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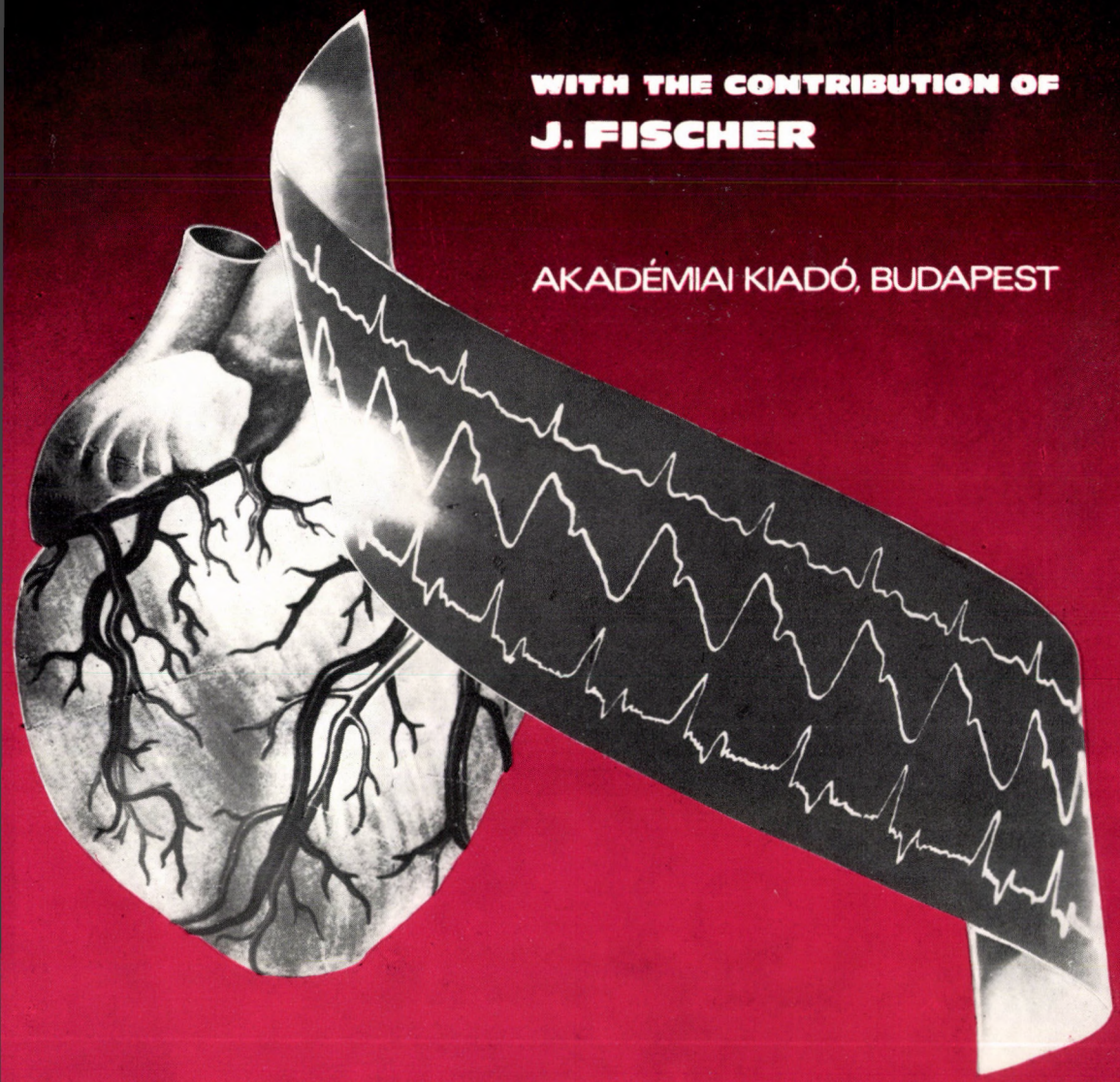
NONINVASIVE EVALUATION OF HUMAN CIRCULATION

CLINICAL, CLINICOPHARMACOLOGICAL AND DATA PROCESSING ASPECTS

WITH THE CONTRIBUTION OF
J. FISCHER

AKADÉMIAI KIADÓ, BUDAPEST



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Noninvasive techniques are being increasingly applied in the study of human circulation. This is due to the fact that direct measurements in the heart applied before cardiac operations are not without danger and can only be performed in well-equipped institutes, the capacity of which is limited even in the most developed countries. Noninvasive procedures being simple and harmless are more suitable for serial investigations. They help in solving not only diagnostic but also epidemiological and clinicopharmacological problems.

In this monograph, the author shows how the first derivative of the carotid pulse follows positive inotropic effects. With this method a series of investigations were made in healthy subjects as well as in cardiac patients at rest, during ergometric exercise and under drug effect. The results help to gain deeper insight into heart failure, and into the pathomechanism of hypertension and essential hyperkinetic heart syndrome. The method may also be applied for clinicopharmacological investigations.

Computer analysis was applied to evaluate the large number of data and to clarify the relations between the changes in parameters. Programs have been devised that are suitable for differentiating between the reactions of healthy subjects and those of cardiac patients thus creating the basis for a mathematical diagnosis.

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by

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Professor György Gábor

CONTENTS

INTRODUCTION

The results presented here are of our own investigations with no attempt having been made to provide a complete review and evaluation of all noninvasive techniques in the study of human circulation.

Originally, our aim was to develop a method for studying the human circulation in a simple and objective way; a method which had to be suitable for investigating large numbers of healthy individuals as well as cardiac patients, after physical effort and therapeutic intervention. In order to achieve our objective a complex investigatory scheme was worked out which uses noninvasive methods. This scheme is most suitable for the assessment of those factors which acutely affect the function of the left ventricle and the systemic circulation. The use of our method enables conclusions to be drawn after a careful consideration of numerous factors—though the technique is not intended to measure every single factor likely to affect the circulation. The emphasis has been, as obviously it should be in all human investigations, on methods which do not produce deleterious effects in the patient.

The direct measurements of flows and pressure gradients in the, heart and great cardiac vessels are now routine. Blood samples may be taken from various parts of the circulatory system for analysis and the circulatory dynamics and anatomical characteristics of heart chambers can also be easily demonstrated. These factors are of considerable help in cardiac surgery, the practice of which is becoming increasingly successful in that such techniques can be applied to accurately establish the diagnosis and to monitor the effects of the operation.

However, these methods can only rarely characterize simultaneously the whole circulatory dynamics even though they undoubtedly yield more accurate results than those achieved by bloodless, noninvasive techniques. Furthermore their use is limited to individual cases and they are unsuitable for large-scale investigations. In this respect, therefore, noninvasive methods are of great value (Snellen 1972).

Pressure pulses generated by the heart, particularly the radial pulse, have been the subject of study for hundreds of years. In ancient times doc-

tors had to rely on their very refined tactile sense. From the feel of the pulse as well as from the appreciation of other physiological phenomena they were able to draw important conclusions.

In the textbook of medicine written by Ti Nei Ching Su Wen, a Chinese physician who lived 2500 years ago, all the pulse characteristics are described in detail. Marey's work (1855) led to the more scientific observation of pulsations when it became possible to record the movements graphically. Marey, quoted by Luisada (1953), wrote: "Science meets with two obstacles, the deficiency of our senses to discover the facts and the insufficiency of our language to describe them. The object of the graphic methods is to get around these two obstacles: to grasp the fine details, which would be otherwise unobserved; and to transcribe them with a clarity superior to that of our words."

The graphic recording of cardiac and arterial pulsations opened up new vistas in the development of cardiology becoming the most important factor in cardiological diagnosis in the second half of the 19th century until the advent of electrocardiography. The development of ECG greatly enhanced the mechanical recording of pulse contour. The simultaneous recording of the mechanical and the electrical events of the cardiac cycle enabled the interpretation and timing of the mechanical recordings to be performed much more accurately.

A fresh impetus was given to cardiography—recording the movements of the heart—which had already been employed by Marey (1855, Luisada 1953, 1959, Benchimol et al. 1960, 1961, 1963, Tafur et al. 1964, Bodor and Kunos 1966, Bodrogi 1966, Denef et al. 1973), to kinetocardiography (Eddlemann 1963), accelerography (Rósa 1947, 1950), to vibrocardiography (Aggress and Wegner 1962), electrokymography (Henny and Boone 1945), radarkymography (Simon et al. 1967, Cohen et al. 1968), and to ballistocardiography (Dock et al. 1953, Starr 1955, 1958, Bodrogi 1956, Gábor and Forgács 1958, 1960, Mihóczy 1964).

The nature of almost every type of pulsation has been investigated using the graphic method permitting Luisada to write that "No manifestation of cardiac action has escaped graphic study".

Recordings made at different points of the vascular system showed the transmission of identical waves, thereby clearly indicating the time needed by the pulse wave to travel between the two points of observation. It also became clear that the pulse waves of the great vessels such as the carotid and subclavian arteries lying near the heart were very similar in form, whereas recordings taken at the periphery essentially resembled the direct intra-arterial recordings of the corresponding vascular bed. A great deal of

knowledge was gained about the vascular patterns obtained in sickness and in health. Full atlases have been published depicting such patterns.

Many investigators have studied external carotid pulse recordings. The initial descriptions were given by Edgren (1889), Huerthle (1893) and MacKenzie (1902). In healthy individuals three principal waves can be identified. The pulse tracing starts with a sharp gradient after the opening of the semilunar valve when the first wave, the percussion wave, appears. Then comes the second, the tidal wave, the final one being the dicrotic wave which follows the incisura (Luisada 1953, Gadermann and Jungmann 1964, Meyer-Heine et al. 1966, Bodrogi 1966*a*, *b*).

The carotid pulse wave is also known as the central pulse curve because of its proximity to the heart. The influence of the peripheral vascular system is relatively less marked on this curve than on those recordings taken at a greater distance from the heart.

Certain points of the pulse wave are indicators of the different phases of the heart beat. The sudden rise at the beginning of the carotid pulse tracing coincides with the beginning of the ejection phase, the incisura with that of the closure of the semilunar valve, and the aortic component of the second heart sound (disregarding the delay which is constant in the same individual and it is in the order of one hundredth of a second, this is the travelling time of the pulse wave from the aortic valve to the point of recording in the carotids). Thus the central pressure tracing is often used as a 'reference curve'. It is, moreover, also used for determining various phases of the cardiac cycle in healthy individuals and in patients suffering from some complaint or other.

With the above factors in mind, we selected the carotid pulse wave analysis to be the main feature for our own noninvasive investigatory techniques. In addition, we monitor cardiac frequency and blood pressure. In acute investigations it has been possible to make continuous recordings of the carotid pulse wave, and this has proved to be extremely useful allowing an analysis of the effects of rapid heart rates on haemodynamic functions. We have introduced as new and relevant parameters the first and second derivatives of the carotid pressure pulse (C): the former being dC/dt, the latter d^2C/dt^2. The derivatives denote the speed of change in pressure, and as we have later demonstrated, the height of the peaks parallels the maximal contractility of the myocardium. This may be regarded as one of the main indicators of the cardiac function. Previously, a reliable noninvasive technique was not available for measuring this function.

Chapter 1 deals with the first derivative of the carotid pressure curve and demonstrates its application in studying the pattern of the carotid

pulse wave and in measuring the duration of the individual phases. The use of the second derivative of the carotid pressure tracing is also demonstrated.

In Chapter 2 we present our results, based on cardiac catheterization in animals as well as in humans, on the use of the pulse height (max dC/dt) as an index of left ventricular contractility. Following positive inotropic stimuli the peaks were higher and the actual change was proportional to the magnitude of the stimulus. Correspondingly, with negative inotropic interventions, the maximum peaks were lower.

The analysis of the amplitude of the changes in the first heart sound was particularly helpful; details are given in Chapter 3.

After having elaborated the basic principles, practical uses of the technique are described in Chapters 4 and 5. One area of application is that of clinical medicine and we have carried out experiments in patients with congestive cardiac failure, in various stages of hypertension and in essential hyperkinetic heart syndrome.

The other field is clinical pharmacology in which noninvasive techniques have important applications. Here the quantification of the effects of drugs with positive and negative inotropic action, and the assessment of sensitivity of patients to noradrenaline and isoprenaline are of paramount importance.

Chapters 6 to 9 outline the analysis of our data by computer. Computerization has greatly facilitated the interpretation of our results. Our primary aim was to find the main differences between healthy individuals and cardiac patients. We feel that our investigations have brought us nearer to the objective evaluation of the state of human circulation by noninvasive techniques.

In the last Chapter we have dealt with the limitations of our methods and have presented our plans for the continuation of our work.

It is felt that our task is by no means complete, even so a great deal of help and cooperation has been needed to reach the present stage.

The initial phase of the investigation was started at the 2nd Department of Medicine, Semmelweis Medical University, Budapest, from 1964 to 1966 after which it was continued in the National Institute of Cardiology until 1967. The work has been continued since then at the Bajcsy-Zsilinszky Hospital, Budapest.

It is fitting to acknowledge the benevolence of the late Professor Gömöri, for having allowed us to commence our trials with what was then a very new technique. We express our gratitude to Professor Gy. Gábor, Director of the National Institute of Cardiology, who at the initial stage as Head of the Cardiology Division, 2nd Department of Medicine, took an active part in

the form of his guidance, advice and criticism in almost every phase of our work.

We are indebted to Prof. I. Fenyő of the Mathematics Department of the Faculty of Electrical Engineering, Technical University, Budapest, who from the outset, and during the entire period of investigation, assisted with the mathematical and physical aspects of the research. His associate, L. Bánsági, constructed the first derivational electronic circuit for adaptation to our apparatus.

The Principal Official of Medicor Works, L. Szabó, is thanked for his technical help.

The complex nature of our research scheme necessitated the formation of working teams of distinguished experts to deal with specific aspects of the problem.

We are grateful to Prof. L. Hársing, Associate Prof. T. Romoda, Senior Lecturer Gy. Somogyi, Head of Section M. Békés, Research Worker Eszter Török, University Lecturers Éva Kiss and B. Kenéz, Chief Physician K. Komor, and to our colleagues working with us at present, M. Szirtes, Zs. Herpai, J. Décsy, I. Vass, F. Szász, and J. Arnold.

The computer work was performed under the direction of the Principal Research Officer of the Hungarian Academy of Sciences, J. Fischer of the Computer and Automation Institute of the Hungarian Academy of Sciences. We express our thanks to Z. Markovics and Mrs. G. Jancsó, whose help in mathematical analyses was highly valuable.

Finally, Director and Physician-in-Chief Gy. Bodrogi and Prof. T. Frey are thanked for their helpful recommendations and advice at the review stage of this book.

PART I

CHAPTER 1

THE FIRST DERIVATIVE OF THE EXTERNAL CAROTID TRACING

WHAT IS A DERIVATIVE?

The derivative in mathematics is an elementary concept. Since this study has been written for medically qualified doctors it is necessary to give a short explanation.

The laws of the rate of change in mathematics are described as functions. This means that the independent variable (x) determines the rate of change of the dependent variable (y), i.e. $y = f(x)$. Geometrically, the x, y coordinate system gives the curve of the function (Figs 1, 2). It also has a meaning in physics. Very often the independent variable is the time (t) and in the majority of cases the motion (S) is the dependent variable, $S = f(t)$ (Fig. 3). The function is composed of an infinite number of points and the connection of these points with an unbroken line may produce the whole function with the necessary accuracy. If on the function curve $y = f(x)$ we mark two points of which the coordinates are a, $f(a)$ and x, $f(x)$ (Fig. 1), the straight line which connects the two points forms an angle α with the x axis and the tangent of this angle, in other words its slope, is

$$\frac{f(x) - f(a)}{x - a}.$$

This quantity can also be described as $\frac{\Delta f(x)}{\Delta x}$ and its value is called differ-

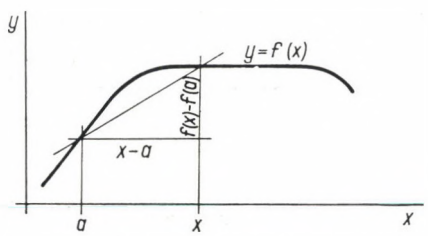


Fig. 1. The slope of the straight line drawn over two points of the function $y = f(x)$, and $\frac{f(x) - f(a)}{x - a}$ is the difference quotient

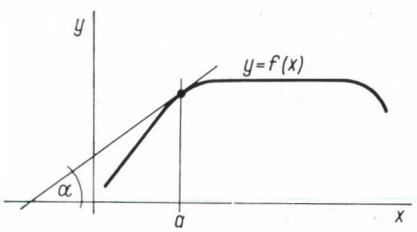


Fig. 2. The slope of the line drawn over point a is given by the differential quotient $\frac{df(x)}{dx}$

ence quotient. If the distance between the two points is of an infinitesimal size, i. e. it approaches zero $[(x - a) = \Delta x \to 0]$, the former quotient tends to its limit, so the differential quotient of the basic function is being constituted; mathematically it is denoted as $\frac{df(x)}{dx}$. It also renders the tangent of the angle α between the x axis and the tangent, drawn at point a. In this way at any point of the function $y = f(x)$ the tangent line can be constructed, and its slope (tangent of the angle) can be described by a second function. This function is the first differential quotient, in other words the first derivative of the basic function and its equation is $y' = f'(x)$. If the $f(x)$ function can be constituted by elementary functional operations, its differential quotient, i. e. derivative function, can also be obtained in a similar way. Geometrically, with the tangent lines drawn to the basic curve, their derivative curve can be constructed in every case. There are some regularities, however, which help in constructing the derivative; this is shown in the upper part of Fig. 3, where S denotes the motion in the function of time $S = f(t)$. Stretch 1–2 is a straight line with a constant gradient and the derivative, which is the lower curve in Fig. 3, is also straight having a constant value. The slope of the upper curve is less steep between points 2 and 3 and the derivative curve turns downwards. Stretch 3–4 on the basic curve is horizontal, the derivative being zero. This is a very relevant assertion, namely the derivative is zero where the basic curve neither ascends nor descends. Its value is constant at extreme or stationary points as well. After point 4, curve $S = f(t)$ again tends downwards and the derivative curve denoted as $\frac{dS}{dt}$ becomes negative.

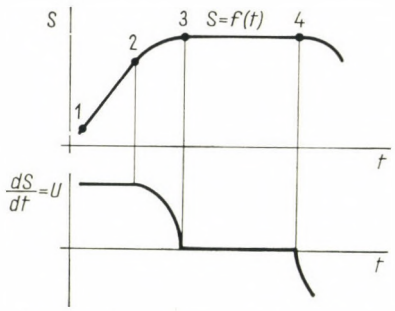


Fig. 3. The differential quotient of the motion function $y = \frac{dS}{dt}$ is the velocity function. The continuous ascendence of stretch 1–2 corresponds to a straight line (constant value). The derivative function related to stretch 3–4 is zero

It is possible to constitute the differential quotient by a computer with a reasonable accuracy. The functional relations which can be described by electrical signals form a special group in the sense that it is possible to produce the derivative of the respective function with a suitable electrical circuit synchronously. This is dealt with in the next section.

The differential quotient or derivative determines certain mathematical relations and in geometry it is the slope of the tangent line. If the relation has a physical or biological meaning the differential quotient has the appropriate implication. Most commonly it means speed and in this case the basic relation is motion. If the basic relation is change of pressure its derivative means the rate of change of pressure. We talk about time derivative if the rate of change is described in the function of time and this is very common in biological recordings. As it can be seen in the following the first derivative of function $y = f(x)$ is also a function $y' = f(x)$ and, in a similar manner from this the second . . . and nth derivative can be derived.

The second derivative in physical terms means velocity $y'' = f''(x) = \frac{d^2y}{dx^2}$.

*

It can be stated that the derivative of the curve is suitable for characterizing speed.

SIMPLE ELECTRONIC DERIVATION OF THE PRESSURE AND PULSE CURVES

The derivative is a new and useful parameter, its construction is simple and can be recorded synchronously with the basic curve. Many biological events are suitable for being converted into electrical signals which may be stored on magnetic tape for further use. The electronic derivation of electric signals is a technique which has been known for a long time. Reeves et al. (1960) and Reeves and Hefner (1962) recorded the pressure curve of the

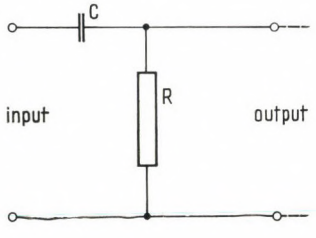


Fig. 4. Diagram of the R-C electric circuit. R = resistance: 50–70 Kohm; C = capacity: 2–4 μF; time constant: 100–150 msec

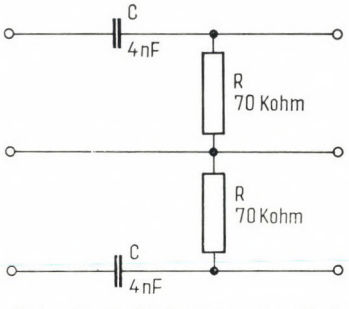


Fig. 5. R-C electric circuit for symmetric amplifier

dog's left ventricle synchronously with its electrical derivative. They found a relationship between the peaks of the pressure curve and the rate of change of contractility in the left ventricle. Gleason and Braunwald (1962) were the first to use this technique in humans.

There are three practical ways for derivation: (*i*) Using an analog amplifier; (*ii*) applying the carrier frequency method; (*iii*) by means of the so-called passive R-C (resistance-capacity) electrical circuit.

The first two techniques are rather complicated and expensive. For our purpose the third possibility was accessible. Considering the accuracy of the basic curve, the precision obtained by R-C derivation is quite satisfactory. It does not require an expensive and complicated equipment. The circuit diagram can be seen in Fig. 4. The highest frequency of the pulse and pressure curves to be derived is about 5 Hz. To secure a suitable signal/noice relationship an R-C electrical circuit was constructed with a time constant of 100–150 msec. The value of 'R' is 50 to 70 Kohm and that of 'C' 2 to 4 nF. The biological amplifier has been constructed with bilateral symmetry. Therefore in these cases the circuit diagram shown in Fig. 5 was applied. The unit used for derivation can be seen in Fig. 6. The basic curve to be

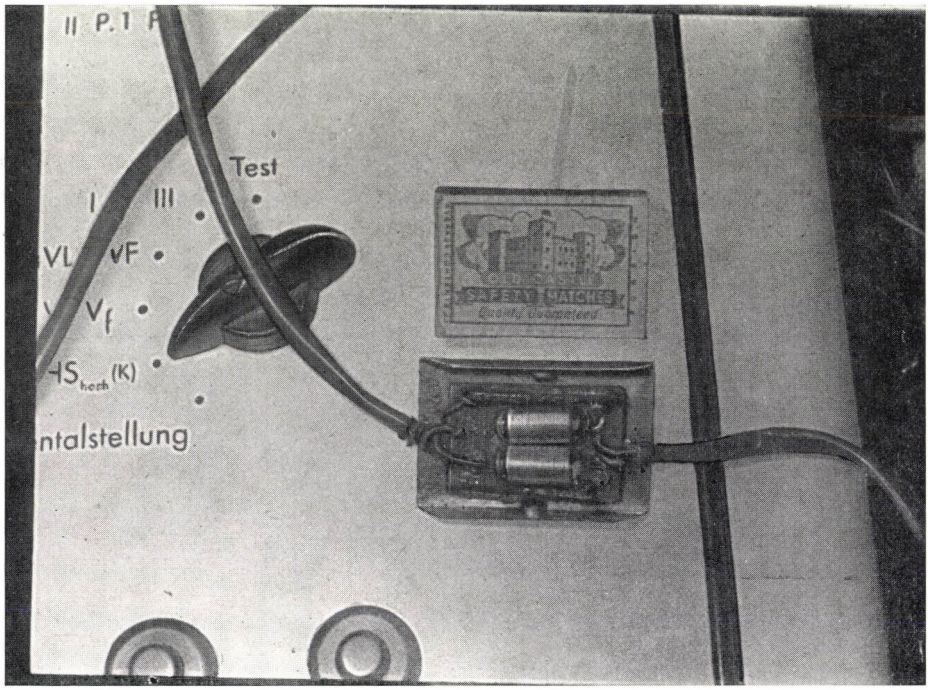
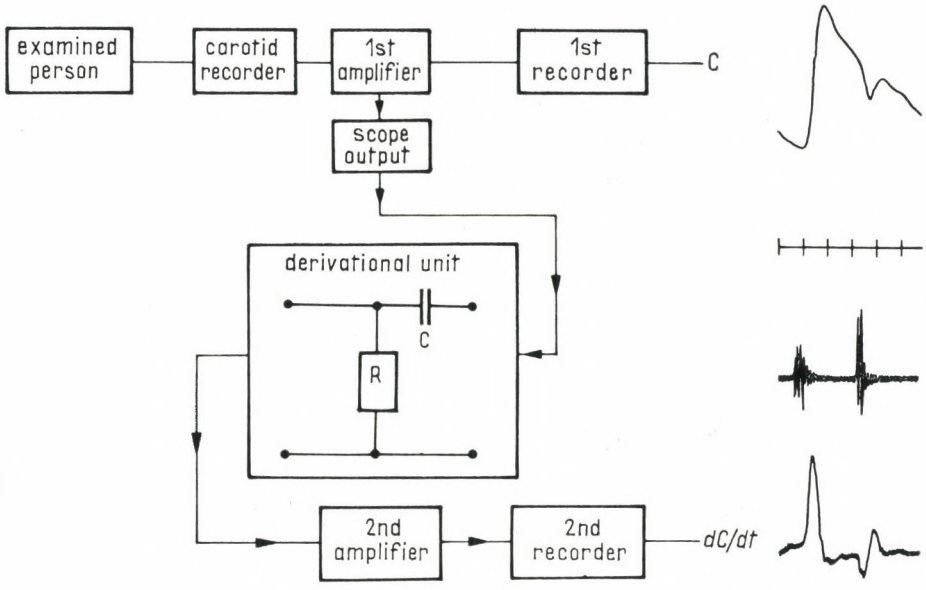
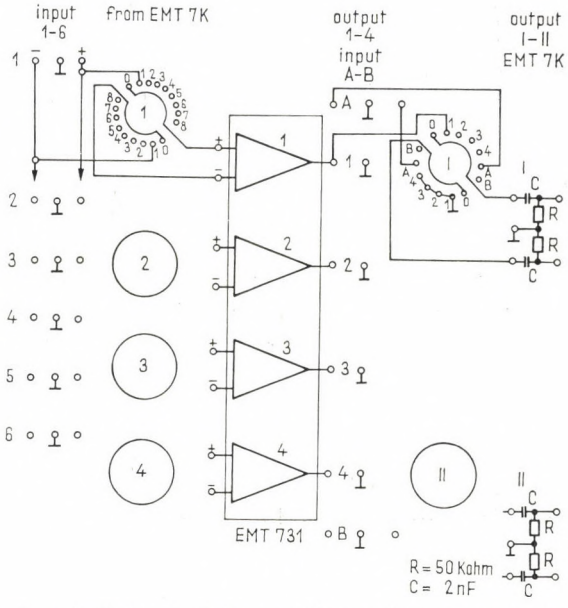


Fig. 6. The unit applied for derivation is not bigger than a matchbox



a



b

Fig. 7.(*a*). The electrical signal of the carotid tracing comes to an amplifier, from this to the first recorder. From the scope output the signal arrives through the unit for derivation to the second amplifier and finally to the second recorder. (*b*) The circuit diagram used with the Elema-Mingograph-61. The signals coming from the output of the scope of the basic instrument are led to the input shown at the left side of the drawing. Switches 1 to 4 make possible the transmission of the signals to an amplifier of the EMT 731 apparatus, and from here with switches 1 and 2 through the R-C electric circuit I and II with a plug into the 20 mV input of the basic instrument. EMT 7K: specification of final amplifier

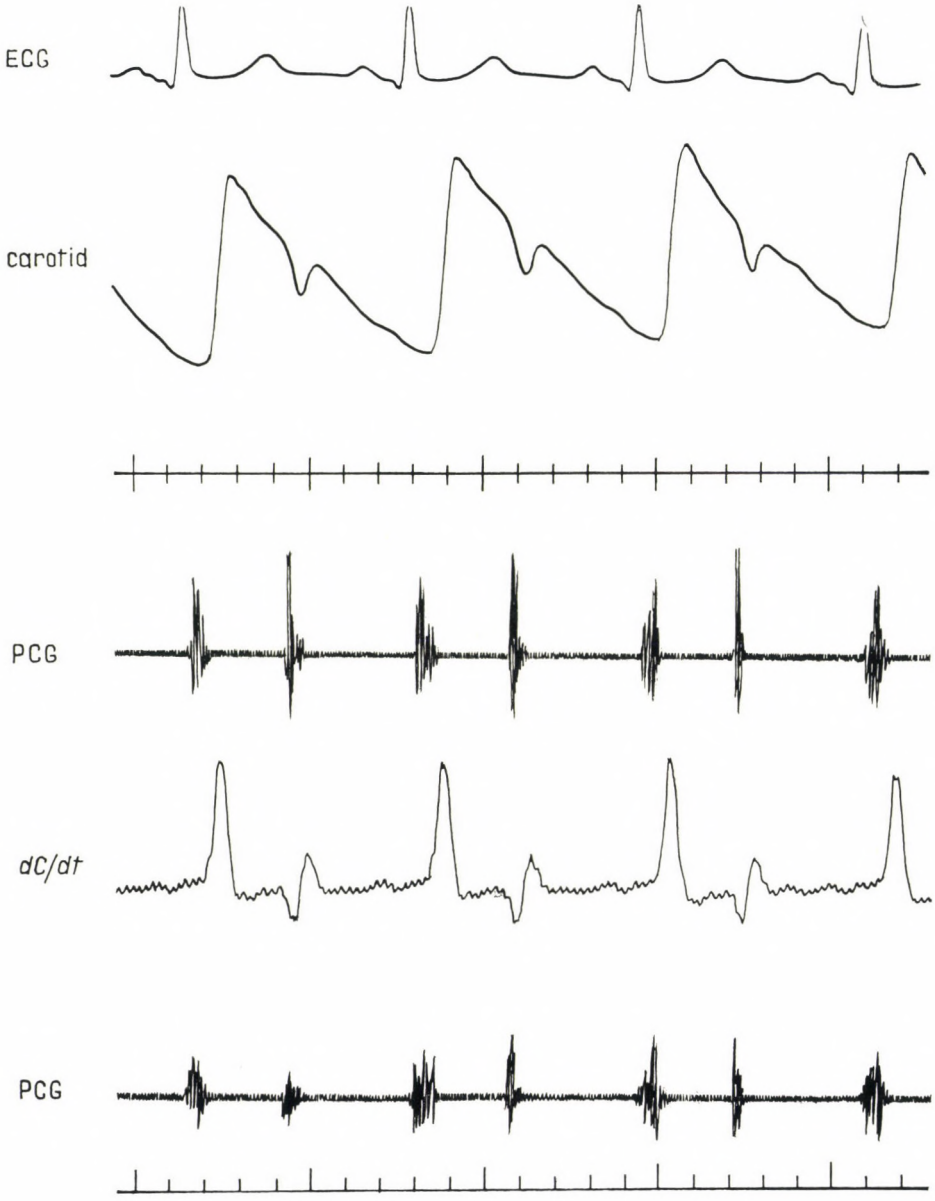


Fig. 8. Hellige multiscriptor, paper speed: 50 mm/sec. In addition to the ECG and PCG of a healthy individual the carotid tracing and its first derivative can also be seen

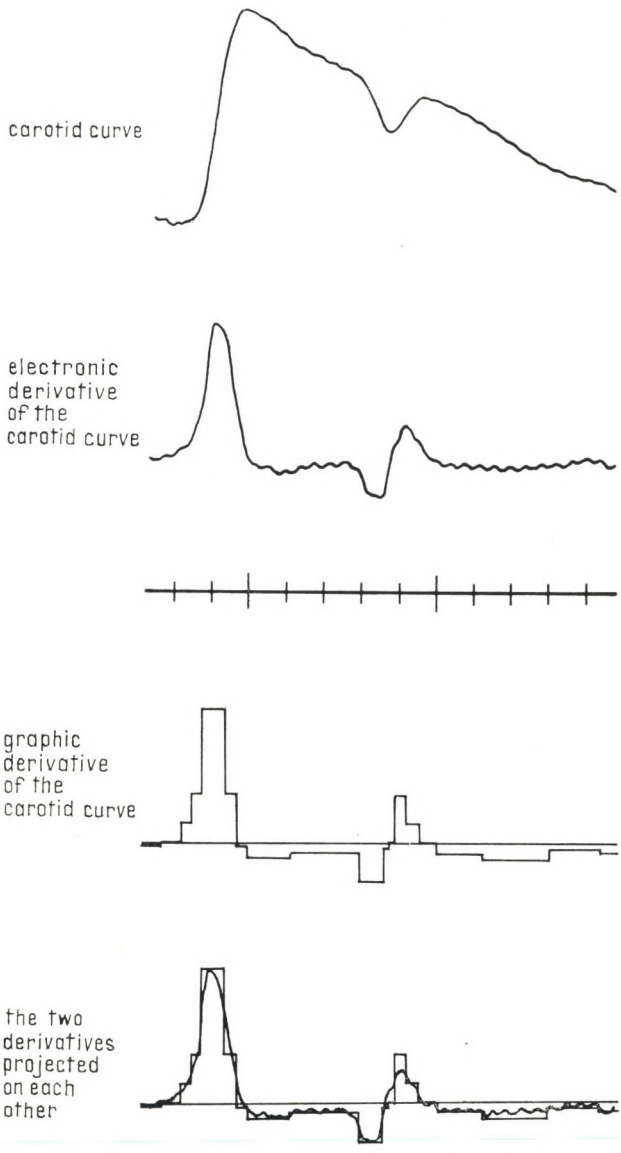


Fig. 9. Hellige multiscriptor, paper speed: 100 mm/sec. The electronic and graphic derivatives are highly similar

derived (in our cases most frequently the external carotid tracing or pressure curve) was recorded through one channel of the multichannel apparatus (Fig. 7*a*, *b*). The carotid curve, in the majority of cases, was taken with a piezo crystal 'information' pick-up. The electrical output of the scope of the same channel was connected with the unit described above. The derivative signal obtained was linked with another channel of the polygraph and registered synchronously with the basic curve. The second derivative was gained by using the same principle; the electrical signal of the first derivative was connected to another R-C electrical circuit and then to the polygraph.

This technique can be applied to almost every equipment used in Hungary. We ourselves worked with this technique on the following instruments: Hellige, Siemens, Elema, Cardotester, Galileo. Figure 8 shows a recording taken with a 6-channel Hellige multiscriptor. The first channel was used for the second lead of the ECG, the second for the carotid curve (*C*), the fifth for the first derivative of the carotid curve and the fourth and sixth channels for the phonocardiogram.

For the sake of comparison and for checking our technique the derivative of the carotid curve was constructed in a healthy individual, both graphically and electrically. The two derivatives revealed great similarity at the relevant points (Fig. 9), with the two curves covering each other. It is beyond doubt, in view of the theoretical considerations of Rushmer (1964), that the electronic derivative is more detailed and accurate (Simonyi et al. 1965, Simonyi and Bánsághi 1966, Simonyi 1973, Spodick 1973).

Since our first publication in 1965, Hungarian authors have used the derivatives of the pressure and pulse curves in exploring haemodynamics [Romoda 1967, Romoda and Istvánffy 1969, Bodrogi et al. 1969, 1970, Bodrogi and Biró 1970, Romoda et al. 1970, Fenyvesi (personal communication) 1970, Thuránszky 1970, Simon et al, 1970, Porubszky et al. 1970, 1972, Simon 1970, 1971, Békés et al. 1971*a*, *b*, Bodrogi 1970*a*, *b*, 1971, 1972, Bodrogi and Bodrogi 1972, 1973, 1974, Bodrogi and Kovács 1972, Son 1972, Kékes et al. 1973, Porubszky and Gábor 1972]. Warrenbourg et al. (1969*a*, *b*), Kahn and Spodick (1972), Spodick (1973), and Nandi and Spodick (1973) also report on the successful use of the carotid derivative. The derivative of the ECG is also used (Kenedi and Müller 1972, Kenedi et al. 1972*a*, *b*).

*

The technique described above is suitable for simple derivation of pulse and pressure curves.

THE FIRST DERIVATIVE OF THE CAROTID PULSE WAVE IN HEALTHY INDIVIDUALS

The first derivative of the carotid tracing (dC/dt) has a characteristic shape; this has been described by us on the basis of analysing 250 curves (Simonyi et al. 1965, 1968). The findings ware confirmed by results obtained after analysing 1,500 curves (Simonyi 1971).

The shape of the derivative curve is determined from the original tracing, i. e. the carotid pulse wave which is recorded as follows. The patient lies in the supine position (Fig. 10). Piezocrystal infration pick-up is placed over the site of maximal pulsation of the carotid artery using a degree of pressure not uncomfortable to the patient. The errors in placing the pick-up affect the shape of the carotid tracing and obviously that of the derivative curve as well. With practice and patience reproducible curves can be recorded. During recording the most important prerequisites are a good pick-up, a well-trained staff and a cooperative patient (Bodrogi 1966). If any of these prerequisites is not fulfilled a good recording is not possible. Occasionally,

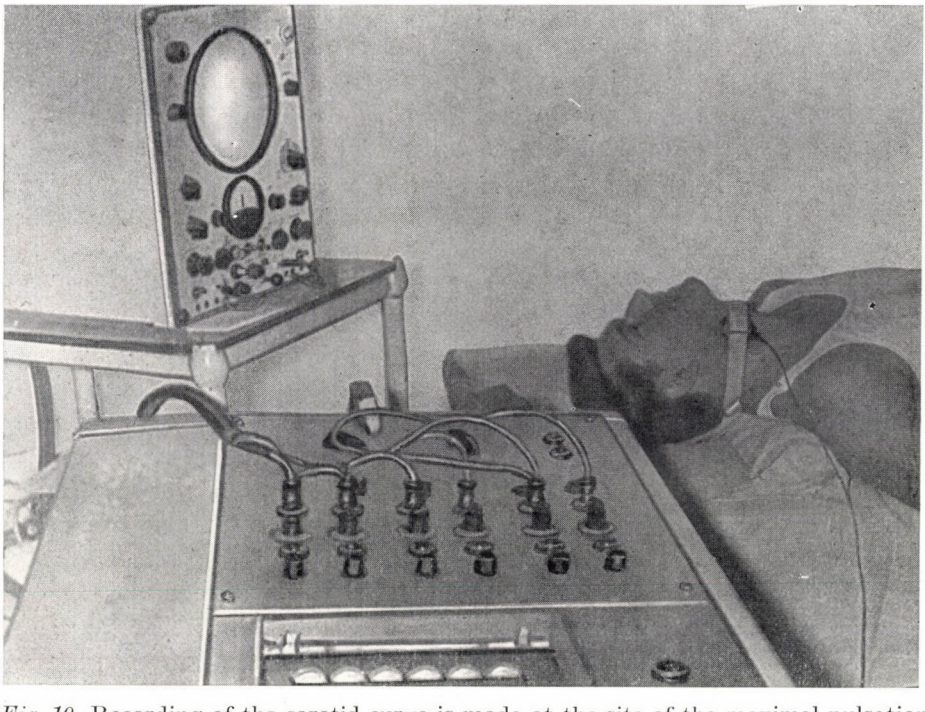


Fig. 10. Recording of the carotid curve is made at the site of the maximal pulsation of the carotid artery

anatomical peculiarities, such as a short neck, thyroid goitre, etc. may cause difficulties. From a good tracing the following can be expected.

1. It should have one or two initial small waves, which characterize the central pulse.

2. After the opening of the semilunar valve it should show a steep rise.

3. The incisura should be visible on the descending limb (unless there is severe aortic regurgitation characterized by the absence of the incisura).

4. In diastole, apart from the dicrotic wave the curve should have a gentle slope to the next presystole (Bodrogi 1966).

It is necessary to carefully analyse the derivative curve, too. It must be checked to ensure that the steeper slope of the tracing corresponds to a higher, and the gentler slope to a smaller derivative curve. Also the positive peak of the derivative should coincide with the steepest part of the tracing. Finally, at the extreme values of the basic curve, as we would expect, the derivative should be on the zero line. In other words, the derivative curve's zero line can be determined by drawing a line on the points representing the extreme values of the original tracing, these being the beginning of the rise, and the highest and lowest point of the incisura. This is relevant because the highest point of the derivative is measured by correlating it to the zero line, and at a first glance the often negative diastolic line may be regarded as the base line. If the preamplifier of the carotid pick-up is disconnected, the zero line of the derivative appears directly on the recordings. The derivative curve in diastole, corresponding to the descending limb of the carotid tracing, generally runs slightly below the zero line. The presystolic wave(s) of the carotid tracing appear on the dC/dt curve as a small positive peak. Simultaneously with the sudden rise of the carotid curve a rise can be seen on the derivative, too. The synchrony of the two points at the beginning of the steep slope helps in identifying them. This is when the first pointed positive wave being a characteristic feature of the differential curve appears reaching its peak when the rise of the carotid tracing is the steepest. After this, it suddenly falls, reaching or even crossing the zero line and becoming slightly negative. In some cases, however, it becomes positive. Before the end of systole there is a regular small negative wave, being smaller than the first positive one, reaching the zero line simultaneously with the deepest part of the incisura. Then in synchrony with the dicrotic wave of the carotid tracing a small positive wave can be seen on the derivative curve, this being followed by the diastolic period; throughout the diastolic phase, up to the presystolic small wave, the curve is slightly in the negative range.

The shape of the carotid tracing in healthy individuals is not uniform. O'Rourke (1971) has pointed out that there is no universal nomenclature as

far as the name of the waves are concerned. Normal variants occur in the shape of the presystolic small waves in the position of the anacrotic notch; in the magnitude of the percussion waves, and in the plateau formation in t waves, in other words the 'catacrotic flexure', in the position of the incisura and of the dicrotic wave, in their size (compared to each other) and in their timing (Luisada 1953, 1959, Gadermann and Jungmann 1964, Dontas 1960, Dontas et al. 1961, Freis et al, 1966). This variability is demonstrated in Figs 8 and 11. The derivatives are not identical but in view of the main waves they show close similarity, and this can be seen at 96.5% of the tracings (cf. Fig. 18). Warrenbourg et al. (1969) gave an account and interpretation of the first derivative of the carotid curve. They mark the waves of the differential curve with A, B, C, D and E. A is the first high, positive, B is the following midsystolic, negative, C the small, positive, D the regular, negative, and E the small, positive wave which corresponds to the dicrotic undulation. Their characterization of tracings obtained in healthy individuals is similar to ours. Wave A runs always higher than wave D, waves A and D reveal less variability. The highest number of variants were found among the midsystolic waves, and their properties are dependent on the plateau formation of the carotid tracing. All the waves are present in young individuals, whereas with advanced age waves B and C often disappear. In the figures by Kahn and Spodick (1972) and Nandi and Spodick (1973) theshape of the first derivative of the carotid curve is similar to that observed by us.

*

The first derivative (dC/dt) of the carotid tracing in healthy individuals is a characteristic (typical) curve.

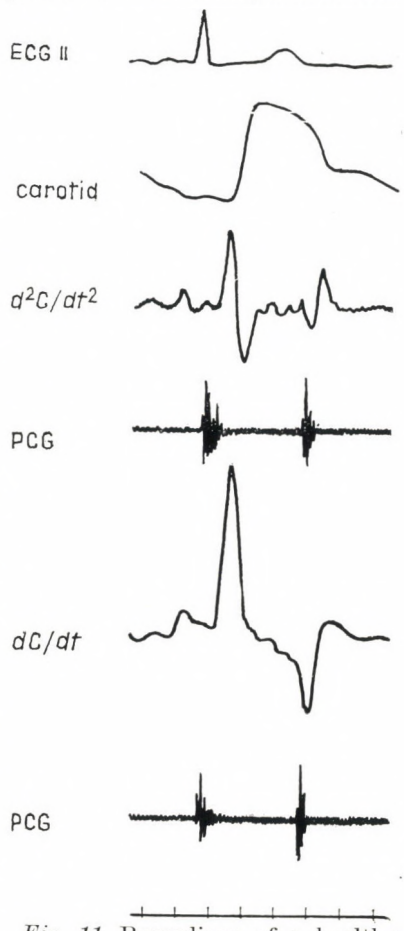


Fig. 11. Recordings of a healthy individual by the Hellige multiscriptor (paper speed: 50 mm/sec). The upstroke of the carotid curve of dC/dt and d^2C/dt^2 begins synchronously indicating the zero line on the corresponding curves and the beginning of the ejection. The first positive wave of dC/dt crosses the zero line at the end of the rapid ejection. The incisura shows the end of the ejection period

THE USE OF THE *dC/dt* CURVE FOR MEASURING SYSTOLIC TIME INTERVALS

The analysis of the differential curve helps in determining the beginning of the ejection phase (Simonyi et al. 1968). The incisura of the carotid tracing marks the end of the ejection period. The incisura can be identified on the derivative curve at a distance of a few hundredths of a second from the deepest point of the derivative, where it crosses the zero line (Fig. 11). Warrenbourg et al. (1969) and Nandi and Spodick (1973) recommend the deepest point of the derivative curve for the same purpose because it is easy to identify. A new step is the estimation of the duration of the first positive notch. This probably indicates the duration of the rapid ejection period. At later stages the velocity decreases during the reduced ejection phase which starts at the end of the rapid ejection and finishes at the incisura. With the simultaneous recording of the PCG and the carotid tracing the length of the whole systole can be estimated. With the duration of the ejection period being subtracted from this the time of the isometric contraction is obtained (Fig. 12). Measurements have been carried out with this technique in 50 healthy individuals. In order to further check our results the phases of the systole were also estimated with a ballistocardiograph (Gábor and Forgács 1958, 1960, Gábor 1964) in the same individuals; the statistical analysis showed a good correlation (Table 1; Simonyi et al. 1965, 1968).

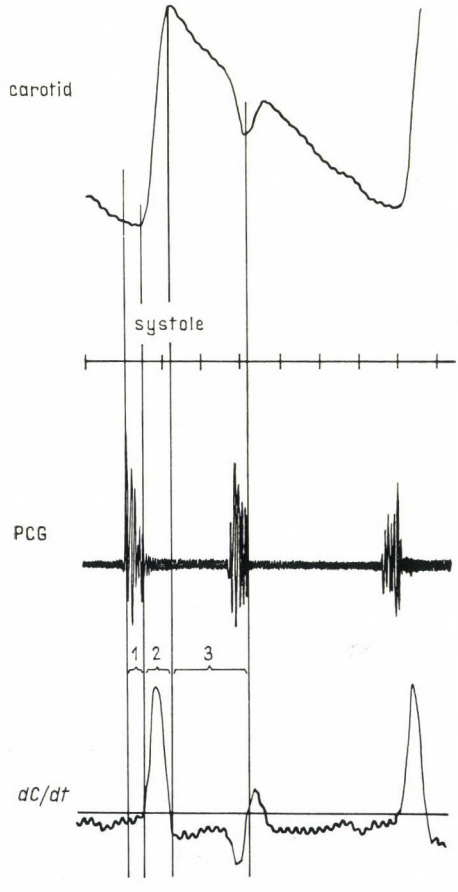


Fig. 12. The measurement of certain phases of the systole can be seen in the PCG, carotid tracing and its first derivative. 1, isometric contraction; 2, rapid ejection; 3, reduced ejection

TABLE 1

Data of systolic time intervals measured on the carotid derivative and ballistocardiographic curves

	Isometric contraction	Rapid ejection	Reduced ejection
	in sec · 10^{-2}		
BCG	3.83 ± 0.90	11.78 ± 1.51	16.75 ± 1.41
dC/dt	3.57 ± 0.76	11.50 ± 1.56	17.36 ± 1.74
t	1.4	0.93	1.78
p	> 0.10	> 0.20	> 0.05

Figures 13 to 15 show the statistical distribution of our results, the two curves represent findings using the two techniques. A close similarity can be noted. Warrenbourg et al. (1969) estimated with the derivative technique

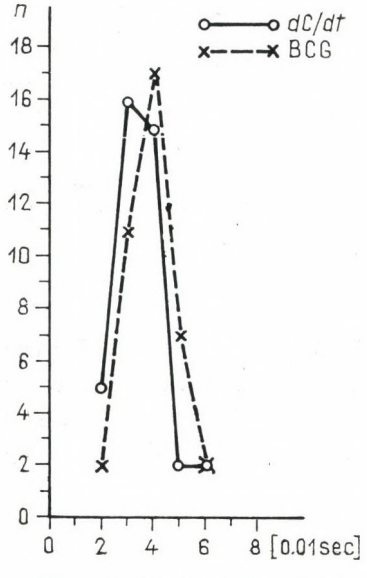


Fig. 13. Abscissa: length of the isometric contraction in hundredth of seconds. Ordinate: number of cases in whom the values were found either with ballistocardiography or with the *dC/dt* curve

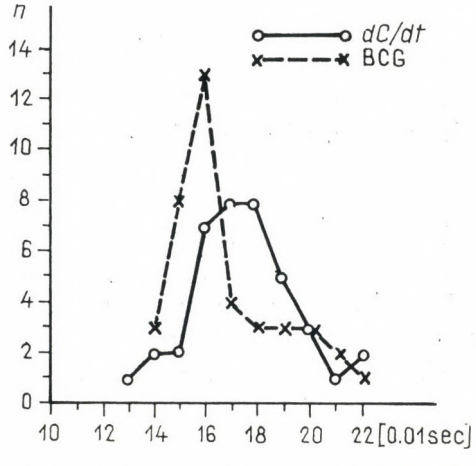


Fig. 14. Abscissa: length of the rapid ejection. Ordinate: number of cases in whom the values were found with ballistocardiography and the *dC/dt* derivative curve

the time of wave *A* and found it to be 80 to 150 (mean 120 msec), and this agrees well with our own measurement which was 111.5±15.6 msec. The time of ejection was found to lie between 250 and 300 msec, our mean value for the same parameter being 188.6 msec.

Estimation of the 'contraction time' of the heart was first made at the beginning of the century. It has since been used as a basis for evaluation of the cardiac function (Hess 1915, Wiggers 1921, 1952, Schultz 1937, Blumberger 1940, Benchimol et al. 1960, 1962, 1963, Weissler and Harris 1968, Weissler et al. 1961, 1964, 1969, Bodrogi 1961, Agress and Wegner1962, Holldack 1966, Harris et al, 1967, Stafford et al. 1970, Willems and Kestelloot 1967, Garrard et al. 1970, Perloff and Reichek 1972, Parks et al. 1973).

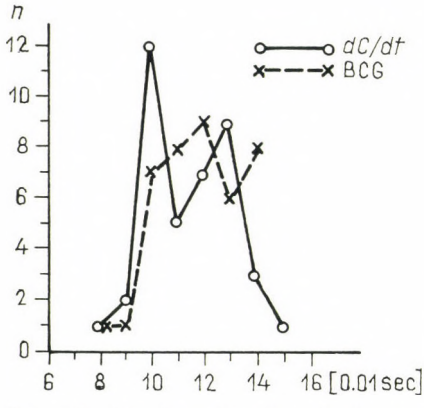


Fig. 15. Abscissa: length of the reduced ejection period; Ordinate: number of cases in whom the values were found with ballistocardiography and the *dC/dt* derivative curve

The first derivative of the apex cardiogram (Reale 1967, Gleichman 1968, Gleichman et al. 1970, 1971, Porubszky and Gábor 1972, Gábor et al. 1972, Kékes et al. 1973, Bodrogi and Bodrogi 1973, 1974, Strausz et al. 1974) and that of the chest impedance cardiogram (Lababidi et al. 1970) may also be used for the same purpose.

It is hoped that the technique describ ed above will serve as a useful aid in estimating certain phases of the systole.

*

The first derivative of the carotid tracing (*dC/dt*) could be used for the measurement of the duration of slow and rapid ejection. The positive wave of the *dC/dt* curve marks the boundary of the rapid ejection period. The results obtained with this technique and with acceleration ballistocardiography showed good correlation.

THE FIRST DERIVATIVE OF THE CAROTID PULSE WAVE UNDER PATHOLOGICAL CONDITIONS

In this section our observations on the derivative curve in patients with atherosclerotic heart disease of varying severity and blood pressure will be reviewed (Simonyi et al. 1968*a*). The grading of disability was done according to the criteria of the New York Heart Association.

A large number of cardiac patients have curves which deviate significantly from those of normals. These differences are in the descending part, insofar as they do not return to the base line steeply, either forming a second peak (Fig. 16), or assuming a dome-like shape (Fig. 17). According to Bodrogi's observations (1972) the time required for the curves in these cases to return to the zero line is definitely longer than in healthy individuals. Figure 18 shows a schematic diagram of the typical and atypical *dC/dt* curves.

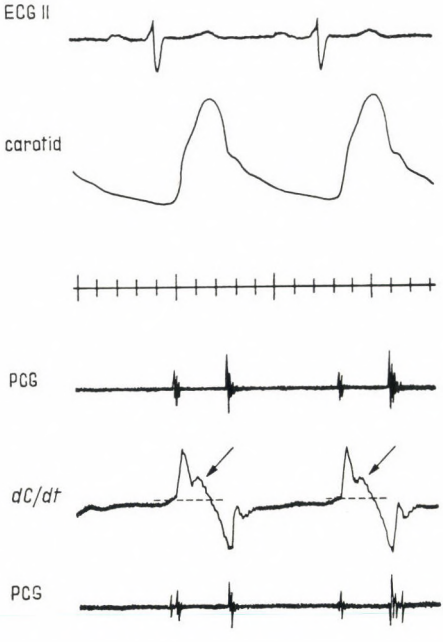


Fig. 16. Atypical *dC/dt* curve. The descending part of the positive wave does not fall steeply but returns to the base line after forming a second peak

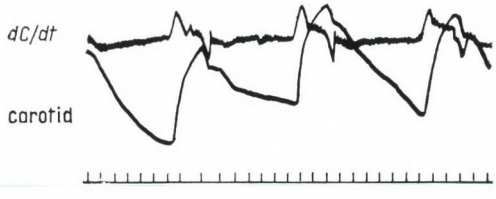


Fig. 17. Atypical *dC/dt* curve. The descending part of the positive wave does not fall steeply but returns to the base line with a dome-like contour

250 *dC/dt* curves were analysed and divided into two groups. In Group I there were 90 individuals without cardiac disease. In Group II, there were 140, all with significant heart disease.

Figure 19 shows that in Group I the percentage of typical *dC/dt* curves was 96.5%, and that of atypical 3.5%. In Group II there were only 41.6% typical

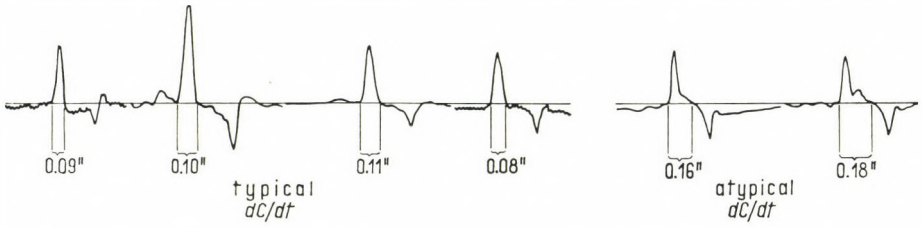


Fig. 18. Typical and atypical *dC/dt* curves. On the typical curve the descending part of the first positive peak returns steeply to the base line, the time between the beginning and the end of the wave being short (0.08–0.14 sec). On the atypical curve the descending part is not steep. Often a second peak or a dome-like shape appears and the derivative crosses the base line after a shorter period

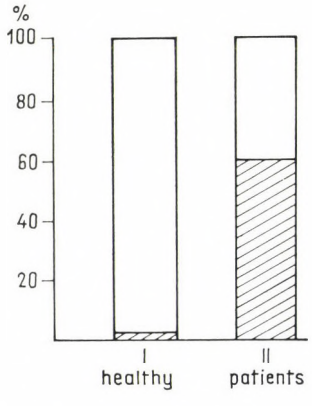


Fig. 19. In the healthy group there are 3.5 per cent atypical curves, in the group of patients there are 58.4 per cent. Empty column: typical *dC/dt*. Cross-hatched column: atypical *dC/dt*

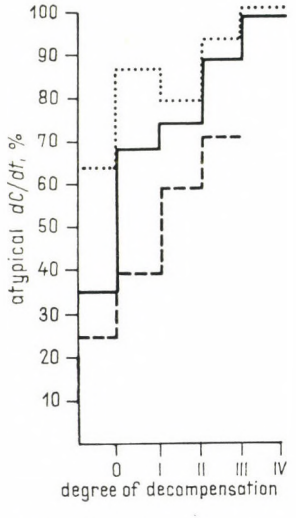


Fig. 20. Atypical curves are more rare among compensated patients, their proportion increases with the severity of decompensation. There are more atypical curves in the hypertensive group. Dotted line: hypertensive. Broken line: normotensive. Solid line: average

and 58.4% atypical curves. A correlation has been found between the clinical picture and the incidence of atypical tracing. Among the patients there were relatively few cases of valvular defects, there being none with aortic valve disease. The few cases with mitral valve abnormalities presented a distinctive picture as far as the derivative curves were concerned. In cases of congestive cardiac failure and in hypertensive disease atypical *dC/dt* curves were often found. For further clarification the patients of Group II were subdivided according to the degree of decompensation, and the number of atypical derivative curves was estimated in the subgroups (Fig. 20). The latter were further separated into normotensive and hypertensive cases. The Figure shows that the smallest number of atypical curves was found in the compensated group, and the frequency of abnormality increased with the grade of decompensation. Among the hypertensive patients there were many more atypical tracings than among those with normal blood pressure. Figure 21 shows the correlation between the height of the blood pressure and the rate of atypical tracings. The greater the systolic pressure the larger was the number of the atypical derivative curves. This was not the case with diastolic pressure, there being more atypical curves in the hypertensive patients with low diastolic pressures.

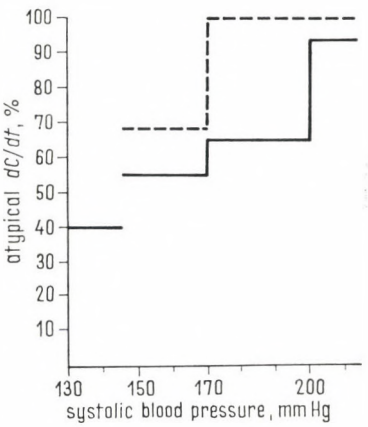


Fig. 21. The curve shows the correlation between the rate of atypical *dC/dt* curves and the height of the blood pressure. With the increase of systolic pressure the frequency of atypical curves increases; this is particularly so if the high systolic pressure is accompanied by a diastolic pressure which is lower than 95 mm Hg. Broken line: diastolic pressure < 95 mm Hg. Solid line: diastolic pressure > 95 mm Hg

Cases with valvular failure were not analysed but it must be pointed out that in aortic stenosis the *dC/dt* derivative greatly accentuates the characteristic vibrations seen on the anacrotic side (Fig. 22) and this might be a useful diagnostic aid (Simonyi 1971).

Warrenbourg et al. (1969) have also investigated the derivatives of the carotid tracing; their work is of great importance because it was carried out in cases in which valvular defects had been demonstrated by cardiac catheterization. They emphasized the value of the derivative in aortic valvular defects. Their tracings of heart disease associated with hypertension are very similar to ours.

Rushmer's view (1964) that the efficiency of the heart is reflected in the 'initial ventricular impulse' is supported by much experimental work. It could be expected that in this phase there are some abnormalities in pathological cases. The analysis of the *dC/dt* curve justifies this assumption. The pressure in the transitional phase between the rapid and reduced ejection period is abnormal. It is known from the experiments of Gábor and his associates (Gábor and Forgács 1958, 1960, Gábor 1964) that in decompensated cardiac failure the rapid ejection phase is relatively lengthened, and when myocardial function improves and there is better compensation, the rapid ejection time shortens. The *dC/dt* tracing shows that the descending part of the positive wave descends more slowly and forms a second peak or dome-like shape before reaching the zero line.

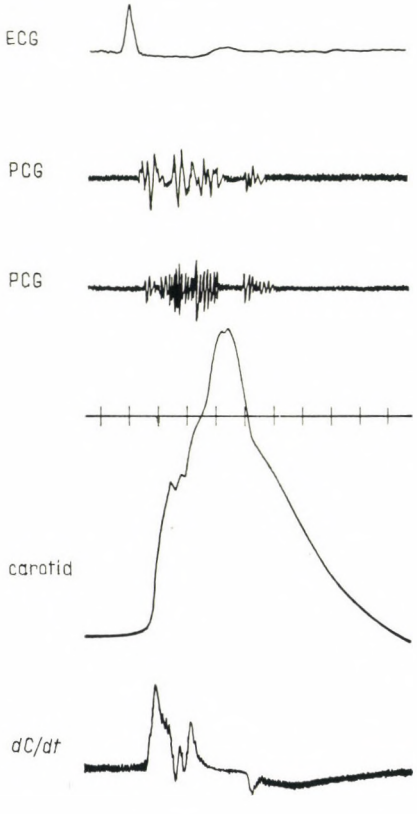


Fig. 22. Tracings taken in patients with aortic stenosis. There are abnormal changes on the carotid pulse contour, with slight 'cock's crow'-like vibrations. In the derivative atypical waves can be clearly seen in the middle of the ejection, accentuating the pathological phenomena of the original curve (Elema Mingograph, paper speed: 50 mm/sec)

The changes in the shape of the *dC/dt* curve can be ascribed to the altered function of the heart. Besides the reason mentioned above, this is further supported by the observations that abnormal *dC/dt* curves often occur in cases without the clinical symptoms of the altered function of the periphery. The frequency of the atypical curves increases with the increasing grade of severity of decompensation in normotensive patients (Fig. 20). Among the possible peripheral factors, the changes in the elasticity of the ascending aorta and the carotid artery should also be mentioned. This is believed to play only a minor role; the altered peripheral resistance is more important. If the cardiac failure is accompanied by hypertension there is a great incidence of curves. Among patients with identical systolic pressures there are

more atypical tracings where the diastolic pressure is low (Fig. 21). This point indicates altered myocardial function but the role of the periphery cannot be ignored.

*

96.5% of the dC/dt curve has a typical shape in healthy individuals, whilst in heart disease this is only so in 41.6% of the cases. The shape of the descending part of the positive wave is atypical and does not reach the base line steeply but forms either a second peak or a dome-like contour. The reason of this is assumed to be due to the changing function of the ventricular myocardium, although higher blood pressure may also play a role. The first derivative of the carotid tracing accentuates the irregular vibrations found in aortic stenosis and this could be a useful diagnostic aid.

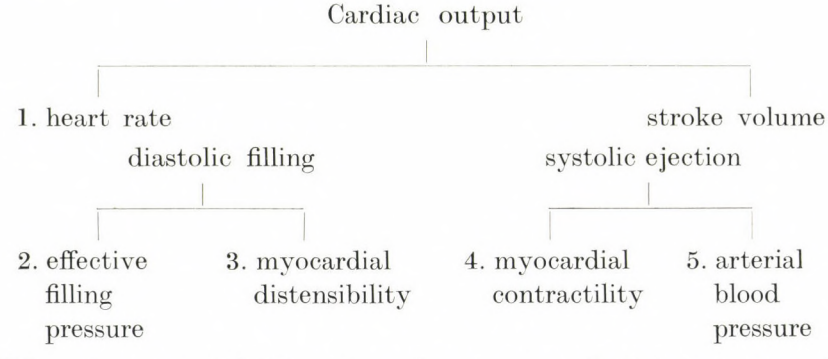
CHAPTER 2

THE DERIVATIVE OF THE CAROTID CURVE AS A SEMIQUANTITATIVE OR QUANTITATIVE METHOD FOR ASSESSING POSITIVE INOTROPIC ACTIONS

CONTRACTILITY OF THE MYOCARDIUM

In the Introduction it has been mentioned that the height of the peaks of the derivatives of the carotid tracings run parallel with the contractility of the ventricular myocardium. It will now be attempted to justify this statement.

Before elucidating this concept it should be mentioned that changes in contractility *per se* do not necessarily determine the variations in cardiac output; contractility is, however, an important determinant of cardiac output. Rushmer's schematic figure (1955) illustrates the interplay of certain factors in influencing changes of cardiac output:



Although many definitions have been proposed, it is not very simple to define 'contractility'. Rutishauser and Krayenbühl (1968) emphasize that contractility or the inotropic state of the myocardium should be defined with appropriate postulates.

Luisada (1953) writes: "The heart has four basic properties: Automaticity, excitability, conductivity and contractility. A fifth, tonus, is under discussion . . ."

"Contractility is the ability of the heart muscle to shorten itself, thus performing work."

Sarnoff's classic definition (1955) states that increase of contractility means that at a given diastolic pressure the external stroke work of the heart increases.

In experimental work a change in the cardiac circumference is regarded as a degree of contractility, this being measured with a Walton–Brodie 'straingauge arch' (Boniface et al. 1953). In man this can be applied only during cardiac surgery (Sonnenblick et al. 1966). A very useful index is the mean systolic ejection rate (the MSER index), which is the quotient of the systolic volume and the ejection time (Gorlin et al. 1964, Mitchell et al. 1966).

Sonnenblick (1962) investigated the isotonic contraction of the cat papillary muscle with the techniques used in the study of the skeletal muscle, i. e. during steady loading. The velocity of the initial shortening was found to be faster by smaller loading. Using different loads on the muscle the force–velocity curve can be constructed. Starting from this theory the force–velocity correlation was studied in intact animals (Ross et al. 1966, Levine et al. 1966, Taylor et al. 1967) and later in man (Downing and Sonnenblick 1964, Glick et al. 1965, Ross et al. 1966, Levine et al. 1966, Sonnenblick 1968). The extrapolated maximum value was regarded as a parameter for contractility increasing after positive and decreasing after negative inotropic interventions.

A further step forward was the introduction of the first derivative of the left ventricular pressure curve (Reeves et al. 1960, Reeves and Hefner 1962, Gleason and Braunwald 1962). The isovolumetric stage on the derivative of the ventricular pressure (dp/dt) is denoted as a pointed peak (max dp/dt) being very sensitive to positive inotropic interventions with an increase and to negative inotropic interventions with a decrease in the peak.

Based upon animal experiments and theoretical considerations, Rushmer (1964) regards the impulse which brings into motion the heart as a distinctive feature of cardiac function, 'initial ventricular impulse, a potential key to cardiac evaluation'. For the quantitative evaluation of contractility of the ventricular myocardium some indices have been introduced. Siegel et al. (1964) recommend the $\frac{\max dp/dt}{IIT}$ index where IIT = integrated isometric tension. Veragut and Krayenbühl (1965) suggested the index $\frac{\max dp/dt}{IP}$, IP being the pressure which can be measured in the ventricle at the time of max dp/dt.

Recently, Mason et al. (1970, 1971) introduced the $\frac{dp/dt}{P}$ index as a measure of contractility, the quotient composed of the derivative and the accompanying pressure (P), all of which can be obtained continuously by electronic monitoring. According to the authors' opinion, the results obtained charac-

terize the beat-to-beat contractility independently of the preload and afterload. Katz (1970) points out that this technique still needs further elaboration.

In spite of these and other new indices (Hugenholtz et al. 1971, Agress et al. 1972, Diamond et al. 1972, Ross and Peterson 1973, McDonald and Hobson 1974, Madias and Cohen 1974, Brundage and Cheitlin 1974, Peterson et al. 1974), new techniques available for studying human haemodynamics as well as that in experimental animals, the first derivatives of the ventricular or aortic pressure tracings are the most widely used techniques. Accepting this view and following the example of the derivatives of the intracavitary pressure the derivative of the carotid tracing has been constructed, the dC/dt which can also be used to follow changes in contractility. This assumption will be elaborated in Chapter 2, now only the proofs are enumerated:

1. In the dog the shape of dC/dt is similar to that of the derivative of the aortic pressure tracing.
2. The max dC/dt is sensitive to the action of well-known drugs in the same manner as is the max dAo/dt.
3. The shape of dC/dt in man is similar to that of dAo/dt.

COMPARATIVE STUDY OF THE FIRST DERIVATIVE OF THE INDIRECT CAROTID PRESSURE CURVE AND THE INTRA-ARTERIAL PRESSURE CURVES IN EXPERIMENTAL ANIMALS

Cross-bred dogs of both sexes weighing 18 to 20 kg were used. After the exposure of the carotid artery under chloralose-urethane anaesthesia a polyvinyl catheter was inserted. Care was taken to ensure that the tip of the catheter reached the aorta just above the aortic valve, and the pressure was measured at this level. An external detector was placed on the intact carotid artery on the opposite side. The tracing of the carotid curve and its derivatives both by the noninvasive and direct intra-arterial techniques was recorded synchronously.

Myocardial contractility was altered by the administration of certain drugs and the changes that occurred in the carotid tracings were correlated with those in their derivatives to see whether there was a good agreement between the two. The drugs used in this experiment were as follows: Nor-

adrenaline (10, 40 and 100 μg) adrenaline (10, 40 and 200 μg), isoprenaline (10 and 40 μg) and the beta receptor-blocking compound propranolol (Inderal, ICI, 10 and 40 μg). All the drugs diluted in saline were given by i. v. infusion.

Thirty-six experiments were carried out in six dogs. The derivatives taken during rest, i. e. before drug administration showed, identical patterns (Fig. 23). During diastole there were either no or at the most negligible changes, i. e. all three derivatives ran horizontally. This horizontal line was chosen as the base line, the upward deflection being designated as positive and the downward as negative. (This base line proved to be identical with the '0' differential line, constructed with the extreme values of the basic tracing.) The derivatives at the early part of the systole form a steep ascending line which ends in a pointed peak indicating the maximum velocity of the pressure gradient. After this initial positive phase, the derivative curve again reaches the base line and runs horizontally. At the end of the systole a negative wave is seen, this, however, being smaller than the positive wave at the beginning of the systole. This negative deflection is followed, but not invariably, by a small positive wave.

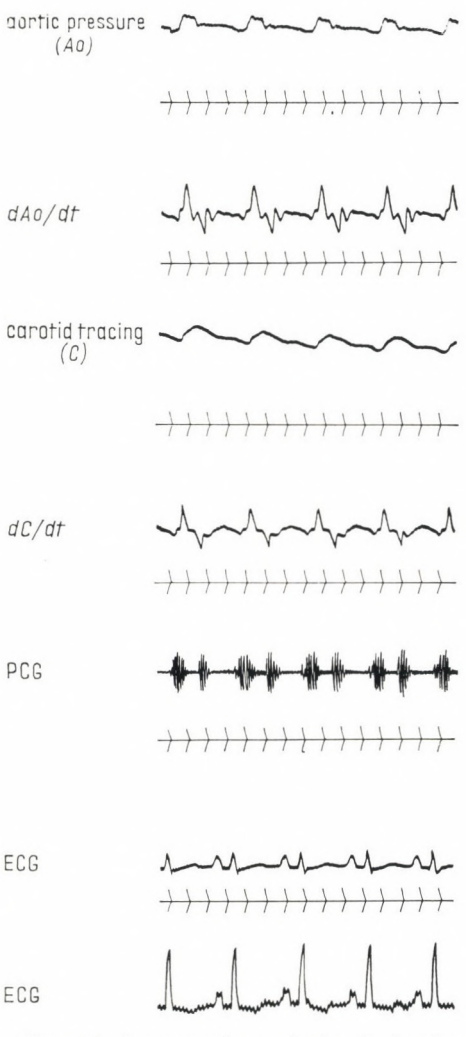


Fig. 23. A comparison of the derivative curve (*dAo/dt*) obtained by intra-aortic (invasive) tracing (*Ao*) and the derivative curve (*dC/dt*) obtained from noninvasive tracing of the carotid tracing (C) (dog, Galileo polygraph, paper speed: 50 mm/sec)

Prior to recording the basic tracings one of the drugs was administered to the experimental animal allowing 10 to 15 minutes, for the peak action of the test compound. This was followed by the administration of the next compound. The order of the drugs was randomized in each animal, in order

to eliminate the synergistic and antagonistic interaction between the different drugs used in the same animal.

After the administration of adrenaline (10, 50 and 100 μg) the height of the peak seen on the tracing increased on both derivatives, this change being dose dependent. In the same animal, change in the maximum values of the derivatives originating from the tracings recorded from the aorta and the carotid artery showed a similar pattern (Fig. 24).

Noradrenaline (10, 40 and 100 μg) like adrenaline caused an enhancement of the peaks on the derivative curves, and the elevation had a similar character as in the case of adrenaline (Fig. 25). Noradrenaline in the majority

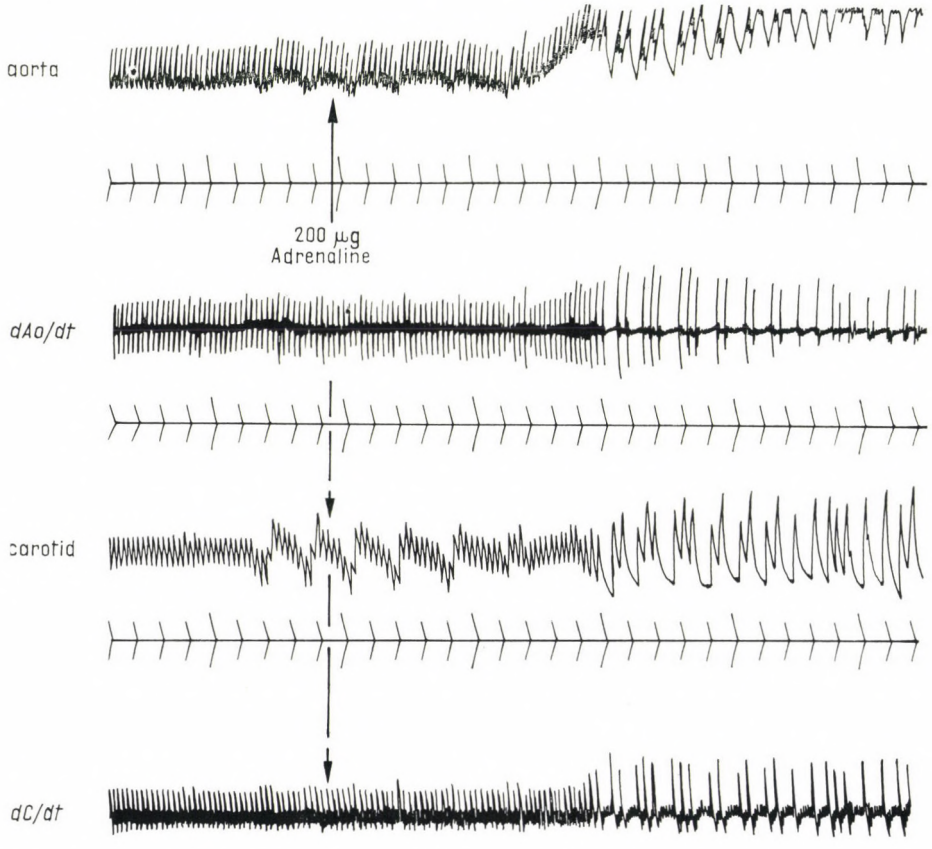


Fig. 24. After the administration of 200 μg adrenaline, the pressure in the aorta increases, there is a significant bradycardia, the derivative of the aortic pressure curve (*dAo/dt*) is similar to the first derivative of the carotid tracing (*dC/dt*) (dog, Galileo polygraph, paper speed: 2 mm/sec)

of the experimental animals caused arrhythmia, mostly ventricular extrasystoles. The extrasystolic peaks on the derivative curves were lower than those of the normal systolic peaks. Here again the three curves revealed similar patterns.

Isoprenaline is one of the drugs which markedly increase the contractility of the myocardium. After the administration of 10 and 40 μg doses the peaks on all three derivative curves became higher (Fig. 26). The above experiments are demonstrated schematically in Fig. 27. The action of isoprenaline was blocked by giving propranolol in advance. In this case the peaks of the derivative curves did not show elevation.

The aim of our investigation was to check whether the derivative of the tracing recorded by noninvasive technique in the experimental animal showed an identical pattern with that of the intra-aortic tracing. By observing the effects of drugs which have a well-known action on myocardial contractility certain conclusions could be drawn concerning the results of changing contractility on the shape of the derivative curve of the pulse tracing.

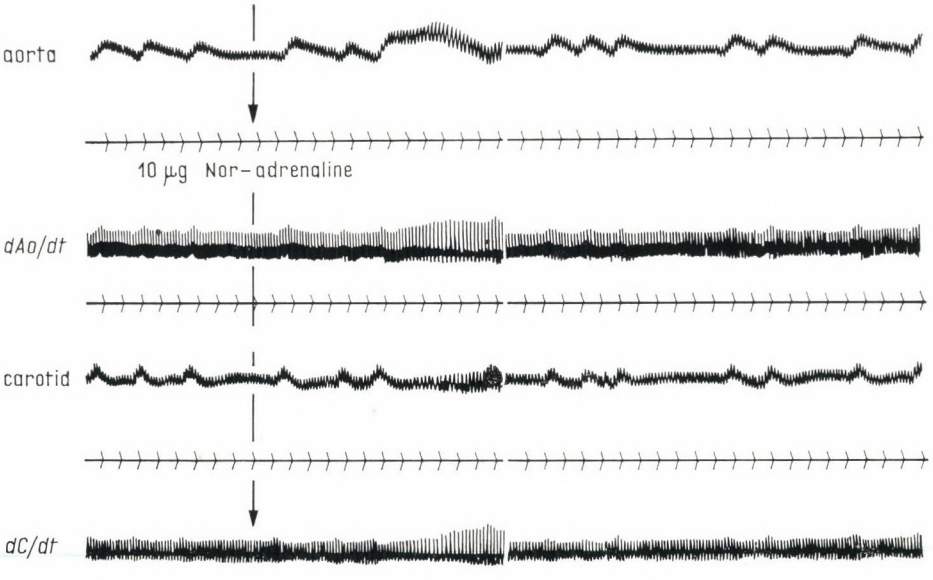


Fig. 25. After the administration of 10 μg noradrenaline the aortic pressure slightly increases, both derivatives obtained from the aortic and the noninvasive carotid tracings showing a slight increase. In the second half of the diagram recovery towards the base line is shown after 8 minutes (dog, Galileo polygraph, paper speed: 2 mm/sec)

Our experiments have borne out our hypothesis, i. e. the peaks on the derivative curves taken by external tracing change in the same direction as the tracing taken by intra-arterial recording. However, differences do exist in the absolute values. Nevertheless, if absolute values are ignored and changes are expressed as percentage of the control value, identical figures are obtained. This allows us to expect the same information from the derivative curve of the external carotid tracing as from the intra-arterial tracing of the aortic pressure.

It can also be concluded that the maximum values of the derivatives of direct and indirect carotid artery tracing both indicate changes in myocardial contractility. This does not apply to cases in which pathological alterations of the outflow tract of the left ventricle and of the proximal part of the aorta may distort the tracing. The results of our animal experiments show an enhancement of the peaks in case of drugs which increase, and a

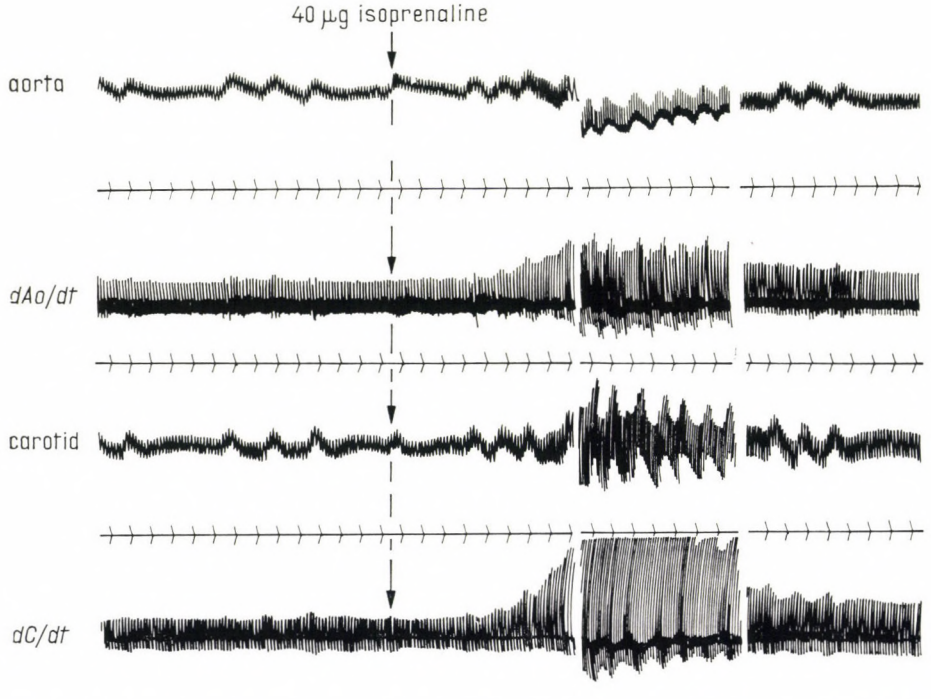


Fig. 26. After the administration of 40 μg isoprenaline the pressure in the aorta decreases. At the same time, both first derivatives obtained from the aortic pressure curve and the carotid tracing show an identical rise. Two minutes after injection, the effect is almost over (dog, Galileo polygraph, paper speed: 2 mm/sec)

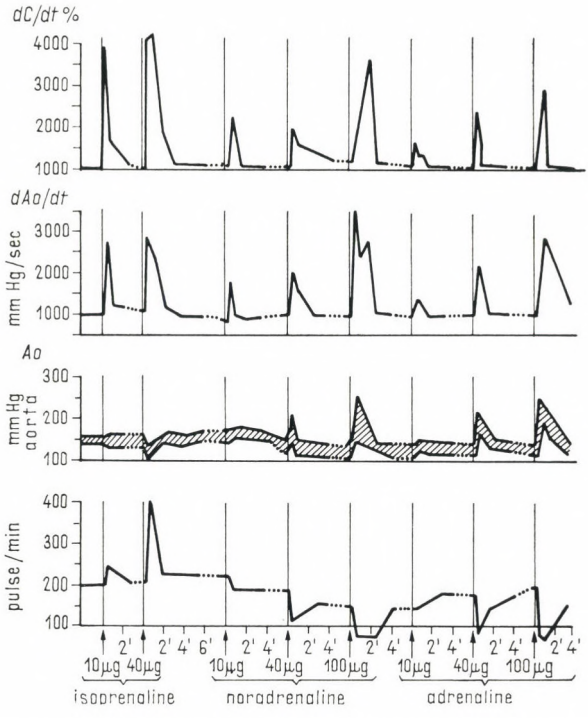


Fig. 27. The first derivative of the carotid tracing taken by the noninvasive technique (*dC/dt*) and that of the invasive intra-arterial tracing of the aortic pressure (*dAo/dt*) show a similar pattern. The changes are dose dependent

lowering in those, which decrease contractility of the myocardium, and this supports our assumption.

*

Deductions from the results obtained in animal experiments allowed the conclusion that the first derivative of the carotid artery tracing can be used to evaluate changes in myocardial contractility (Gábor et al. 1968).

FIRST DERIVATIVE OF THE CAROTID TRACING: A NONINVASIVE TECHNIQUE TO ASSESS THE POSITIVE AND NEGATIVE INOTROPIC INTERVENTIONS

In the previous section it has been attempted to prove the applicability of the first derivative of the external carotid arterial trace as an index of changes in contractility of the myocardium in the experimental animal. Here, the application of this technique in man is dealt with.

The carotid tracing was recorded in the patient lying supine. The piezo-crystal 'infraton' carotid pick-up was held at a position on the neck where the amplitude of arterial pulsation was maximal. The tracing and the derivative were obtained using the technique described in Chapter 1 (p. 27).

During the experiments in which drugs were administered, the patient lay still and received the test compound through a cannula inserted previously, so that he was not aware of the time of injection. To measure the pressure in the left ventricle and in the aorta the catheter was introduced percutaneously through the femoral artery by the 'Seidlinger' technique. (These investigations were carried out on patients in whom cardiac operation had been envisaged, with the aim to establish the correct diagnosis. This was done in the Haemodynamic Laboratory of the National Cardiological Institute, Budapest.)

The dp/dt was calibrated by our own method (Simonyi et al. 1968). The pressure curves in the aorta with its derivatives were recorded at the same time as the external carotid tracing and its derivative. In agreement with our earlier observations the derivative of the left ventricle was found to reach its maximum in the isometric phase and that of the dC/dt at the beginning of the ejection phase. There is a similarity between the derivatives of the direct pressure tracing and those of the indirect carotid pulse (Fig. 28).

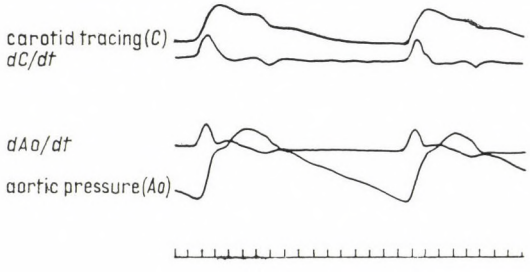


Fig. 28. Elema-Mingograph. Paper speed: 50 mm/sec. The derivatives of the aortic and indirect carotid tracings are highly similar

The peak of the left ventricular pressure derivative increases following the well-known inotropic action of isoproterenol. A similar enhancement of the peak occurs in the case of the derivative of the right ventricle and the derivatives of the directly recorded aortic and femoral artery pressure tracings. The peaks on the carotid derivative increase in parallel with the

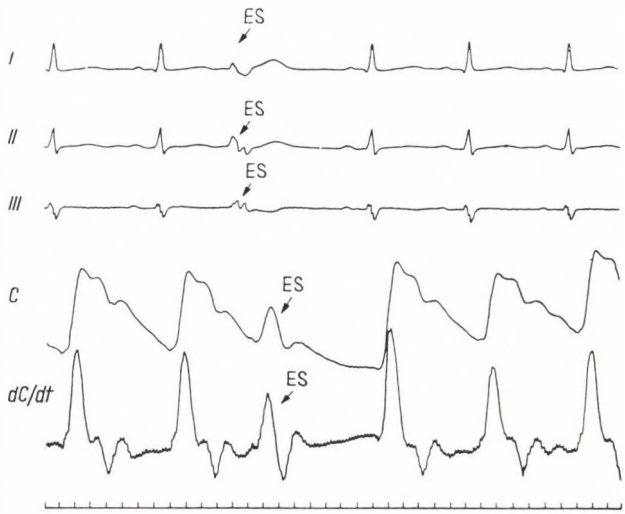


Fig. 29. Siemens-Cardirex (paper speed: 25 mm/sec). After an extrasystole (ES) the compensatory pause is followed by a high peak on the *dC/dt* curve and the 'potentiated' heart contraction reveals an increased inotropic action

intracavitary derivatives mentioned above during simultaneous recordings proving that the max *dC/dt* is influenced by inotropic changes in the heart.

It is known that the compensatory pause after an extrasystole is followed by a powerful 'potentiated' contraction. This is illustrated in Fig. 29, which shows that the peak of the derivative of the carotid tracing is higher in the post-extrasystolic beat.

The action of a very small dose of isoprenaline is shown in Fig. 30. Thirty seconds after the injection of the drug the max *dC/dt* is almost doubled. The time course of action produced by the small dose of drug is demonstrated in the record taken at a slow speed (Fig. 31). It will be seen here that at rest the height of the peaks of the max *dC/dt* are fairly uniform. With isoprenaline, after a temporary increase, the peaks of the max *dC/dt* return to their original position. The greatest increase in height was found after isoprenaline administration; with doses of 10 μg adrenaline, 10 μg noradrenaline and

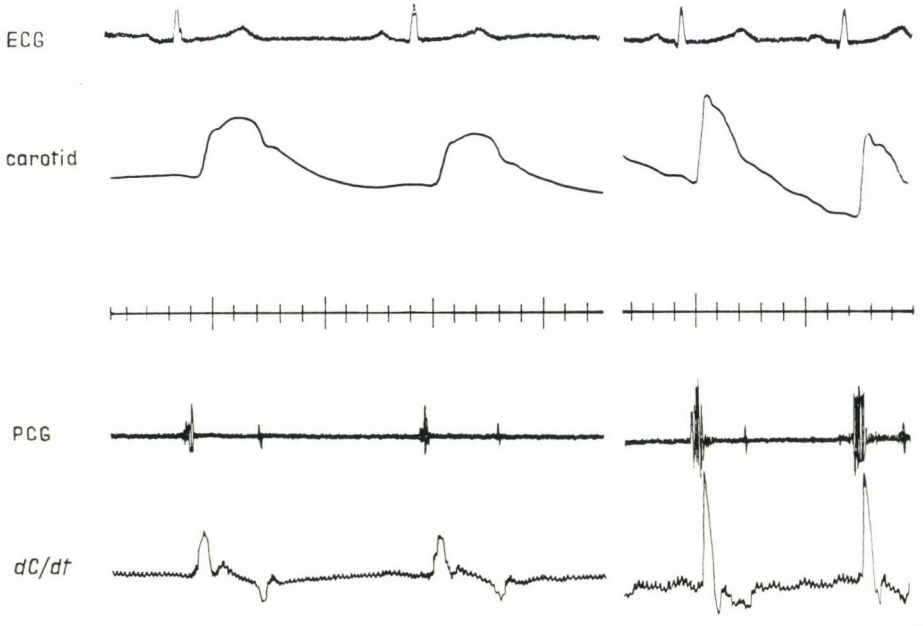


Fig. 30. Hellige multiscriptor (paper speed: 50 mm/sec). Thirty seconds after the administration of 5 μg isoprenaline the max dC/dt increases significantly

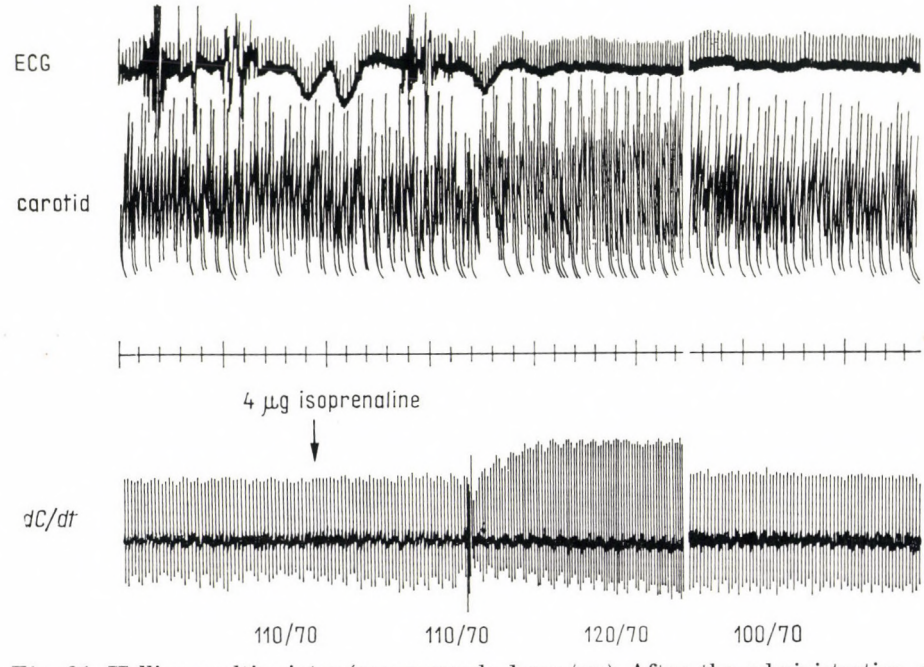


Fig. 31. Hellige multiscriptor (paper speed: 1 mm/sec). After the administration of 4 μg isoprenaline the max dC/dt inreases, returning 6.5 min later to the initial value

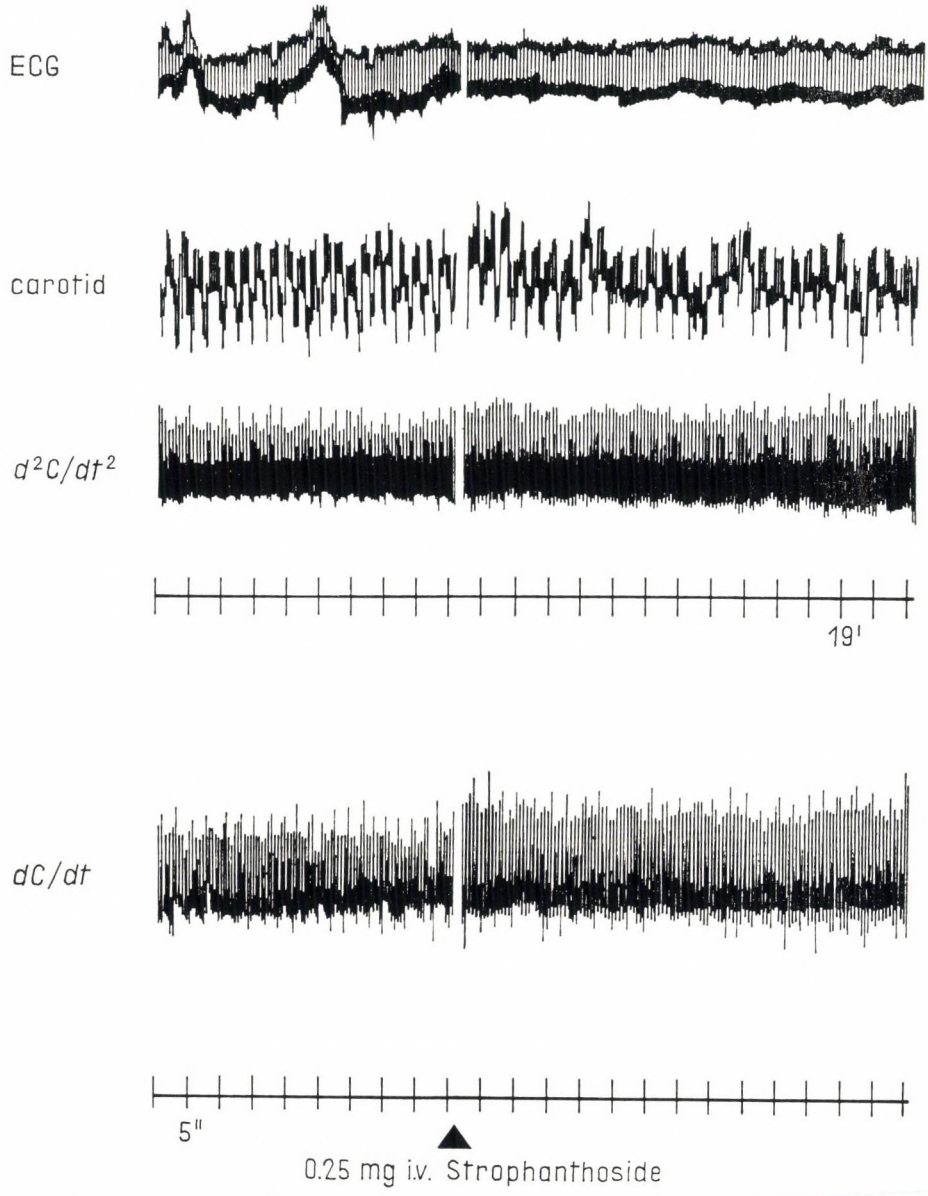


Fig. 32. In response to Strophanthoside (0.25 mg dose) the peaks of the derivatives increase slightly

0.25 mg of strophantoside we have seen only small increases (Fig. 32). The changes in the max dC/dt are also very good indicators of negative inotropic interventions. In patients suffering from essential hyperkinetic heart syndrome the max dC/dt decreases conspicuously after the administration of a small dose of propranolol (Simonyi et al. 1968*b*, Simonyi 1969*a*, *b*, 1971).

Similar observations have been published by Kahn and Spodick (1972) who found that the dD/dt quotient (D = displacement pulse) yielded from the time derivative of the carotid curve increases due to isoproterenol and decreases due to propranolol administration [dD/dt ratio means the height of the positive wave in percentage of the total height of the whole (positive + negative) derivative curve].

*

The first derivative of the carotid tracing and the derivatives of the intracavitary curves have a similar pattern and they react similarly to isoprenaline. The higher max dC/dt which can be seen after the compensatory pause which follows an extrasystole is indicative of an increased inotropic activity of the myocardium. After the administration of drugs with well-known inotropic actions the max dC/dt behaves predictably; in the case of drugs with positive inotropic action it increases and in the case of compounds with negative inotropic actions it decreases.

On the basis of these observations, it is believed that the use of dC/dt in man is a suitable technique to study changes in the negative and positive inotropic effects in the heart.

CALIBRATION OF THE CAROTID DERIVATIVE AND ITS RELATION TO OTHER PARAMETERS

The distance between the base line and the highest point on the derivative curve of the carotid tracing indicates the levels of the systolic and diastolic pressures. Our calculation of the max dC/dt value was based on this assumption. The blood pressure was measured by Korotkoff's technique in the brachial artery. The slope of the curve was estimated at a level of 0.01 sec, by taking advantage of the vertical lines of the time signals. The 0.01 sec time line seemed to us a short interval, adequate for obtaining the real value of the max dC/dt. The value of the medium height was calculated with the aid of the principle of proportionality, the result being given in relation to 1 sec (Fig. 33) and expressed in mm Hg per sec.

The determination of cardiac output was carried out by the measurement of the differences in O_2 concentration in samples taken from the femoral

artery and the right atrium, and the results were .calculated by using the Fick principle. In some cases the estimation was made with ^{131}I tagged albumin with the isotope dilution technique. The carotid tracing was recorded at the same time as the *dC/dt*. The ejection period was measured from the carotid curve.

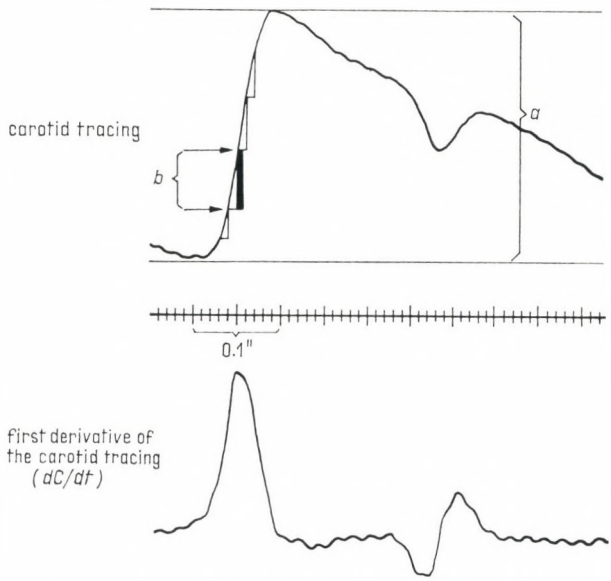


Fig. 33. Calculation of max *dC/dt*. Hellige multiscriptor (paper speed: 100 mm per sec). Max $dC/dt = 100 \times \frac{b}{a} \times$ pulse pressure mm Hg per sec. $a =$ = the distance between the highest point of the carotid curve and the base line, this being equivalent to the difference between the systolic and diastolic pulse pressure; b = the greatest increase of the carotid curve at 0.01 sec coinciding with the peak of the derivative

The calculation was made as follows:

$$\text{MSER (Mean Systolic Ejection Rate)} = \frac{\text{stroke volume}}{\text{ejection time}} \text{ ml/sec.}$$

$$\text{MSER index} = \frac{\text{stroke volume/body surface m}^2}{\text{ejection time}} \text{ ml/sec.}$$

The max *dC/dt* was determined in 44 individuals, among whom 18 did not have any cardiovascular disease, whereas 26 were ill, the majority

suffering from coronary artery disease. Thirteen suffered from heart failure during the investigation. The figures varied between 545 and 3200 mm Hg per sec. For comparison, the figures obtained by Gleason and Braunwald (1962) in the left ventricle ranged between 870 and 3200 mm Hg per sec. Neither these authors nor we have found any relation between the maximum value of the derivative and the degree of cardiac decompensation. However, there was a close correlation between the values of the max *dC/dt* and the systolic pressure, as well as between the product of the systolic pressure and heart rate (Fig. 34). In the diagram the values representing the severely decompensated cases are crossed out with a horizontal line. Nevertheless, we were unable to draw any conclusion from the location of these points.

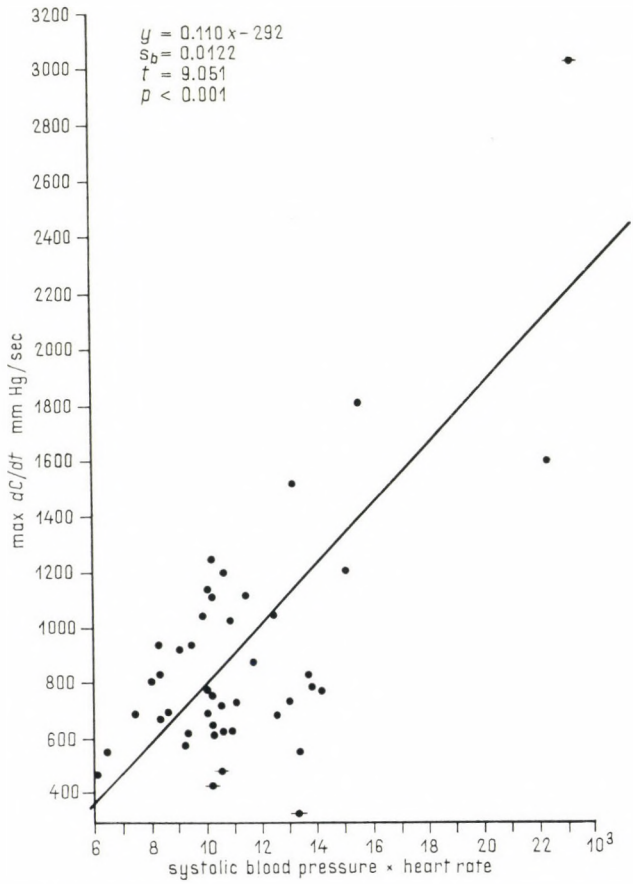


Fig. 34. There is a close correlation between the max *dC/dt* and the product of the systolic pressure and the heart rate

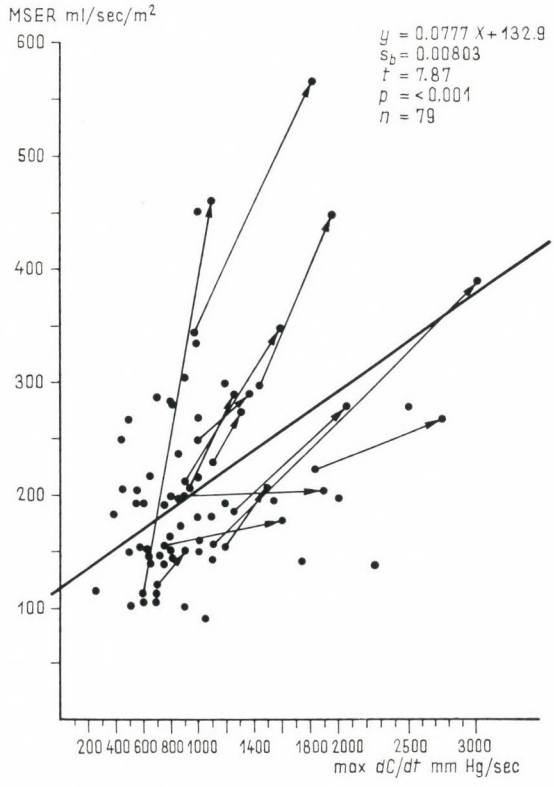


Fig. 35. The MSER and the max dC/dt are interrelated. The arrows indicate the changes after isoprenaline administration

There is a striking similarity between these findings and those of Gleason and Braunwald (1962).

The correlation between the systolic blood pressure (P_s) and the peak derivative (PD) is close and may be described by the following regression line:

$$PD = 15.3\, P_s - 254.$$

Between the peaks of the carotid derivatives and the systolic pressure (measured with Korotkoff's technique) the following regression line was found:

$$\max dC/dt = 14.9\, P_s - 1124\,.$$

The regression coefficients of the two curves do not differ significantly ($t = 0.91$, $p > 0.20$).

The correlation between the peak derivatives (PD) and the product of the ventricular systolic pressure and the heart rate (HR) was:

$$PD = 0.157\ P_s \cdot HR - 149.$$

The following regression line for the carotid derivative was calculated:

$$\max dC/dt = 0.110\ P_s - 292.$$

There was no significant difference ($t = 0.27$; $p > 0.50$) for the two regressions.

The observations in the decompensated subjects were very similar to those seen in compensated failure; however, except for a few instances, the peak derivatives were lower than the product of the systolic pressure and the pulse rate (Simonyi et al. 1968*b*, Simonyi 1969*a*, *b*, 1971).

The MSER index and the max dC/dt were computed simultaneously in 79 patients, in addition, the effect of isoprenaline was studied in 18 of these patients. These findings are shown in Fig. 35, and the changes due to isoprenaline are indicated by arrows. The close correlation between the two indices is obvious.

*

In summary, our findings outlined above allow the following conclusions:

1. The value of the max dC/dt can be calibrated by the systolic and diastolic pressures. The levels are in the same range as those calculated by Gleason and Braunwald, measured in the ventricles.
2. As in the case of ventricular dp/dt, the max dC/dt show a close correlation with the systolic pressure, and the product of the systolic pressure and the heart rate.
3. The max dC/dt and the MSER index are interrelated although the latter measures contractility using an entirely different principle.
4. The max dC/dt and MSER index both increase when isoprenaline is administered and the two parameters alter in a parallel fashion.

These observations support our view that the derivative of the carotid tracing can be used to assess changes in myocardial contractility.

CHAPTER 3

THE COMBINED USE OF THE AMPLITUDE OF THE FIRST HEART SOUND AND THE FIRST DERIVATIVE OF THE CAROTID TRACING FOR THE SEMIQUANTITATIVE ESTIMATION OF NEGATIVE INOTROPIC ACTION

Laurens (1964), Sakamoto et al. (1965) and Luisada et al. (1971, 1974) have demonstrated that the amplitude of the first heart sound is related to the peaks of the first derivative of the ventricular pressure (dp/dt). The derived peaks of the ventricular pressure (dp/dt) and the amplitude of the first heart sound alter in the same manner to the effects of drugs which affect inotropism. From these observations the authors concluded that changes in contractility influence, or rather determine the amplitude of the heart sound.

During the course of our previous investigations it was found that in externally recorded tracings taken simultaneously with phonocardiograms, the heart sounds reacted with a significant increase in their amplitude after positive inotropic interventions. It was, therefore, investigated whether changes in the amplitude of heart sounds was indicative of directional changes in the inotropic state.

The change in the amplitude of the first heart sound was compared with the peak of the carotid derivative to explore the possible correlation between them, the type of correlation seen in healthy subjects and in patients suffering from ischaemic heart disease, to see the changes which might occur after the administration of isoprenaline and after exercise on a bicycle ergometer.

The recordings were performed according to the technique described in the preceding Chapters. However, in this series also the heart sounds were recorded in the low frequency range. This was done with an apparatus mainly letting through vibrations of 25 Hz.

The description of the details of exercise on ergometer will be given on p. 64.

To evaluate the effects of isoprenaline and exercise a phonotransducer was fixed over the cardiac apex. Care was taken to ensure that the microphone remained in the same site and that the present pressure did not alter. Recording was made at rest, 0.5, 1, 1.5, 2, 3, 4 and 5 minutes after exercise and drug administration.

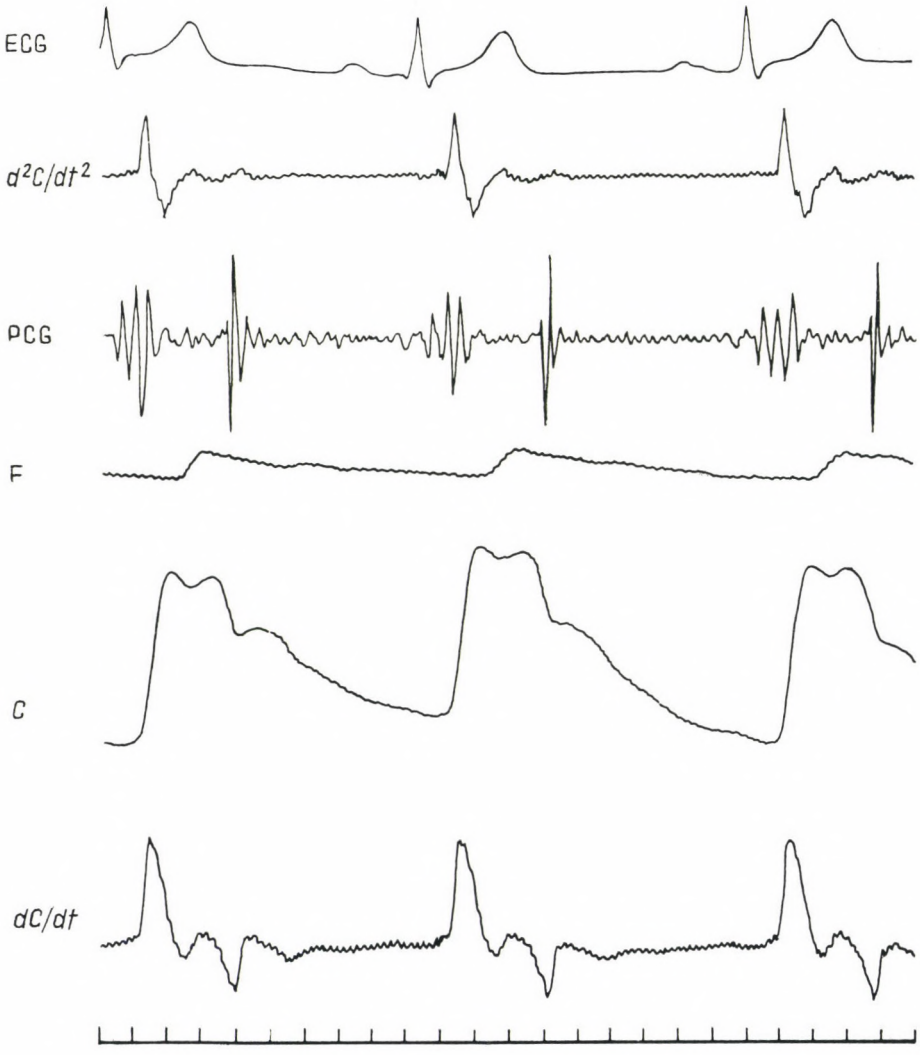
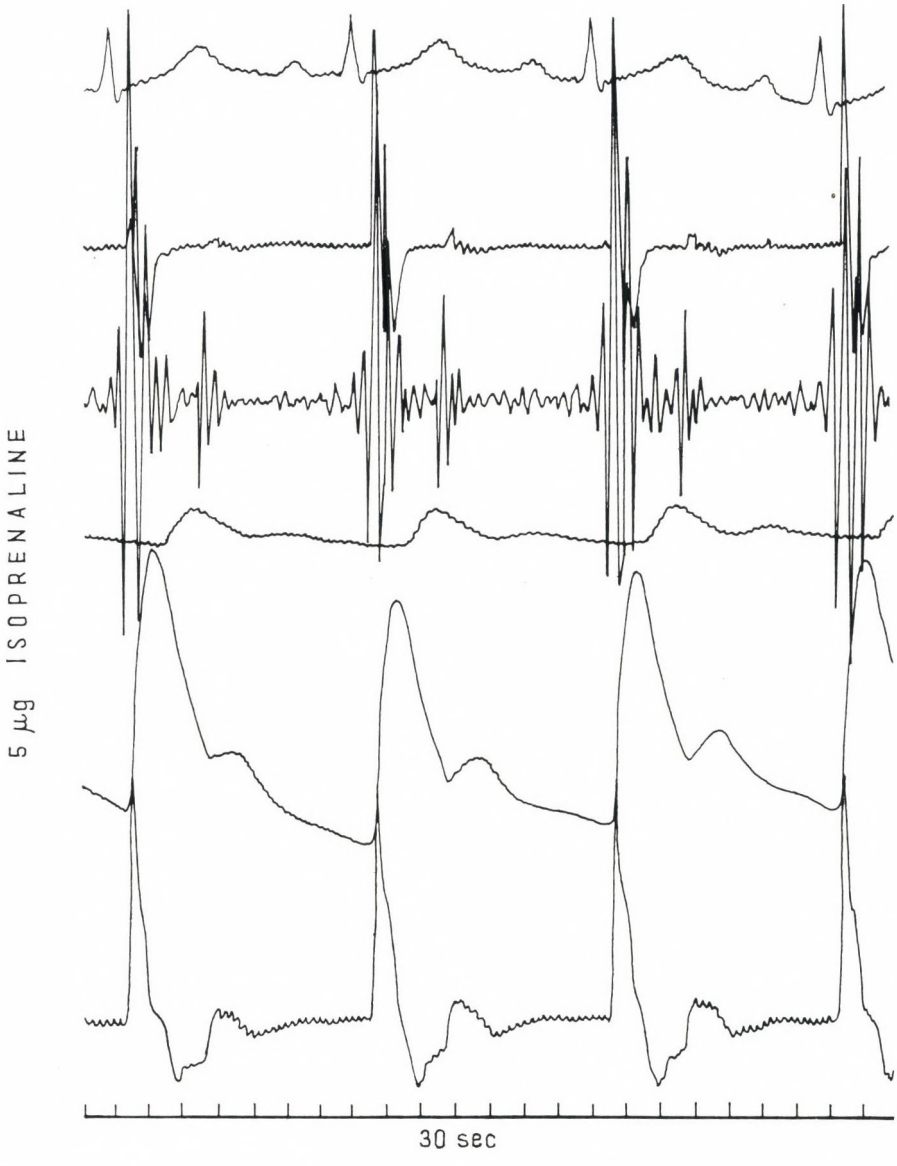


Fig. 36. The carotid tracing, its first and second derivatives and the first heart sound (25 Hz). The derivative curves of the carotid and the amplitude of the heart sound



change synchronously. They increase as a result of the administration of isoprenaline. (Elema Mingograph, paper speed: 100 mm/sec) F = finger plethysmogram

The amplitude of the first sound was assessed by measuring the distance between the maximal and minimal oscillations in five cycles and after isoprenaline administration. The control values were taken as 100 per cent and changes due to interventions were compared to them. (The results did not differ greatly from those obtained with measurements, with only the positive oscillations being considered.) On the derivative curves the relative changes of the high positive deflections were followed.

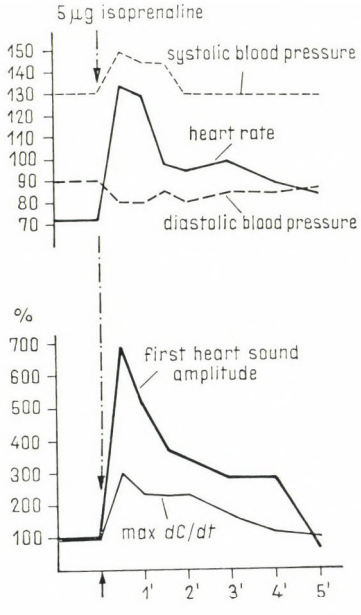


Fig. 37. Changes in a healthy individual after the administration of 5 μg isoprenaline. The amplitude of the first heart sound is increased considerably as is the max dC/dt. Tachycardia occurs and the pulse pressure is widened. The effect is over within a few minutes

The investigations were carried out partly in healthy individuals and partly in patients suffering from decompensated coronary artery disease (degree of decompensation II and III according to the criteria of the New York Heart Association).

Following the administration of isoprenaline there is tachycardia with the carotid curve developing characteristic features; and its first and second derivatives increase in height as does the amplitude of the first heart sound (Fig. 36).

After increased ergometric exercise similar changes were observed. The greatest changes occurred after 0.5 to 1 minute with these parameters gradually returning to the base line (Fig. 37). It is noteworthy that the changes in the heart sound were more marked than those in the derivative peaks.

In this Chapter the interrelationship between the changes in the amplitude of the heart sound and those in the derivative peaks was examined. The data obtained during the investigation of 53 individuals were analysed statistically. In 20 healthy individuals and in 16 cardiac patients the effects of isoprenaline, and in 10 healthy individuals and 7 cardiac patients the effects of increased exercise were studied. The relative changes in the derivative and those in the heart sound were followed during various phases of the effects and compared to each other in 382 cases. The overall results are shown in Fig. 38.

The behaviours of the parameters investigated are closely interrelated. This is more striking, if the changes in the amplitude of the heart sounds are expressed on a logarithmic scale ($r = 0.62$; $p < 0.001$).

A correlation was also found, if the results were divided into groups, i. e. to healthy individuals and to patients; however, the results were not identical in every case. Statistically, the greatest differences could be seen in the data after exercise during which an increase in the amplitude of the heart sound was greater (Fig. 38; the values are marked with crosses). In line with our previous observations, it can be clearly seen in Fig. 39 that in the case of healthy individuals (Group I), the max dC/dt value is increased by 100 per cent or more. In the case of patients suffering from

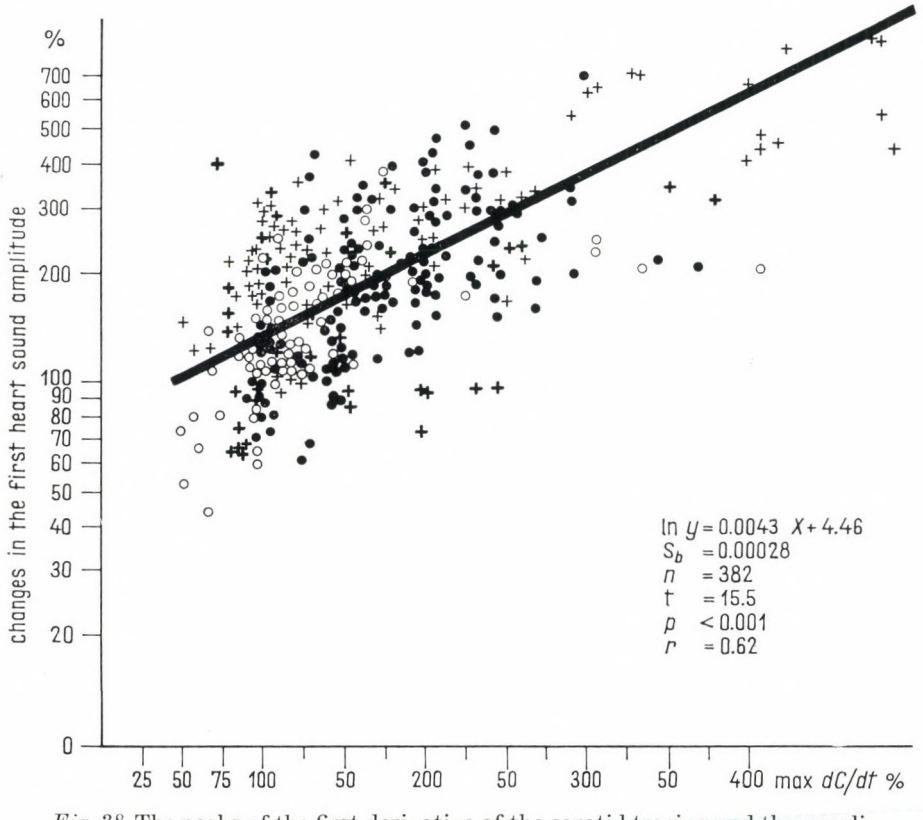


Fig. 38. The peaks of the first derivative of the carotid tracing and the amplitude of the heart sound change in a similar manner as a result of the inotropic action of isoprenaline. On the abscissa the changes in the max dC/dt and on the ordinate the changes in the first heart sound are shown. Closed circles: healthy individuals. Open circles: patients following isoprenaline administration. Thick crosses: effects of exercise tests on cardiac patients. Thin crosses: those of healthy individuals

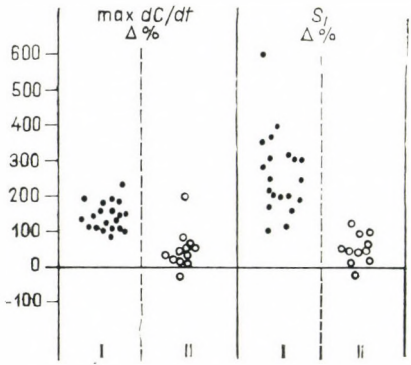


Fig. 39. In Group I (healthy individuals) the max dC/dt value increases more than in Group II (in case of ischaemic heart patients) in response to 5 μg isoprenaline. S_I = first heart sound amplitude

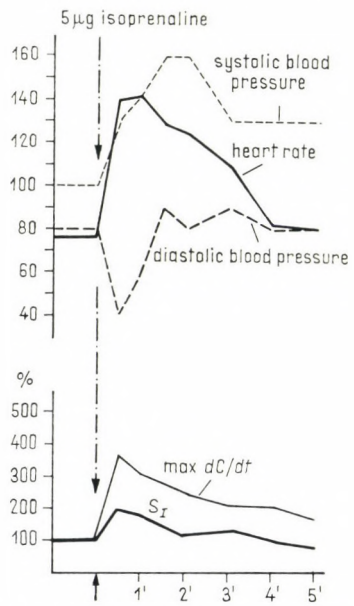


Fig. 40. Due to individual variation in sensitivity, the diastolic blood pressure after the administration of 5 μg isoprenaline decreases more than might be expected, the max dC/dt and the amplitude of the heart sound (S_I) also increase but the latter is less marked than in the case of healthy individuals

coronary artery disease, who were only slightly decompensated (Group II) the max dC/dt values were lower with only one exception. Differences occurred between these two groups and were caused by changes in the amplitude of the first heart sound (Simonyi et al. 1971*a*, *b*).

Figures 40 to 42 illustrate cases in which the type of response differs from that of the most commonly observed ones (shown in Fig. 37).

The changes in the amplitude of the heart sounds and the max carotid derivative are in the same direction allowing us to check the changes in these parameters against each other. The carotid derivative reaches its maximum during the ejection phase, therefore, it cannot provide information about the pre-ejection period. The first heart sound occurs in the preejection period and it could be regarded as a consequence of the dynamic process of that period. Our results are in accord with those of Laurens (1964) and Sakamoto et al. (1965) supporting our view that dynamic factors have an important role in the origin of the first heart sound. At the same time, it is clear that the first heart sound can be used as a measure of the inotropic state, and since it clearly originates in the interior of the heart during the pre-ejection period, it is more independent of peripheral influences than the carotid derivative. The use of the phonocardiogram for such an investigation resembles methods recording mechanically the movements of the cardiac apex. These

methods are becoming increasingly important especially since their derivatives are also investigated (Reale 1967, Gleichmann et al. 1971). The combined procedure, i. e. the analysis of the carotid derivative and the changes in the amplitude of the heart sound, seems to be a very useful method. Figure 37 shows the most common pattern seen in many healthy individuals. By showing other cases, attention has been drawn to the fact that variations in the pattern of response give an insight to what extent the cardiac factors are responsible for the changes and the alteration of the peripheral resistance. As a result changes brought about by exercise or isoprenaline can be separated (and statistics provide significant differences) by haemodynamic analysis using a combined technique (Fig. 38). This is in line with the data in the literature which state that the effects of iso-

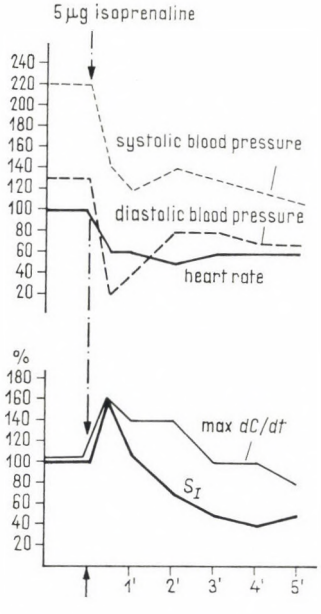


Fig. 41. Due to vagal effects the blood pressure falls markedly, bradycardia develops and the amplitude of the heart sound (S_I) and the change in the derivative tracing are minimal, they may even fall below the convalues

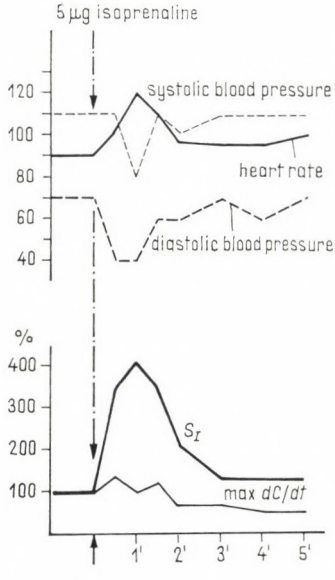


Fig. 42. Changes in a patient suffering from aortic stenosis. Due to the action of isoprenaline the amplitude of the heart sound (S_I) increases with the increase in max *dC/dt* being less striking. There is an increase in the contractility of the ventricle, while due to aortic valve stenosis, the effect cannot reach the periphery

prenaline resemble the haemodynamic modifications due to exercise being, however, not identical with them (Krasnow et al. 1964).

It can be seen in Fig. 39 that as in the case of the derivative of the carotid tracing, the changes in the amplitude of the heart sound can help in differentiating healthy individuals and patients suffering from heart disease. The fact that the amplitude of the first heart sound and the max dC/dt do not change in a parallel fashion, emphasizes the limitations imposed by this technique. In spite of this it is possible to obtain a better understanding of the state of cardiac haemodynamics in patients than by simple clinical means.

*

In response to inotropic interventions both the highest derivative of the carotid tracing and the amplitude of the first heart sound increase. In 389 cases the variations in the two parameters have been compared. In both healthy individuals as well as in cardiac patients, a correlation between the changes due to the effects of isoprenaline and exercise on a bicycle ergometer has been demonstrated.

On the basis of the present work, it can be suggested that changes in the amplitude of the heart sound may be used as an index of changes in contractility.

The combined use of the two techniques is useful as the response to each manoeuvre may be checked against each other. In certain cases they can also be helpful in differentiating between the intra- and extracardiac circulatory effects. The first heart sound occurring in the pre-ejection phase provides information about the intracardiac events, while the max dC/dt points to changes in the circulation after the opening of the aortic valve. The monitoring takes place near the heart but it is not completely free of peripheral effects.

CHAPTER 4

INVESTIGATIONS WITH EXERCISE STRESS AND CATECHOLAMINE STIMULATION

INTRODUCTION

In the previous Chapters it has been demonstrated that the first derivative of the carotid pulse tracing, and the changes in the amplitude of the first heart sound provide useful information about the contractility of the left ventricle. In this section the investigations are discussed which were made under various clinical conditions. In order to test the validity of our method, the factors regulating the contractility of the heart were studied, namely the differences between healthy individuals and patients, and the possibility to quantify these differences.

The circulation of a healthy individual and of a patient with heart disease does not, in many cases, differ greatly. Different types and magnitudes of stress loads are therefore necessary to recognize the marginal pathological states. It is, naturally, important to standardize the loading conditions; parameters which change linearly with the loading may yield useful information.

The exercise on a bicycle ergometer was gradually increased, and pharmacological stress was produced by the administration of isoprenaline which is well known for its effect on the circulation.

At first, it was necessary to examine the responses in a healthy individual. The effect of exercise using bicycle ergometer is discussed on p. 64.

Subsequently, the effects of different doses of isoprenaline in healthy subjects were demonstrated. In both instances it was found that there was a correlation between the magnitude of the exercise load and the dose of the drug on the one hand, and the intensity of the response, on the other (p. 68).

Using these methods, some problems of ischaemic heart and cardiac decompensation are treated on p. 90, while on p. 71 hypertension and on p. 79 essential hyperkinetic heart syndrome are dealt with.

EFFECT OF GRADED EXERCISE IN HEALTHY INDIVIDUALS

The aim of these investigations has been to test the behaviour of the circulation by standardized and graded physical work. The results obtained not only give a clear picture about the physiology of the circulation but also provide an opportunity to use the changes as the basis for understanding pathological responses. Numerous data are available on the effects of different grades of loading on pulse rate, blood pressure, cardiac output, O_2 consumption and CO_2 production.

The adaptation of the circulatory system depends on numerous factors: on the type and duration of exercise, on sex, age, training, as well as on environmental factors.

The most commonly used technique is the two-step Master test (Master and Oppenheimer 1929). In our first investigation a simple type of exercise was used: the person under investigation steps up and down a 40-cm-high step at a predetermined speed. The weight, the height and the number of steps per min give the size of the output (Simonyi et al. 1963, 1964).

In recent years methods of exercise have been introduced allowing the maximal or submaximal capability of the examined person to be assessed. This is achieved either by graded exercise, or by calculated grade of stress or by the maximum pulse rate reached, and/or by O_2 consumption; in every case, sex and age should be taken into consideration (Eldahl 1934, Eskildsen et al. 1950, Donald et al. 1954, Fraser and Chapman 1954, Slonim et al. 1954, Mechelke and Nusser 1955, Holmgren et al. 1957, Mellerowicz 1962, Simonyi et al. 1964, Bellet and Roman 1967, Epstein et al. 1967, Ellestad et al. 1969, Endresz et al. 1971, Hille et al. 1971, Rautenberg and Hultsch 1971, Bruce et al. 1974, McDonough et al. 1974, Ludbrook et al. 1974).

Our complex method using the max dC/dt and the amplitude of the first heart sound (see Chapter 3) by simultaneously measuring blood pressure, pulse rate, ejection time, pressure time and minute index, enabled to obtain useful data about the contractility of the heart.

Gorlin et al. (1962) showed that the MSER of the left ventricle, in other words the ratio of systolic volume and ejection time, is the first parameter revealing the differences in the regulation of the healthy and pathological hearts. Valuable information was expected from the behaviour of the max dC/dt, which after exercise is in close correlation with the MSER. In order to follow changes in the carotid tracing and its derivative after ergometric exercise an adjustable head support was developed on the

'Elema' ergometer (Simonyi 1968*a*). The person under investigation was in the sitting position, his head being supported by this device. With a few exceptions, with this setup curves were obtained which could be evaluated. In normal cases 200, 400, 600, 800 and 1200 kg-m force was applied each time, and the experiment lasted 3 min. The changes in the circulation were recorded at 0.5, 1, 1.5, 2, 3, 4 and 5 minutes after exercise; in some cases recording was also taken during exercise.

Blood pressure was examined by noninvasive means. Both the systolic and diastolic pressure were obtained. The 'mean blood pressure' was calculated from the arithmetic mean of systolic + diastolic pressures. It should be pointed out, however, that we wanted to follow the trend, rather than the absolute values of the 'mean blood pressure'. The calculation of the mean pressure is dealt with later (Chapter 6, p. 132) in which the mean pressure is derived from the area under the curve using a computer. In Chapters 4 and 5, the mean pressure values were calculated by simple means, because the figures agreed well with those obtained by the computer. Variations of the *dC/dt* produced by exercise or drug were related to the control value (Chapter 1, p. 28), the latter being taken as 100 per cent. In some cases the max *dC/dt* was calibrated according to the method given in Chapter 2, p. 50. The pressure time per min index (*PTM*) was calculated from the mean pressure × ejection time and the heart rate. Deviations from the values obtained during rest are given in percentages.

In the following section, data of experiments carried out on 70 healthy individuals of both sexes (age 18–44 years) are presented. Loads of 200 to 400 kg-m were applied in both sexes, the higher loads being used only in males. The 200 to 600 kg-m load was tolerated remarkably well but loads larger than these caused sweating and fatigue.

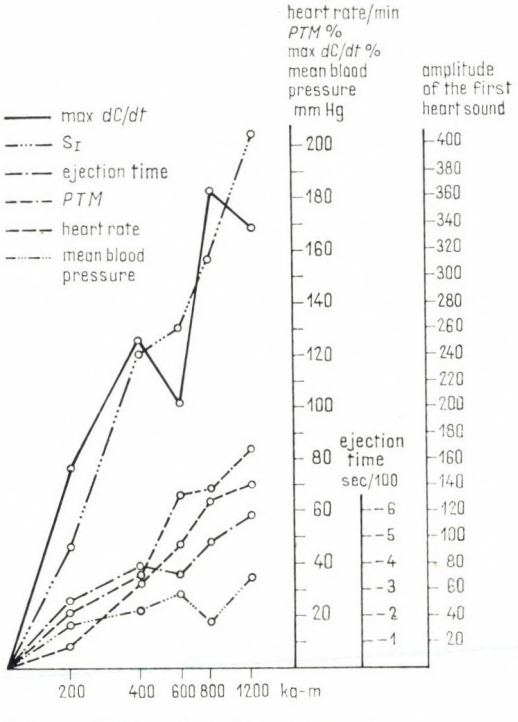


Fig. 43. Effect of graded ergometric exercise (3 min) on maximal changes of circulatory parameters in healthy individuals. S_I = amplitude of the first heart sound

In healthy individuals no change in the ECG was observed after exercise (Figs 43 and 44).

Changes were observed in all parameters immediately after the exercise. These results can be taken as identical with those at the end of the exercise.

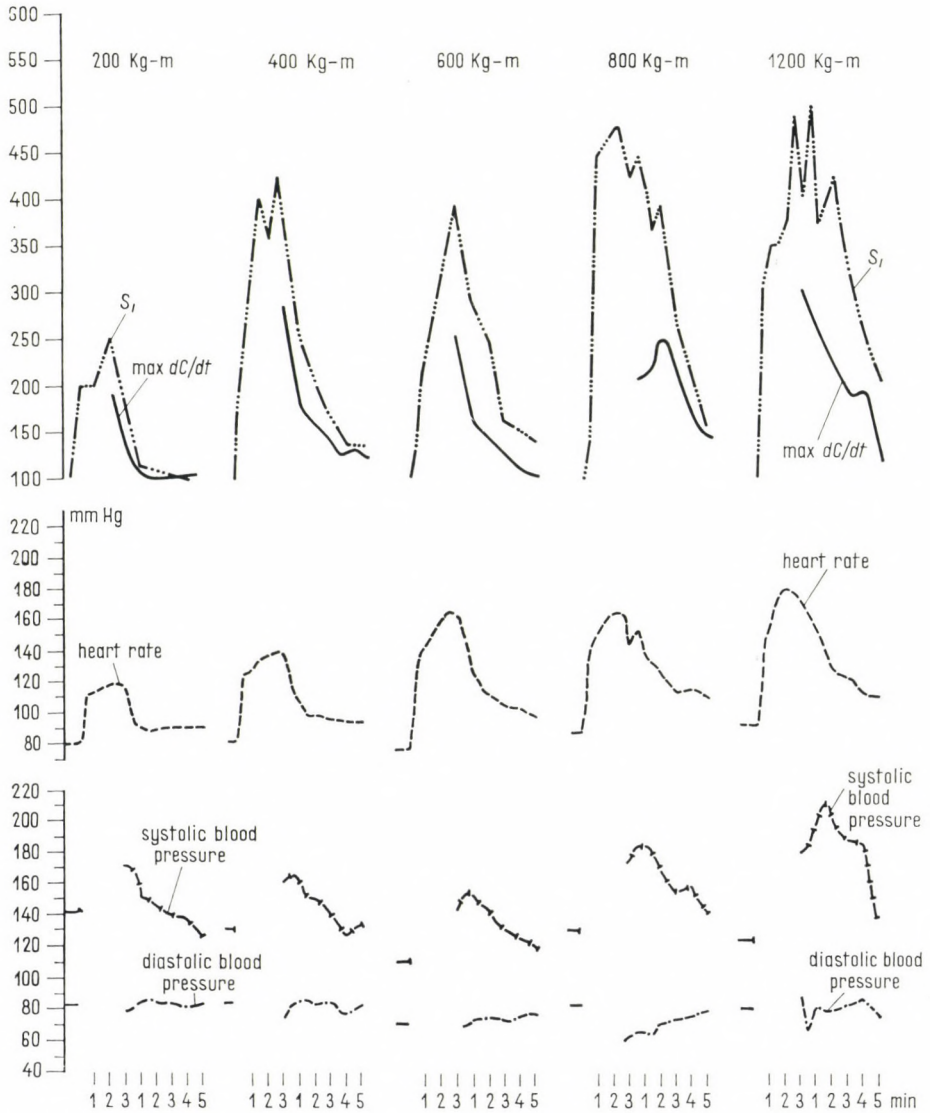


Fig. 44. The haemodynamic effects of graded ergometric exercise (3 min). S_I = amplitude of the first heart sound

Blood pressure: The systolic pressure increased in parallel with the magnitude of the exercise: at 200 kg-m 30.8 mm Hg, at 1200 kg-m 70 mm Hg. The diastolic pressure showed hardly any change from 200 to 600 kg-m, with greater exercise, however, it slightly decreased.

Mean pressure: There was a consistent increase by 10 to 20 mm Hg, at 1200 kg-m it was 34 mm Hg.

Pulse rate: At 200 kg-m it increased by 8.6, at 400 kg-m by 34, at 600 kg-m by 47.7, at 800 kg-m by 63 and at 1200 kg-m by 70. The increase was proportional to the magnitude of the exercise.

Ejection time: The greater the exercise, the shorter the ejection time.

Max dC/dt: It increased with the size of the exercise, the increase being greater than that in the pulse rate.

The amplitude of the first heart sound: The same change occurred as has been outlined in the previous parameter, the increase, however, being even greater.

The growth of the *PTM* is proportional but it is smaller.

The results of groups exposed to 200 and 400 kg-m were compared according to sex. There was hardly any difference in the reactions between males and females. Responses of healthy young and healthy older people did not differ significantly when subjected to work loads in excess of 400 kg-m (see Chapter 4, pp. 72, 92–93).

Five minutes after exercise with greater kg-m the haemodynamic effects have not been completed.

Examining the results obtained from different parameters, these have been found to be in agreement with those in the literature and with our own previous observations (Simonyi et al. 1963, 1964, 1968*c*, Békés et al. 1968).

As it can be seen in Fig. 43, there is a semilogarithmic relationship between the grade of the load and the haemodynamic effects. A 200 kg-m load for 3 minutes is regarded as a small one; on the other hand, 1200 kg-m is almost equal to the submaximal tolerance. The increase in pulse rate, corresponding to the figures in the literature, varied with the extent of exercise, at 1200 kg-m almost reaching the maximum for the particular age. Concomitantly, the ejection time decreased, the mean pressure increased as did the *PTM* which represents the 'afterload'. From the max *dC/dt* and the changes in the amplitude of the heart sound it can be clearly seen that the increase in the contractility of the myocardium plays an important role in the adaptive response to exercise. Nevertheless, this does not deplete all the reserves because after administration of isoprenaline contractility shows further increase (Chapter 4, p. 70).

*

The techniques recommended by us are suitable to measure haemodynamic parameters by noninvasive means. The indices of contractility appear to be of great value.

This experience obtained during the investigation of healthy individuals with graded exercise encouraged us to carry out further comparative studies in various circulatory disorders.

CATECHOLAMINE SENSITIVITY INVESTIGATION

Catecholamines play an important role in the regulation of the circulation. There are many publications on the effect of sympathetic nerve stimulation and that of drugs administered. The subject has become of greater interest since the identification of adrenergic receptors of various types (Ahlquist 1948, 1973). The alpha-type receptors mediate changes in the arteriolar tone and thereby regulate peripheral resistance. The beta-type responses are characterized by positive inotropic actions on the myocardium, this being accompanied by dilatation of peripheral vessels (besides the bronchodilator and other effects which do not influence the circulation).

It seems justified to obtain an insight into the pathomechanism of various cardiovascular diseases by using noradrenaline which acts relatively selectively on the alpha receptors and isoprenaline which acts specifically on beta receptors. The changes in different cardiac states in response to these amines may allow differences to be clarified. In our studies, the effects of propranolol on essential hyperkinetic heart syndrome have been investigated.

In the case of noradrenaline Komor and Polgár (1965*a*, *b*) suggested the use of an optimum dose of 5 μg. In addition, our method has also been used. Investigations with propranolol are described later in this Chapter (pp. 83, 113).

The isoprenaline effect closely mimics that of exercise. There are, however, some differences. It increases pulse rate and stroke-volume as well. The strength of the contraction is enhanced, as may be seen from the increasing MSER (Bruce et al. 1958, Krasnow et al. 1964, Benchimol et al. 1966). Even a very small dose of isoprenaline may cause the elevation of the peak of the first derivative of the right and left ventricles' pressure curves (Gleason and Braunwald 1962). It can also be seen from the preceding Chapters that the first derivative of the carotid tracing behaves similarly. It seemed to be worthwhile to analyse with our method the effects of various doses of the drug.

To overcome the occasional anxiety every patient received 2 tablets of Seduxen (Richter; 10 mg diazepam) 2 hours before the test. The patients received the drug in the supine position through an intravenous cannula

after 15 minutes of rest in rapid injection. The doses were as follows: 5 μg noradrenaline (Noradrenalin, Richter), 0.5–15 μg isoprenaline (Isuprel, Winthrop), 0.5 and 5.0 mg propranolol (Inderal, ICI).

Recordings were made according to the techniques described previously, and the same parameters were used for investigation. Figure 45 shows the results of investigations carried out in 59 healthy individuals.

Isoprenaline causes alterations in the carotid curve, the amplitude increases, the percussion wave is moderately elevated, the *t* wave becomes smaller and the incisura is found further down the pressure curve. A similar pattern can be seen in the figure of Krasnow et al. (1964); Freis et al. (1966) had the same experience when analysing the modifications of the carotid tracing after isoprenaline by an electronic computer. Isoprenaline has a slight and not definite effect on mean blood pressure and *PTM*.

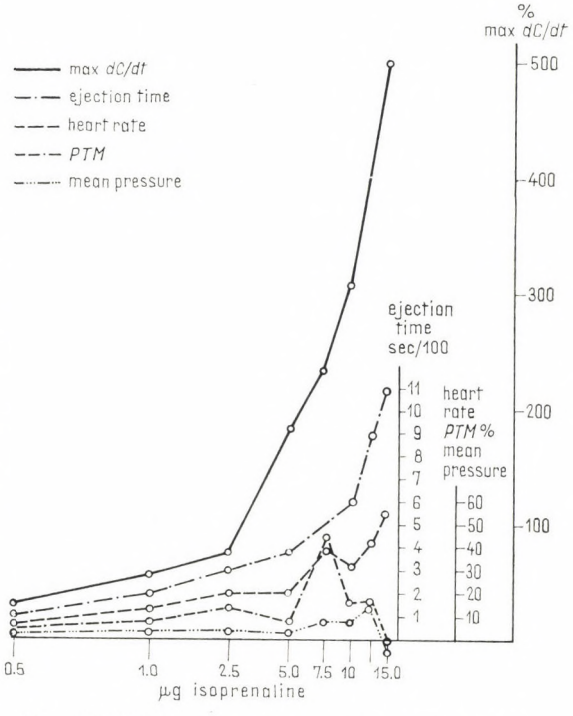


Fig. 45. Effect of i.v. isoprenaline on the maximum changes in circulatory parameters

In proportion to the change in the dose of isoprenaline, the max *dC/dt* and tachycardia increase with the ejection time shortening (see also Chapter 7, p. 151). The most sensitive index is the max *dC/dt*, and the statistical correlation is the highest in this case.

Many authors maintain that in the adaptation of the circulatory system the most sensitive factor is the pulse rate (Blinks and Koch-Weser 1963, Covell et al. 1966, Mitchell et al. 1963, Sonnenblick et al. 1966). From our results it has become clear that in healthy individuals isoprenaline affects the *dC/dt* parameter more effectively. Since this is a sensitive index of contractility, it is assumed that the drug has a direct action on myocardial contractility.

Dodge et al. (1960), Krasnow et al. (1964) and Ross et al. (1965), using different methods, came to the same conclusion. In the overall effects, the

action on the peripheral tone plays an important part. The main difference between exercise and the action of isoprenaline on the circulation concerns mainly this factor. In the latter, the mean pressure and the pressure time per minute index (*PTM*) being characteristic for the 'afterload' hardly increase.

Krasnow et al. (1964) have written about the 'afterload', i. e. the tension the ventricular myocardium develops as a result of the resistance it encounters following the onset of ventricular ejection. These authors and Benchimol et al. (1966) have described observations being very similar to ours.

If our present results are compared with those obtained by ergometric exercise (described previously), it is notable that at almost identical derivative heights the pulse rate is markedly different.

	% max dC/dt	Pulse rate (min)
Exercise with 200 kg-m	+ 78	+ 8.6
2.5 μg isoprenaline	+ 77	+20.0
Exercise with 800 kg-m	+187	+63.0
5.0 μg isoprenaline	+183	+20.0
15.0 μg isoprenaline	+503	+55.0

This means that with smaller exercise and smaller isoprenaline doses the degree of tachycardia is less, whereas in the case of higher exercise stress tachycardia is greater. Fifteen μg of isoprenaline increases the derivative by 503%. Such an increase could not be achieved by maximal exercise stress. This supports the view that the regulation of the heart rate and contractility is not mediated precisely in the same way.

In agreement with data from the literature, our observations form an appropriate basis for studying the haemodynamic effects of isoprenaline. The method described here has been found suitable by us for the investigation of isoprenaline sensitivity in various diseases (Simonyi et al. 1969, Simonyi 1969*a–c*, 1971, Simonyi and Bönsch 1971).

*

The altered sensitivity to nordrenaline and isoprenaline as well as to propranol in various circulatory diseases can be analysed by the previously described noninvasive method.

The max dC/dt readily responds to the haemodynamic effects of isoprenaline in doses of 0.5 to 15 μg.

SOME PROBLEMS IN HYPERTENSION

When Frank created the expression 'hypertension' in 1911, he meant the increase in the tone of the small arteries in the whole body; this is in contrast to the symptomatic hypertension, especially that of renal origin. The precise cause of the increase in muscle tone has remained unclarified. Wollheim and Moeller (1960) express the view that although the aetiology is not clear as yet, it is a well-defined clinical entity in which high blood pressure is the dominant manifestation being by no means the only one. Some authors (Page and Corcoran 1949, White 1951, Bilecky 1955) defined 'essential' hypertension as follows: hypertension is essential if no clearly defined cause for the high blood pressure can be established. The authors agree that this is the most common form of hypertension. According to White (1951), 95 per cent of patients suffer from this form of the hypertensive disease. The central nervous system may have an important role in the pathogenesis and perpetuation of the disorder (Lang 1953, Mjasznikov 1952, Gömöri et al. 1960, Shapiro 1960) but it is not the primary cause.

The stresses of life resulting from the differences in life style affect the organism primarily through the central nervous system. From the environmental (external) factors nutrition and particularly salt intake might have a paramount role (Szabó 1962). Nevertheless, external factors alone do not cause hypertensive disease but a predisposition in the organism is important. This includes inherited and acquired factors ultimately, reflecting the 'reactivity' of the whole body. It influences the neuro-endocrine system and through it, the regulation of blood volume and the tone of the arterioles affecting both cardiac and renal function.

The clear definition of hypertension is complicated by the fact that its natural history has various stages: latent, prehypertensive and labile phases without organic change leading to the final, often fatal, stage during which structural complications occur.

During the initial stages, the normotensive period is interrupted only at times by swings of blood pressure, the so-called 'one-day hypertension', but opinions whether this leads to the development of hypertensive disease, are not uniform (Hines, jr. 1940, Giraud and Latour 1953, Perera 1955, Wollheim and Moeller 1960, Gottsegen and Török 1961). It has been suggested that essential hypertension begins with a long and symptomless phase without hypertension and with non-specific complaints.

The salt loading tests reveal even at this stage similarities with the fully developed hypertension, particularly in mineral and fluid balance (Aviram et al. 1965, Polgár and Komor 1973). To cold stresses (Hines 1940) and to

noradrenaline administration (Komor and Polgár 1965*a*, *b*) the response of these patients resembles those of 'hyperreactors'.

The general view (Pickering 1955) is that in hypertension an increased peripheral resistance is characteristic; recent investigations suggest that in the early stages high blood pressure is caused by higher cardiac output (Widimsky et al. 1967, Varnauskas 1955, Erich et al. 1962, Bello et al. 1965). The change of heart regulation at the early stage of hypertension and, at a later stage, the damage of the myocardium justify that the latter's role and the reaction of the vessels should be investigated simultaneously. Our noninvasive method allows us to carry out such investigations. For these experiments individuals who did not have any symptoms of heart disease were selected.

EFFECT OF ERGOMETRIC EXERCISE

The effect of ergometric exercise was investigated in 29 individuals: 10 individuals were exposed to 200 kg-m, 15 individuals to 400 kg-m, 2 to 600 kg-m, 1 to 800 and 1 to 1200 kg-m load, each for 3 minutes.

A number of the patients who had labile hypertension were at the time of the investigation normotensive, while the others were hypertensive. The exercise was carried out with a bicycle ergometer.

The exercise was tolerated well by all patients. The ECG recorded during exercise did not show signs of ischaemia.

In response to exercise, the systolic pressure increased. This, however, was not as marked as that in the healthy individuals. In some cases, the increase reached 60–80 mm Hg. Five minutes after exercise, the systolic pressure often fell below the control value, the mean blood pressure behaving similarly. The ejection time and the pulse rate did not show any difference from those of the healthy individuals, and after loading the max dC/dt, in general, showed a similar pattern. It was noteworthy that 5 minutes after exercise the values often fell below the initial level. The PTM rose only in isolated cases to a higher level than that of the controls.

INVESTIGATIONS ON NORADRENALINE AND ISOPRENALINE SENSITIVITY

In this section the results of our investigations concerning noradrenaline and isoprenaline sensitivity in healthy individuals, in essential hyperkinetic heart syndrome and at various stages of essential hypertension are presented.

According to symptoms, the patients were divided into the following groups:

1. Healthy (control) group; 10 individuals with no signs of circulatory disease (resting pulse rate below 90/min, blood pressure below 140/90 mm Hg, no mention of hypertension in the family history).
2. Essential hyperkinetic heart syndrome [criteria are given by Gottsegen and Török (1962) and by Török and Matos (1967)] in 7 patients.
3. Patients with essential hypertension who, at the beginning of the investigation and on the previous day, had no increase in blood pressure (RR below 140/90 mm Hg; 16 patients).
4. Patients suffering from hypertension who, at the beginning of the experiment and on the previous days, had a higher than 145/95 mm Hg blood pressure (16 patients). This group was later subdivided on the basis of their reaction to antihypertensive drugs.

In all groups only those patients are included who did not show any sign of congestive heart failure and who, apart from sedatives, did not take any drug during the days before the experiment (for details of the method see p. 68).

The effects of 5 μg noradrenaline may be seen in Figs 46 and 47. It is clear that in Groups 1 and 2 the systolic, diastolic and the mean blood pressures showed virtually no increase whereas in Groups 3 and 4, in other words, in patients having hypertension, the increase was statistically significant.

To a small dose of noradrenaline there was slight bradycardia, no more than 10/min. In parallel with the fall in the heart rate the ejection time lengthened. No change occurred in the max dC/dt values in any of the groups.

The effects of 5 μg isoprenaline are shown in Figs 47 and 48. In controls and in hyperkinetics, the pulse amplitude increased, but the mean blood pressure hardly changed. In hypertension, the mean blood pressure rose to higher values as it could be seen after the administration of 5 μg noradrenaline. This originated in Group 3 primarily from the increase in the systolic pressure. The diastolic pressure decreased in all four groups. Whereas the increase in the blood pressure was somewhat surprising, the increase in the heart rate, the decrease in the ejection time and the elevation of the peak

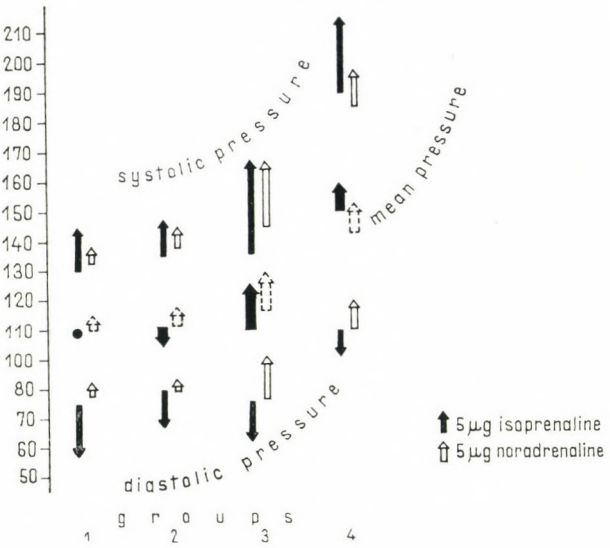


Fig. 46. Effect of 5 μg of isoprenaline (black arrows) and 5 μg noradrenaline (empty arrows) on the systolic, diastolic and mean blood pressure. Due to the effect of isoprenaline in every group the systolic pressure increased, and the diastolic pressure decreased. In the control (1) and in the essential hyperkinetic heart syndrome (2) groups the antagonizing effects led to compensation, so the mean pressure remained unchanged. In Group 3 (essential hypertension but no raised blood pressure during the examination), and Group 4 (hypertensives) the mean blood pressure is enhanced. After the administration of noradrenaline in Groups 1 and 2, the blood pressure remained almost at the same level, in Groups 3 and 4 it increased

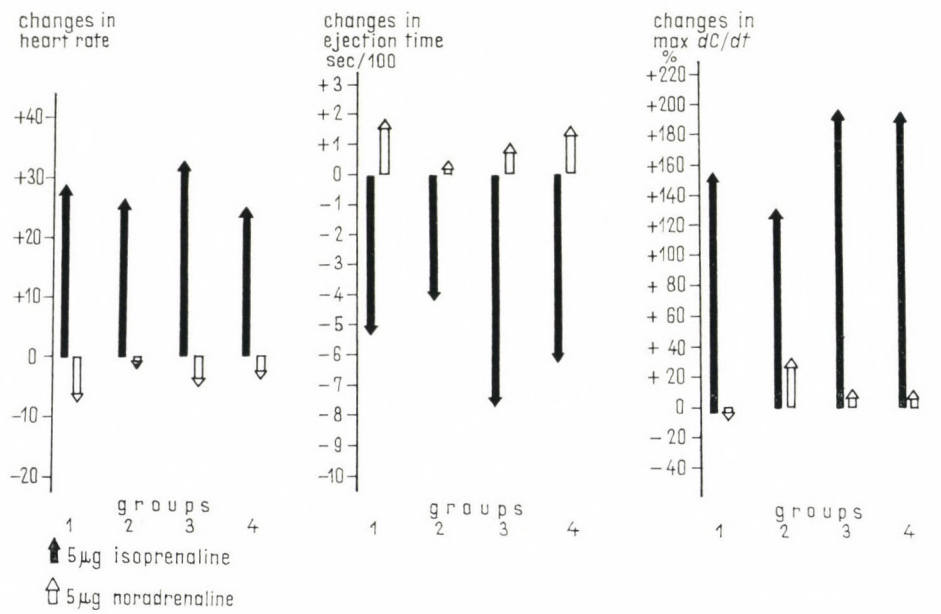


Fig. 47. Changes in heart rate, ejection time and max dC/dt due to the action of 5 μg isoprenaline (black arrows) and 5 μg noradrenaline (empty arrows). The four groups are as follows: 1 = control; 2 = essential hyperkinetic heart syndrome; 3 = hypertension but with no elevated blood pressure during the investigation; 4 = hypertensives

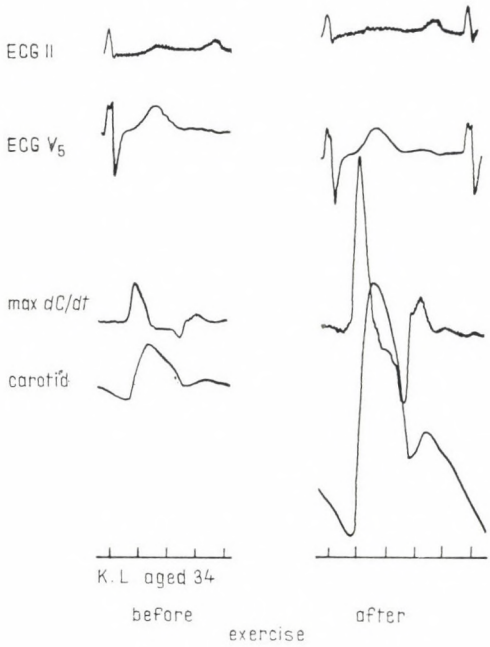


Fig. 48. Carotid tracing and its derivative of a healthy individual after 400 kg-m exercise, 3 min (Siemens Cardirex, paper speed: 50 mm/sec)

of the carotid derivative after the administration of isoprenaline were predictable. There was a considerable scatter around the means in the case of the three parameters, and thus the differences were statistically not significant.

EVALUATION OF REACTIONS IN HYPERTENSION

Taylor et al. (1957), Varnauskas (1955), Sannerstedt (1966) have demonstrated that the blood pressure after identical exercise stress rises to a higher level in hypertensives than in normotensives. Amery et al. (1967) have investigated 61 hypertensives with gradual bicycle ergometric exercises. The maximum oxygen consumption, the cardiac output and the increase in systolic blood pressure depended on age as it was found in the controls. In the younger age group (19–34 years) there was no increase in blood pressure in hypertensives after exercise compared with the healthy individuals. In the older age groups (35–49 and 50–60 years) the blood pressure rose to a higher level than in the controls. In the medium group the circulatory

reaction with every type of exercise was identical with those of the normal controls but in the oldest group the maximum value of the cardiac output was less. The maximum oxygen consumption and the cardiac output decreased significantly with the severity of the hypertension. Wong et al. (1969) examined the influence of hypertension on the maximum working capacity. They investigated 61 patients: 13 were without complications, 15 had retinopathy as a complication, in 22 cases the complication was hypertrophy of the left ventricle and in 11 cases coronary insufficiency. To establish the maximum working capacity, they investigated their patients by using a treadmill in which the slope was increased at 3-minute intervals. They stopped the experiment if the individual complained of fatigue, dyspnoea or anginal pains. The heart function was continuously monitored with bipolar chest electrodes. They also stopped the experiment in case of arrhythmia. The blood pressure in the hypertensive group without complication was at least 160/90 mm Hg at rest. The working capacity of this group was similar to that of the controls. However, it diminished in complicated hypertension particularly if there was a heart complication, to the most marked extent in cases with coronary insufficiency. There was no increase of maximum pulse rate in the 'no complication' group, a smaller increase in the group with complication, and the smallest in the coronary insufficiency group, similar to the control values. In the last group the systolic blood pressure rose only slightly whilst in the other hypertensive groups systolic pressure was higher initially with a further increase. In the 'no complication' group the diastolic pressure decreased slightly. In patients with coronary insufficiency it increased slightly.

Levy et al. (1967) carried out detailed haemodynamic investigations in 20 non-treated labile young hypertensives, with treadmill exercise. They measured cardiac output, intra-arterial blood pressure as well as its first derivative. The peaks of the first derivative of the radial pulse changed in parallel with the MSER and the ejection time index, this being corrected for the pulse rate. This shows that in controls and in hypertensives the peaks of the derivatives of the radial pulse mirror the contractility of the myocardium after exercise, although the monitoring is greatly removed from the heart. Among the patients, they found initial cardiac output only in three cases. All the parameters indicating the behaviour of the heart ran parallel both in hypertensives and in healthy individuals. These are pulse rate, cardiac output and the systolic volume, MSER and the max dC/dt. The extent of increase was also the same in the two groups, except the initial level being higher in hypertensives. The systolic and mean blood pressure increased significantly. The diastolic pressure, being small, rose only in a

fraction of the cases. Sarnoff's tension–time index per min value started from a higher level increasing to the same extent as in the control group. The authors concluded that the vascular hyperreactivity had a dominant role at this stage of the disease.

Our data correspond to those in the literature. We obtained an answer to the main question, i. e. the regulation of myocardial contractility is similar in hypertensives and in normals if there is no complication as far as the heart is concerned. This is in agreement with our previous observations, that the max dC/dt in patients and controls rose similarly after administration of isoprenaline, any variation from this pattern indicating complication (Simonyi et al. 1969, 1970*a-e*, Komor et al. 1970, 1971*a*, *b*) (see also p. 96). As was found by Amery et al. (1967) we did not find very high blood pressure in every case after exercise. All the patients' age was over 30 years.

Our present results with noradrenaline confirm those mentioned in the Introduction, showing a pronounced increase in blood pressure after the administration of this catecholamine. This also seems to corroborate a previous report of ours that in the early stage of hypertension (with normal blood pressure) the administration of 5 μg noradrenaline in one dose can separate the 'neurotics' from those with essential hypertension.

The results with isoprenaline investigations were somewhat surprising. They showed that the effect of catecholamine selectively stimulating the beta-adrenergic receptors had changed in hypertension. In healthy individuals and in patients suffering from essential hyperkinetic heart syndrome a dose of 5 μg does not influence mean blood pressure, in hypertensives it causes a significant increase. The mean is, however, lower than that found after noradrenaline, using the same dose. This denotes that in these patients, apart from the alpha-type hyperreaction, on the effect of isoprenaline there is an increase in blood pressure which is called 'paradox beta hyperreaction'. This is important because after the administration of isoprenaline in this dose, the change in other parameters did not deviate from the predicted values, and there was no variation among the groups investigated.

Preliminary investigations were carried out to find the right dose. The majority of patients received subsequently 0.5, 1.0, 2.5 and 5 μg isoprenaline. With the first two doses there was no measurable change in blood pressure. After 2.5 μg and 5 μg the increase was apparent in the paradox hyperreactions. For reasons discussed later, eventually 5 μg was administered.

It is worth mentioning that at the non-hypertensive stage the elevation of the mean blood pressure in hypertensives is due to an increase primarily in systolic blood pressure, whereas at the hypertensive stage the diastolic pressure contributed as well.

The 'paradox beta hyperreaction' in hypertensives could be a possible explanation of the depressor action of propranolol (Prichard and Gillam 1964) and nethalide (Schröder and Werkő 1964). Both propranolol and nethalide are beta-blocking drugs. The above-mentioned authors found a lasting vasodepressor effect from beta-adrenergic-blocking drugs in mild hypertensives. In severe cases, propranolol given as an adjunct to hypotensive drugs also produced lowering of blood pressure, this being later confirmed by other authors. The mechanism of action, according to Ulrich et al. (1968) and Frohlich et al. (1968), is due to the reduction of cardiac output. See also Chapter 5, in which the finding that guanethidine stops the 'paradox beta reaction', is described, and Chapter 6, in which a detailed analysis of the action of isoprenaline at various stages of the disease are presented.

There is a discussion in the literature whether essential hyperkinetic heart syndrome can be regarded as an early stage of hypertension (cf. Chapter 4, p. 86). Our investigations showed this to be not so. In hypertension there is an increased sensitivity of the sympathetic nervous system to the alpha-receptor stimulant action of noradrenaline and paradoxically to typical beta stimulants which both precipitate alpha-type reaction from the point of view of blood pressure regulation. In essential hyperkinetic heart syndrome the symptoms of beta sensitivity predominate (cf. Chapter 4, p. 86), characterized by increased systolic volume, cardiac output at rest, greater 'mean systolic ejection rate' and the max dC/dt. After slight exercise and the administration of isoprenaline and noradrenaline in small doses, there is no enhancement of blood pressure. This, however, does not exclude the possibility of one disease progressing to the other. It is quite possible that the metabolism of the catecholamines has a congenital or acquired defect and this is becoming more apparent during the progression of the disease and can be measured in more than one parameter.

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Ergometric exercise was carried out in 29 patients, in one group during the normotensive stage. The haemodynamic parameters changed in the manner suggested in the literature. In some cases the increase in blood pressure was greater than in healthy individuals. The isoprenaline sensitivity experiments showed that hypertension *per se* does not influence contractility of the myocardium. The decrease in the reaction may indicate a cardiac complication.

Thirty-five cases were investigated as controls. In patients suffering from essential hyperkinetic heart syndrome and in hypertensives of various stages, the effect of the administration of 5 μg noradrenaline and 5 μg

isoprenaline, resp., was examined. The drugs were given i.v. in one dose and injected rapidly. The effects of the drugs were tested on the mean blood pressure, pulse rate, ejection time and max. carotid derivative (max dC/dt).

From our experiments it may be seen that in healthy individuals catecholamines do not cause any increase in the blood pressure, whereas in hypertensives (also in the early normotensive phase) both drugs produce increase of blood pressure. Our results confirmed the earlier observations, namely that in hypertension there is an alpha-type hyperreaction. During the action of isoprenaline in the same patients 'paradox beta hyperreaction' develops with the elevation of the blood pressure. This phenomenon could explain the depressant action of the beta-receptor-blocking drugs. The other parameters did not reveal any difference between controls and patients. The normotensive phase of hypertension on the basis of increased alpha and the 'paradox beta sympathetic' pressure reaction can be separated from that of the essential hyperkinetic heart syndrome where the greater beta-receptor sensitivity dominates.

SOME PROBLEMS OF ESSENTIAL HYPERKINETIC HEART SYNDROME

Although no exact data are available, it is well known that the number of patients suffering from psychosomatic, in other words functional, diseases is growing all over the world. Mechelke and Christian (1960) reported on patients of nine different cardiac out-patient and in-patient departments. Of 22,500 patients 4000 (17.75%) proved to be suffering from a 'functional' disease. However, the percentage varies: Christian et al. (1954) in Heidelberg and Master (1952) in New York found 38.4%, other authors (Edwards and White 1934, White and Jones 1931) found only 10%. The figure is probably higher than that (Simonyi 1963). This clinical entity has attracted increasing attention since the initial publications of Da Costa (1871) and Myers (1870) cit. by Mechelke and Christian (1960). It became clear that the 'functional disorder' does not represent a single entity but may have several variants. In one of these with well-defined features, besides the 'nervous' complaints, there is an overactive and rapid heart beat with labile systolic blood pressure. This was described by Gorlin et al. (1959), and Gorlin (1962) as 'idiopathic high output state', and later 'hyperkinetic heart syndrome'. The decreased peripheral resistance and increased MSER were considered to be characteristic, and the enhanced contractility of the myocardium was regarded as the most striking feature of the clinical picture. Gábor

(1961), using ballistography, demonstrated that in this syndrome the ratio of the dynamic phases of the heart changes, the isometric contraction and the rapid ejection being all shortened.

This problem is still of interest and under investigation (Gottsegen and Török 1962, Török et al. 1963, Török and Matos 1967, Juchems 1964, 1966, 1969, Juchems and Kaffarnik 1966, Juchems and Wertz 1969, Christian et al. 1966, Graf 1966; Graf and Ström 1966, Laberke 1967, Solti et al. 1968, Lohmöller and Lydtin 1969, Kálmán et al. 1970, Kenedi 1970). In our own investigations (Simonyi 1969*a–c*, Simonyi et al. 1963*a)* in the majority of patients suffering from 'cardiovascular neurosis' increased cardiac output and systolic volume, decreased peripheral resistance and augmented circulating blood volume were found. The investigation of the systolic phase revealed that the rapid ejection was shortened compared with the reduced ejection. As a consequence of this, the heart ejects more rapidly the augmented stroke volume into the circulation. The increased cardiac output occurring in the first half of systole may be associated with systolic murmurs. The increased volume of the heart is in agreement with these findings (Simonyi and Bogsch 1963). The circulatory parameters in patients reveal the same pattern at rest as may be seen in healthy individuals after minor loading (Simonyi 1963*a–c*).

Since the main interest is focussed on the regulation of contractility of the myocardium, our noninvasive technique was used for studying this problem. The conclusion was drawn that the increased function of the beta-adrenergic system was responsible for the alterations in circulatory parameters (Simonyi 1968, 1969*a–c*, Frohlich et al. 1969), in the essential hyperkinetic heart syndrome.

The following investigations were carried out in patients with an essential hyperkinetic heart syndrome:

Exercise in controls and in patients;
Isoprenaline sensitivity;
Noradrenaline sensitivity;
Propranolol sensitivity.

The patients were selected according to the criteria laid down by Gottsegen and Török (1962) and Török and Matos (1967).

The individuals were tested for 3 minutes with Elema ergometer under standardized conditions, in the sitting position and with 400 kg-m (approx. 60 watts). The exercise and recording were performed with techniques described in Chapter 4, p. 64. Seventeen controls and 11 patients were investigated, the age varying between 18 and 30 years (Simonyi et al. 1968*c*).

In the controls there was no strain during the testing period: the ECG did not change but the pulse amplitude increased transiently. This, however, was not significant. The ascending part of the carotid curve became steeper, the occasional anacrotic notch disappeared and the incisura shifted to a lower position. The first positive wave of the derivative increased significantly, its negative wave becoming steeper.

Pulse rate: From a mean value of 83/min (range 64–100) immediately after exercise it went up to 106/min (78–124). After 0.5 min it was 92/min and 1 min after completion of the test it returned to the resting value.

Mean blood pressure: It was 106.1 mm Hg (100–112.5) at rest, immediately after exercise it was 121.8 (100.0–142.5) with a gradual decrease to reach the base line 3 min later.

Max dC/dt: Before the experiment it was 753 mm Hg per sec (range 420–1530) and it rose to 1431 (723–3750) mm Hg per sec. Thereafter, it decreased gradually but 10 min after completion of the test it was still higher than the base line; The increase immediately after exercise was 185 per cent (142–243) (Figs 49 and 50).

PTM: From 2212 mm Hg per sec (1820–2920) after exercise it went up to 3117 mm Hg per sec (2540–3920), then it became gradually lower and reached the base line at 10 min. The mean increase was 140.8 per cent (120–200). The values are shown in Figs 49 and 50.

In the group with essential hyperkinetic heart syndrome, the exercise was well tolerated by the patients without any ECG changes. The pattern of the carotid curve and its derivative was similar to those of the controls.

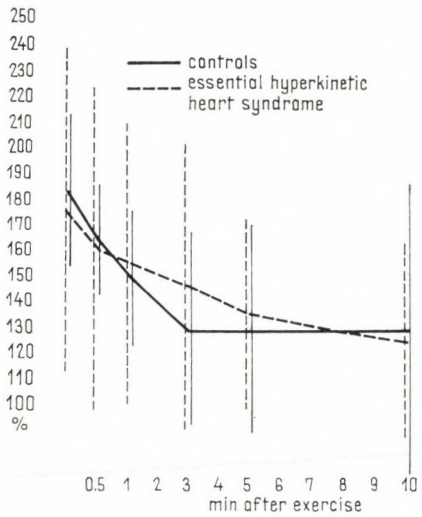

Fig. 49. The max *dC/dt* of patients suffering from essential hyperkinetic heart syndrome and of controls after 400 kg-m exercise for 3 min

Pulse rate: At rest it was 95/min (81–111). Immediately after exercise it was 124/min (105–155), by 3 min it returned to the base line. As in the controls, the mean pulse rate in this group was higher at rest as well as after exercise.

Mean blood pressure: It was 112.3 mm Hg (102–125) at rest, going up to 130 mm Hg (110–140) followed by a gradual decrease by 3 min, nearly reaching the pre-exercise level, but it did not return completely to the original level even by 10 min. The mean blood pressure of this group was higher than that of the controls.

Max dC/dt: From 1040 mm Hg per sec (700–2750) it rose to 1819 mm Hg per sec (800–4190), then decreased gradually without reaching the base line at 10 min. The mean of the group was higher than that of the controls. Because of the great scatter of the individual values the difference was not significant statistically. The percentage increase was 178 (95–332), there being no difference between this value and that of the controls.

PTM: 2355 mm Hg per sec (2100–2870) was the resting value, and it rose up to 2370 mm Hg per sec (2810–3770). After this peak it went down, being close to the base line at 3 min. However, it did not reach it at 10 min. The mean *PTM* values were, generally, higher than those of the controls but the differences were statistically significant only at 1 and 10 min.

The average increase was 139.5 per cent (124.5–175.5), similar to that of the controls (see Figs 49 and 50).

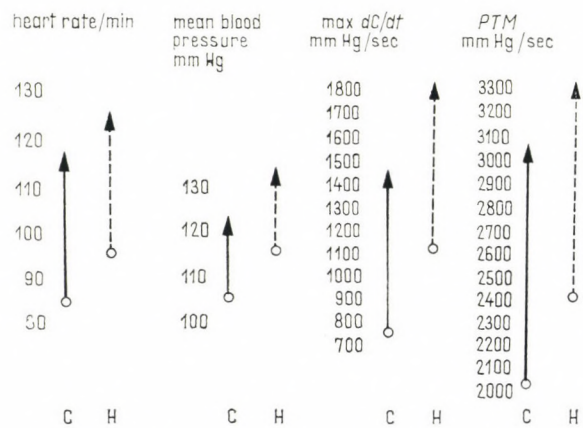

Fig. 50. Values of the controls and of hyperkinetics after 400 kg-m exercise for 3 min. C = controls (solid line). H = hyperkinetics (broken line)

EXPERIMENTS ON ISOPRENALINE SENSITIVITY

The results of our experiments on isoprenaline sensitivity can be seen in Chapter 4, pp. 73–74 and Figs 46 and 47. In these experiments the 5 μg isoprenaline in a single dose, injected rapidly in hyperkinetics, as in controls, increase the systolic and decrease the diastolic pressure. The mean blood pressure decreases slightly. As it has been mentioned previously, there is a significant difference compared with patients suffering from essential hypertension. In the latter group the isoprenaline precipitates the increase of the mean blood pressure. The degree of tachycardia produced by the drug, the shortening of the ejection and the change of the max dC/dt are uniform in every group.

In spite of these, the reactions of the hyperkinetics are somewhat less pronounced. This is due to the elevated beta-adrenergic state found at rest in these patients.

In Chapter 7 the effects of various doses of the drug in this disease are discussed. From the investigations it could be seen that the experiments carried out with 5 μg isoprenaline separate out these patients from those with labile essential hypertension (Komor et al. 1970, 1971*a*, *b*).

EXPERIMENTS ON NORADRENALINE SENSITIVITY

For results of our experiments on noradrenaline sensitivity see pp. 73–74 and Figs 46 and 47.

5 μg of noradrenaline injected in a single dose produced a moderate increase in the systolic, diastolic and mean pressures. There was no difference in this respect between the controls and hyperkinetics. However, the hypertensive groups greatly deviated from this pattern. In the latter groups the same dose of noradrenaline caused a pronounced elevation of the systolic, diastolic and mean blood pressures. The drug produced a minor bradycardia with lengthening of the ejection period in all the groups. The increase in max dC/dt in the hyperkinetic group was the greatest (beta-type reaction due to noradrenaline effect), but the scatter was considerable and the difference did not reach statistical significance (Komor et al. 1970, 1971*a*, *b*).

EXPERIMENTS ON PROPRANOLOL SENSITIVITY

In this study 0.5 mg and 2.5 mg propranolol (Inderal, ICI) were administered to essential hyperkinetic heart syndrome patients and to controls. It was assumed that in these patients due to their increased sympathetic tone, the small dose of beta-receptor-blocking drug used might provoke changes which may not influence the circulation of the controls.

Twenty-three controls and 31 patients suffering from essential hyperkinetic heart syndrome were investigated (Rausch et al. 1969, Török et al. 1969*a*, *b*, Matos et al. 1971). The average age of the controls was 27 years and that of the patients, 22 years. The male : female ratio in the healthy group was 11 : 12, and in the patient group 15 : 16.

In the supine position, patients were given 0.5 mg and 2.5 mg i.v. propranolol at a speed of 1 mg per min. After the completion of the injection, recordings were taken according to the techniques described previously.

In evaluating the results statistically the following questions were considered:

1. The differences between the patients and the controls at rest. Pulse rate: controls: 77 ± 3, hyperkinetics: 93 ± 3 ($p < 0.001$). Mean arterial blood pressure: controls: 103 ± 2, hyperkinetics: 112 ± 2 ($p < 0.01$). Ejection time: controls: 29 ± 0.6 hundredth of sec, hyperkinetics: 27 ± 0.6 ($0.02 > p > 0.01$). Pressure time: controls: 2347 ± 97 mm Hg per sec, hyperkinetics 2778 ± 108 ($p < 0.01$). Max *dC/dt:* controls: 854 ± 54, hyperkinetics: 1214 ± 109 ($p \cong \cong 0.01$).

All parameters tested indicated statistical significance.

2. The difference between the controls and hyperkinetics on the effect of 0.5 mg propranolol. In controls there was no change in any of the parameters. In hyperkinetics this small dose reduced the heart rate ($p < 0.01$) and also decreased the *dC/dt* and the *PTM* ($p < 0.001$).

The difference between controls and hyperkinetics was also significant ($p < 0.01$).

3. The difference between the controls and hyperkinetics after 2.5 mg propranolol. In the control group, propranolol reduced the heart rate significantly ($p < 0.001$), and the pressure time index also became shorter ($p < 0.001$). There was no change in the other parameters.

In essential hyperkinesis, all the parameters were altered significantly. Mean blood pressure: $0.05 > p > 0.02$. Pulse rate: $p < 0.001$. Ejection time: $p < 0.001$. *PTM:* $p < 0.001$. Max *dC/dt:* $p < 0.001$.

Between the two groups there was a statistical difference in ejection time ($0.05 > p > 0.02$) and in max *dC/dt* ($p < 0.01$).

4. The possibility of a difference between the effect of 0.5 mg and 2.5 mg doses.

In the control group (Fig. 51) the only significant difference was in the reduction of the heart rate ($0.01 > p > 0.001$).

In hyperkinetics there was a difference in lengthening of the ejection time ($0.01 > p > 0.001$).

In some cases propranolol produced changes in the ECG.

1. ST-T deviations, often found in the hyperdynamic circulatory state, were seen in 9 of 31 patients and in 3 of the 23 controls. These changes disappeared after 0.5 and 2.5 mg propranolol.

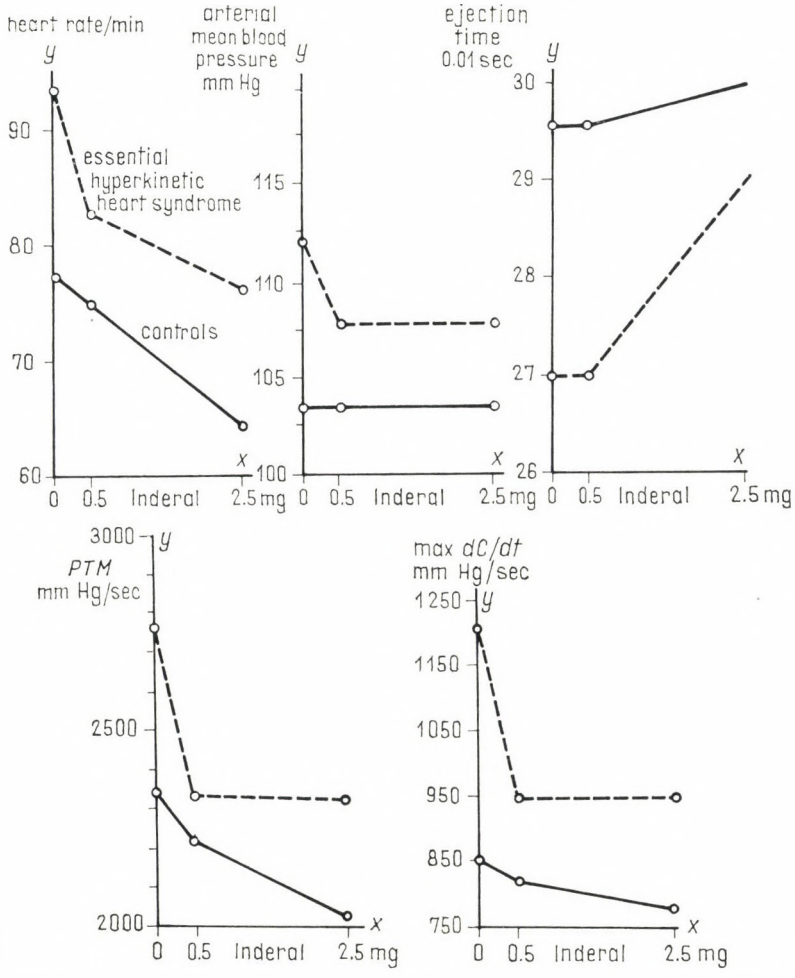

Fig. 51. Correlation between the dose of Inderal and the effects on the circulation. In hyperkinetics (broken line) 0.5 mg Inderal produces changes in haemodynamics, as seen from the effects on the max *dC/dt*, *PTM* and mean blood pressure. The reactions do not increase after 2.5 mg dose. However, the pulse rate slows and the ejection time increases

2. Frequent, unifocal ventricular extrasystoles were found in 2 patients in the hyperkinetic group. The extrasystoles disappeared after 0.5 mg propranolol.

3. In one hyperkinetic individual, after 0.5 mg propranolol PQ time at rest (0.18 sec) revealed a transient lengthening (0.23 sec).

EVALUATION OF REACTIONS IN HYPERKINESIS

Our results show that in essential hyperkinetic heart syndrome there are parameters which differ from those found in the controls even at rest. The enhanced max dC/dt indicates increased contractility, the pulse rate is higher, the ejection time is shorter and the mean arterial pressure and the pressure time per min increase. These findings support the view that the disorder is related to the increased tone of the beta-adrenergic system.

In exercise with relatively small loads, patients were found to tolerate it well, and their parameters changed similarly to those of the controls. In our previous work (Simonyi et al., 1963*a*) it was shown that the patients were unable to react similarly to the controls when greater loads were used. The patients appeared to achieve greater cardiac output being necessary for coping with a greater load by an increase in pulse rate rather than by that in the systolic volume. This adaptation has a greater energy demand.

Our experiments with isoprenaline were promising, because in hyperkinetic heart disease the beta-adrenergic system has a decisive role and the stimulant action of this drug is akin to the enhanced beta-adrenergic state. Frohlich et al. (1966) found an increased sensitivity in these patients. On examining the pulse rate, Polgár and Komor (1972) came to the same conclusion. Hence, they regard the patients as beta hyperreactors in contrast to alpha hyperreactors (i. e. individuals with increased sensitivity to noradrenaline, being at the normotensive stage of hypertension) (see Chapter 4, p. 78). They also suggest the existence of individuals with mixed sensitivity. The 5 μg isoprenaline used in our experiments could not differentiate the controls from the hyperkinetics but showed the division between hyperkinetics and patients suffering from essential hypertension. In the latter, by raising the mean blood pressure, the isoprenaline creates an alpha-type reaction. This reaction was reverted after blocking the alpha-receptors with guanethidine, i.e. isoprenaline reduced the mean blood pressure in hypertonics as well (Simonyi et al. 1970*a–e*).

The reactions of the hyperkinetics after administration of 5 μg noradrenaline were similar to those of the controls. However, the max dC/dt in the hyperkinetics showed a greater increase. This may suggest that the typical

alpha stimulator noradrenaline in this disease acts as a moderate beta stimulant. This is strikingly different from those with hypertension.

The question emerges whether hyperkinetic heart syndrome is related to essential hypertension. Gottsegen and Török (1962) found that among parental relatives of hyperkinetics there were more hypertensives than in the controls. The ratio is similar to what is found among the relatives of hypertensives. Gottsegen et al. (1964) using Jablons' angiotensin test found great similarity with the reaction type in hyperkinetics and with that of patients with essential hypertension.

Our investigations being in agreement with those of other authors have revealed marked differences between the two diseases. More evidence is needed to verify the hypothesis that hyperkinetic heart syndrome may change into hypertension. Moreover, it is neither quite sure that labile hypertension may develop into stable hypertension. Christian et al. (1966), experts in this field, deny the possibility of hyperkinetic heart syndrome transforming into hypertension. Investigations outlined in Chapter 7 indicate that in hyperkinetic heart syndrome, peripheral vasodilatation has a decisive role in the regulation of myocardial contractility. This reminds us of the experiments of Naszlady (1967) in which by the reduction of peripheral resistance, a model of the hyperkinetic circulation could be produced (see also Graf 1966).

The specific blockade of the beta-adrenergic system gave an opportunity for further clarification. A very small dose of propranolol (0.5 mg), which does not provoke any changes in controls, normalizes the raised parameters found at rest in hyperkinetic heart syndrome. The increase of the dose to 2.5 mg produced no further effect on the parameters.

0.5 mg and 2.5 mg i.v. injected propranolol affected only the ejection time being lengthened significantly after 2.5 mg, but not done so after 0.5 mg. The max dC/dt decreased after 0.5 mg propranolol and thus indicated more sensitively the reduction in contractility than did the lengthening of the ejection time.

Schmidt and Schmier (1967) have shown in animal experiments that the negative inotropic action of the beta-blocking agents is composed of two actors: of the adrenolytic effect of the catecholamines stored in the heart, and of the direct negative inotropic action on the myocardium. This latter seems to be independent of the beta-blocking action requiring 6 times the beta-blocking dose for it to be apparent. In our opinion, the reduction of the max dC/dt represents the normalization of the contractile force which is due to beta-adrenergic stimulation rather than to a pathological reduction in myocardial force. The beneficial effect of the beta-adrenergic-blocking

agents in this disesase has also been observed by others. Warketin and Valenca (1965) have found a reduction in systolic volume, cardiac output, left ventricular ejection rate and the first derivative of its pressure curve (dp/dt), together with an increase in the left ventricular ejection time and the peripheral resistance. The hyperdynamic circulation of the hyperkinetic individual became nearly normal. Bollinger et al. (1965, 1966, 1967) have shown that after partial blocking of the beta-receptors, the increase in heart rate became proportional to the work produced. The working capacity of the patients increased and the raised blood flow in the skeletal muscle and the increased cardiac output decreased.

This agrees well with our own observations: after propranolol on loading there is a slight tachycardia in hyperkinetics and the increase in blood pressure as well as in max dC/dt and S_I is smaller.

Nordenfelt (1965) showed that the ECG signs due to alterations in sympathetic tone following postural changes could be prevented by 5 mg Inderal. Suzman (1966) stated that the ST-T changes which appear in anxiety or in hyperventilation and postural changes can either be prevented or greatly reduced by beta-blockade. After the administration of 0.5 mg and 2.5 mg propranolol it was found that the ST-T changes, being characteristic of sympathetic excess, disappeared as did the ESs.

Kenedi (1970) presented similar data on the disappearance of the murmurs linked with the greater and accelerated ejection after a beta-blocking agent (Kálmán et al. 1970). Our experience was similar, too.

0.5 mg i.v. propranolol in healthy individuals leaves the circulatory parameters unchanged. After 2.5 mg propranolol in these individuals, there is a marked negative chronotropic effect and a reduction of the pressure time index as well. However, no negative inotropic action was found and the max dC/dt and the ejection time did not change significantly. 5 mg i.v. propranolol caused a negative inotropic action in the controls, as was shown by Lydtin et al. (1967). They concluded that in the healthy human heart at rest there is a beta-adrenergic stimulation. The effect of the catecholamine present in the myocardium at rest is much less than it is in hyperkinetic heart syndrome. After 2.5 mg propranolol the peak value of the derivative of the carotid curve, which changes in parallel with contractility, does not decrease significantly, whereas in hyperkinetics after 0.5 mg propranolol there is a marked change.

Our results obtained with the administration of a beta-receptor-blocking agent agree with those published in the literature. In addition, the majority of the abnormal variables of the circulation could be normalized with very small doses of the beta-blocker. This had not been previously recognized.

Such doses did not influence the haemodynamic variables in the controls. The pathogenesis of the essential hyperkinetic heart syndrome is uncertain. Our results support the view that in the development of the disease the beta-adrenergic system contributes by its increased activity and this can be influenced with a very small dose of propranolol. It is thus not surprising that beta-blocking agents are being used for the diagnosis and treatment of the disorder.

Krüger (1967) and Solti et al. (1968) used propranolol to establish the diagnosis in hyperkinetic heart syndrome and obtained good therapeutic effect. Frohlich et al. (1966), on the basis of two patients with exaggerated symptoms of beta-adrenergic activity, described a circulatory syndrome differing from the essential hyperkinetic heart syndrome. It is influenced by Inderal. The good therapeutic effect of propranolol and other beta-blocking agents was reported by Laberke (1967), Kuemmerle and Fitzgerald (1968), Török (1969) and Juchems and Wertz (1969).

On a short-term basis, we have had good results with this form of therapy, but so far we cannot be certain of the long-term effects.

*

In patients suffering from essential hyperkinetic heart syndrome investigations by complex, noninvasive techniques were carried out concerning the effect of (*i*) 400 kg-m exercise for 3 min; (*ii*) 5 μg isoprenaline; (*iii*) 5 μg noradrenaline; (*iv*) 0.5 mg and 2.5 mg propranolol. The results were compared with those in the controls.

In hyperkinetic heart syndrome, increased beta-adrenergic tone can be demonstrated at rest. The response to small ergometric exercise was not different from that of the controls. However, 5 μg isoprenaline separate out the disease from hypertension. The same may be said about noradrenaline. 0.5 mg propranolol, which has no effect on the circulation in controls, normalizes the hyperkinetic circulation.

All this supports the assumption that in this disease the elevated beta-adrenergic tone is characteristic. Beta-blocking agents have a good therapeutic effect in the syndrome of essential hyperkinetic circulation.

SOME PROBLEMS OF CARDIAC FAILURE

Cardiac failure is a central problem of the medical sciences, since it limits the human productivity, moreover, human life, stated Schwiegk and Riecker (1960) in a monograph on the pathophysiology of cardiac failure. The ancient medical descriptions show that the clinical manifestations and the symptoms of the heart's insufficient working capacity appear in other organs or groups of organs. With the deterioration of the peripheral circulation the changes of respiration, kidney function, the working capacity of the skeletal muscle, the disturbances of the salt and mineral balance with oedema appear often earlier than the reduction of the cardiac function which is very difficult to recognize. In 1894 Osler (cit. by Bing et al. 1968) did not deal with cardiac failure in a separate chapter but he very well described the symptoms: "One does not know what is going on inside these hearts but they lose their reserve energy and with this the capacity to maintain the circulation on heavy load." The full explanation is still wanting, there being many conceptual differences. Bing et al. (1968) could not answer their own question what cardiac insufficiency is. This is so because there are important technical limitations and, in addition, there may not be a simple single answer.

"It is generally agreed that heart failure is the disease state in which an abnormality of myocardial function is responsible for the heart's failure to pump blood at a rate commensurate with the body's requirements", said Pool and Braunwald (1968). They emphasized that the basic mechanisms have not yet been clarified.

Cardiac failure in man is a general term embracing a wide spectrum of clinical forms. It is very difficult to grade and compare them with each other. The difficulties are also mentioned by others (Reindell 1968, Wollheim 1968, Hecht 1968).

Proximal to the affected part of the heart congestion (backward failure) occurs but the diseased heart is unable to cope with the demand of the arterial side either (forward failure). Gömöri (1955) is correct in saying that there is a failure in areas proximal as well as distal to the heart. It is impossible to categorize heart failure simply as either 'forward' or 'backward'. The two forms almost always coexist: 'backward failure' is the consequence of 'forward failure'.

"Clinically, heart failure is usually recognized when there are symptoms of congestion. But not all heart failure patients have congestive heart failure" . . . "it is reasonable to differentiate between the pump function of the whole heart and the muscle function of the myocardium" (Roskam 1974).

Mechanical factors, among them myocardial hypertrophy, play an important role in the genesis of heart failure. The hypertrophy is initially compensatory to meet the increased demand, but myocardial efficiency does, nevertheless, decrease (Meerson 1965, Chidsey et al. 1966). Spann et al. (1967) by constricting the pulmonary arteries of the cat produced first hypertrophy of the right ventricle and then cardiac failure. In either case the contractility of the isolated fibres of the heart decreases. In the isolated papillary muscle, the maximum velocity of the fibre shortening (V_{max}) is reduced, as is the maximum isometric tension (P_0). These changes were more pronounced if cardiac failure developed.

Similar studies were undertaken by Krames et al. (1967) and Spann et al. (1967) in undamaged hearts. It appeared that hypertrophied muscle *in toto* was able to maintain compensation for a long time.

A great number of studies have been made on the ultrastructure of the myocardium in healthy individuals and in patients with cardiac failure. The chronic myocardial ischaemia due to the disease of the coronary vessels causes lasting hypoxia and heart failure develops even without extra loading. It is quite obvious that after infarction provoked by acute or chronic antecedents a part of the myocardium does not contribute to the work of the heart, the remaining myocardium having to perform greater work. However, this often cannot be achieved because hypoxia damages the intact myocardium as well. An extensive research is centred on clarifying the biochemical background of cardiac failure. It was assumed that there is a disorder of energy production (Szekeres and Schein 1959, Gertler 1961, Schwartz and Lee 1962, Wollenberger et al. 1963, Argus et al. 1964). Others believe that the fault is in the storage of energy (Furchgott and De Gubareff 1958, Furchgott and Lee 1961, Feinstein 1962, Fleckenstein 1964, Fox et al. 1965), while some others that it is in the transformation of the energy to work (Olson 1959, Minton et al. 1960). Nevertheless, Buckley and Tsuboi (1961) and Bing (1965) found no abnormality in this process. The ATPase present in the contractile myofibrils might have an important role. The decrease of this enzyme was reported by Chandler et al. (1967) and Pool and Braunwald (1968), and these authors consider this an explanation for the reduction in the velocity of all energetic processes. Their hypothesis is that in cardiac failure the liberation of calcium from the sarcoplasmic reticulum is insufficient, and as a consequence, the activation of the contraction is inhibited.

A significant role was also attributed in producing heart failure to the adrenergic nervous system. Some difficulty has arisen from the fact that there is still no agreement on the parameter, the changes in which are specific

in defining cardiac failure. Moreover, the measurements are also biassed by psychological impulses. Reindell (1968) recommends the use of the speed of the pressure development (dp/dt) and the spiro-ergometric methods. The complex noninvasive technique recommended by us seemed to be highly suitable for studying the pathomechanism of cardiac failure because it can be applied for following changes in the contractility of the myocardium, this being the focal point of the whole problem.

EFFECT OF EXERCISE

400 kg-m load was applied for 3 min in controls and in patients suffering from ischaemic cardiac failure, and the difference in max dC/dt values was noted (for technique and calculation see Chapter 4, p. 64).

In the control group, there were 13 individuals between the age of 50 and 70. The 14 patients with ischaemic heart failure were selected from persons of similar age who reacted with an effort angina; the majority also had positive ECG changes. Nevertheless 400 kg-m load did not precipitate these symptoms. The members of this group of patients at the time of the experiment had a compensated cardiac failure. The duration and the severity of the disease varied.

Elderly healthy individuals

All of them carried out the test without difficulties, there were no ECG abnormalities. The carotid pulse recording before exercise showed the pattern characteristic for this age as is well known from the literature.

Pulse rate: Before exercise it was 79/min (55–93), it rose to 92/min (70–125) and one minute after exercise it went back to the initial value. There was a smaller increase in pulse rate compared to that in the younger age group (see Chapter 4).

Mean blood pressure: 114 mm Hg (95–125) before exercise, immediately after exercise it was 132 mm Hg (107–160), then 3–5 minutes after completing the exercise it returned to the base line. The mean blood pressure before and during the exercise was higher in the older group (see Chapter 4).

Max dC/dt: At rest 794 mm Hg per sec (362–1150), immediately after exercise 1392 mm Hg per sec (795–2272), then it gradually decreased; 10 minutes after testing it was still above the base line.

The maximum increase was 184 per cent (130–390). There was no difference between the older and the younger age groups.

PTM: At rest 2260 mm Hg per sec (1240–3180), immediately after exercise it was 3050 mm Hg per sec (2140–4590), then it gradually decreased to reach the base line.

The maximum increase was 137.3 per cent (114.5–171.0), there being no difference between the older and the younger individuals.

Ischaemic cardiac failure

The patients tolerated the exercise well, there was no aggravation of the ischaemic ECG findings. On the carotid tracing anadicrotic angulation and irregular pattern of the derivative were found even before exercise (in 6 patients of the controls). These changes were worse and occurred more frequently after exercise (in 8 cases, compared to 1 in the controls) (Fig. 52).

Pulse rate: From 74/min (56–87) it rose to 95/min (72–122), one minute later it became normal. There was no deviation from that of the control group.

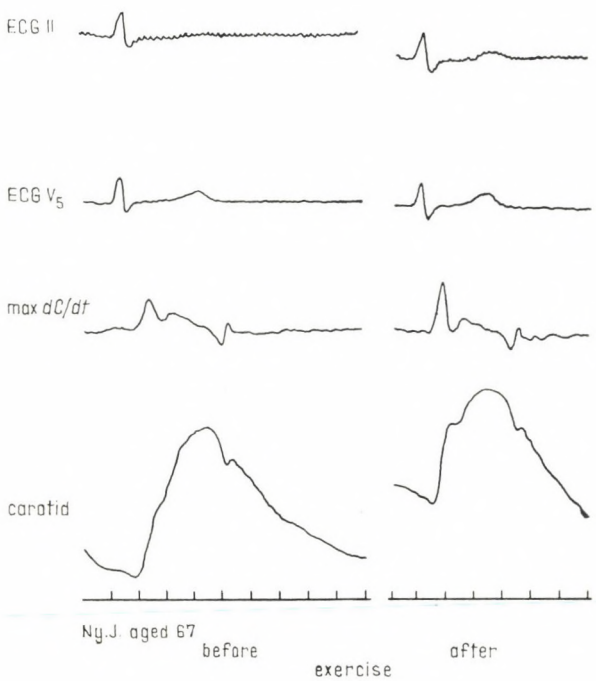

Fig. 52. Effect of ergometric exercise on ischaemic heart disease

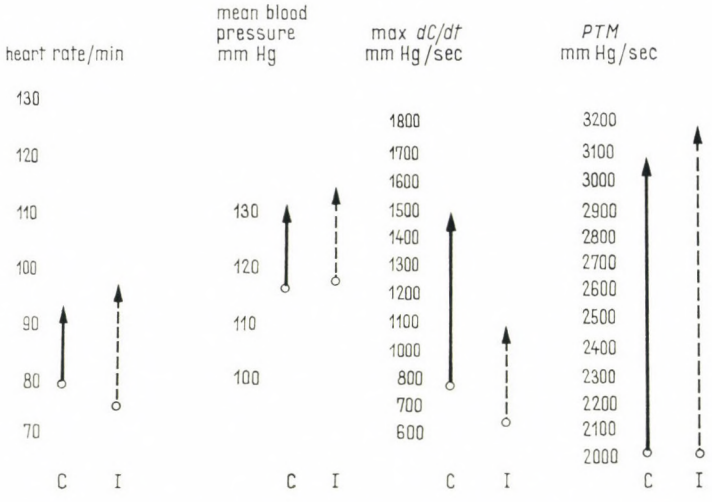

Fig. 53. Effect of exercise (3 min, 400 kg-m) on the pulse rate, mean blood pressure, max dC/dt and PTM. The main difference between the two groups was found in the dC/dt. C = older controls (solid line). I = patients with ischaemic heart disease (broken line)

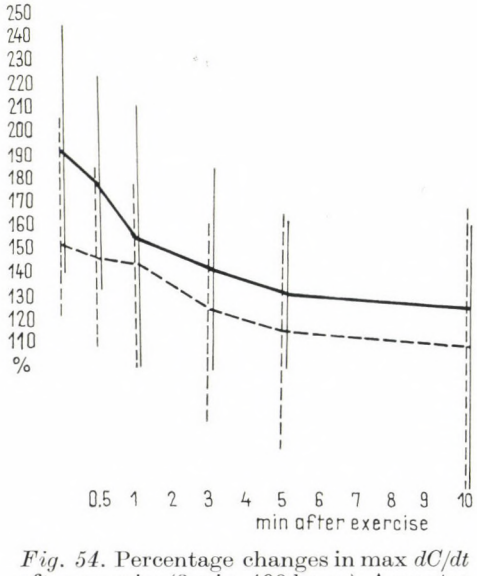

Fig. 54. Percentage changes in max dC/dt after exercise (3 min, 400 kg-m). A greater increase was found in the controls. Solid line: older controls. Broken line: patients with ischaemic heart disease

Mean blood pressure: The base line was 115.2 mm Hg (95.0–132.5) from that it went up to 132.3 mm Hg (105–160) while gradually decreasing in the 5th minute, it returned to the base line. Between controls and patients no difference was found.

Max dC/dt: From 632 mm Hg per sec (266–1100) it rose to 930 mm Hg per sec (370–2400), then it decreased gradually, reaching the base line 10 minutes later. The maximum increase was 143% (80–240) (see Fig. 54). Both the value at rest and the increase after exercise were less than that found in the control group.

PTM: 2200 mm Hg per sec (1530–3160) at rest, going up to 3208 mm Hg (2420–4280) immediately after exercise, and coming down to the base line in the 10th minute. The increase was 150.1% (117.5–199.5). The value at rest was the same in both groups, in the patient group it rose somewhat higher. The only difference between the two groups was a slower normalization in the patients.

The data in the ischaemic group can be seen in Figs 53 and 54 (Békés et al. 1968, Simonyi 1971).

INVESTIGATIONS ON NORADRENALINE SENSITIVITY

As in the investigations described previously, the patients received 5 μg i. v. noradrenaline in a single dose in the supine position.

The experiments were carried out in 12 patients with decompensated cardiac failure. Of the 12 patients, 11 had ischaemic cardiopathy and/or hypertrophic cardiomyopathy, in one case there was a combined mitral valve defect.

At every 0.5 min after the administration of noradrenaline, pulse rate and blood pressure were measured. In 11 cases noradrenaline increased the blood pressure, in one case it lowered it by 20 mm Hg. In 4 cases greater than 20/15 mm Hg increase was found in the blood pressure (50/20, 60/30, 40/30, 75/20). The pulse rate rose slightly in all but one case; in the case which behaved exceptionally pronounced tachycardia was found (Vass et al. 1972).

The experiments were carried out as described on p. 68 of Chapter 4.

The values in Figs 55 and 56 show the maximum changes with respect to the effect of the drug. The experiments were performed in controls and in decompensated cardiac patients, the latter showing different grades of de-

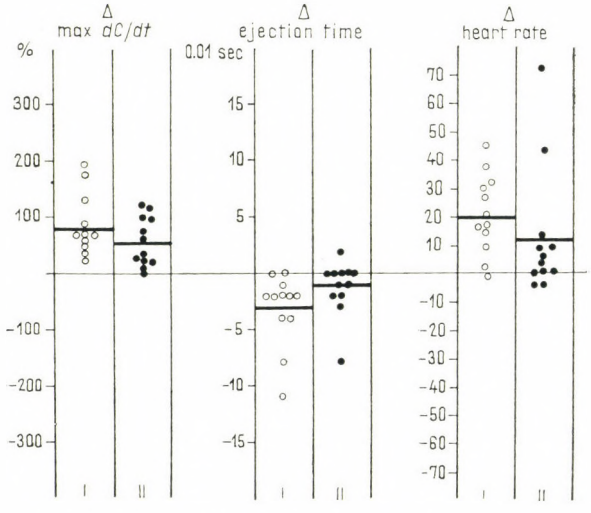

Fig. 55. Relative change in the max dC/dt, changes in ejection time, pulse rate after 2.5 μg isoprenaline. There is no marked difference between the two groups. I = controls. II = cardiac patients

compensation. For controls, individuals were selected without history or symptoms of cardiac disease. Some of them, however, had higher blood pressure. The grade of decompensation was established according to the classification of the New York Heart Association. The isoprenaline (Isuprel, Winthrop) was given i.v. in single non-cumulative doses of 2.5 μg and 5 μg, respectively.

2.5 μg dose was given to 12 controls and 12 cardiac patients; 5 μg was administered to 30 controls and 16 cardiac patients. At rest there was no difference between the two groups as far as heart rate and ejection time were concerned, whereas the mean blood pressures of the patients were higher. This might be due to the fact that ischaemic heart disease is often associated with hypertension. In the control group individuals with increased blood pressure showed similar results to those of the other individuals in the group.

After the administration of 2.5 μg isoprenaline the responses of both groups were similar (Fig. 55).

After a dose of 5 μg, there was a significant difference (Fig. 56) which could be best seen in the pattern of the max dC/dt change. Out of 30 individuals without cardiac disease, the increase was greater than 100 per

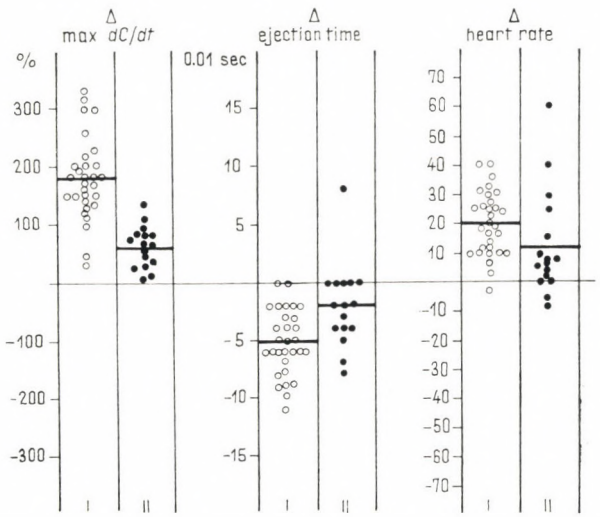

Fig. 56. Changes of dC/dt, ejection time, pulse rate after 5 μg isoprenaline. The max dC/dt increases more markedly in the control group than in the patient group. I = controls. II = cardiac patients

cent in 28 cases, whereas among 16 decompensated cardiac patients it was only greater in 2 cases. These two were lower than 180 per cent being the average increase found in the controls. In patients' group, the greatest increase was 131 per cent, whilst in the control group, it was 330 per cent. There was a marked difference in the ejection time as well. In the control group, its shortening was more pronounced. Although the deviation of means was statistically significant, there was an overlap in the individual values.

Blood pressure was not substantially different in the two groups, however, in the controls, the widening of the pulse amplitude was more prominent. The acceleration of the heart rate was more or less the same in both groups. In a few cases the tachycardia was more marked (72 and 60/min).

In healthy individuals, both isoprenaline doses increased the pulse rate by 20/min, while the increase of the max dC/dt was greater after the higher dose. In patients, there was hardly any change after doubling the dose.

EVALUATION OF REACTIONS IN CARDIAC FAILURE

The cardiac output of patients with heart disease did not deviate from that of the normals at rest in every case. Stead et al. (1948) found that cardiac output, in 82 per cent of the controls, was higher than 4.51 per min, whereas in 48 patients with chronic cardiac failure, in 78 per cent, it was lower. It may be expected that the cardiac output in severe decompensation is less, but it is greater than might be anticipated from the clinical picture as claimed by Schwiegk and Riecker (1960). Harrison (1935) found in a few decompensated patients greater cardiac output than in normals. Beside the 'low output heart failure' a new concept, the 'high output heart failure' has thus developed (McMichael 1947).

In any event, barring the most severe cases, the cardiac output change at rest is not a distinct feature in most cases of heart failure. It is agreed that more information can be obtained by measuring the behaviour of the heart in exercise under various stress conditions. It was concluded that cardiac output and the systolic volume were inadequate and less than in controls. Hickam and Cargill (1948), Messer et al. (1962), Gorlin et al. (1962). Levine et al. (1962), Binckelmann et al. (1963), Messer et al. (1963), Gorlin et al. (1964) showed that the MSER index, which is systolic volume/ejection time is characteristic of the contractility of the myocardium at rest, and of the reactions to loading. In case of adaptation the increase of MSER is greater in controls than in patients. It has already been shown that the peaks of the first derivative of the carotid tracing change in parallel with the MSER. On the basis of this observation the problem with the former method has been examined.

At the time of the experiment our patients were in a compensated state. However, they had myocardial damage as may be surmised from the presence of ischaemic heart disease. Taking this point into consideration, a small load was applied which, according to our previous experiments (Chapter 4, pp. 64, 92-93) caused an increase in pulse rate and a slight elevation in mean blood pressure and max dC/dt. The same load in ischaemic cardiac patients did not produce angina or the development of ischaemic signs on the ECG (Békés 1966, 1967). The selected 60 Watt (400 kg-m) output lasting for 3 minutes complied with the conditions. The pulse rate and the

blood pressure changed in parallel with both the control and the patient group indicating that the load was not excessive for the patients.

The blood pressure in the controls aged 50 to 70 years was slightly higher than in the younger control group. However, there was no difference in pulse rate, max dC/dt and in PTM. In the ischaemic heart disease the increases in pulse rate and blood pressure were similar to those of the controls. The main difference was found in the max dC/dt which is an index of myocardial contractility. The mean for the patient group was lower at rest and the increase after exercise was substantially lower than in the control group. The method used by us demonstrated the disorder of the myocardium with small load and no other method was suitable to achieve this.

Sarnoff's PTM index (1955) reveals a greater increase in the patient group, but this increase compared to the controls is not significant. With a greater load the difference becomes more pronounced (Gábor et al. 1964*a–c*).

In the carotid tracing in patients the anadicrotic angulation and irregular derivative are more common findings. These alterations after exercise were more marked, indicating in part the increasing resistance of the periphery (Dontas et al. 1961, Freis et al. 1966, Gadermann and Jungmann 1964, Naszlady 1967), and in part the intrinsic disorder of the myocardium as well (Simonyi et al. 1968*a*).

The patient group was not homogeneous. This may explain the differences in the haemodynamic parameters. Some of the patients behaved in a similar manner to the controls, and more than half of the group deviated from those, this being reflected by the smaller increase in max dC/dt. At rest, there was a difference only in the two means, and the individual values revealed a large scatter. After exercise the patients with pathological reactions were demarcated from the controls. There was a reproducibility of reactions in the same individuals. The more severe the disease the more severe were the reactions.

Our findings prove that after a small load, the contractility of the myocardium is the same in the younger and older healthy individuals. However, myocardial contractility in ischaemic heart disease is abnormal.

Catecholamines have a prominent role in the regulation of circulation (Raab 1960, Moran 1963, Valori et al. 1967). The interest in this problem was generated by the discovery of different types of adrenergic receptors (Ahlquist 1948). One part of our investigations deals with the alpha-receptor stimulant noradrenaline, and the second part with the beta-receptor stimulant isoprenaline.

Chidsey et al. (1962) demonstrated that in cardiac failure, as a symptom of increased sympathetic activity, the circulating noradrenaline in blood

increases and its excretion in urine is greater than in normals. Chidsey et al. (1965) have also shown that in muscle removed during operation the noradrenaline reserve is diminished. Chidsey et al. (1964) and Spann et al. (1965) described similar findings in animal experiments. The activity of the tyrosine hydroxylase enzyme, which influences the speed of the noradrenaline synthesis, decreases (Pool et al. 1967).

The effect of 5 μg noradrenaline in heart failure was examined, and following the experiments of Komor and Polgár (1965*a*, *b*) investigations were carried out at various stages of hypertension and essential hyperkinetic heart syndrome. In agreement with previous observations it was found that in the early phase of hypertension the patients react with a greater increase of blood pressure, whilst in controls and hyperkinetics hardly any change is apparent. There is bradycardia and almost no change in max dC/dt.

It was concluded that the effect of noradrenaline on the blood pressure is independent of the decompensation of the heart. In cardiac patients there were some who behaved like 'hyperreactors' and others as 'normoreactors'. In the group of decompensated patients, unlike those in the other groups, pulse rate increased moderately. In one patient (K. V., 78-year-old female) after 5 μg noradrenaline the pulse rate rose from 92 to 160 at 0.5 min. It then decreased gradually and at 5 min it was 90/min.

In order to investigate the role of the beta-receptors, it was found that isoprenaline imitates closely (but not exactly) the effect of exercise on the circulation (Krasnow et al. 1964, Bruce et al. 1958). It thus became of interest to investigate whether the sensitivity to isoprenaline changed in cardiac decompensation. The effects of 2.5 μg were identical in the controls and in patients but after a 5 μg dose there was a clear separation between the two groups.

The max dC/dt may be elevated following an extrasystole and in atrial fibrillation, in the latter the height of the peaks being variable. The peak of the derivative was higher in patients with a pacemaker with fixed heart rate. These observations were also made by authors using different techniques (Ross et al. 1965, Benchimol et al. 1966). From this it may be inferred that the increase of inotropy is independent of changes in the heart rate. Our previous findings, namely that the drug does not act similarly on pulse rate and max dC/dt, appears to confirm this suggestion. With the increase in pulse rate, the time of ejection shows a consistent decrease (Willems and Kesteloot 1967).

According to Krasnow (1971), isoprenaline alters the haemodynamics in heart failure towards normal. Elliot et al. (1963) and Dodge et al. (1960) did not find any difference in the response of healthy individuals and pa-

tients with heart failure given isoprenaline. This agrees with our observation, i.e. there was no variation in the reactions of patients and controls after 2.5 μg isoprenaline. The technique used by us allows the monitoring of very rapid effects on the circulation. Thus it was found that after 5 μg isoprenaline the responses of the two groups were clearly separable. Although in a few cases 10 μg isoprenaline was administered to patients and controls, the 5 μg dose was chosen because this was helpful in separating the two groups, apart from being free of side effects. It is not surprising that the separation occurs only with 5 μg isoprenaline, since some load is tolerated by every patient. 'Insufficiency' occurs only if the load exceeds a certain limit.

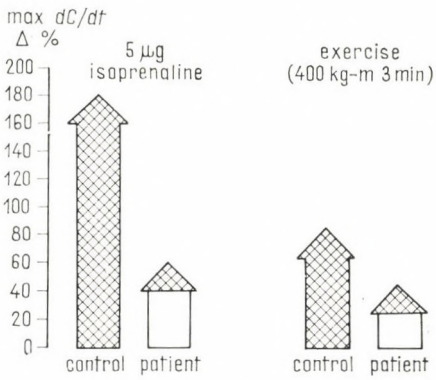

Fig. 57. The max *dC/dt* in the control group shows a greater increase after exercise as well as after isoprenaline loading

The data agree with the experience of Covell et al. (1966), namely that in experimental heart failure after the stimulation of the postganglionic nerve, the inotropic and chronotropic responses are smaller than in controls. This is in agreement with the conclusion of Pool and Braunwald (1968). ". . . the response of the intact circulation to stress may require adrenergic support. In the presence of congestive heart failure this support may, to a great extent, be lost . . ."

Taking all these factors into account, it may be stated that the endogenous adrenergic drive or the stimulant action of isoprenaline given exogenously, as it were, lead to a smaller increase in contractility in heart failure than in patients with healthy heart muscle (Fig. 57). This alteration of contractility is the dominant aspect of the clinical picture of heart failure.

The responses enable us to recognize the early signs of heart failure at a stage when there are no overt manifestations. The ergometric exercise imitates physiological stresses. The isoprenaline loading, however, separates more clearly the two groups. The ergometric exercise is suitable for a screening test. For clinical diagnosis, the isoprenaline sensitivity test is more suitable.

*

The effect of bicycle ergometric exercise, 400 kg-m, lasting for 3 min was investigated in controls and in patients having ischaemic heart failure.

Every individual completed the test without difficulty. In patients there were no ECG signs of increasing ischaemia and no symptoms of angina. The difference between younger and older controls could be found only in the mean blood pressure, this being higher in the older group. The pulse rate, the peaks of the max *dC/dt* (derivative of the carotid tracing) and the *PTM* index reacted in a similar way in both groups. In patients, the indicator of myocardial contractility, the max *dC/dt*, also lower at rest, on exercise remained lower than in the controls. In more severe cases, the max *dC/dt* was conspicuously low. The patients during the investigation were compensated and apart from the max *dC/dt* changes mentioned above and ECG findings in a few cases, did not show any deviations from the older controls. It was concluded that in patients with ischaemic heart failure the signs of deteriorating myocardial contractility have been present before the development of decompensation.

In 12 uncompensated cardiac failure cases the effect of 5 μg i.v. noradrenaline was examined. The action of noradrenaline on the blood pressure is independent of the grade of decompensation. In patients with decompensation there was a slight increase in pulse rate, whereas in our former investigations there was a tendency toward bradycardia. In one patient with severely damaged myocardium, marked bradycardia developed.

In controls and in uncompensated patients (altogether in 70 cases) the effect of 2.5 μg and 5 μg isoprenaline was investigated. The reactions of both groups were similar on 2.5 μg dose, but on 5 μg dose the max *dC/dt* increase was much greater in controls than in patients. In this respect the two groups sharply differed.

CHAPTER 5

CLINICOPHARMACOLOGICAL INVESTIGATIONS

INTRODUCTION

The evaluation of the efficiency of therapy is a difficult task. The course of the disease in the same individual depends on various factors and the assessment of the changes, particularly the identification of the precise cause of a change often is a complex exercise. A very careful analysis is needed to distinguish between fortuitous and causal origin. At the evaluation of a drug's effect one should avoid the uncritical use of the *post hoc ergo propter hoc* principle. Environmental factors, nutrition, physical or mental strain may improve or worsen the course of the disease. Faith or distrust in therapy or drug is an additional component to a good or bad therapeutical effect. Experimental medicine is in a position whereby it can standardize the circumstances and this is a great advantage compared to clinical medicine. Nevertheless, the main objective is to cure the patient and assess the therapy.

The therapy with drugs usually requires various steps, nevertheless these are often not considered logically being as follows:

1. The diagnosis.
2. The planning of the therapy the aim of which is to eliminate the cause of the disease, and at the same time to alleviate symptoms.

In the initial planning one should consider whether one wants to attack at one or more points with special consideration for the main actions and side effects as well as dangers in relation to the drug sensitivity of the individual.

3. The form of administration in adequate and effective dosage.
4. The monitoring of immediate and later effects in groups of patients.
5. The assessment of the therapy at individual level.
6. Drawing conclusions from groups of patients treated by the same method.

The administration of drugs with well-known actions is done in this way. The therapy with drugs and clinical work cannot be dissociated. 'Human pharmacology' must be studied in special and well-equipped institutes.

Drugs with well-known actions do not act identically in different diseases, nor indeed in the same disease at different stages. The differing response may be a characteristic feature of pathophysiology. This may be used for diagnostic purposes as well, e. g. if the uncomfortable oppression in the chest disappears after nitroglycerine this makes the diagnosis of coronary artery disease highly probable.

The experiments with drugs which have not been introduced into human medicine are being performed accordingly. The new discipline which undertakes this task is clinical pharmacology. The development of it as a discipline was necessitated by the large number of drugs which have recently appeared for evaluation. Laurence (1971) considers it highly important to work out new and sophisticated techniques. It is especially important to develop new research methods, and to improve the earlier ones for the purposes of clinical pharmacology.

The experimental methods should be suitable for providing information that is intersubjective, significant and unbiassed (Dettli 1971). If the method is quantitative in nature, it makes the statistical evaluation feasible (Joubert et al. 1971). The modern way of doing this is the use of a computer (Spindelberger and Spitzy, 1971). The great advantage here is that it is not onerous for the patient and it is exact and reproducible. This is a prerequisite for performing a large number of investigations under identical circumstances. With regard to these points, our combined technique being based on the use of the first derivative of the carotid tracing seems to be suitable for clinicopharmacological studies, preferably, for studying short-term actions which affect inotropy, either in a positive or in a negative direction. The vast area of the potential use for the method enables a quantitatively objective assessment of details in a number of situations. In the case of drugs with inotropic actions, the relative increases in the peaks of the carotid derivative demonstrate dose–effect relationships.

In this Chapter we do not intend to give a detailed account of the subject but to emphasize some principles, some forms underlying the use of our method.

In the first part of this Chapter, interventions directly influencing inotropic state, in the second part indirect interventions altering the response of catecholamines under various forms of treatment are dealt with.

ACTIONS DIRECTLY AFFECTING INOTROPY

In this series it was investigated how an i.v. administered drug affects the following parameters: pulse rate, blood pressure, relative change of max *dC/dt*, relative change of the amplitude of the first heart sound, ejection time.

The investigations were made in patients lying supine, the measurements and calculations were carried out as described previously.

Answers were sought to the following questions: Does the drug influence inotropy, and if so in which direction? Is there a relationship between the dose and the response? Are there any differences between controls and patients?

THE INOTROPIC EFFECT OF ISOPRENALINE

Controls

Investigations on the effects of isoprenaline have already been dealt with (Chapter 4, p. 68). Nevertheless, it is thought worth while to mention it here because this is the reference drug for comparison of agents with positive inotropic properties. The potency of drugs with inotropic effect is tested against isoprenaline. The effect of this drug in the range of 0.5–15.0 μg can be followed with our technique (see Fig. 45).

There is a logarithmic correlation between the dose and the graded relative increases in the max *dC/dt* (Fig. 58).

Patients with heart failure

In these patients the effects of the drug are less marked in relation to the increases in the dose. After 2.5 μg, there is no difference in the effect between controls and patients, after 5 μg the max *dC/dt* increases further in controls, but not in the patients (Chapter 4, pp. 96–97; Figs 55–56).

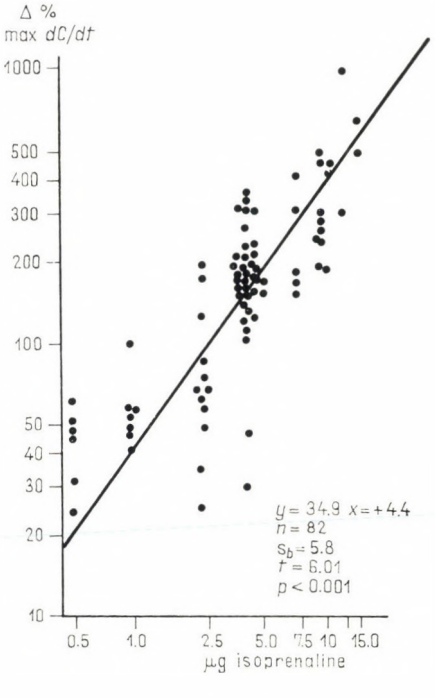

Fig. 58. There is a logarithmic correlation between the dose and the relative increase of the max *dC/dt* in healthy individuals

Circulatory-pharmacological investigations in healthy individuals with 1-(3-methoxy-4-oxyphenyl)2-isopropylamino-1-ethanol-HCl (EGYT-402), also known as MOXA

Isoprenaline is a characteristic stimulant of the beta-receptors of the adrenergic nervous system. It is active in very small doses, suggesting that it has a high degree of physiological affinity for beta-receptors.

It seemed worth while to study the metabolites of the catecholamines in respect of their beta-stimulant actions. One of them, MOXA, has been synthetized in a chemically pure form. This compound is produced in the organism by the enzyme catechol-orthomethyl-transferase (COMT). This drug in larger doses has a beta-receptor-blocking effect. However, it was later found that in smaller doses the same drug has a beta-stimulant effect (Thuránszky 1970).

Pharmacological investigations in animal experiments were carried out by Thuránszky (1970). No human investigations have so far been reported. The effects of MOXA have been investigated in a large number of individuals and our complex technique could be used to advantage.

Altogether 70 healthy individuals were examined in the following distribution.

MOXA (mg)	No. of individuals
80	17
60	9
40	8
30	8
20	7
10	6
5	8
2	7
Total:	70

In every individual, isoprenaline sensitivity was tested by giving i.v. 5 μg isoprenaline (INA; Isuprel, Winthrop). After completion of the effect, the dose–effect relationship with various doses of MOXA was investigated.

Results. MOXA has a demonstrable positive inotropic action. It increases contractility of the myocardium, the effect being dose dependent. This can be seen in Fig. 59 which shows that the first derivative of the carotid

tracing (dC/dt) increases markedly after 80 mg of MOXA. Figure 60 shows the effects of 80 mg MOXA and 5 μg isoprenaline. The max dC/dt becomes higher after both drugs but the isoprenaline effect lasts 5 min, whilst that of MOXA persists even after 25 min.

A similar pattern could be seen in the pulse rate. Systolic pressure and consequently pulse amplitude increased after isoprenaline in the first few minutes, decreasing subsequently, the effects of the two drugs being virtually identical.

The additional figures demonstrate the dose–effect relationship and its effects on various parameters. On the left side of Fig. 61, the relationship between the dose of MOXA and the change of the max dC/dt is indicated. As it may be seen, the relationship is logarithmic.

In Fig. 61 on the right, the changes in max dC/dt may be seen. The response to MOXA is illustrated as a percentage of the response in the same individual after 5 μg isoprenaline. After either intervention max dC/dt changes show similar patterns.

For comparison, the dose–effect relation curve for isoprenaline is demonstrated (Fig. 58). In this case, the correlation is also logarithmic. As far as pulse rate is concerned, if the initial angulation is disregarded, the correlation is linear. A similar linear correlation exists between the total duration of the reaction and its half-time.

The evaluation of the correlation between ejection time and the magnitude of the dose is difficult because of the wide scatter of results. The change in the blood pressure does not appear to depend on the dose.

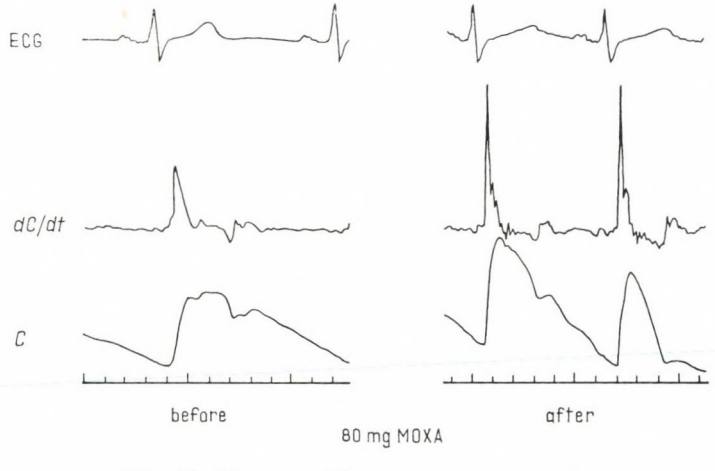

Fig. 59. The max dC/dt increases markedly due to the action of MOXA

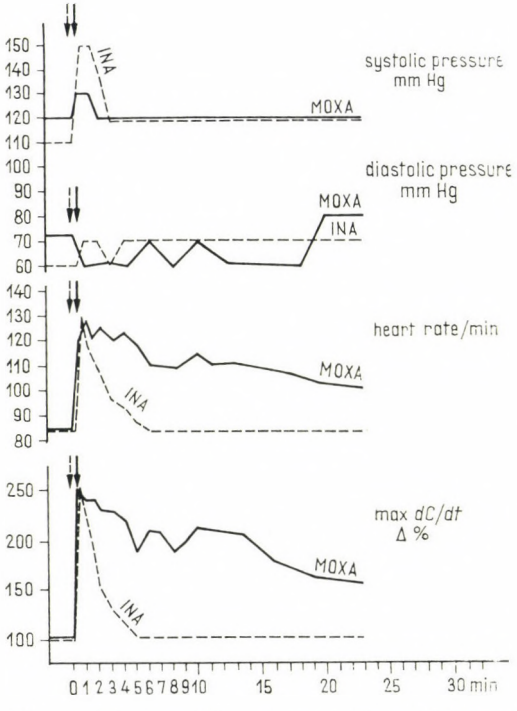

Fig. 60. Effects of 5 μg isoprenaline (INA) and 80 mg MOXA. The max *dC/dt* and the pulse rate show similar changes. The effect of isoprenaline lasts for 5 min, that of MOXA is still present after 25 min

Summarizing these results, the decrease of mean blood pressure and the increase of pulse amplitude were found.

There are marked differences, as in animal experiments, between the half decay time and the total duration of the effect. For these parameters the values are dose dependent but they are greater than those found after 5 μg isoprenaline. In this case the half-time is 2 min and the total duration of effect is 5 min.

The responses to 5 μg isoprenaline were equivalent to those of 80 mg MOXA. In animal experiments, the INA : MOXA ratio is 1 : 300–400, whereas in man it is 1 : 16,000. This may be due to species differences.

The doses given by us are in the range in which Thuránszky found stimulating effect. Nevertheless, it was not possible to give higher doses in man.

In 70 individuals, no unpleasant side effects were found, apart from palpitation in a few cases. In preliminary studies it was noticed that the effect of MOXA in healthy individuals deviated from that found in patients.

*

Following enzymatic actions in the organism 1-(3-methoxy-4-oxyphenyl)-2-isopropylamino-1-ethanol-HCl is formed and it acts, in all probability, on beta-receptors.

Pharmacological investigations were performed on the human circulation, and positive inotropic actions were found in the dose range used. There was a logarithmic correlation between contractility and the magnitude of the dose, whereas it was linear between the latter and the pulse rate. The mean

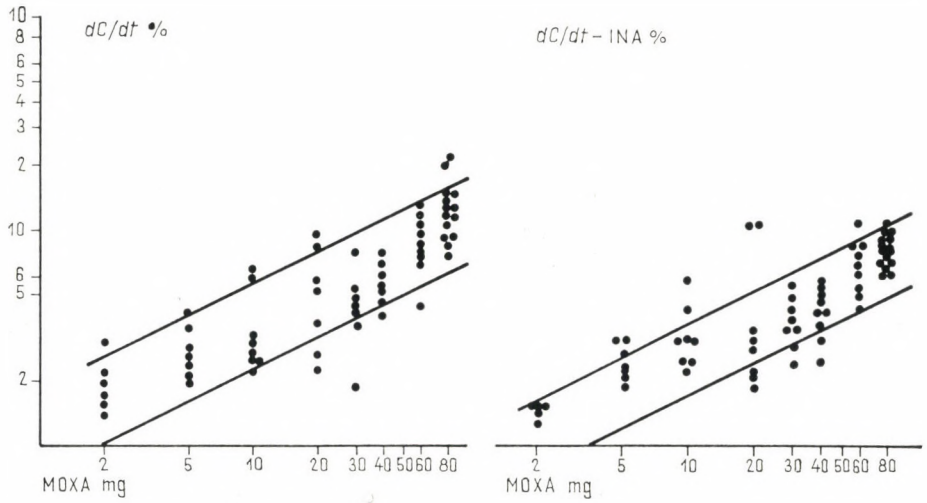

Fig. 61. At the left: correlation between the changes of the max *dC/dt* and MOXA administered in doses ranging from 2 mg to 80 mg. At the right: changes of max *dC/dt* due to increasing doses of MOXA. The results are expressed in percentage of the action of 5 μg isoprenaline

blood pressure slightly decreased, the pulse amplitude increased especially at higher doses. The ejection time generally decreased.

As far as the effect of 5 μg isoprenaline was concerned, the dose was equivalent to that of 80 mg MOXA. This ratio in animal experiment is 1 : 300 or 1 : 400, in man it is 1 : 16,000. The duration of effect and the half-time of the effect of MOXA are longer than those of INA and they are dose dependent.

Circulatory-pharmacological investigations with MOXA in patients suffering from circulatory disorders

The effect of MOXA is not known in individuals suffering from circulatory disorders. This was investigated because the compound may have therapeutic applications. For the purposes of comparison in the majority of cases the effect of 5 μg isoprenaline was also measured in the same patient.

Experiments were carried out in 58 patients, 23 of whom had congestive cardiac failure; 22 of the patients had ischaemic cardiac disease and in one there was severe combined mitral valve defect with failure.

Nine patients from this group were investigated after treatment with ouabain.

Ten patients had atrioventricular block and 8 patients had an implanted pacemaker. Eight patients had chronic bronchial asthma or asthmatic bronchitis. In these patients the chronic effects of respiratory disease on the pulmonary circulation was evident.

Results. Systolic, diastolic and mean blood pressures in this group were similar to those in controls. The pulse rate responses to isoprenaline were also similar but somewhat reduced. The changes in ejection time were similar to those in the controls. In patients, the max *dC/dt* after 80 mg MOXA and 5 μg isoprenaline increased only to a minor extent (Fig. 62), and this was clearly evident in patients with A-V block developing after infarction. Treatment with K-strophantoside produced no change in the parameters examined.

The duration and the half decay time of MOXA effect were shorter in patients.

It might be expected that complete atrioventricular block would be the main indication for the therapeutic use of MOXA. In 9 out of 10 patients

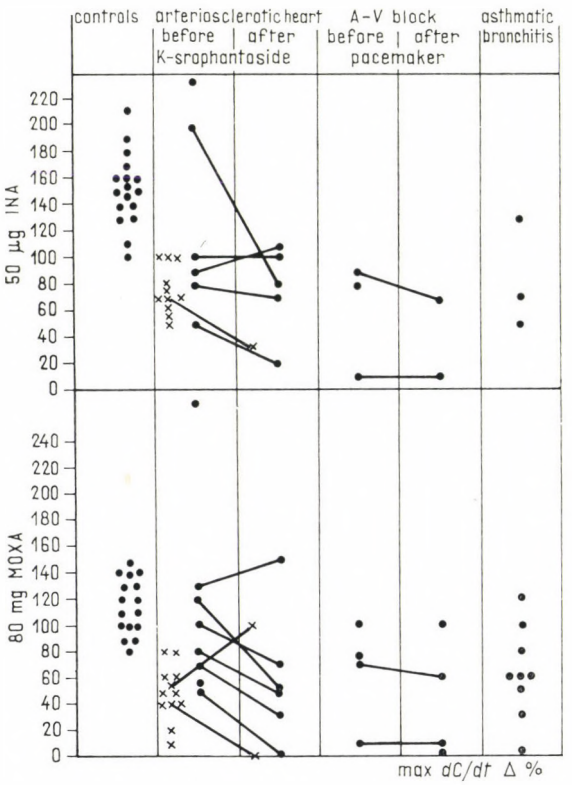

Fig. 62. Upper part: effect of isoprenaline (INA). Lower part: effect of MOXA on the percentage changes in the max *dC/dt*. The groups are controls, patients with arteriosclerotic heart disease (before or after K-strophantoside), patients with atrioventricular block (before and after the implantation of a pacemaker), and patients with asthmatic bronchitis. Crosses indicate hypertensives. The figures for the same individual before and after K-strophantoside treatment or before or after pacemaker implantation are connected with a line. In the groups of patients with heart disease, lower max *dC/dt* was found after INA and MOXA treatment

the compound could not reverse the slow rate in heart block, nor could it prevent the occurrence of Adams–Stokes attacks. Moreover, the hypotensive effect of the drug in these patients was disadvantageous. It was impossible to enhance the effect on pulse rate by increasing the dose (Fig. 63). The infusion of isoprenaline in a patient with Adams–Stokes attack, after an unsuccessful use of MOXA, led to a beneficial effect which enabled pacemaker implantation under more favourable conditions. In a younger patient, who apparently had congenital complete heart block, MOXA raised heart rate and, during ergometric exercise, the max *dC/dt* increased indicating enhanced myocardial contractility (Fig. 64). It seems that patients with A-V block developing after myocardial lesions of arteriosclerotic origin respond differently from those with congenital lesions producing heart block. This suggestion is in agreement with the finding of Boda (1969) who could prevent Adams—Stokes attacks in a patient with congenital A-V block by administering MOXA. In arteriosclerotic heart disease, in A-V block developing after infarction and giving rise to Adams—Stokes attacks,

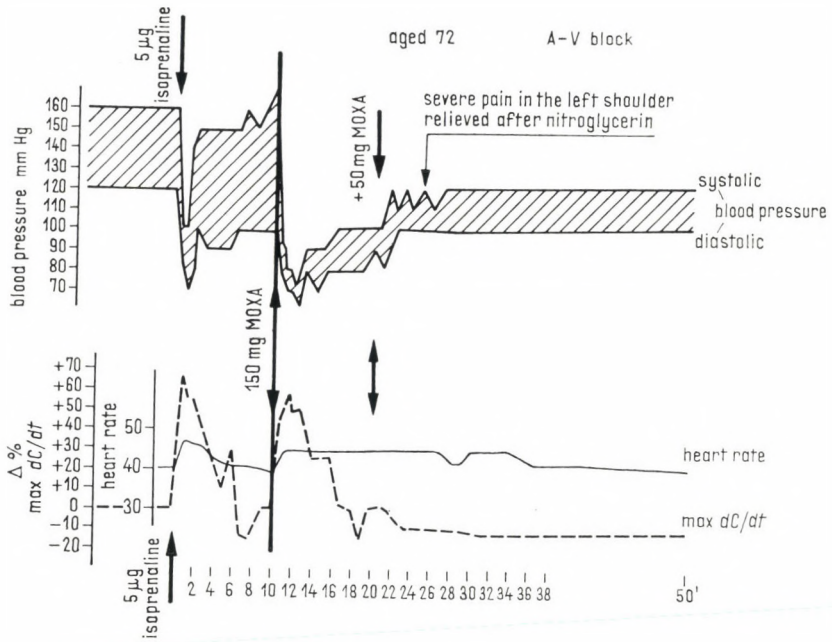

Fig. 63. Effect of 5 µg isoprenaline + 150 mg + 5 mg MOXA in A-V block after infarction. Isoprenaline produced a more transient depression of blood pressure than MOXA. The second dose of MOXA did not result in a positive inotropic action

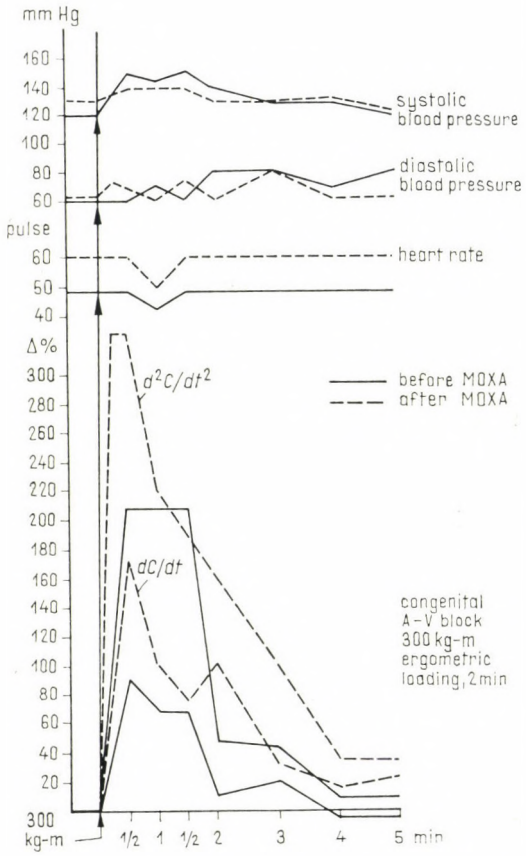

Fig. 64. After MOXA, the tolerance of the patient with congenital A-V block improves

MOXA is not helpful. In these cases, isopropyl-noradrenaline infusions are needed.

In a younger patient with sinus bradycardia and in congenital complete A-V block MOXA increased heart rate. In the latter case oral MOXA was better tolerated but the patient did complain of an unpleasant oppressive sensation.

A favourable effect was observed after i.v. and oral treatment, without side effects, in chronic asthmatic bronchitis and asthmatic attack.

*

The cardiovascular actions of i.v. administered MOXA were compared with those of 5 μg isopropyl-noradrenaline. As with INA, MOXA increased the max dC/dt in cardiac patients only slightly and this effect did not improve with K-strophantoside. MOXA decreased blood pressure to a lesser extent than isopropyl-noradrenaline.

In heart diseases with bradycardia of arteriosclerotic origin it was not possible to increase pulse rate and prevent the Adams—Stokes attacks. With an increase in the dose of MOXA the therapeutic effect did not increase even though blood pressure and max dC/dt were reduced and unpleasant side effects appeared. It was observed that in these doses beta-blocking properties of the compound were more apparent.

In a case of bradycardia not due to arteriosclerotic heart disease and in another case of congenital A-V block, the i.v. and oral administration of MOXA increased pulse rate to the desired level. However, in these cases unpleasant sensations were produced. In one of these, an increased tolerance to the loading stress was found.

INVESTIGATIONS WITH PROPRANOLOL

These investigations have been described on p. 83 of Chapter 4. Here it is examined whether the drug has an effect on myocardial contractility in controls and in patients.

In the case of isoprenaline and MOXA the changes in the positive inotropic actions are analysed, whereas in the case of propranolol, the analysis was done on the negative effects.

As regards clinicopharmacological analysis, it is necessary to distinguish normals from patients with hyperkinetic heart syndrome. 0.5 mg propranolol (Inderal, ICI) reduced the max dC/dt in patients, but no further effect was seen when the dose was increased to 2.5 mg. In controls, there was virtually no effect with 0.5 mg, but definite effects were seen at higher doses.

In order to quantify the effect of a beta-receptor-blocking drug, the inhibitory action of the compound on the increase in the max dC/dt by isoprenaline is recommended (Békés et al. 1971*a*, *b*) (Chapter 5, p. 122).

CHANGES IN CATECHOLAMINE SENSITIVITY

On the basis of our findings described above, the question naturally arises whether the drug under study modifies the sensitivity of different adrenergic receptors, i. e. whether its effects are stimulant or inhibitory.

In the following section such investigations on the effects of some antihypertensive drugs [guanethidine, i.e. Sanotensin (EGYT) and its derivative Sanegyt (EGYT)], and antiarrhythmic drugs with various points of attack (lidocaine, quinidine, Trasicor) are dealt with.

ANTIHYPERTENSIVE DRUGS

Changes in catecholamine sensitivity during guanethidine treatment

Various data testify to the increased reactivity of the sympathetic nervous system in hypertension. In our experiments it has been found that a small dose of noradrenaline produced an 'alpha'-type hyperreaction. When given in an equivalent dose, isoproterenol led to 'paradoxical beta-hyperreaction'. Both reactions have been observed in the early stages of hypertension, even at a stage when the blood pressure is not elevated.

It is well known that the majority of antihypertensive drugs act by depressing the function of the sympathetic nervous system. The drugs, which inhibit synthesis of catecholamines or which prevent their action in any

part of the sympathetic nervous system, are the most efficient antihypertensive agents. In these experiments the effect of guanethidine on the reactivity of alpha- and beta-receptors and the changes in the sensitivity of the latter to noradrenaline and isoprenaline were investigated.

The patients were divided in 5 groups according to clinical symptoms.

1. Healthy individuals, control group;
2. Essential hyperkinetic heart syndrome;
3. Hypertensives, having normal blood pressure;
4. Hypertensives, before treatment, having increased blood pressure;
5. Hypertensives who were on a small dose of guanethidine treatment for one week, and whose blood pressure was still high ($>$ 145/95).

The patients in these groups were identical to those mentioned on p. 73 of Chapter 4, however, the patients in Group 4 were divided in two further subgroups.

Every patient was examined at least twice within 7 to 10 days. They received 10 mg of diazepam (Seduxen, Richter) to avoid anxiety.

A detailed description of the methods has been presented on p. 68 of Chapter 4.

The values obtained are presented in the following order: (*i*) Values at rest; (*ii*) values reflecting the maximal change after administration of catecholamine (usually 1/2 to 1 1/2 min after administration); (*iii*) differences between the values at rest and the values measured after the drug (guanethidine) action.

After the first examination the patients usually received 3×10 mg guanethidine (Sanotensin, EGYT). The dose was increased if there was no reduction in standing blood pressure. The maximal dose was 50 mg per day, with this dose every patient having some reduction in standing blood pressure. It was not intended to normalize the blood pressure (Group 5). Seven to ten days after the initial measurements, a second examination was performed. The values obtained after guanethidine treatment were compared with those obtained prior to treatment with the differences evaluated statistically.

The effect of 5 μg isoprenaline administration is demonstrated in Fig. 65. The thick arrows represent the pretreatment values, the subsequent thin arrows show the figures obtained after one week of guanethidine treatment plus isoprenaline administration.

There was no change in mean blood pressure in controls and hyperkinetics. In hypertensives at the early (normotensive) stage there was an increase in blood pressure (see Chapter 4, pp. 73). On guanethidine treatment the

'paradoxical beta-reaction' ceased to exist. Instead there was a blood pressure reducing effect. The guanethidine treatment potentiated the increases in pulse rate and the ejection time decreasing action in every group without modifying the reactions of the derivatives of the carotid tracing.

In Fig. 66, it can be seen that with increasing doses of isoprenaline the pulse rate increases, the ejection time shortens and the peak effect on the derivative is enhanced. In this respect there was no difference between controls and patients. This was not so with the blood pressure, there being discrepancies in the results between the groups with no dose–effect relation. The effect of guanethidine treatment was apparent mainly after the administration of 5 μg isoprenaline, the results being significant. On this dose the 'paradoxical beta-reaction' caused by isoprenaline reversed the increase of heart rate, and the decrease of ejection time became more expressed, at the same time the response with max dC/dt was unchanged (Fig. 66, thin arrows).

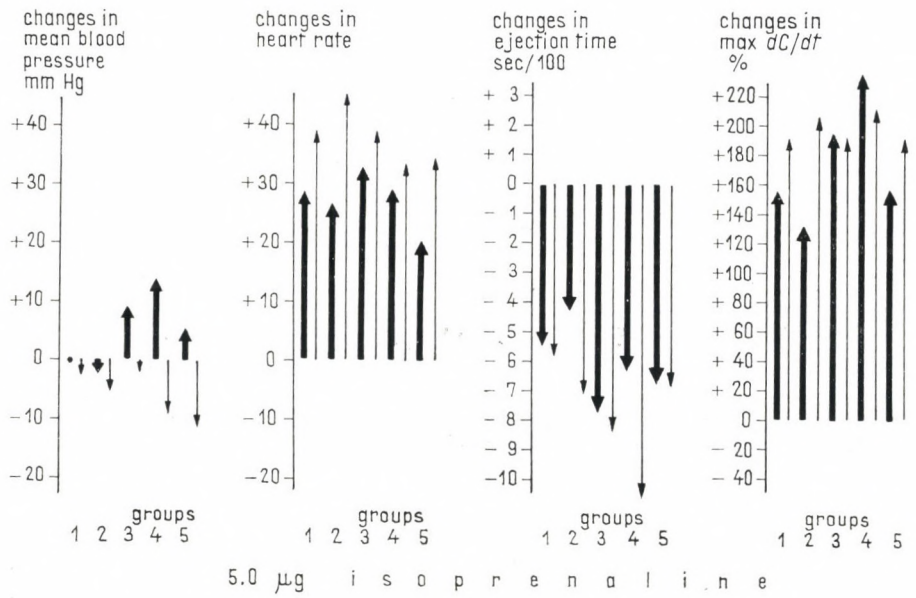

Fig. 65. Thick arrows represent the effects of 5 μg isoprenaline before guanethidine treatment in (1) controls, (2) patients with essential hyperkinetic heart syndrome, (3) hypertensives in the normotensive phase, (4) hypertensives responsive to treatment, (5) hypertensives not responsive to treatment. Thin arrows indicate isoprenaline responses after guanethidine treatment. The prominent feature is the hypotensive effect, particularly in hypertensive groups; the drug potentiates the effects on heart rate and ejection time without a change in max dC/dt

The changes on 5 μg noradrenaline are displayed in Fig. 67. Five μg noradrenaline raises the blood pressure to a higher level, reduces heart rate further lengthening the ejection time. There is no change in the effect on max dC/dt.

We intended to find the mechanism whereby guanethidine influences alpha- and beta-reactions provoked by the two catecholamines in these

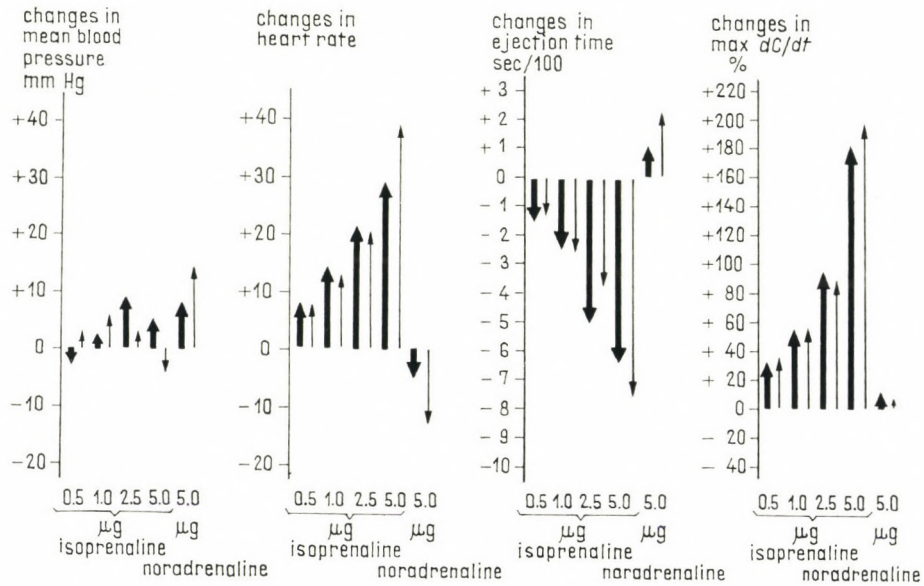

Fig. 66. For symbols see Fig. 65. The figure summarizes the effects in every group following varying doses of isoprenaline and 5 μg noradrenaline, resp. The effects of isoprenaline on heart rate, ejection time and max dC/dt are dose dependent since the trend in changes is similar in each group. As far as the mean blood pressure is concerned, due to differing responses in different patients, dose-dependent changes were not apparent. After guanethidine treatment 5 μg isoprenaline produced an inverse blood pressure response and the effects on heart rate and ejection time were potentiated; the effects of noradrenaline on blood pressure, heart rate and ejection time were also increased

patients. In agreement with the data in the literature (Gaffney and Braunwald 1963) we found a moderate slowing down effect on the heart rate, and at the same time a lengthening of the ejection time. Our results confirm the earlier findings, namely that guanethidine potentiates the action of noradrenaline (Mendlowitz et al. 1965). From our investigations it has become clear that this could be demonstrated with a relatively small dose (30 to 50 mg per day for 7 to 10 days) even if the blood pressure did not decrease.

The effect of guanethidine treatment on isoprenaline responses deserves comment. The 'paradoxical beta-reaction' observed in hypertensives, implying an increase in blood pressure, is reversed, i. e. in patients treated with guanethidine, isoprenaline injection causes again reduction in blood pressure. This occurred also in patients after an unsuccessful antihypertensive treatment with guanethidine.

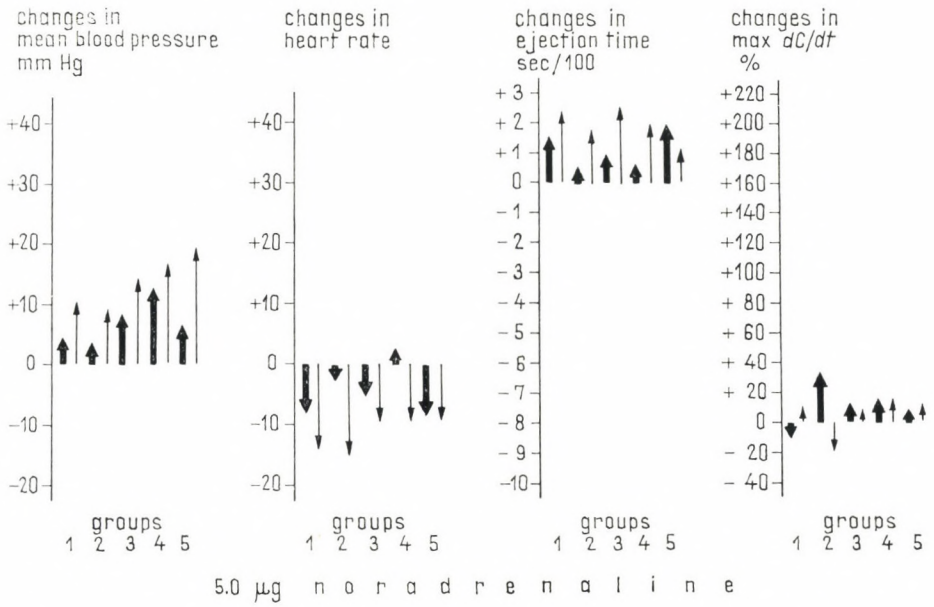

Fig. 67. For symbols see Fig. 65. After treatment with guanethidine 5 μg noradrenaline causes more marked changes in mean blood pressure, heart rate and ejection time

Guanethidine in every group potentiated the accelerating effect of isoprenaline on the pulse rate and the shortening of the ejection time but did not change the reaction of max dC/dt. Consequently, guanethidine, in this dosage, does not depress myocardial contractility. This is of interest in view of the fact that Gaffney and Braunwald (1963) reported a deleterious effect of guanethidine on the heart muscle of decompensated patients. This risk is not a serious one in the case of healthy or slightly damaged myocardium. On the contrary, the lower peripheral resistance decreases the work load on the heart which might be advantageous. The fact that guanethidine affects the actions of noradrenaline and isoprenaline on the heart rate without changing max dC/dt, confirms our previous conclusion that the control of

cardiac frequency and contractility do not necessarily run parallel in every case. The dosage administered by us seems ideal for the treatment of hypertension. The question whether the dose of guanethidine should be further increased or whether another antihypertensive drug should be introduced in addition to guanethidine, is not discussed here.

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The effects of guanethidine treatment (7 to 10 days, relatively small dose) on responses produced by catecholamines were investigated. As described in the literature, it was also found that the changes provoked by catecholamines were greater after guanethidine treatment. Thus guanethidine treatment potentiates the reflex-depressant action of noradrenaline on heart rate and the delaying action on the ejection time. Similarly it was found to potentiate the positive chronotropic action and to accentuate the shortening effect on ejection time by isoprenaline. Guanethidine treatment in every group also potentiated the vasopressor effect of noradrenaline. The 'paradoxical beta-reaction' on isoprenaline, i.e. increase in blood pressure in hypertensives, changes following guanethidine, shows an inverse response.

There was a tendency towards bradycardia on guanethidine. Hence the ejection time of the heart was prolonged and at the same time the dC/dt, which reflects changes in myocardial contractility, did not alter. In the dose studied, the drug appears to be ideal for the treatment of hypertension.

Experiments with 2-guanidino-methyl-1-monoazo-cyclo-octane sulphate (Sanegyt)

The guanethidine preparations (Sanotensin, Ismelin) are widely used for treatment in moderate and severe hypertension. However, they may produce unpleasant side effects, especially orthostatic hypotension (which may cause collapse). In addition, there is an uncertainty about the proportion of the drug absorbed when given orally. Thus an attempt was made to produce a compound which has similar hypotensive properties as guanethidine without the disturbing side effects. The 2-guanidino-methyl-1-monoazo-cyclo-octane sulphate (by other name alpha-guanidino-methyl-heptamethylenimine sulphate monohydrate), a derivative of guanethidine, in the course of pharmacological investigations proved to be superior to guanethidine (Komlós et al. 1968, Varga and Molnár 1968). Jávor (1968) reported favourable results with the drug in 15 patients. Studies were made with the compound to find the smallest clinical dose of the Sanegyt (EGYT) which might

modify the sensitivity of alpha- and beta-receptors of the autonomic nervous system.

The patients were divided into 5 groups in an identical manner as in the investigations previously performed with guanethidine (see above). The patients had compensated cardiac disease not requiring drug therapy apart from sedatives during the weeks preceding the investigations.

After the initial examination the patients received 3×10 mg dose. This was increased later but only in patients who did not experience orthostatic symptoms after 3 days of treatment with the drug. The maximal dose was 60 mg per day. With this dosage there was a postural drop in blood pressure. It was not intended to achieve normal levels of blood pressure. Seven to ten days after the initial catecholamine injection the test was repeated.

In 70 patients, the mean systolic and diastolic blood pressures (calculated without grouping) decreased significantly. The pulse rate decreased from 81.5 to 71.5 (means), and the ejection time increased from 27.1 to 28.3 sec/100 (means).

Figure 68 shows the effect of isopropyl-noradrenaline (INA) before and after Sanegyt treatment. With INA, the systolic pressure usually increased and remained high or even rose further during Sanegyt treatment. With INA effect in all except the 2nd group an insignificant reduction in diastolic pressure was observed. The effect lasted over the course of Sanegyt treatment (from -3.9 to -4.3). There was a more pronounced reduction in the group with idiopathic hyperkinetic heart syndrome but the number of patients in this group was small there being a wide scatter in the results. Hence, the data here need to be interpreted with caution.

The mean blood pressure rose to higher levels in the groups of hypertensives. During Sanegyt treatment, the increase caused by the INA was greater than that seen without treatment except for patients in group 5.

The Sanegyt treatment increased further only in controls the tachycardia which is obligatory after catecholamines. As far as the ejection time is concerned there was a change only in Group 1. The mean of max dC/dt (calculated without grouping) did not show a change. Deviation from this pattern was only seen in Group 4, i.e. in labile hypertensives.

In Fig. 69 the effect of 5 μg noradrenaline is shown before and after Sanegyt treatment. Mean blood pressure rose in every group, markedly so in Groups 3 and 4 (hypertensives) and did not change after Sanegyt treatment. A slight reduction was caused by the Sanegyt treatment in Group 5.

Heart rate decreased due to the effect of Sanegyt treatment. With noradrenaline it became slightly lower with or without Sanegyt treatment.

Ejection time was prolonged only slightly after noradrenaline. Sanegyt treatment caused a further minor increase (from +0.2 to +0.8 sec/100).

Max *dC/dt* remained virtually unchanged. There was no difference between the treated and non-treated phases.

In Fig. 68 the effect of 5 μg isoprenaline is demonstrated before and after Sanegyt treatment. In the untreated patients, in agreement with our previous findings, the 'paradoxical beta-reaction' was observed. Whereas due to guanethidine treatment the reaction became inverse, during Sanegyt administration the paradoxical reaction intensified slightly and could be demonstrated in the controls as well. The paradoxical reaction was abolished only in Group 5 and the mean blood pressure showed an 'inverted' trend. The heart rate under the action of isoprenaline during guanethidine treat-

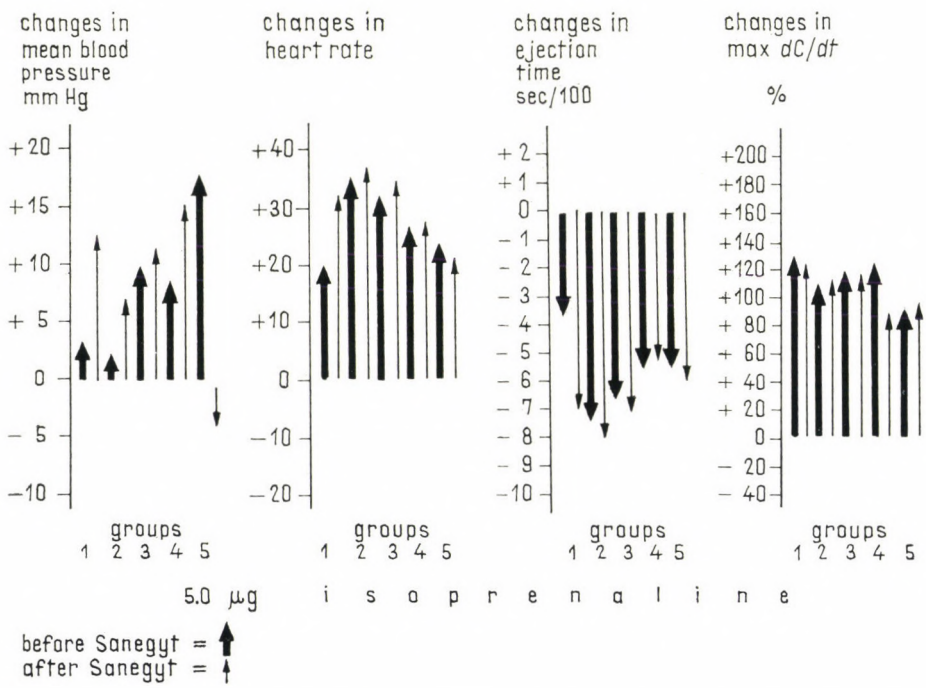

Fig. 68. The change in isoprenaline sensitivity on the effect of Sanegyt. The thick arrows show the figures before, and the thin arrows the figures after Sanegyt treatment. Controls (1), essential hyperkinetic heart syndrome (2), hypertension, normotensive (3), hypertension, responsive (4), hypertension, nonresponsive (5). The thin arrows represent the values after Sanegyt treatment. The administration of Sanegyt in contrast to guanethidine did not modify the effects of noradrenaline

ment increased further but not during treatment with Sanegyt. The same effects were seen in the case of ejection time. The max *dC/dt* was not altered by isoprenaline either after guanethidine or Sanegyt.

Sanegyt administration did not modify the increase in blood pressure due to noradrenaline (Fig. 69). In can be clearly seen that noradrenaline, in general, reduces heart rate and prolongs the ejection time but does not affect the max *dC/dt*. Neither guanethidine nor Sanegyt alter the responses in some patients. They do, however, enhance reactivity.

As a matter of fact, there are many similarities between the effects of guanethidine and Sanegyt (EGYT), although differences are seen as well. The latter can be explained partly by the fact that Sanegyt depletes catecholamines to a lesser extent (Varga and Molnár 1968). This might account for the less frequent occurrence of postural hypotension during Sanegyt treatment. Jávor et al. (1968) and Petrányi (1968) have published clinical reports on the use of Sanegyt, and on the basis of their studies it would ap-

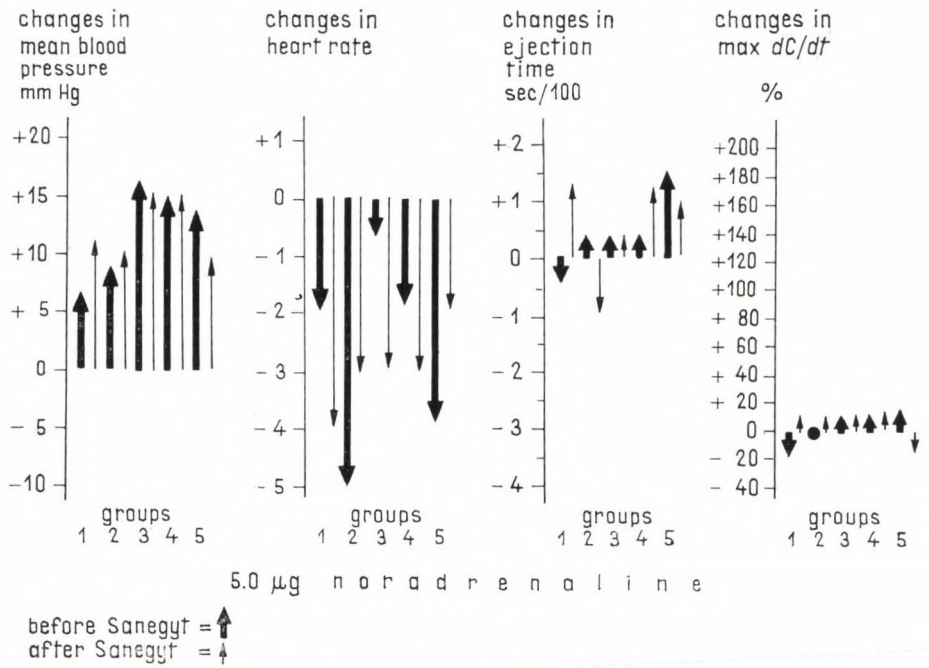

Fig. 69. Change in sensitivity to noradrenaline due to Sanegyt treatment. The thick arrows represent the effect of 5 μg noradrenaline before Sanegyt treatment. The grouping is the same as in previous experiments. Sanegyt treatment, unlike guanethidine does not influence the effects produced by 5 μg isoprenaline

pear that the new guanethidine derivative might have advantages in the treatment of hypertension

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The changes caused by small doses of catecholamines were investigated before, and 7 to 10 days after Sanegyt treatment. The results were compared to those obtained by guanethidine (Sanotensin, EGYT) administration. 30 to 50 mg per day is suffcient from Sanegyt to produce measurable changes in blood pressure and in some other reactions. The most marked effects are as follows:

1. The 'paradoxical beta-reaction' in hypertension, i.e. the increase in mean blood pressure after isoprenaline on guanethidine treatment ceased to exist, in other words the blood pressure became lower. On Sanegyt treatment this 'inversion' could be seen only in patients with higher blood pressure. In normotensive patients the usual paradoxical reaction was present and slightly increased.
2. Both the increase in heart rate and the shortening of the ejection time following isoprenaline were intensified by guanethidine treatment. Sanegyt had no effect on either response.
3. The vasopressor effect of noradrenaline became prominent on guanethidine treatment, whereas such an action was absent during Sanegyt administration. This was so in all three groups with hypertension.
4. The max dC/dt did not change after noradrenaline. It became higher after isoprenaline, but remained unchanged on guanethidine or Sanegyt treatment.

CHANGE IN THE SENSITIVITY OF BETA-RECEPTORS BY ANTIARRHYTHMIC DRUGS (LIDOCAINE, PROCAINAMIDE, QUINIDINE AND TRASICOR)

Catecholamines, particularly the beta-receptor stimulants, apart from positive inotropic and chronotropic actions also have arrhythmogenic effects. They increase cardiac automaticity and thus enhance the tendency to ventricular extrasystole, ventricular tachycardia and fibrillation. In experimental animals it was found that beta-stimulants lowered the threshold of the ventricular fibrillation (Csapó et al. 1970, Papp and Szekeres 1968).

It is also known that extrasystoles or ventricular fibrillation occurring in atrial fibrillation with low ventricular rate, and in atrioventricular block can be prevented by isoprenaline. Recently, Békássy et al. (1970) reported

good results with isoprenaline in 'low heart rate-type' paroxysmal ventricular or atrial fibrillation.

It has been shown (Szirtes et al. 1970) that 5 μg isoprenaline in healthy individuals rarely produces extrasystoles. In patients with heart disease it does, however, induce extrasystoles within five minutes, the difference from healthy individuals being significant. Considering our finding that in heart failure 5 μg isoprenaline increases myocardial contractility only minimally (Chapter 4, p. 90), it seemed worth while to investigate whether antiarrhythmics modify isoprenaline sensitivity.

The investigations were carried out in individuals who had no cardiocirculatory symptoms. Our noninvasive technique, described previously in this book, was used.

The individuals received 5 μg Isuprel (Winthrop) and the effect was tested for 5 minutes. Subsequently, antiarrhythmic agents were given and isoprenaline sensitivity was investigated again. Lidocaine (EGYT) was given i.v. in a dose of 2 mg per kg; INA sensitivity test was performed 4 minutes later. Procainamide was administered in the form of Novocamide (Hoechst) 4 mg per kg i.v. and the isoprenaline sensitivity tested 4 minutes after the injection. Quinidine (Alkaloida) was given orally in a dose of 5×200 mg on a day which was between the first and second isoprenaline assay. The investigation on Trasicor (Ciba and Chinoin) was carried out in the same way, the drug being administered in a 3×20 mg dose on the day between two isoprenaline tests.

In all our investigations using 5 μg isoprenaline there was a marked tachycardia; dC/dt became higher and pulse pressure widened. The results are summarized in Fig. 70.

There was an increase in max dC/dt in 3 out of 8 patients receiving Lidocaine. The peak of the first derivative of the carotid tracing was enhanced with isoprenaline and in one case the isoprenaline sensitivity was not altered. In 2 cases it decreased. The rate-increasing effect on the heart and the effect on blood pressure following isoprenaline remained unchanged after Lidocaine.

After procainamide the increase of max dC/dt was less in every case. The effect on heart rate and blood pressure was difficult to evaluate. Oral quinidine suppressed almost uniformly the stimulant effect of isoprenaline on max dC/dt and heart rate. There was no consistent effect on blood pressure. Trasicor inhibited all actions of isoprenaline (Fig. 70).

The aim of antiarrhythmic treatment is to abolish arrhythmias and to improve cardiovascular function. Hence a knowledge of the action of antiarrhythmic agents is of paramount importance. An agent is considered ideal

if in doses in which it has antiarrhythmic effects it does not depress the circulation. The haemodynamic actions of this class of drugs are relatively well known, even though conflicting data are found in the literature (Butterworth 1963, Jewitt et al. 1968, Jewitt 1970, Szekeres 1970, Szekeres and Papp 1971).

Our findings revealed discrepancies in the haemodynamic effects of isoprenaline. Trasicor blocked all effects of isoprenaline, quinidine reduced the positive inotropic and chronotropic effects of isoprenaline. Procainamide

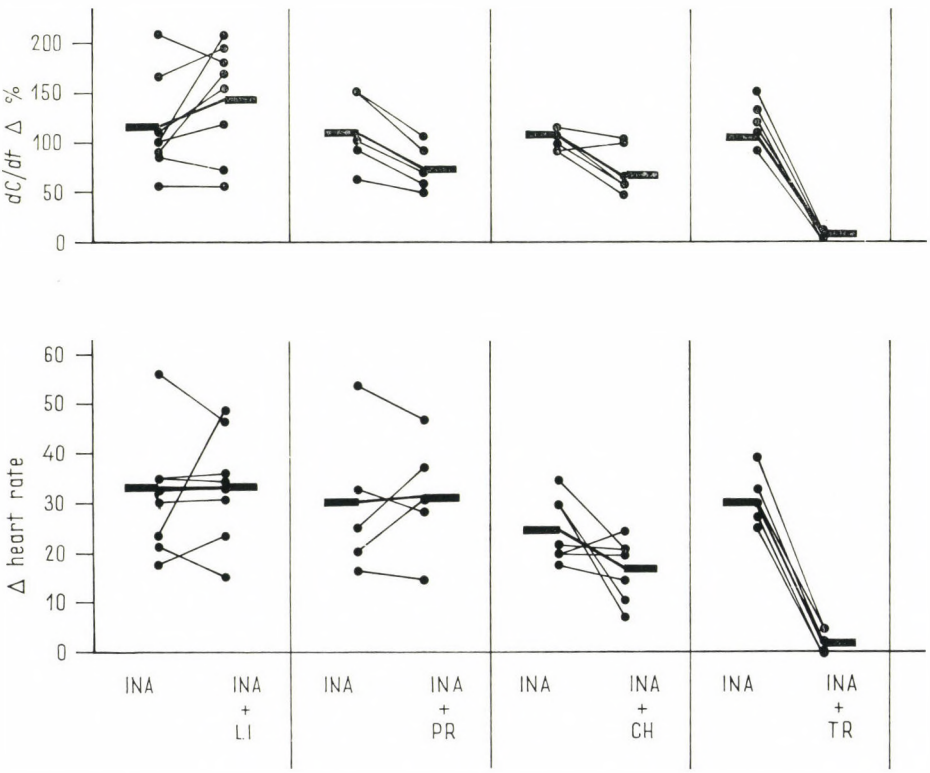

Fig. 70. In the upper part, the points represent the percentage increase in max dC/dt with 5 μg isoprenaline. The values before and after the administration of anti-arrhythmic drugs are connected with a line. In the lower part, the effect of INA on the heart rate is demonstrated in the same way. Lidocaine (2 mg/kg) i.v. enhances the action of isoprenaline on the increase in max dC/dt. Procainamide, 4 mg/kg, i.v. and quinidine (5×200 mg) orally reduces, and Trasicor (3×20 mg), orally, prevents this action. The accelerating action of 5 μg isoprenaline on heart rate is not affected by lidocaine and procainamide, quinidine reduces it and Trasicor abolishes it altogether. INA = isopropyl-noradrenaline, LI = lidocaine, PR = procainamide, CH = quinidine, TR = Trasicor

decreased the chronotropic effect only slightly, but produced a severe attenuation of the isoprenaline effect on the max dC/dt. The divergent effects of procainamide and Lidocaine on contractility, previously thought to have similar effects, were particularly striking. Lidocaine, in the majority of cases, increased the positive inotropic actions of isoprenaline. To our knowledge this is a new finding further supporting the suggestion that Lidocaine in the dose clinically used is not a cardiodepressant drug (Bigger and Mandel 1970, Stanard et al. 1968, Harrison et al. 1963, Binnion 1968, Schumacher et al. 1968). For antiarrhythmic therapy, it is advantageous to have a drug which has no myocardial depressant action.

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Antiarrhythmic drugs do not consistently affect sensitivity to isoprenaline. Trasicor prevents the increasing action on contractility and the accelerating action on heart rate. Quinidine reduces both but does not abolish them completely. Procainamide decreases the isoprenaline-induced positive inotropic effect without affecting the change in heart rate. Lidocaine does not affect the latter, and further enhances the increase in contractility. This may be important because in the case of Lidocaine we have an agent which has antiarrhythmic effects in doses which do not produce cardiocirculatory depression.

PART II

CHAPTER 6

BASIC CONCEPTS, DATA AND CALCULATIONS USED IN COMPUTER ANALYSIS

INTRODUCTORY REMARKS ON MATHEMATICAL PROCESSING

In the previous chapters it has been shown that the complex of noninvasive methods yields much valuable information about the condition of the cardio-circulatory system. The new parameters, the first and second derivative of the carotid tracing, indicate changes in myocardial contractility.

By the use of these and other parameters it was concluded that the state of circulation may be characterized even better if the investigations included not only the rest period but also the period following ergometric exercise and administration of drugs, especially catecholamines. The method proved to be of value for monitoring positive and negative inotropic actions in a quantitative manner. From the point of view of clinical medicine it enabled us to analyse variations in myocardial contractility in various disease entities.

The information obtained by 3, and later 6 records taken simultaneously represented data which could not be analysed by simple statistical methods, when consideration was given to the number of groups investigated, the time selected to examine the drug effect, etc. The evaluation was complicated by the fact that the large amount of data represented records of events which took place simultaneously and which were interdependent. To overcome this problem a computer had to be used, and even so the number of data which were fed into the computer had to be limited.

Our main purpose was to find ways and means to obtain an early diagnosis of myocardial damage. During the planning of the investigations we made use of our earlier experience. In conformity with other investigators, we have shown that with respect to haemodynamic effects the specific stimulant of beta-receptors, isoprenaline, is very similar to physical exercise (Chapter 4, p. 64). In cardiac insufficiency, the damaged heart muscle is unable to meet the increased demand caused by exercise and it cannot respond to the action of isoprenaline in the same way as the healthy myocardium (Chapter 4, p. 68). The response seen after the administration of 5 μg isoprenaline may be used to separate patients with healthy myocardium from those with disease almost as well as the changes after 400 kg-m ergometric exercise for 3 min. On the basis of these observations, the effects

of isoprenaline (isopropyl-noradrenaline, INA), given i.v. and in various dosages were analysed by using a computer.

By examining the correlations within the group of patients and between groups, attempts have been made to characterize mathematically the differences between the normal and the diseased heart considering the administered dose of isoproterenol. An attempt was also made to see the differences between the clinical diagnosis and that arrived at by mathematical analysis. In this way 'important' and 'less important' parameters could be identified.

METHODS, PREPARATION OF DATA FOR INVESTIGATION AND PATIENT MATERIAL

The experiments were carried out in the same way as has been described earlier. The patients were supine, they received a sedative, isoprenaline (Isuprel, Winthrop) was given i.v. in doses from 0.2 μg to 15 μg.

Records were taken 0.5, 1, 1.5, 2, 3, 4, and 5 minutes after the injections. Simultaneously with Korotkoff's method, the blood pressure over the brachial artery was measured. Lead II of the ECG and the carotid tracing were also recorded (with a piezocrystal infraton detector). In addition, the first derivative of the carotid tracing was also registered with the R-C circuit, as has been described earlier. The recordings were performed partly with a 3-channel Hellige '9400 T' multiscriptor, partly with a 6-channel Elema-Mingograph-61.

A data card was completed during every examination. One side of this contained the data used for identifying the subject: serial number, sex, age, weight, grouping according to disease (see later), the dosage of isoprenaline. The other side contained the obtained results. Apart from blood pressure all data were read from the recordings:

a. Systolic blood pressure.

b. Diastolic blood pressure.

c. Pulse rate (measured by using the R-R distance on the ECG).

d. Height of the incisura measured from the base line, in mm.

e. Ejection time, in 0.01 sec (the period from the rapid upstroke of the carotid tracing to the incisura).

f. Height of the carotid tracing (taken at the highest point of the tracing with respect to the base line).

g. The time taken to reach the highest point on the carotid tracing. This was measured from the beginning of the upstroke, in 0.01 sec.

h. Height of the anadicrotic notch measured from the base line.

i. Distance of the anadicrotic notch from the beginning of the upstroke, in 0.01 sec.

j. The greatest elevation of the carotid tracing related to 0.01 sec, in mm (see Chapter 2, p. 50) (this reference value for calibration was given only in the rest period).

k. Peak height of the carotid tracing's first derivative (max dC/dt) related to the base line, in mm.

Each value (except *j*) was recorded in the rest period and after the administration of the drug, i. e. eight times. So the record sheet contained a matrix which had 8 items of data in the horizontal, and 11 items of data in the vertical lines.

The details of the record sheet were transferred to the tape and calculations were performed with a Gier, a CDC 3300, and a Minsk-32 type computer, according to the method which will be described later.

The equations of the mathematical correlations used in this study are given in Chapter 9.

The patients were divided into 7 groups:

Group 1. These individuals were healthy from the point of view of their circulatory system. They did not have high blood pressure, and there was no history of hypertension. Their resting pulse rate was not faster than 90/min, blood pressure. $<$ 145/95.

Group 2. At the time of investigation they had normal blood pressure, but most of them were hyperkinetic. The resting pulse rate was faster than 90/min. Some of them had history of high blood pressure. There were no symptoms of cardiac decompensation; RR $<$ 145/95.

Group 3. Elevated blood pressure, 145/95 $<$ RR $<$ 175/110. No symptoms of cardiac decompensation.

Group 4. Increased blood pressure, RR $\geqq$ 175/95, no symptoms of cardiac decompensation.

Groups 1 to 4 could be regarded as healthy as far as their heart was concerned.

Group 5. Decompensated arteriosclerotic heart disease (grade of decompensation: I, II and III); RR $<$ 145/95.

Group 6. Decompensated arteriosclerotic heart disease (grade of decompensation: I, II and III); 145/95 $\leqq$ RR $<$ 175/110.

Group 7. Decompensated arteriosclerotic heart disease (grade of decompensation: I, II and III), RR $\geqq$ 175/95.

TABLE 2

Distribution of the computerized cases according to isoprenaline dose and patient groups

Dose of isoprenaline μg	Groups							Total
	1	2	3	4	5	6	7	
0.2	2	1						3
0.5	19	21	11	6	3	2	3	65
1.0	17	15	12	7	2	3	2	58
2.5	14	21	6	3	6	3	2	55
5.0	66	52	17	14	19	14	14	196
7.5	4	1						5
10.0	16	10	1		9	6	1	43
12.5	2							2
15.0	2							2
Total	142	121	47	30	39	28	22	429

The grade of decompensation was given according to the tabulation of the New York Heart Association.

Data were used from 429 individuals.

Table 2 contains the distribution of the patients on the basis of the doses of isoprenaline in the various groups.

CALCULATION OF ARTERIAL MEAN PRESSURE

The blood pressure is a central problem in the study of the circulation. Therefore, it seemed essential for us to have a closer look at the quantitative measure of blood pressure and its mean by a bloodless method. It is hoped that this will be used by other investigators as well.

The first measurement of blood pressure was performed by Hales (1733) in a horse, by an invasive method. The equipment of Hales was called piezometer; 100 years later Poiseuille (1828) constructed a mercury manometer. This enabled serial measurements of blood pressure in experimental animals by the invasive method; in man, this was only done under exceptional circumstances. In human medicine, the measurement of blood pressure became popular with the introduction of bloodless blood pressure measurement (von Basch 1880, 1893, Riva-Rocci 1896, Korotkoff 1905).

Since the pressure in the systemic circulation is maintained by the rhythmic contraction of the left ventricle, the pressure curve of the aorta during systole is identical with that in the left ventricle, except during the isometric phase (provided there is no aortic stenosis or obstruction). However, in

diastole the pressure does not decrease to zero but remains at a so-called diastolic level until the next systole if there are no anatomical abnormalities. The height of the arterial pressure and the shape of the pulse wave are not identical at every point in the circulation. If no other marking is used the 'systolic blood pressure' is equal to the pressure measured over the brachial artery. Under certain pathological conditions, as in aortic coarctation, it is essential to measure the femoral blood pressure. To standardize a uniform technique, some guide-lines have been published by the New York Heart Association and the British Cardiac Society. There are some points which may interest the clinician:

1. The systolic pressure varies with physiological conditions.
2. Under pathological conditions the diastolic pressure is often more informative than the systolic pressure.
3. The so-called mean blood pressure is based on the arithmetical means of the systolic and diastolic pressures (Best and Taylor 1945, Grosse-Brockhoff 1950). Korotkoff's pulse wave integral gives the real value of the mean blood pressure. An approximate value of this is the diastolic pressure plus 43 per cent of the pulse pressure. A prerequisite for the validity of this is the normal shape of the central pulse wave (Wezler and Böger 1939).
4. The pulse pressure is the difference in the systolic and diastolic pressures and it is proportional to the cardiac output.

In calculating the mean blood pressure, the quoted authors add one-half, one-third or 43 per cent of the pulse pressure to the diastolic pressure. Experimental data have only been published by Wezler and Böger. They give the 43 per cent value by considering the area below the tracing of the subclavian artery in 15 individuals. No data have appeared in the literature on the large-scale investigation of this issue.

In our present investigations the following questions have been dealt with.

1. Is it possible to use the central pulse tracing (taken by indirect means) for determining the factor of the arterial mean pressure (α) and the systolic mean blood pressure (β) which multiplied by the pulse pressure yields a value to which the diastolic pressure can be added to obtain the mean blood pressure? For this purpose the direct aortic pressure curves were compared with the indirect carotid tracings.
2. By analysing 303 carotid tracings what kinds of numerical values are obtained for factors α and β?
3. How do the factors change in hypertension, in cardiac decompensation, and after isoprenaline administration?

The pressure curve of the aorta was recorded by a catheter inserted through the femoral artery. The tracing was taken with an Elema-Mingograph and with the transducer belonging to the apparatus. (Catheterization was done at the National Institute of Cardiology, for diagnostic purposes.) The indirect recording of the blood pressure was taken over the brachial artery using Korotkoff's method, and the indirect carotid tracing was recorded simultaneously with a piezocrystal A-C infraton detector. In some cases recordings were made with Elema-Mingograph and in others with Hellige multiscriptor 9400 T.

The area below the tracing was determined from curves obtained both by direct and indirect means, starting from the beginning of the upstroke until the start of the next contraction. Thus the factor (α) was calculated

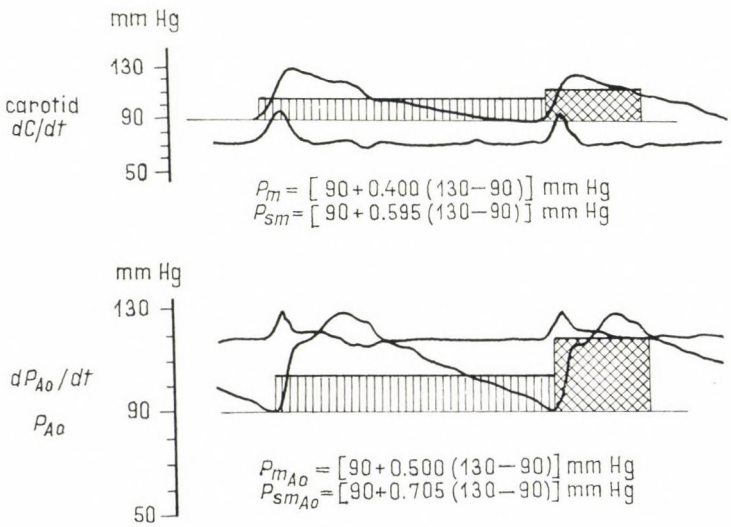

Fig. 71. The two upper lines are the carotid tracing and its first derivative recorded by noninvasive means. The two lower lines are the aortic pressure curve and its derivative recorded by direct means. The oblong represents the whole period, its upper side corresponding to the mean blood pressure. In the second period, the oblong represents the systole and the systolic mean pressure. The equations were used for the calculation of the mean blood pressure and the systolic mean blood pressure. In both recordings, the systolic blood pressure P_s = 130 mm Hg and the diastolic pressure P_d = 90 mm Hg (the subscript A_0 refers to aortic pressures)

which multiplied by the pulse amplitude and the result being added to the diastolic value, the mean blood pressure (P_m) value is obtained

$$\alpha = \frac{\text{area below the curve}}{\text{time of one heart period}}.$$

The calculation of the systolic mean pressure differs from the above-mentioned method in that instead of the area and the time below the whole curve, only the time and area concerning the systole were used for calculation

$$\beta = \frac{\text{area below the curve up to the incisura}}{\text{ejection time}}$$

1. $$P_m = P_d + \alpha(P_s - P_d)$$

2. $$P_{sm} = P_d + \beta(P_s - P_d)$$

where P_s = systolic blood pressure

P_d = diastolic blood pressure

P_m = mean pressure

P_{sm} = systolic mean pressure (Fig. 71).

In cases where the direct and indirect measurements were compared, the two measurements were made simultaneously.

For the calculation of the area below the carotid tracing the highest point of the anadicrotic notch (A), that of the tracing (M) and the incisura (I)

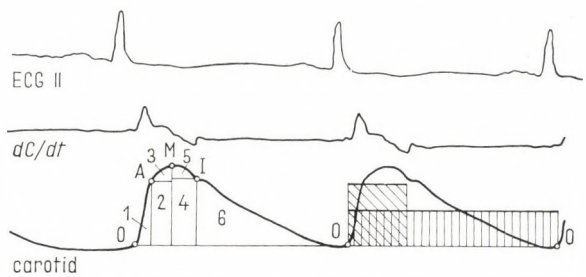

Fig. 72. Lead II of the ECG, the first derivative of the carotid tracing recorded by noninvasive means. In the carotid tracing, the points are indicated which served as markers and supports for constructing triangles and oblongs for the considerably accurate measurement of the area of the whole and the systolic period. O = beginning of the upstroke, A = anacrotic notch, M = maximal height, I = incisura. The second revolution shows the calculated areas

calculated from the base line and the time of these points calculated from the beginning of the upstroke of the carotid tracing up to the beginning of the next cycle were used (Fig. 72).

Three hundred and three measurements were performed by this technique. 101 individuals were grouped according to the principles mentioned in the previous section. In the same number of patients calculations were also made 1.5 minutes after the administration of 5 μg isoprenaline (Isuprel, Winthrop). For technical questions and dosage of the drug see the previous section.

The calculation of α and β values was performed with an electronic calculator and for the comparison of the results Student's t test was used.

The distribution of the cases in the groups were as follows,

Group	No. of individuals
1.	33
2.	33
3.	6
4.	7
5.	7
6.	6
7.	9
Total:	101

Table 3 contains the results of the mean blood pressure obtained by direct and indirect means. First of all, the behaviour of factor α was studied, this being 0.441 ± 0.048 in the aorta and 0.430 ± 0.040 in the carotid. No statistically significant difference has been found.

In Table 4 a comparison is drawn between the values of the factors of the systolic mean blood pressures (β). In the aorta this is 0.621 ± 0.06 and in the carotid artery it is 0.640 ± 0.050. There is no significant difference between the two values.

Three hundred and three carotid tracings recorded by noninvasive method showed the following figures: $\alpha = 0.400 \pm 0.079$, $\beta = 0.655 \pm 0.070$.

The α values obtained in various groups were around 0.4, without statistically significant differences (Table 5).

After isoprenaline administration, in the majority of the cases the α value have not changed markedly except in the group of cardiac patients (Group 7) where they showed a moderate but significant increase related to the controls (Table 6).

TABLE 3

Comparison of the factors used for calculating the mean blood pressure. Recordings were made by noninvasive and direct means

No.	Name, sex	Age	Diagnosis	Noninvasive			α	Aorta			α
				P_s	P_d	P_m		P_s	P_d	P_m	
1	B. B. male	19	essential hyperkinetic heart syndrome	140	80	107.3	0.456	140	80	104.9	0.415
2	H. Gy. female	30	mitral stenosis	100	70	81.7	0.390	120	80	97.0	0.425
3	L. M. female	18	Fallot's tetralogy	95	50	69.8	0.440	95	50	68.6	0.412
4	G. F. male	24	mitral stenosis + mitral regurgitation	125	80	96.2	0.360	70	40	51.1	0.430
5	M. M. female	20	mitral stenosis	110	60	85.0	0.500	100	60	74.4	0.360
6	K. E. female	22	essential hyperkinetic heart syndrome	130	50	87.0	0.475	132	50	90.0	0.488
7	M. A. female	16	mitral stenosis + mitral regurgitation	120	70	91.0	0.423	100	70	83.1	0.470
8	Z. I. female	40	mitral stenosis, aortic stenosis	120	70	91.5	0.431	120	90	104.2	0.472
9	H. Z. male	30	essential hyperkinetic heart syndrome	130	70	94.0	0.400	130	70	100.0	0.500
							mean: 0.430 S. D.: ±0.040				mean: 0.441 S. D.: ±0.048

$t = 0.47$
$p > 0.60$

TABLE 4

Comparison of the factors for calculating the systolic mean pressure. Recordings were carried out by intracavitary (direct) and noninvasive means

No.	Name, sex	Age	Diagnosis	Noninvasive			β	Aorta			β
				P_s	P_d	P_{sm}		P_s	P_d	P_{sm}	
1	B. B. male	19	essential hyperkinetic heart syndrome	140	80	118.4	0.640	140	80	117.8	0.530
2	H. Gy. female	30	mitral stenosis	100	70	88.6	0.620	120	80	105.4	0.635
3	L. M. female	18	Fallot's tetralogy	95	50	78.2	0.650	95	50	79.6	0.660
4	G. F. male	24	mitral stenosis + mitral regurgitation	125	80	105.2	0.560	70	40	57.1	0.570
5	M. M. female	20	mitral stenosis	110	60	95.0	0.700	100	60	84.0	0.600
6	K. E. female	22	essential hyperkinetic heart syndrome	130	50	106.6	0.710	132	50	103.2	0.650
7	M. A. female	16	mitral stenosis + mitral regurgitation	120	70	105.0	0.700	100	70	88.0	0.600
8	Z. I. female	40	mitral stenosis, aortic stenosis	120	70	100.8	0.617	120	90	106.4	0.547
9	H. Z. male	30	essential hyperkinetic heart syndrome	130	70	105.6	0.595	130	70	102.2	0.705
							mean: 0.640 S. D.: ± 0.050				mean: 0.621 S. D.: ± 0.060

$t = 0.72$
$p > 0.50$

TABLE 5

Factor α for mean arterial blood pressure compared in the different groups. The figure for α in every group is around 0.4, there is no significant difference (for definition of α see p. 134) Ø = $p > 0.05$

Group	1	2	3	4	5	6	7	Group
n	33	33	6	7	7	6	9	
α	0.42	0.43	0.45	0.39	0.42	0.44	0.43	
S. D.	0.06	0.07	0.07	0.07	0.05	0.06	0.07	
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	1
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	2
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	3
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	4
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	5
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	6
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	7

TABLE 6

Factor $\alpha_{1.5}$ for mean arterial blood pressure. $\alpha_{1.5}$ = α value 1.5 min after injection of 5 μg isoprenaline. These values do not differ significantly except in Group 7 (heart disease + hypertension), where $\alpha_{1.5}$ is slightly higher, Ø = $p > 0.05$, + = $p < 0.05$, +++ = $p < 0.01$

Group	1	2	3	4	5	6	7	Group
n	33	33	6	7	7	6	9	
$\alpha_{1.5}$	0.39	0.37	0.40	0.40	0.39	0.41	0.44	
S. D.	0.06	0.08	0.08	0.07	0.05	0.08	0.06	
	Ø	Ø	Ø	Ø	Ø	Ø	+	1
	Ø	Ø	Ø	Ø	Ø	Ø	+++	2
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	3
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	4
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	5
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	6
	+	+++	Ø	Ø	Ø	Ø	Ø	7

TABLE 7

Factor β for systolic mean blood pressure. The β values are around 0.65, in Groups 6 and 7 (heart disease and hypertension), they are around 0.7. The differences in Group 7 are significant. (For definition of β see p. 136) Ø $= p > 0.05$, + $p < 0.05$, +++ $= p < 0.01$

Group	1	2	3	4	5	6	7	Group
n	33	33	6	7	7	6	9	
β	0.67	0.68	0.64	0.64	0.64	0.71	0.73	
S. D.	0.06	0.07	0.07	0.10	0.05	0.06	0.06	
	Ø	Ø	Ø	Ø	Ø	Ø	+++	1
	Ø	Ø	Ø	Ø	Ø	Ø	+	2
	Ø	Ø	Ø	Ø	Ø	Ø	+	3
	Ø	Ø	Ø	Ø	Ø	Ø	+	4
	Ø	Ø	Ø	Ø	Ø	+	+++	5
	Ø	Ø	Ø	Ø	+	Ø	Ø	6
	+++	+	+	+	+++	Ø	Ø	7

The factor applied for the calculation of the systolic mean pressure showed significant differences in Group 7, $\beta > 0.7$ (Table 7), in the other groups it was around 0.65. After isoprenaline the β values have not changed significantly, except in Group 7 (Table 8).

TABLE 8

Factor $\beta_{1.5}$ for systolic mean pressure. $\beta_{1.5}$ = 1.5 min value of β after injection of 5 μg isoprenaline. No change after the administration of the drug. β denotes the systolic mean pressure coefficient Ø $= p > 0.05$, + $= p < 0.05$, +++ $= p < 0.01$

Group	1	2	3	4	5	6	7	Group
n	33	33	6	7	7	6	9	
$\beta_{1.5}$	0.65	0.64	0.64	0.65	0.63	0.68	0.72	
S. D.	0.05	0.07	0.05	0.07	0.05	0.07	0.02	
	Ø	Ø	Ø	Ø	Ø	Ø	+++	1
	Ø	Ø	Ø	Ø	Ø	Ø	+++	2
	Ø	Ø	Ø	Ø	Ø	Ø	+	3
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	4
	Ø	Ø	Ø	Ø	Ø	Ø	+	5
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	6
	+++	+++	+	Ø	+	Ø	Ø	7

The importance of the indirect measurement of blood pressure has not decreased, it is frequently used in office practice in the intensive care units. It is often incorporated into an automatic monitoring system. In some units it is controlled by a computer (Rastelli 1968). The mean blood pressure calculated from the noninvasive measurement yields valuable information for physical and pharmacological loading studies.

For Sarnoff's pressure time index, the mean systolic pressure is necessary. This index is a good indicator of the O_2 consumption of the myocardium (Gábor et al. 1964*a–c*, 1966, 1969).

From the initial part of our investigation, it became clear that the mean blood pressure calculated either from the area below the aortic, or carotid pulse tracings is similar. Therefore, the application of noninvasive measurement seems justified. Our method differs from that of Wezler and Böger (1939) in that they have used the subclavian artery tracing as the central pressure curve.

On the basis of our 303 examinations it has been concluded that for the calculation of the arterial mean blood pressure 40 per cent of the pulse pressure should be added to the diastolic pressure, the formula being

$$P_m = P_d + \alpha(P_s - P_d)$$
$$(\alpha = 0.400 \pm 0.079).$$

The recommended α value has a relatively small standard deviation, so 0.400 is a reasonable factor. The error does not exceed the error of Korotkoff's method of blood pressure measurement. This figure is nearly identical with that (0.43) of Wezler and Böger. 0.655 is recommended as a factor for the calculation of the mean systolic pressure. This is justified because of the small standard deviation (S. D. $= \pm 0.070$).

In one-third of the cases, it was studied whether the α and β factors recommended by us could be applied in pathological cases, and after the administration of drugs. No difference was found between the control and the hyperkinetic, prehypertensive and hypertensive groups, there being a difference, however, between controls and decompensated cardiac patients if the latter had hypertension as well. In this group, as seen in Table 6, the indices are higher.

These results encourage us to calculate mean blood pressure by using the blood pressure measurement over the brachial artery and the area below the carotid tracing.

*

The most accurate calculation of the mean arterial blood pressure could be made from the area below the tracing. An approximation to this is possible if to the diastolic value the α or β pulse pressure rate is added. This reasoning is supported by the following facts.

1. There is no difference between the values of factors α, which is the factor for the mean arterial pressure, and β, which is the factor for systolic pressure, if they are calculated either from the aortic (direct) or carotid (noninvasive) tracings.

2. On the basis of 303 examinations $\alpha = 40.0 \pm 7.9$ per cent and $\beta = 65.5 \pm 7.0$ per cent.

Because of the small standard deviation these index figures are considered adaptable for use.

3. By comparing the control and patients' groups at rest and after 5 μg isoprenaline it was found that deviations from these figures could only be seen in patients, who in addition to cardiac decompensation also had hypertension. In these patients the figures were higher.

4. In our studies the blood pressure measurements and the area below the carotid tracing were used for the calculation of mean blood pressure.

CALCULATIONS REGARDED AS THE ANALYTICAL BASIS OF OUR COMPUTER STUDIES

In this section some simple calculations are presented. This procedure is called 'basic calculations' because initially the results obtained immediately have been evaluated. Subsequently, they have been used as basic figures for further calculations.

These basic calculations can be seen in the computer sheet (Table 9). The figures found in different individuals are shown separately. These data were grouped according to the principle given on p. 131. In front of every individual's results there are figures for identification. The first digit groups are serial numbers, the next denote sex, 01 = male, 02 = female, the next three digits refer to age, the last ones to cardiac condition, 000 = = healthy (no cardiac disease), 001 = cardiac patient.

Each parameter is represented by its resting value, obtained 1.5 min after isoprenaline, the integral of these values from 0 to 5 min, the maximal value after isoprenaline and the relation of the latter to the 1.5 min value.

The printed 'basic data' are as follows:

1. Incisura index
2. Peripheral index -1

TABLE 9

A sample of basic cardiovascular data (Patient Group No. 1)

IDENTIFIER: 027 02 016 000 56

	INCIS. IND.	PERIPHR. 1	PERIPHR. 2	MAX dC/dt	P_m	P_{ms}	ALPHA	BETA
0 MIN.	0.74	4.50	5.43	576.92	81.84	98.88	0.36	0.65
1.5 MIN.	0.43	6.03	7.36	1794.07	106.07	129.58	0.45	0.74
INTEGRAL	0.41	4.77	5.95	1407.05	89.24	111.03		
MAXIMUM	0.74			3333.33				
MAX/1.5	1.72			1.86				

IDENTIFIER: 033 02 042 000 57

	INCIS. IND.	PERIPHR. 1	PERIPHR. 2	MAX dC/dt	P_m	P_{ms}	ALPHA	BETA
0 MIN.	0.49	4.12	4.58	500.00	94.56	105.14	0.36	0.63
1.5 MIN.	—	375.73	—	1400.00	7439.40	—	91.99	—
INTEGRAL	—	218.68	—	1050.00	4968.15	—		
MAXIMUM	9999.00			1900.00				
MAX/1.5				1.36				

IDENTIFIER: 034 02 042 000 58

	INCIS. IND.	PERIPHR. 1	PERIPHR. 2	MAX dC/dt	P_m	P_{ms}	ALPHA	BETA
0 MIN.	0.45	4.11	4.42	375.00	101.28	108.86	0.38	0.63
1.5 MIN.	—	338.29	—	1125.00	7780.57	—	96.13	—
INTEGRAL	—	234.47	—	858.75	6097.09	—		
MAXIMUM	9999.00			1725.00				
MAX/1.5				1.53				

IDENTIFIER: 028 02 016 000 59

	INCIS. IND.	PERIPHR. 1	PERIPHR. 2	MAX dC/dt	P_m	P_{ms}	ALPHA	BETA
0 MIN.	0.35	3.72	4.12	625.00	88.94	98.65	0.47	0.72
1.5 MIN.	—	527.42	—	5000.00	7763.63	—	77.04	—
INTEGRAL	—	261.40	—	3043.75	5211.44	—		
MAXIMUM	9999.00			6250.00				
MAX/1.5				1.25				

IDENTIFIER: 201 02 028 000 60

	INCIS. IND.	PERIPHR. 1	PERIPHR. 2	MAX dC/dt	P_m	P_{ms}	ALPHA	BETA
0 MIN.	0.68	5.54	6.27	1704.55	115.15	130.41	0.50	0.81
1.5 MIN.	0.67	5.56	6.39	1846.59	110.04	126.52	0.40	0.73
INTEGRAL	0.66	5.41	6.09	1924.72	114.85	129.35		
MAXIMUM	0.70			2130.68				
MAX/1.5	1.05			1.15				

3. Peripheral index —2
4. Max dC/dt
5. P_m (arterial mean pressure)
6. P_{ms} (systolic mean pressure)
7. alpha
8. beta

1. The height of the incisura divided by the height of the highest point of the carotid tracing.

According to data in the literature (Gadermann and Jungmann 1964, Dontas et al. 1961) the incisura is higher if the peripheral resistance increases and it is lower if the resistance decreases.

2. $$\frac{\text{Arterial mean blood pressure}}{\text{ejection time} \times \text{heart rate}} .$$

The arterial mean blood pressure is printed under 5, the ejection time is given as 0.01 sec.

It was expected that this index would give us valuable information because it has been shown in Chapter 2 that the max dC/dt correlates well with the MSER index:

$$\frac{\text{stroke volume}}{\text{ejection time}} = \frac{\text{cardiac output}}{\text{pulse rate} \times \text{ejection}} .$$

The max dC/dt refers to a central regulation, whereas the other data on the analogy of the calculation of peripheral resistance (mean pressure included), refer rather to a peripheral regulation.

3. The difference between this and item 2 is that instead of the arterial mean pressure here the systolic mean pressure is used.

4. The calculation of the max dC/dt was made at zero time, according to the method outlined on p. 27 of Chapter 1.

$$\max dC/dt = \frac{j(a-b)}{g} \text{ mm Hg sec}$$

where j = elevation of the carotid tracing during 1/100 sec, a = systolic, b = diastolic blood pressure difference, g = the time to the peak of the carotid tracing.

The values after the drug were obtained by taking the peak on the curve at zero time as 100 per cent (k_0), the values after isoprenaline being related to this

$k_n : n = 0, 1, 1.5, 2, 3, 4, 5$

$$\max dC/dt = \frac{100\, j_0(a_0 - b_0)}{g_0}$$

$$\max dC/dt = \frac{k_n \cdot \max dC/dt_0}{k_0}.$$

The P_m, P_{ms}, alpha and beta calculations were elaborated in the previous section. Here these values are used according to this description.

From the other parameters the incisura index and the maximal change of the max dC/dt were used at zero time. The selection of these parameters was based on random calculations. The maximum information was expected from these parameters. In terms of the same reasoning no other parameters were made use of.

The behaviour of the max dC/dt at rest and its relative increase after 5 μg isoprenaline in various groups of patients was examined. Further grouping was made in the control group, and subgroups formed: from 0 to 29 years = a, from 30 to 55 years = b, from 56 years = c.

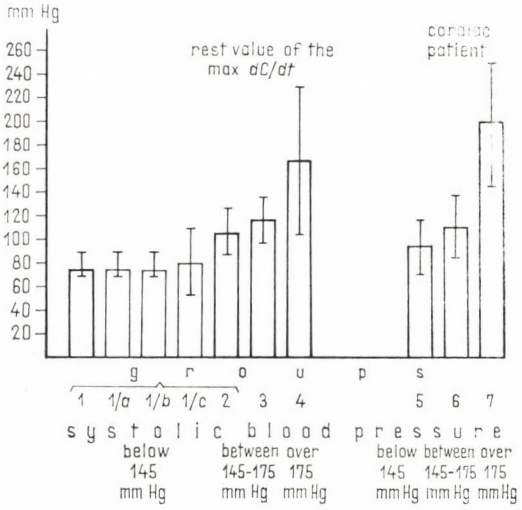

Fig. 73. The rest value of the max dC/dt is greater if the blood pressure is higher. There is no difference between cardiac patients and controls with similar blood pressure (Groups 1–5, 3–6, 4–7), the age has no influence (1/a up to 29 yr, 1/b between 30–55 yr, 1/c over 55 yr)

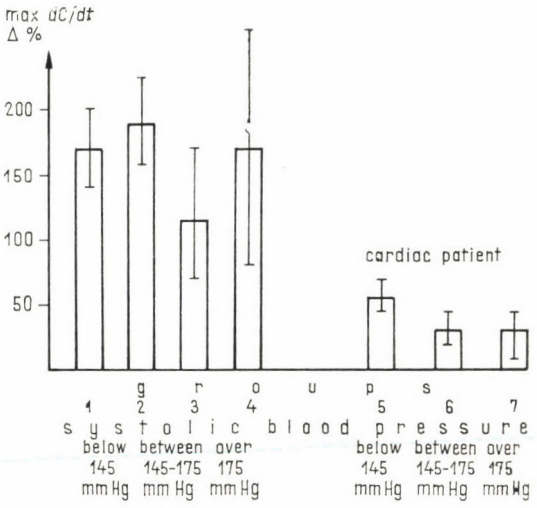

Fig. 74. Relative change of max dC/dt after 5μg isoprenaline. The max dC/dt shows a smaller increase in patients with heart disease

Figure 73 shows that the max dC/dt in controls is the same in every age group, and the cardiac patient with high blood pressure and the hypertonic patient with the same blood pressure (but without heart disease) have a similar max dC/dt value. However, the max dC/dt in patients with higher blood pressure is greater.

Figure 74 shows changes in the dC/dt after 5 μg isoprenaline. It can be seen that this parameter remains significantly lower in Groups 5, 6, 7, i.e. in groups with cardiac patients.

After these preliminary calculations the number of patients – being low in these groups – was increased.

The pulse rate and the incisura index behaved similarly to the max dC/dt, but for some reason to a lesser extent. The trend was found more informative than the absolute figure, the upward standard deviation being higher.

Considering that between the changes of the max dC/dt and the dose of isoprenaline a logarithmic correlation exists, a logarithmic scale was used in the subsequent calculations.

*

From the figures of the data sheets some parameters were calculated which do not need complicated computation. The usefulness of these parameters was interpreted at random. For further calculations the max dC/dt at zero time, the maximal value after isoprenaline administration, the values of the incisura index at the same time intervals and the mean blood pressure were used.

CHAPTER 7

PARTIAL LOGARITHMIC REGRESSIONS OF ISOPRENALINE-EVOKED max dC/dt ALTERATIONS

REGRESSION ANALYSIS WITH VARYING DOSES OF ISOPRENALINE

The patients were investigated according to the grouping described previously. The following parameters have been studied:

1. The maximal change in max dC/dt;
2. The dose of isoprenaline;
3. The change in mean blood pressure;
4. The change in ejection time;
5. The change in heart rate;
6. The change in incisura index.

The figures for parameters in points 3, 4, 5, 6 were calculated at a time when the change in max dC/dt was maximal. This was made as follows. The computer was programmed to derive the time of the maximal change in max dC/dt (this was usually 0.5, 1 or 1.5 min), and to find the related data for parameters in 3, 4, 5 and 6.

In the present study, firstly, the value of each parameter and secondly, the value of multiple parameters were investigated, considering the relation to a particular disease state. The values related to the control value and logarithmic scale were used. The preliminary calculations showed that the selection of time intervals and other parameters promised to yield an efficient basis for further evaluation. This was anticipated from the type of the standard deviation of the single parameters within and outside the groups, and from the fact that the combined distribution could be described by linear correlation. (For the logarithmic correlation dose–max dC/dt see p. 105.)

Partial logarithmical regression analysis was made. For calculations, the maximal change of max dC/dt was selected as dependent variable, on the basis of our previous experience with this parameter. The calculations were aimed at finding out the strength of the correlation and the significance of the single parameters (Table 10). The first part of the tables contains the means calculated from the natural logarithm of the dose and the circulatory parameters and it also contains the standard deviation. The following scheme

TABLE 10

Partial logarithmic regression with varying doses (Patient Group No. 2)

SAMPLE SIZE: 098

MAX dC/dt	DOSE	P_m	EJECT. TIME	PULSE RATE	INCIS. IND.
MEAN: 0.4008	0.6737	0.0075	−0.0823	0.0707	0.3191
S. D.: $34.8503 \cdot 10^{-2}$	$10.0275 \cdot 10^{-1}$	$86.7393 \cdot 10^{-3}$	$13.8271 \cdot 10^{-2}$	$13.2264 \cdot 10^{-2}$	$51.0312 \cdot 10^{-2}$
CORR. MATR.: 1.0000	0.6562	0.0758	−0.5504	0.5043	0.1620
0.6562	1.0000	0.1259	−0.5781	0.3519	0.1880
0.0758	0.1259	1.0000	0.0452	0.1590	−0.3955
−0.5504	−0.5781	0.0452	1.0000	−0.4326	−0.1559
0.5043	0.3519	0.1590	−0.4326	1.0000	−0.0055
0.1620	0.1880	−0.3955	−0.1559	−0.0055	1.0000
DISPERSION COEFF.:	$42.5383 \cdot 10^{-2}$				
TOTAL CORR. COEFF.:	$53.4885 \cdot 10^{-2}$				
PART. CORR.:					
$-18.0000 \cdot 10^{-1}$	$46.2385 \cdot 10^{-2}$	$41.4137 \cdot 10^{-4}$	$-17.5445 \cdot 10^{-2}$	$33.3233 \cdot 10^{-2}$	$70.1313 \cdot 10^{-3}$
REGRESSION PARAMETERS:					
$19.7829 \cdot 10^{-2}$	$15.8848 \cdot 10^{-2}$	$12.9309 \cdot 10^{-3}$	$-40.1113 \cdot 10^{-2}$	$72.3014 \cdot 10^{-2}$	$36.9441 \cdot 10^{-3}$
F TEST:	21.1601				
REL. ERROR:	$\sim 59.2940 \cdot 10^{-2}$				
T TEST:	$50.0186 \cdot 10^{-1}$	$39.7230 \cdot 10^{-3}$	$-17.0932 \cdot 10^{-1}$	$33.9002 \cdot 10^{-1}$	$67.4336 \cdot 10^{-3}$
COV. MATR.:					
$12.1454 \cdot 10^{-2}$	$22.9310 \cdot 10^{-2}$	$22.9181 \cdot 10^{-4}$	$-26.5210 \cdot 10^{-3}$	$23.2450 \cdot 10^{-3}$	$28.8184 \cdot 10^{-3}$
$22.9310 \cdot 10^{-2}$	$10.0550 \cdot 10^{-1}$	$10.9496 \cdot 10^{-3}$	$-80.1555 \cdot 10^{-3}$	$46.6683 \cdot 10^{-3}$	$96.1892 \cdot 10^{-3}$
$22.9181 \cdot 10^{-4}$	$10.9496 \cdot 10^{-3}$	$75.2371 \cdot 10^{-4}$	$54.1741 \cdot 10^{-5}$	$18.2457 \cdot 10^{-4}$	$-17.5046 \cdot 10^{-3}$
$-26.5210 \cdot 10^{-3}$	$-80.1555 \cdot 10^{-3}$	$54.1741 \cdot 10^{-5}$	$19.1188 \cdot 10^{-3}$	$-79.1193 \cdot 10^{-4}$	$-10.9973 \cdot 10^{-3}$
$23.2450 \cdot 10^{-3}$	$46.6683 \cdot 10^{-3}$	$18.2457 \cdot 10^{-4}$	$-79.1193 \cdot 10^{-4}$	$17.4938 \cdot 10^{-3}$	$-36.8904 \cdot 10^{-5}$
$28.8184 \cdot 10^{-3}$	$96.1892 \cdot 10^{-3}$	$-17.5046 \cdot 10^{-3}$	$-10.9973 \cdot 10^{-3}$	$-36.8904 \cdot 10^{-5}$	$26.0418 \cdot 10^{-3}$
CORR. MATR.:					
$21.5001 \cdot 10^{-1}$	$-98.2667 \cdot 10^{-2}$	$-69.1955 \cdot 10^{-4}$	$34.2161 \cdot 10^{-2}$	$-58.9960 \cdot 10^{-2}$	$-11.6309 \cdot 10^{-3}$
$-98.2667 \cdot 10^{-2}$	$21.0070 \cdot 10^{-1}$	$-34.2607 \cdot 10^{-2}$	$69.6076 \cdot 10^{-2}$	$11.0559 \cdot 10^{-2}$	$-26.2041 \cdot 10^{-3}$
$-69.1955 \cdot 10^{-4}$	$-34.2607 \cdot 10^{-2}$	$12.9846 \cdot 10^{-1}$	$-25.9781 \cdot 10^{-2}$	$-19.1910 \cdot 10^{-2}$	$53.7471 \cdot 10^{-3}$
$34.2161 \cdot 10^{-2}$	$69.6076 \cdot 10^{-2}$	$-25.9781 \cdot 10^{-2}$	$17.6905 \cdot 10^{-1}$	$38.9106 \cdot 10^{-2}$	$-11.1811 \cdot 10^{-3}$
$-58.9960 \cdot 10^{-2}$	$11.0559 \cdot 10^{-2}$	$-19.1910 \cdot 10^{-2}$	$38.9106 \cdot 10^{-2}$	$14.5783 \cdot 10^{-1}$	$67.5354 \cdot 10^{-3}$
$-11.6309 \cdot 10^{-2}$	$-26.2041 \cdot 10^{-2}$	$53.7471 \cdot 10^{-2}$	$-11.1811 \cdot 10^{-3}$	$67.5354 \cdot 10^{-3}$	$12.7928 \cdot 10^{-1}$

is a correlation matrix with a pattern of 6×6. In appropriate places in this matrix the correlation coefficients indicating the strength of the correlation can be found. The correlation is considered strongly positive if the correlation coefficient is positive also statistically, i.e. significantly different from zero. The figures in Table 10 having no sign are to be considered positive. For the figures with a negative sign the negative correlation was evaluated in a similar manner. The remaining poor correlations, independently of their sign, indicate a lack of relationship. The 'dispersion coefficient' and the 'total correlation coefficient' denote a common variation of the parameters and the strength of the relationship, resp.

The partial correlation coefficient characterizes the correlation between the single parameter and the max dC/dt, with the exclusion of the bias given by the four other parameters.

The parameters of the regression function yield the coefficients of the linear regression equation:

$$y = a_1 + a_2x_2 + a_3x_3 + a_4x_4 + a_5x_5 + a_6x_6$$

from which the best equation (first grade) was calculated for the max dC/dt, as a dependent variable, and the other parameters, as independent variables. (The equation is 'best' in the sense that from the theoretically possible equations just the $a_1 \ldots a_6$ values are substituted thus approaching the values of max dC/dt which are actually measured.) As additional data the F test, the 'relative error' and the t test, which indicate the strength of the regression connection, the correctness of the approximation and the strength of the relationship with single independent variables are also given.

The covariance matrix and the correlation matrix (included for the sake of completeness) are not evaluated.

The F test indicates that, in general, there is a significant correlation between the change of the max dC/dt and the other parameters examined. It is a general rule that the values of the mean blood pressure have not changed and have not influenced the correlations significantly.

The other parameters show marked alterations in every group. The detailed analysis of these parameters is as follows.

The ejection time and the pulse rate both have an important role but they are inversely related, i.e. an increase in pulse rate is associated with a shortening of the ejection time. The diverse alterations can be seen in the correlation matrix as well. The related t tests indicate that in the groups containing 'non-heart' patients, the ejection time shows a lesser correlation with max dC/dt than with the pulse rate, whereas in the groups of 'cardiac patients' the reverse holds true. The same discriminative power can be

expected from the two parameters, this being the justification for using them interchangeably.

In contrast to the two above-mentioned parameters, the incisura index shows no relationship to the height of the blood pressure or the type of heart disease. There is a correlation, however, with the mean blood pressure. This suggests that the incisura index is more of an indicator of the peripheral resistance than of myocardial contractility.

From studies of the dose–effect correlations, it can be stated that in the control group the relationship to max dC/dt is extremely close. This is also so in Group 2 and in both groups this correlation is closer than that of the dose and the ejection time. In Groups 3, 4, 5–7, the dose has the closest correlation with the ejection time. The dose–pulse rate relationship is not so strong as the ejection time–dose relationship.

*

The parameters have, in general, a correlation with the change of the carotid derivative. The mean blood pressure hardly plays a role, the behaviour of the incisura index is not constant. Ejection time and the alteration of the pulse rate indicate strong negative correlation. In the 'non-heart' patient groups, ejection time shows a poorer correlation with max dC/dt, whereas this is close with the heart rate in the group of 'cardiac patients'.

The effect of the varying doses of isoprenaline is indicated most sensitively by max dC/dt.

CALCULATIONS WITH FIXED ISOPRENALINE DOSES

In our previous studies the dose of isoprenaline was greatly variable, and the magnitude of the dose biased markedly the most important parameters. Therefore, the results obtained after administration of 5 μg isoprenaline were analysed. Experiments were also made with 10 μg isoprenaline, though it was found that this gave no further information.

The results have been analysed in two ways:

1. At the time of maximal elevation of dC/dt (see p. 147);
2. At a fixed time, 1.5 min, which, in general, is the starting point of the decline in the reaction provoked by isoprenaline.

The measurement outlined in point 1 was performed in every group. Point 2 was studied only in Group 2, this being only a preliminary study. It was concluded that the investigation at 1.5 min was less informative.

The parameters were identical with those described on p. 147, except that the dose was fixed.

The F tests, in contrast to what was found in cases with changing doses, were not significant, or their values were smaller. The t tests were in general not significant. There was one exception: in Groups 3 and 4, the changes of the ejection time and max dC/dt showed significant difference (see later).

All these imply that with fixed dose, the parameters are independent of each other giving more information on individual events.

It should be noted that the max dC/dt and the changes in the pulse rate in every group had little or no correlation (Chapter 4, pp. 64, 68, 96). Consequently, the two parameters used as independent entities enabled us to distinguish individuals and groups according to their cardiac condition.

The parameters in the groups were studied with the help of the correlation matrices (Table 11).

Group 1. Controls

a. Max dC/dt increases independently of other parameters. It goes further than might be expected from the increasing heart rate.

b. Heart rate changes markedly. This shows close negative correlation with the ejection time, but it is not dependent on other parameters.

c. The incisura index varies readily but has no relationship to other parameters.

d. The mean blood pressure does not change.

Based on these facts it can be stated that healthy circulation reacts remarkably to 5 μg isoprenaline: contractility increases (max dC/dt), there is a higher heart rate, and peripheral resistance decreases (incisura index). From the point of view of the parameters, the compensatory mechanisms are independent. having considerable reserves (see p. 195).

Group 2 Mainly hyperkinetics

a. Max dC/dt increases markedly, however, this is not independent. It shows close correlation with the incisura index, which indicates a decrease in peripheral resistance, and in some individuals with the decrease in blood pressure.

b. Pronounced increase in heart rate, but the heart rate–ejection time correlation ceased to exist.

c. The change of the incisura index is not independent, nevertheless, beside max dC/dt it correlates with the changes in mean blood pressure as well.

TABLE 11

Partial logarithmic regression with fixed dose (Patient Group No. 1)

DOSE = 5

SAMPLE SIZE: 063

	MAX dC/dt	P_m	EJECT. TIME	PULSE RATE	INCIS. IND.
MEAN:	0.9111	−0.0271	−0.2439	0.3394	0.5509
S.D.:	$24.9478 \cdot 10^{-2}$	$13.5575 \cdot 10^{-2}$	$12.8804 \cdot 10^{-2}$	$16.2050 \cdot 10^{-2}$	$55.0223 \cdot 10^{-2}$
CORR. MATR.:	1.0000	0.1017	−0.2102	0.0793	0.0293
	0.1017	1.0000	−0.0201	0.1614	−0.3383
	−0.2102	−0.0201	1.0000	−0.3540	0.0815
	0.0793	0.1614	−0.3540	1.0000	0.1982
	0.0293	−0.3383	0.0815	0.1982	1.0000
DISPERSION COEFF.:		$79.2944 \cdot 10^{-2}$			
TOTAL CORR. COEFF.:		$62.4599 \cdot 10^{-3}$			
PART. CORR.:	$-10.0000 \cdot 10^{-1}$	$12.9775 \cdot 10^{-2}$	$-21.4751 \cdot 10^{-2}$	$-41.7011 \cdot 10^{-3}$	$95.5953 \cdot 10^{-3}$
REGRESSION PARAMETERS:	$80.6352 \cdot 10^{-2}$	$25.7445 \cdot 10^{-2}$	$-44.9988 \cdot 10^{-2}$	$-71.2531 \cdot 10^{-3}$	$47.4809 \cdot 10^{-3}$
F TEST:		$96.6006 \cdot 10^{-2}$			
REL. ERROR:		$26.5127 \cdot 10^{-2}$			
T TEST:		$99.6769 \cdot 10^{-2}$	$-16.7456^{\Gamma} \cdot 10^{-1}$	$-31.7863 \cdot 10^{-2}$	$73.1382 \cdot 10^{-2}$
COV. MATR.:	$62.2395 \cdot 10^{-3}$	$34.3890 \cdot 10^{-4}$	$-67.5507 \cdot 10^{-4}$	$32.0549 \cdot 10^{-4}$	$40.1958 \cdot 10^{-4}$
	$34.3890 \cdot 10^{-4}$	$18.3806 \cdot 10^{-3}$	$-35.0609 \cdot 10^{-5}$	$35.4597 \cdot 10^{-4}$	$-25.2357 \cdot 10^{-3}$
	$-67.5506 \cdot 10^{-4}$	$-35.0609 \cdot 10^{-5}$	$16.5905 \cdot 10^{-3}$	$-73.8854 \cdot 10^{-4}$	$57.7624 \cdot 10^{-4}$
	$32.0549 \cdot 10^{-4}$	$35.4597 \cdot 10^{-4}$	$-73.8854 \cdot 10^{-4}$	$26.2602 \cdot 10^{-3}$	$17.6696 \cdot 10^{-3}$
	$40.1958 \cdot 10^{-4}$	$-25.2357 \cdot 10^{-3}$	$57.7624 \cdot 10^{-4}$	$17.6696 \cdot 10^{-3}$	$30.2746 \cdot 10^{-2}$
CORR. MATR.:	$10.6662 \cdot 10^{-1}$	$-14.9225 \cdot 10^{-2}$	$24.7804 \cdot 10^{-2}$	$49.3663 \cdot 10^{-3}$	$-11.1695 \cdot 10^{-2}$
	$-14.9225 \cdot 10^{-2}$	$12.3962 \cdot 10^{-1}$	$-17.1482 \cdot 10^{-2}$	$-34.9407 \cdot 10^{-2}$	$50.6946 \cdot 10^{-2}$
	$24.7804 \cdot 10^{-2}$	$-17.1482 \cdot 10^{-2}$	$12.4835 \cdot 10^{-1}$	$50.2763 \cdot 10^{-2}$	$-26.6646 \cdot 10^{-2}$
	$49.3662 \cdot 10^{-2}$	$-34.9407 \cdot 10^{-2}$	$50.2763 \cdot 10^{-2}$	$13.1388 \cdot 10^{-1}$	$-42.0997 \cdot 10^{-2}$
	$-11.1695 \cdot 10^{-2}$	$50.6946 \cdot 10^{-2}$	$-26.6646 \cdot 10^{-2}$	$-42.0997 \cdot 10^{-2}$	$12.7993 \cdot 10^{-1}$

(TABLE 11 cont.)

Patient Group No. 2

SAMPLE SIZE: 050

	MAX dC/dt	P_m	EJECT. TIME	PULSE RATE	INCIS. IND.
MEAN:	0.9157	−0.0886	−0.2766	0.2749	0.6460
S. D.:	$22.7084 \cdot 10^{-2}$	$13.8003 \cdot 10^{-2}$	$10.4249 \cdot 10^{-2}$	$14.3180 \cdot 10^{-2}$	$53.0319 \cdot 10^{-2}$
CORR. MATR.:	1.0000	−0.3462	0.0314	0.1824	0.3863
	−0.3462	1.0000	−0.0146	0.0980	−0.4854
	0.0314	−0.0146	1.0000	−0.4929	−0.2780
	0.1824	0.0980	−0.4929	1.0000	0.3634
	0.3863	−0.4854	−0.2780	0.3634	1.0000
DISPERSION COEFF.:		$58.2441 \cdot 10^{-2}$			
TOTAL CORR. COEFF.:		$22.5651 \cdot 10^{-2}$			
PART. CORR.:	$-10.0000 \cdot 10^{-1}$	$-22.4319 \cdot 10^{-2}$	$19.5371 \cdot 10^{-2}$	$19.4638 \cdot 10^{-2}$	$20.7472 \cdot 10^{-2}$
REGRESSION PARAMETERS:	$83.9615 \cdot 10^{-2}$	$-40.5156 \cdot 10^{-2}$	$44.2446 \cdot 10^{-2}$	$34.5788 \cdot 10^{-2}$	$10.4470 \cdot 10^{-2}$
F TEST:		$32.7834 \cdot 10^{-1}$			
REL. ERROR:		$21.8231 \cdot 10^{-2}$			
T TEST:		$-15.4413 \cdot 10^{-1}$	$13.3634 \cdot 10^{-1}$	$13.3113 \cdot 10^{-1}$	$14.2272 \cdot 10^{-1}$
COV. MATR.:	$51.5671 \cdot 10^{-3}$	$-10.8505 \cdot 10^{-3}$	$74.4356 \cdot 10^{-5}$	$59.3192 \cdot 10^{-4}$	$46.5157 \cdot 10^{-3}$
	$-10.8505 \cdot 10^{-3}$	$19.0447 \cdot 10^{-3}$	$-21.0281 \cdot 10^{-5}$	$19.3654 \cdot 10^{-4}$	$-35.5227 \cdot 10^{-3}$
	$74.4357 \cdot 10^{-5}$	$-21.0281 \cdot 10^{-5}$	$10.8678 \cdot 10^{-3}$	$-73.5674 \cdot 10^{-4}$	$-15.3668 \cdot 10^{-3}$
	$59.3192 \cdot 10^{-4}$	$19.3654 \cdot 10^{-4}$	$-73.5674 \cdot 10^{-4}$	$20.5004 \cdot 10^{-3}$	$27.5935 \cdot 10^{-3}$
	$46.5157 \cdot 10^{-3}$	$-35.5227 \cdot 10^{-3}$	$-15.3668 \cdot 10^{-3}$	$27.5935 \cdot 10^{-3}$	$28.1239 \cdot 10^{-2}$
CORR. MATR.:	$12.9141 \cdot 10^{-1}$	$31.7971 \cdot 10^{-2}$	$-26.2306 \cdot 10^{-2}$	$-28.1558 \cdot 10^{-2}$	$-31.5069 \cdot 10^{-2}$
	$31.7971 \cdot 10^{-2}$	$15.5588 \cdot 10^{-1}$	$-13.7788 \cdot 10^{-2}$	$-51.3523 \cdot 10^{-2}$	$81.5161 \cdot 10^{-2}$
	$-26.2306 \cdot 10^{-2}$	$-13.7788 \cdot 10^{-3}$	$13.9583 \cdot 10^{-1}$	$64.7272 \cdot 10^{-2}$	$24.7389 \cdot 10^{-2}$
	$-28.1558 \cdot 10^{-2}$	$-51.3523 \cdot 10^{-2}$	$64.7272 \cdot 10^{-2}$	$16.2039 \cdot 10^{-1}$	$-54.9440 \cdot 10^{-2}$
	$-31.5069 \cdot 10^{-2}$	$81.5161 \cdot 10^{-2}$	$24.7389 \cdot 10^{-2}$	$-54.9440 \cdot 10^{-2}$	$17.8579 \cdot 10^{-1}$

(TABLE 11 cont.)

Patient Group No. 3

SAMPLE SIZE: 016

	MAX dC/dt	P_m	EJECT. TIME	PULSE RATE	INCIS. IND.
MEAN:	0.8609	−0.05447	−0.2612	0.2835	0.2681
S. D.:	$22.4565 \cdot 10^{-2}$	$15.2306 \cdot 10^{-2}$	$11.0228 \cdot 10^{-2}$	$15.7457 \cdot 10^{-2}$	$60.0672 \cdot 10^{-2}$
CORR. MATR.:	1.0000	0.2456	0.4780	0.1326	−0.0191
	0.2456	1.0000	0.1070	0.0888	−0.7723
	0.4780	0.1070	1.0000	−0.4642	0.0518
	0.1326	0.0888	−0.4642	1.0000	0.1562
	−0.0191	−0.7723	0.0518	0.1562	1.0000
DISPERSION COEFF.:		$35.1611 \cdot 10^{-2}$			
TOTAL CORR. COEFF.:		$40.7529 \cdot 10^{-2}$			
PART. CORR.:	$-10.0000 \cdot 10^{-1}$	$63.2706 \cdot 10^{-3}$	$56.2903 \cdot 10^{-2}$	$39.5443 \cdot 10^{-2}$	$-35.9367 \cdot 10^{-3}$
REGRESSION PARAMETERS:	$10.5377 \cdot 10^{-1}$	$13.6397 \cdot 10^{-2}$	$13.8272 \cdot 10^{-1}$	$63.8479 \cdot 10^{-2}$	$-19.7006 \cdot 10^{-3}$
F TEST:		$18.9158 \cdot 10^{-1}$			
REL. ERROR:		$20.0786 \cdot 10^{-2}$			
T TEST:		$21.0266 \cdot 10^{-2}$	$22.5879 \cdot 10^{-1}$	$14.2793 \cdot 10^{-1}$	$-11.9266 \cdot 10^{-2}$
COV. MATR.:	$50.4294 \cdot 10^{-3}$	$83.9977 \cdot 10^{-4}$	$11.8331 \cdot 10^{-3}$	$46.8809 \cdot 10^{-4}$	$-25.7429 \cdot 10^{-4}$
	$83.9977 \cdot 10^{-4}$	$23.1972 \cdot 10^{-3}$	$17.9598 \cdot 10^{-4}$	$21.3070 \cdot 10^{-4}$	$-70.6582 \cdot 10^{-3}$
	$11.8331 \cdot 10^{-3}$	$17.9598 \cdot 10^{-4}$	$12.1501 \cdot 10^{-3}$	$-80.5749 \cdot 10^{-4}$	$34.2901 \cdot 10^{-4}$
	$46.8809 \cdot 10^{-4}$	$21.3070 \cdot 10^{-4}$	$-80.5749 \cdot 10^{-4}$	$24.7928 \cdot 10^{-3}$	$14.7695 \cdot 10^{-3}$
	$-25.7429 \cdot 10^{-4}$	$-70.6582 \cdot 10^{-3}$	$34.2901 \cdot 10^{-4}$	$14.7695 \cdot 10^{-3}$	$36.0807 \cdot 10^{-2}$
CORR. MATR.:	$16.8785 \cdot 10^{-1}$	$-15.6139 \cdot 10^{-2}$	$-11.4555 \cdot 10^{-1}$	$-75.5615 \cdot 10^{-2}$	$88.9422 \cdot 10^{-3}$
	$-15.6139 \cdot 10^{-2}$	$36.0818 \cdot 10^{-1}$	$-10.5532 \cdot 10^{-1}$	$-12.6386 \cdot 10^{-1}$	$30.3577 \cdot 10^{-1}$
	$-11.4555 \cdot 10^{-1}$	$-10.5532 \cdot 10^{-1}$	$24.5375 \cdot 10^{-1}$	$15.7370 \cdot 10^{-1}$	$-12.0975 \cdot 10^{-1}$
	$-75.5615 \cdot 10^{-2}$	$-12.6386 \cdot 10^{-1}$	$15.7370 \cdot 10^{-1}$	$21.6321 \cdot 10^{-1}$	$-14.0985 \cdot 10^{-1}$
	$88.9422 \cdot 10^{-3}$	$30.3577 \cdot 10^{-1}$	$-12.0975 \cdot 10^{-1}$	$-14.0985 \cdot 10^{-1}$	$36.2916 \cdot 10^{-1}$

(TABLE 11 cont.)

Patient Group No. 4

SAMPLE SIZE: 014

	MAX dC/dt	P_m	EJECT. TIME	PULSE RATE	INCIS. IND.
MEAN:	0.8236	−0.0895	−0.2441	0.2642	0.3611
S.D.:	$36.8790 \cdot 10^{-2}$	$12.3295 \cdot 10^{-2}$	$10.4461 \cdot 10^{-2}$	$18.6831 \cdot 10^{-2}$	$63.3501 \cdot 10^{-2}$
CORR. MATR.:	1.0000	−0.1219	−0.4757	0.0077	−0.2046
	−0.1219	1.0000	−0.3570	−0.0210	−0.3993
	−0.4757	−0.3570	1.0000	−0.1917	0.0214
	0.0077	−0.0210	−0.1917	1.0000	0.2910
	−0.2046	−0.3993	0.0214	0.2910	1.0000
DISPESRION COEFF.:		$58.6898 \cdot 10^{-2}$			
TOTAL CORR. COEFF.:		$45.2462 \cdot 10^{-2}$			
PART. CORR.:	$-10.0000 \cdot 10^{-1}$	$-50.5158 \cdot 10^{-2}$	$-62.5722 \cdot 10^{-2}$	$-18.3610 \cdot 10^{-3}$	$-41.6889 \cdot 10^{-2}$
REGRESSION PARAMETERS:	$21.4133 \cdot 10^{-2}$	$-15.2856 \cdot 10^{-1}$	$-23.0384 \cdot 10^{-1}$	$-28.6715 \cdot 10^{-3}$	$-22.7275 \cdot 10^{-2}$
F TEST:		$18.5930 \cdot 10^{-1}$			
REL. ERROR:		$33.1341 \cdot 10^{-2}$			
T TEST:		$-17.5600 \cdot 10^{-1}$	$-24.0648 \cdot 10^{-1}$	$-55.0924 \cdot 10^{-3}$	$-13.7593 \cdot 10^{-1}$
COV. MATR.:	$13.6006 \cdot 10^{-2}$	$-55.4198 \cdot 10^{-4}$	$-18.3257 \cdot 10^{-3}$	$52.9214 \cdot 10^{-5}$	$-47.7921 \cdot 10^{-3}$
	$-55.4198 \cdot 10^{-4}$	$15.2016 \cdot 10^{-3}$	$-45.9808 \cdot 10^{-4}$	$-48.3234 \cdot 10^{-5}$	$-31.1846 \cdot 10^{-3}$
	$-18.3257 \cdot 10^{-3}$	$-45.9808 \cdot 10^{-4}$	$10.9121 \cdot 10^{-3}$	$-37.4072 \cdot 10^{-4}$	$14.1566 \cdot 10^{-4}$
	$52.9214 \cdot 10^{-5}$	$-48.3235 \cdot 10^{-5}$	$-37.4072 \cdot 10^{-4}$	$34.9060 \cdot 10^{-3}$	$34.4369 \cdot 10^{-3}$
	$-47.7921 \cdot 10^{-3}$	$-31.1846 \cdot 10^{-3}$	$14.1566 \cdot 10^{-4}$	$34.4369 \cdot 10^{-3}$	$40.1324 \cdot 10^{-2}$
CORR. MATR.:	$18.2636 \cdot 10^{-1}$	$93.3326 \cdot 10^{-2}$	$11.9182 \cdot 10^{-1}$	$26.5282 \cdot 10^{-3}$	$71.3026 \cdot 10^{-2}$
	$93.3326 \cdot 10^{-2}$	$18.6908 \cdot 10^{-1}$	$10.8615 \cdot 10^{-1}$	$-28.0657 \cdot 10^{-3}$	$92.2090 \cdot 10^{-2}$
	$11.9182 \cdot 10^{-1}$	$10.8615 \cdot 10^{-1}$	$19.8645 \cdot 10^{-1}$	$22.9014 \cdot 10^{-2}$	$56.8325 \cdot 10^{-2}$
	$26.5282 \cdot 10^{-3}$	$-28.0657 \cdot 10^{-3}$	$22.9014 \cdot 10^{-2}$	$11.4297 \cdot 10^{-1}$	$-34.3231 \cdot 10^{-2}$
	$71.3026 \cdot 10^{-2}$	$92.2090 \cdot 10^{-2}$	$56.8325 \cdot 10^{-2}$	$-34.3231 \cdot 10^{-2}$	$16.0171 \cdot 10^{-1}$

(TABLE 11 cont.)

Patient Group No. 5

SAMPLE SIZE: 019

	MAX dC/dt	P_m	EJECT. TIME	PULSE RATE	INCIS. IND.
MEAN:	0.6467	−0.0126	−0.1498	0.2286	0.2246
S. D.:	$29.9322 \cdot 10^{-2}$	$69.6488 \cdot 10^{-3}$	$12.5764 \cdot 10^{-2}$	$16.7889 \cdot 10^{-2}$	$39.5108 \cdot 10^{-2}$
CORR. MATR.:	1.0000	−0.4017	−0.4512	0.0052	0.2568
	−0.4017	1.0000	0.6299	−0.0308	−0.4246
	−0.4512	0.6299	1.0000	−0.3481	−0.5127
	0.0052	−0.0308	−0.3481	1.0000	0.3694
	0.2568	−0.4246	−0.5127	0.3694	1.0000
DISPERSION COEFF.:		$49.6385 \cdot 10^{-2}$			
TOTAL CORR. COEFF.:		$24.4722 \cdot 10^{-2}$			
PART. CORR.:	$-10.0000 \cdot 10^{-1}$	$-11.4105 \cdot 10^{-2}$	$-29.4923 \cdot 10^{-2}$	$-15.3350 \cdot 10^{-2}$	$52.2069 \cdot 10^{-3}$
REGRESSION PARAMETERS:	$55.3884 \cdot 10^{-2}$	$-58.7245 \cdot 10^{-2}$	$-92.9780 \cdot 10^{-2}$	$-27.7446 \cdot 10^{-2}$	$42.3820 \cdot 10^{-3}$
F TEST:		$11.3405 \cdot 10^{-1}$			
REL. ERROR:		$40.2258 \cdot 10^{-2}$			
T TEST:		$-42.9749 \cdot 10^{-2}$	$-11.5487 \cdot 10^{-1}$	$-58.0650 \cdot 10^{-2}$	$19.5607 \cdot 10^{-2}$
COV. MATR.:	$89.5935 \cdot 10^{-3}$	$-83.7394 \cdot 10^{-4}$	$-16.9866 \cdot 10^{-3}$	$26.2571 \cdot 10^{-5}$	$30.3668 \cdot 10^{-3}$
	$-83.7393 \cdot 10^{-4}$	$48.5096 \cdot 10^{-4}$	$55.1719 \cdot 10^{-4}$	$-35.9572 \cdot 10^{-5}$	$-11.6846 \cdot 10^{-3}$
	$-16.9866 \cdot 10^{-3}$	$55.1719 \cdot 10^{-4}$	$15.8166 \cdot 10^{-3}$	$-73.4929 \cdot 10^{-4}$	$-25.4760 \cdot 10^{-3}$
	$26.2571 \cdot 10^{-5}$	$-35.9572 \cdot 10^{-5}$	$-73.4929 \cdot 10^{-4}$	$28.1867 \cdot 10^{-3}$	$24.5029 \cdot 10^{-3}$
	$30.3668 \cdot 10^{-3}$	$-11.6846 \cdot 10^{-3}$	$-25.4760 \cdot 10^{-3}$	$24.5029 \cdot 10^{-3}$	$15.6110 \cdot 10^{-2}$
CORR. MATR.:	$13.2402 \cdot 10^{-1}$	$18.0921 \cdot 10^{-2}$	$51.7239 \cdot 10^{-2}$	$20.6042 \cdot 10^{-2}$	$-74.0717 \cdot 10^{-3}$
	$18.0921 \cdot 10^{-2}$	$18.9878 \cdot 10^{-1}$	$-10.8169 \cdot 10^{-1}$	$-45.7249 \cdot 10^{-2}$	$37.4100 \cdot 10^{-2}$
	$51.7239 \cdot 10^{-2}$	$-10.8169 \cdot 10^{-1}$	$23.2313 \cdot 10^{-1}$	$63.8527 \cdot 10^{-2}$	$36.3087 \cdot 10^{-2}$
	$20.6042 \cdot 10^{-2}$	$-45.7249 \cdot 10^{-2}$	$63.8527 \cdot 10^{-2}$	$13.6349 \cdot 10^{-1}$	$-42.3341 \cdot 10^{-2}$
	$-74.0717 \cdot 10^{-3}$	$37.4100 \cdot 10^{-2}$	$36.3087 \cdot 10^{-2}$	$-42.3341 \cdot 10^{-2}$	$15.2039 \cdot 10^{-1}$

(TABLE 11 cont.)

Patient Group No. 6

SAMPLE SIZE: 014

	MAX dC/dt	P_m	EJECT. TIME	PULSE RATE	INCIS. IND.
MEAN:	0.3550	−0.0082	−0.1112	0.2065	0.1809
S. D.:	$12.4957 \cdot 10^{-2}$	$11.3932 \cdot 10^{-2}$	$14.5404 \cdot 10^{-2}$	$14.0033 \cdot 10^{-2}$	$43.2987 \cdot 10^{-2}$
CORR. MATR.:	1.0000	0.0956	−0.1795	0.2213	0.2001
	0.0956	1.0000	0.1567	0.4466	−0.7239
	−0.1795	0.1567	1.0000	−0.3431	−0.0841
	0.2213	0.4466	−0.3431	1.0000	−0.2341
	0.2001	−0.7239	−0.0841	−0.2341	1.0000
DISPERSION COEFF.:		$47.0314 \cdot 10^{-2}$			
TOTAL CORR. COEFF.:		$20.9616 \cdot 10^{-2}$			
PART. CORR.:	$-10.0000 \cdot 10^{-1}$	$31.8693 \cdot 10^{-2}$	$-18.2232 \cdot 10^{-2}$	$53.9708 \cdot 10^{-3}$	$39.5883 \cdot 10^{-2}$
REGRESSION PARAMETERS:	$30.0419 \cdot 10^{-2}$	$55.6678 \cdot 10^{-2}$	$-16.3489 \cdot 10^{-2}$	$55.1757 \cdot 10^{-3}$	$16.3339 \cdot 10^{-2}$
F TEST:		$59.6716 \cdot 10^{-2}$			
REL. ERROR:		$31.2972 \cdot 10^{-2}$			
T TEST:		$10.0867 \cdot 10^{-1}$			
COV. MATR.:	$15.6143 \cdot 10^{-3}$	$13.6149 \cdot 10^{-4}$	$-32.6197 \cdot 10^{-4}$	$38.7162 \cdot 10^{-4}$	$10.8252 \cdot 10^{-3}$
	$13.6149 \cdot 10^{-4}$	$12.9806 \cdot 10^{-3}$	$25.9629 \cdot 10^{-4}$	$71.2468 \cdot 10^{-4}$	$-35.7119 \cdot 10^{-3}$
	$-32.6197 \cdot 10^{-4}$	$25.9629 \cdot 10^{-4}$	$21.1424 \cdot 10^{-3}$	$-69.8541 \cdot 10^{-4}$	$-52.9750 \cdot 10^{-4}$
	$38.7162 \cdot 10^{-4}$	$71.2468 \cdot 10^{-4}$	$-69.8541 \cdot 10^{-4}$	$19.6091 \cdot 10^{-3}$	$-14.1946 \cdot 10^{-3}$
	$10.8252 \cdot 10^{-3}$	$-35.7119 \cdot 10^{-3}$	$-52.9750 \cdot 10^{-4}$	$-14.1946 \cdot 10^{-3}$	$18.7478 \cdot 10^{-2}$
CORR. MATR.:	$12.6521 \cdot 10^{-1}$	$-64.2170 \cdot 10^{-2}$	$24.0694 \cdot 10^{-2}$	$-78.2307 \cdot 10^{-3}$	$-71.6084 \cdot 10^{-2}$
	$-64.2170 \cdot 10^{-2}$	$32.0919 \cdot 10^{-1}$	$-80.4941 \cdot 10^{-2}$	$-10.6760 \cdot 10^{-1}$	$21.3402 \cdot 10^{-1}$
	$24.0694 \cdot 10^{-2}$	$-80.4941 \cdot 10^{-2}$	$13.7887 \cdot 10^{-1}$	$69.6924 \cdot 10^{-2}$	$-35.1694 \cdot 10^{-2}$
	$-78.2307 \cdot 10^{-3}$	$-10.6760 \cdot 10^{-1}$	$69.6924 \cdot 10^{-2}$	$16.6064 \cdot 10^{-1}$	$-30.9797 \cdot 10^{-2}$
	$-71.6084 \cdot 10^{-2}$	$21.3402 \cdot 10^{-2}$	$-35.1694 \cdot 10^{-2}$	$-30.9797 \cdot 10^{-2}$	$25.8602 \cdot 10^{-1}$

(TABLE 11 cont.)

Patient Group No. 7

SAMPLE SIZE: 013

	MAX dC/dt	P_m	EJECT. TIME	PULSE RATE	INCIS. IND.
MEAN:	0.5665	−0.0403	−0.1789	0.2031	0.2454
S. D.:	$41.3196 \cdot 10^{-2}$	$84.2572 \cdot 10^{-3}$	$10.5387 \cdot 10^{-2}$	$15.2590 \cdot 10^{-2}$	$40.5987 \cdot 10^{-2}$
CORR. MATR.:	1.0000	0.2964	−0.5107	0.6045	0.3400
	0.2964	1.0000	−0.1122	0.0034	−0.1969
	−0.5107	−0.1122	1.0000	−0.8120	−0.1229
	0.6045	0.0034	−0.8120	1.0000	0.4078
	0.3400	−0.1969	−0.1229	0.4078	1.0000
DISPERSION COEFF.:		$34.2080 \cdot 10^{-2}$			
TOTAL CORR. COEFF.:		$48.2999 \cdot 10^{-2}$			
PART. CORR.:	$-10.0000 \cdot 10^{-1}$	$40.3613 \cdot 10^{-2}$	$-60.5757 \cdot 10^{-3}$	$29.6045 \cdot 10^{-2}$	$23.5890 \cdot 10^{-2}$
REGRESSION PARAMETERS:	$27.3214 \cdot 10^{-2}$	$16.0409 \cdot 10^{-1}$	$-32.0508 \cdot 10^{-2}$	$12.2197 \cdot 10^{-1}$	$21.4068 \cdot 10^{-2}$
F TEST:		$18.6847 \cdot 10^{-1}$			
REL. ERROR:		$52.4405 \cdot 10^{-2}$			
T TEST:		$12\,4773 \cdot 10^{-1}$	$-17.1649 \cdot 10^{-2}$	$87.6639 \cdot 10^{-2}$	$68.6572 \cdot 10^{-2}$
COV. MATR.:	$17.0731 \cdot 10^{-2}$	$10.3182 \cdot 10^{-3}$	$-22.2400 \cdot 10^{-3}$	$38.1144 \cdot 10^{-3}$	$57.0336 \cdot 10^{-3}$
	$10.3182 \cdot 10^{-3}$	$70.9928 \cdot 10^{-4}$	$-99.6732 \cdot 10^{-5}$	$43.6732 \cdot 10^{-6}$	$-67.3707 \cdot 10^{-4}$
	$-22.2400 \cdot 10^{-3}$	$-99.6732 \cdot 10^{-5}$	$11.1063 \cdot 10^{-3}$	$-13.0573 \cdot 10^{-3}$	$-52.5999 \cdot 10^{-4}$
	$38.1144 \cdot 10^{-3}$	$43.4264 \cdot 10^{-6}$	$-13.0573 \cdot 10^{-3}$	$23.2836 \cdot 10^{-3}$	$25.2631 \cdot 10^{-3}$
	$57.0336 \cdot 10^{-3}$	$-67.3707 \cdot 10^{-4}$	$-52.5999 \cdot 10^{-4}$	$25.2631 \cdot 10^{-3}$	$16.4826 \cdot 10^{-2}$
CORR. MATR.:	$19.3423 \cdot 10^{-1}$	$-63.2685 \cdot 10^{-2}$	$15.8116 \cdot 10^{-2}$	$-87.2845 \cdot 10^{-2}$	$-40.6833 \cdot 10^{-2}$
	$-63.2685 \cdot 10^{-2}$	$12.7039 \cdot 10^{-1}$	$16.9219 \cdot 10^{-2}$	$38.0645 \cdot 10^{-2}$	$33.0880 \cdot 10^{-2}$
	$15.8116 \cdot 10^{-2}$	$16.9219 \cdot 10^{-2}$	$35.2248 \cdot 10^{-1}$	$31.1352 \cdot 10^{-1}$	$-85.7083 \cdot 10^{-2}$
	$-87.2845 \cdot 10^{-2}$	$38.0645 \cdot 10^{-2}$	$31.1352 \cdot 10^{-1}$	$44.9416 \cdot 10^{-1}$	$-10.7824 \cdot 10^{-1}$
	$-40.6833 \cdot 10^{-2}$	$33.0880 \cdot 10^{-2}$	$-85.7083 \cdot 10^{-2}$	$-10.7824 \cdot 10^{-1}$	$15.3782 \cdot 10^{-1}$

The myocardium is not affected in this disease, the regulation of the circulation has changed and an increased beta-adrenergic tone is a characteristic feature (Chapter 4, pp. 79, 83). The present results point to the paramount role of the decrease in peripheral resistance. In this respect the patients differ from the controls and also from the hypertensives. This is in agreement with the finding that it is possible to produce a model of hyperkinesis under experimental conditions by a sudden increase in the peripheral resistance through artificial shunts (Naszlady 1967).

Group 3. Mild hypertension, systolic pressure between 145 and 175

a. Max dC/dt increases markedly but it is not fully independent. It has a positive correlation with the change in ejection time.

b. Pulse rate increases but has no correlation with ejection time.

c. The incisura index and mean blood pressure show a negative correlation.

In this group the regulation of peripheral resistance has an important role, indicated by the correlation between ejection time and mean blood pressure. This, however, does not affect the regulation of contractility (max dC/dt). This latter is connected with the lengthening of the ejection time. From the groups investigated this connection could only be found in Group 3. It is known that greater systolic output can lengthen the ejection time. It is obvious that this is so if peripheral resistance is not too high. At this stage (see pp. 71, 73, Chapter 4) the greater systolic output is a common finding. On the basis of the regression analysis it seems that in the response after isoprenaline the volume reaction is important, in addition to the increase in peripheral resistance.

Group 4. Marked hypertension, systolic pressure $>$ *175 mm Hg*

a. Max dC/dt increases markedly and correlates negatively with the ejection time.

b. Pulse rate increases considerably without having a correlation with the ejection time.

c. There is a negative correlation between the changes in mean blood pressure and the incisura index.

In marked hypertension the most important feature is the increase in peripheral resistance (resistance hypertension). The regulation of contractil-

ity has a negative correlation with the changes of the ejection time, as in the group of cardiac patients. In this respect there is a difference between this group and Group 3.

In Groups 2, 3 and 4 the reactions, shown by the parameters, are somewhat similar. In all three groups the correlation between heart rate–ejection time ceased to exist. There is, however, a correlation between incisura index and mean blood pressure. This could be ascribed to the more important role of the regulation of the peripheral resistance in this group than in the controls. The trend in Group 2 is decreasing and in Groups 3 and 4 it is increasing.

Group 5. Cardiac patients, no hypertension

a. Max dC/dt has a marginal reaction and it has a negative correlation with the changes in ejection time and mean blood pressure.

b. The pulse rate increases inconsiderably without having a correlation with the ejection time.

c. The incisura index reacts more sluggishly.

d. The ejection time decreases only slightly.

Group 6. Heart disease, mild hypertension, systolic blood pressure between 145 and 175 mm Hg

a. Max dC/dt shows a sluggish reaction.

b. There is a negative correlation between max dC/dt and ejection time, the reaction of the pulse rate being weak.

c. The reaction of the incisura index is also sluggish, there is an inverse correlation between this parameter and the mean blood pressure.

d. There is a slight change in ejection time.

Group 7. Cardiac patients, marked hypertension, systolic pressure above 175 mm Hg

a. The reaction of max dC/dt is slow, correlating negatively with the change in ejection time, at the same time, it has a positive correlation with the heart rate.

b. The pulse rate increases sluggishly, there is an inverse correlation between this parameter and the changes in ejection time.

c. The incisura index reveals a retarded reaction.

d. Ejection time shows a sluggish reaction.

In groups with cardiac patients (Groups 5, 6 and 7) it is common that (*i*) reaction of all the parameters is sluggish; (*ii*) there is a negative correlation between max dC/dt and ejection time; (*iii*) there is a negative correlation between heart rate and the changes of ejection time.

These groups compared to the controls show sluggish and more interrelated reactions.

To obtain a better insight into the possible concordance, the groups with and without heart disease were compared.

Comparison of Groups 1 and 5. Common: heart rate–ejection time change inversely. Deviations: in Group 5 the parameters react sluggishly, in Group 1 the reactions are marked. In Group 5 the changes of max dC/dt, the ejection time and mean blood pressure have a negative correlation among themselves whereas there is no such negative correlation in Group 1.

Comparison of Groups 3 and 6. Common: there is a positive correlation between the changes in mean blood pressure and incisura index. Deviations: the parameters react sluggishly in Group 6, whereas there is a vigorous reaction in Group 3. In the latter, there is a positive correlation between max dC/dt and ejection time, this, however is not so in Group 6. (The heart disease stops this connection, and, similarly to the observations in Groups 5 and 7, it pushes toward a negative correlation.) In Group 6 there is a negative correlation between ejection time and heart rate, whereas this does not exist in Group 3.

Comparison of Groups 4 and 7. Common: a negative correlation between max dC/dt and the changes of ejection time. Deviations: the reactions reflected by the parameters in Group 7 are sluggish, this is not so in Group 4. In Group 7 there is a negative correlation between heart rate and ejection time. There is no such correlation in Group 4. A positive correlation between max dC/dt exists only in Group 7.

As a basis for most cardiac diseases, there is deteriorating contractility of the myocardium (Chapter 4, p. 96).

All parameters show decreased adaptability, there is a reduced reserve and the mechanisms are not independent.

The max dC/dt, which is an index of contractility, shows a smaller increase, and it is not independent of the decrease in ejection time. The latter, however, is dependent on the pulse rate. The appearance of hypertension does not disturb the negative correlation between pulse rate and ejection time. In Group 6 there is a new regulatory measure: the incisura–mean

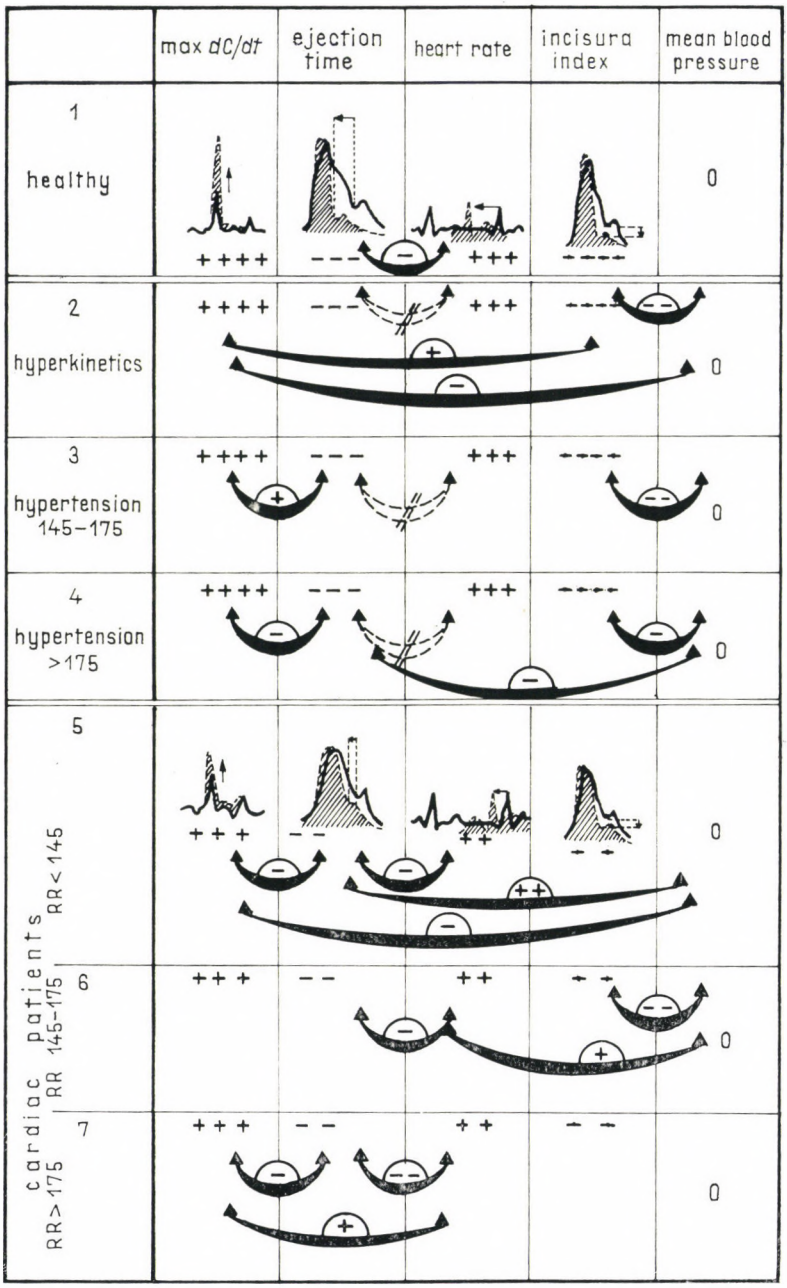

Fig. 75. Regression analysis after administration of 5 μg isoprenaline. The arrows connect those parameters which show a regular correlation with partial logarithmic regression analysis. The positive (+) signs on the arrows indicate the strength of the correlation. The broken line denotes the discontinuation of the correlation. The negative (−) signs below the single parameters show the significance and trend of the change. According to the examinations, in the controls the parameters show relatively independent and significant changes (Group 1). Under pathological conditions the reactions become more dependent and interrelations depending on the pathomechanism develop (Groups 2, 3 and 4). In groups with heart disease (Groups 5, 6 and 7), the parameters react more sluggishly, becoming interdependent

pressure regulation. Nevertheless, it has no place in Group 7 where pulse rate seems to have a paramount role.

The most seriously ill patients can be found in Group 7, and in this group, beside diminished contractility, the peripheral reactivity has also decreased. Here, the pulse rate seems to be the most important factor in the regulation. If the patient is unable to use the latter mechanism, he has angina (Tábor 1968), or his working capacity diminishes further (Endersz et al. 1972) (Fig. 75).

*

Investigations were carried out in controls and patients with various circulatory diseases and partial regression analysis was performed on the results. The effect of 5 μg isoprenaline was studied using the following parameters: max dC/dt, mean blood pressure, ejection time, heart rate and incisura index.

In controls (Group 1) these parameters change independently from each other, the changes being significant.

In patients different correlations were observed which can be related to the pathomechanism of the disease outlined on the basis of previous clinical investigation.

In Group 2 containing mainly hyperkinetics, the computer analysis supports the view that the decrease in peripheral resistance has a paramount role in the development of the contractility.

Group 3, which contains the mild hypertonics, shows in contrast to the other groups, that the max dC/dt is positively correlated with the change in ejection time. This explains the frequent occurrence of 'volume hypertension' in this group.

In Group 4 including patients with marked hypertension, there is a close correlation between incisura index and mean blood pressure, indicating the 'resistance hypertension' character of the group.

In contrast to the previous groups, in Groups 5, 6 and 7 with heart diseases, the parameters show a slower alteration, being less independent of each other. This suggests that, in addition to the diminishing of the regulation of contractility (which is an essential feature of the disease), the mechanism for the regulation of pulse rate and peripheral resistance has a smaller room for manoeuvre. In Groups 6 and 7, with heart disease combined with hypertension, the changes in most parameters are accompanied by changes of the pulse rate, the latter being the determinant of the circulatory reactions of the patient.

CHAPTER 8

SEQUENCE AND EVALUATION OF VARIOUS DISCRIMINANT ANALYSES

LINEAR LOGARITHMIC DISCRIMINANT ANALYSES IN CASES OF VARIOUS GROUPINGS OF PATIENTS

In this section, an analysis is presented in which individuals with and without heart disease are distinguished by using some parameters with the help of discriminant analysis.

Five μg isoprenaline was administered as in cases described in the previous section. The same patients were examined, using the parameters already calculated.

a. The maximum increase of max dC/dt,

$$\frac{\text{maximal value}}{\text{zero time value}};$$

b. Control (zero time) pulse rate;

c. Relative changes of pulse rate,

$$\frac{\text{pulse rate at the time of the highest max } dC/dt}{\text{zero time pulse rate}}.$$

The blood pressure was taken into consideration by selecting the groups according to zero time blood pressure (Chapter 7, p. 151), and by studying the changes in blood pressure, i.e. those of mean blood pressure; those of the systolic pressure; disregarding the changes in blood pressure and integrating the patients into two groups: with and without heart disease, with identical blood pressures; disregarding the blood pressure at rest.

Thus, Groups 1 to 4 without heart disease are confronted with Groups 5 to 7 with heart disease.

In selecting these parameters our previous experience was utilized (Chapter 7, pp. 147, 150), showing that these had yielded relatively good information. They also have a practical value, namely, they are easily measurable.

A logarithmic scale had been used for calculation also based on previous experience. Since the parameters showed a satisfactory linear correlation, the method of logarithmic discriminant calculation was chosen.

The aim of the linear discriminant analysis is to find the linear combination of the parameters used for discrimination, in other words, the sum of the products with constants which separate the groups most efficiently. This means that the computer is programmed to find the constants for the single parameters with which combined figures can be produced, indicating the condition of the myocardium and being suitable for most reliably separating groups with and without heart disease. A generally accepted criterion for optimum separation is the highest grade of significance between the two groups with Student's t test.

Table 12 contains the following items:

S-1 matrix: This is the sum of the products, matrix of the changes of the three variables which are the bases of evaluation (covariance-matrix multiplied by n—1 degree of freedom), in groups clinically considered being without heart disease.

S-2 matrix: The same in the corresponding group with heart disease.

S matrix: The sum of S-1 and S-2. (Every element of the matrix is equal to the sum of the corresponding S-1 and S-2 matrix.)

S inverse: The inverse matrix of the previous matrix multiplied with the S matrix yields the unit matrix.

Lambdas: Discriminant coefficients obtained by multiplying the vectors (differences of the means) by the S inverse.

Mahalanobis' D^2: In analyses with more variables (between groups characterized by vectors) this is the habitual D^2 distance, which in our case marks the separation of groups confronted (heart disease or not) on the basis of all parameters. The D value gives the deviations between the means of the groups mentioned above, related to the standard deviation inside the group.

F test: It yields the significance of the distance mentioned previously, using the F tables.

Z alphas: They are the values of the individuals obtained by discriminant analysis, by multiplying the parameters of the examined individual with the corresponding lambdas, and by adding up these figures.

Table 12 further contains the individuals to be compared according to the magnitude of the Z alphas, their group-affiliation, serial number and number for identification.

The denotation *Z alpha* was applied according to the accepted usage of the statistical literature: Z means the combined figures mentioned above, while alpha refers to the group.

TABLE 12

Discriminant analysis
(Patient Groups 1 to 4 vs. 5 to 7)
a Basic calculations

DOSE = 5

SAMPLE NO. AND SIZE:

GROUP 104 : 149

GROUP 507 : 047

	I GREATEST INCREASE IN LOG MAX dC/dt	II INITIAL TIME LOG PULSE RATE	III LOG PULSE RATE INCREASE AT I
MEAN:			
GROUP 104	0.8983	4.4105	0.3031
GROUP 507	0.5239	4.4252	0.2129
DIFFERENCE OF MEANS:	0.3744	−0.0147	0.0902
S-1 MATRIX:	9.1584	0.2816	0.6251
	0.2816	4.6708	−2.1192
	0.6251	−2.1192	3.7366
S-2 MATRIX:	4.8485	0.1828	0.6021
	0.1828	2.3718	−0.5082
	0.6021	−0.5082	1.0550
S MATRIX:	14.0070	0.4644	1.2272
	0.4644	7.0426	−2.6273
	1.2272	−2.6273	4.7916
S INVERSE:	0.0743	−0.0151	−0.0273
	−0.0151	0.1816	0.1034
	−0.0273	0.1034	0.2724
LAMBDAS:	0.0256	0.0010	0.0128
MAHALANOBIS' D^2:	2.0796		
F TEST	− 24.5120		
Z ALPHAS:			
MEAN:			
GROUP 104	0.0313		
GROUP 507	0.0206		
S. D.:			
GROUP 104	0.0069		
GROUP 507	0.0090		

(TABLE 12 cont.)

b Discriminant scores

NO.	IDEN-TIFIER	GROUPS 1, 2, 3, 4	GROUPS 5, 6, 7
0001	0407		0.0053
0002	0623		0.0057
0003	0626		0.0084
0004	0628		0.0085
0005	0564		0.0096
0006	1176		0.0099
0007	0020	0.0105	
0008	0620		0.0123
0009	0383		0.0144
0010	0051		0.0146
0011	0846		0.0149
0012	1333		0.0154
0013	0622		0.0156
0014	0621		0.0156
0015	0003	0.0159	
0016	0402		0.0162
0017	0517		0.0162
0018	1331		0.0164
0019	1355		0.0165
0020	0891	0.0169	
0021	0381	0.0171	
0022	0001	0.0177	
0023	1364		0.0181
0024	1301		0.0182
0025	0055		0.0183
0026	0624		0.0184
0027	0508	0.0185	
0028	1303		0.0186
0029	0761	0.0188	
0030	0629		0.0196
0031	0390	0.0200	
0032	0445	0.0202	
0033	1366		0.0205
0034	1001	0.0205	
0035	1178		0.0206
0036	1262		0.0212
0037	1199		0.0213
0038	1249		0.0213
0039	0853		0.0215
0040	1201		0.0217
0041	0848	0.0217	
0042	0928	0.0219	
0043	1275		0.0224
0044	1250		0.0224

(TABLE 12*b* cont.)

NO.	IDEN-TIFIER	GROUPS 1, 2, 3, 4	GROUPS 5, 6, 7	DISCRIMI-NANT THRESHOLD
0045	1214		0.0226	
0046	0529		0.0226	0.0228
0047	0492	0.0231		
0048	0375	0.0231		
0049	0343		0.0234	
0050	0962	0.0238		
0051	1229		0.0240	
0052	0565	0.0240		
0053	0519	0.0242		
0054	0518	0.0244		
0055	0987	0.0245		
0056	1180		0.0245	
0057	0509	0.0246		
0058	0991	0.0247		
0059	0486	0.0249		
0060	0607		0.0250	
0061	0512	0.0253		
0062	0352	0.0257		
0063	0885	0.0260		
0064	0793	0.0260		
0065	0888	0.0260		
0066	0361	0.0261		
0067	0606		0.0261	
0068	0379	0.0263		
0069	0977	0.0264		
0070	1191		0.0264	
0071	0354	0.0265		
0072	0903	0.0265		
0073	0530	0.0265		
0074	0883	0.0267		
0075	0844	0.0268		
0076	0821	0.0270		
0077	0344		0.0270	
0078	0877	0.0272		
0079	0485	0.0275		
0080	0969	0.0275		
0081	0372	0.0275		
0082	0974	0.0276		
0083	0989	0.0277		
0084	0017	0.0277		
0085	0863	0.0277		
0086	0359	0.0279		
0087	0934	0.0280		
0088	0380	0.0281		

(TABLE 12*b* cont,)

NO.	IDEN-TIFIER	GROUPS 1, 2, 3, 4	GROUPS 5, 6, 7
0089	0392		0.0281
0090	0869	0.0281	
0091	0857	0.0284	
0092	0879	0.0285	
0093	0489	0.0285	
0094	0873	0.0288	
0095	0897	0.0290	
0096	0439	0.0291	
0097	0855	0.0293	
0098	0833	0.0293	
0099	0523	0.0293	
0100	0355	0.0293	
0101	0871	0.0294	
0102	0865	0.0294	
0103	0875	0.0295	
0104	0552	0.0295	
0105	0859	0.0297	
0106	0881	0.0297	
0107	0790	0.0297	
0108	0919	0.0297	
0109	0818	0.0298	
0110	0942	0.0302	
0111	0913	0.0303	
0112	1309		0.0303
0113	0456	0.0304	
0114	0358	0.0305	
0115	0806	0.0306	
0116	0068	0.0306	
0117	0922	0.0308	
0118	0487	0.0309	
0119	0799	0.0312	
0120	0059	0.0312	
0121	0804	0.0313	
0122	0825	0.0314	
0123	0520	0.0314	
0124	0815	0.0314	
0125	0353	0.0314	
0126	0830	0.0316	
0127	0809	0.0317	
0128	0360	0.0318	
0129	0495	0.0319	
0130	0812	0.0320	
0131	0985	0.0323	
0132	0434	0.0323	

(TABLE 12*b* cont.)

NO.	IDEN-TIFIER	GROUPS 1, 2, 3, 4	GROUPS 5, 6, 7
0133	0838	0.0323	
0134	0861	0.0325	
0135	0002	0.0325	
0136	0662	0.0328	
0137	0356	0.0329	
0138	0840	0.0331	
0139	0562	0.0332	
0140	0400	0.0332	
0141	0365	0.0336	
0142	0500	0.0338	
0143	0910	0.0338	
0144	0345	0.0339	
0145	0979	0.0339	
0146	1357		0.0341
0147	0403	0.0341	
0148	0965	0.0341	
0149	0597	0.0342	
0150	0362	0.0343	
0151	0836	0.0344	
0152	0550	0.0345	
0153	0341	0.0345	
0154	0525	0.0346	
0155	0916	0.0347	
0156	0515	0.0350	
0157	0521	0.0355	
0158	0550	0.0357	
0159	0776	0.0357	
0160	0369	0.0358	
0161	0348	0.0360	
0162	0449	0.0361	
0163	0038	0.0362	
0164	0545	0.0363	
0165	0061	0.0363	
0166	0030	0.0365	
0167	0971	0.0368	
0168	0850	0.0376	
0169	0669	0.0380	
0170	0419	0.0381	
0171	0397	0.0382	
0172	0900	0.0386	
0173	0828		0.0390
0174	0466	0.0390	
0175	0493	0.0391	
0176	0869	0.0395	

(TABLE 12*b* cont.)

NO.	IDEN-TIFIER	GROUPS 1, 2, 3, 4	GROUPS 5, 6, 7
0177	0572	0.0398	
0178	0983	0.0402	
0179	0394	0.0402	
0180	0497	0.0406	
0181	0460	0.0413	
0182	0507	0.0426	
0183	0014	0.0430	
0184	0758	0.0431	
0185	0503	0.0431	
0186	0405	0.0435	
0187	0349	0.0436	
0188	0342	0.0437	
0189	0541	0.0438	
0190	0012	0.0442	
0191	0409	0.0452	
0192	0437		0.0453
0193	0465	0.0470	
0194	0404	0.0475	
0195	0684		0.0513
0196	0451	0.0528	

In Table 12 the clinically 'fit' persons were arranged in the left-hand column, whereas the 'sick' persons in the righ-hand column.

Since the Z values are arranged vertically following each other according to their magnitude, the result is that, according to the mathematical prediction, in the upper part of the column are those being 'more sick', while at the bottom those being 'more healthy'. On the basis of this tabulation, the best discriminant border line was chosen so that the conformity between 'clinical' and 'mathematical' diagnosis be the greatest. In other words it means that the standard deviation of the Z values of the clinically 'healthy' and 'sick' groups, resp., should have the smallest overlap. As a matter of fact, such a division could only be made imperfectly. The individuals belonging to the opposite side of the dividing line, according to the clinical evaluation, were marked as 'erroneously listed'. Thus, there were cases with 'erroneously healthy' (clinically sick, but mathematically fit) and 'erroneously sick' (clinically healthy but mathematically sick) listing.

In the following the problem how many 'erroneous' listings have been made in the various comparative studies is dealt with and finally these cases are discussed individually.

DISCRIMINANT ANALYSIS IN GROUPS SELECTED ACCORDING TO THE CHANGES IN MEAN BLOOD PRESSURE

On the basis of the zero time blood pressure, matched groups of controls and cardiac patients were compared:

Group 1	with Group	5
Group 2	with Group	5
Group 1+2	with Group	5
Group 3	with Group	6
Group 4	with Group	7

Moreover, each group was divided on the basis of its reaction to 5 μg isoprenaline: the increase was higher or lower than 10 mm Hg. The subgroups were also compared in pairs.

This method yielded the significant separation of the two groups in every case where the alteration of the mean blood pressure was below 10 mm Hg (this was done using the χ^2 test). In subgroups with higher than 10 mm Hg increase of mean blood pressure, the number of cases was not sufficient to calculate mathematical significance.

In the groups deviating significantly, the change of max dC/dt had the most important role, as did that of the pulse rate. The pulse rate at rest played a subordinate role.

Of the 89 individuals clinically considered 'healthy' (the change in mean blood pressure being not greater than 10 mm Hg), mathematical analysis found 79 (89 per cent) 'correct' listing and 10 (11 per cent) 'erroneous' listing. At the same time, of the 30 individuals clinically considered 'sick' 26 (87 per cent) were listed correctly and 14 (13 per cent) incorrectly.

The method has an error, namely that a considerable number of individuals (39 per cent) in whom mean blood pressure increased by more than 10 mm Hg, were not evaluated.

DISCRIMINANT ANALYSIS IN GROUPS SELECTED ACCORDING TO THE CHANGES IN SYSTOLIC PRESSURE

In this part, comparisons were made identically to the previous ones with the difference that the 10 mm Hg limit was related to the systolic pressure. In view of the experience gained previously, Groups 1 and 2 were combined. The comparisons, except in Group 1, have yielded significant results. In this

grouping each case could be evaluated, however, the weight of the parameters used for separation varied.

Summarizing the results, it was found that of the clinically 'healthy' people 136 (91 per cent) were 'healthy' using mathematical criteria, and 13 (9 per cent) were sick. Of 47 patients with clinical heart disease 37 (79 per cent) were 'sick' mathematically and 10 (21 per cent) were healthy. The error, calculated in percentage, was nearly identical in the groups above and below 10 mm Hg blood pressure change produced by isoprenaline.

DISCRIMINANT ANALYSIS WITHOUT CONSIDERING THE CHANGES IN BLOOD PRESSURE

The groups and method were similar as in the two previous experiments, except that we disregarded the changes after isoprenaline.

If Groups 1 and 2 were confronted with Group 5 there was a statistically significant difference, the overlap, however, was considerable, so the method is not suitable for individual separation.

Group 4 confronted with Group 7 did not reveal significant difference, the overlap being also great. On the contrary, Group 3 confronted with Group 6 showed a marked difference. In this series of 31 cases only one proved to be erroneously listed.

CUMULATIVE DISCRIMINANT ANALYSIS. PATIENTS WITH AND WITHOUT HEART DISEASE

In this comparison all patients with heart disease were confronted with patients without heart disease. The methods were similar to those used previously.

Of the clinically 'healthy' people ($n = 149$) 137, (92 per cent) had concordant and 12 (8 per cent) discordant mathematical listing. Of the 47 clinically 'sick' patients, 34 (72 per cent) agreed and 13 (28 per cent) disagreed with the mathematical characterization.

The coefficients of the discriminant analysis obtained by group division, according to blood pressure, showed greater oscillations than those with no division. It must be admitted that the groups divided according to blood pressure are much smaller. Nevertheless, the trends in these groups are also identical and support the conclusions drawn from the discriminant analysis performed in the non-divided groups. It is clear that the changes

of the max dC/dt and the pulse rate give more information for the characterization of the heart's condition. The logarithms of the changes reveal that the values of the max dC/dt have double weight, in other words related to the original value they are present in squares, compared to the ratio of the heart rate, which is linear.

The discriminant scores calculated on pp. 167–71 according to the Z alpha values separate the 'cardiac patients' from those of the 'healthy' individuals at 0.0228. The individuals having a lower value are sick, those with a higher value are healthy. The lambda corresponding to the max dC/dt is 0.0256, to the zero time pulse rate it is 0.0010 and to the pulse rate coinciding with the greatest change of the max dC/dt it is 0.0128.

It can be stated that by excluding the zero time pulse rate, if the (max $dC/dt)^2$ multiplied by the pulse rate after administration of isoprenaline becomes greater than 4.2025 times the base line value, the individual is healthy. If it is smaller, the patient is sick (see later).

The function dividing the two groups is as follows:

$$z = \frac{4.2025}{x^2}$$

where

$$x = \frac{\text{the greatest value of max } dC/dt \text{ after isoprenaline}}{\text{zero time value of max } dC/dt};$$

$$z = \frac{\text{pulse rate at time } (x)}{\text{zero time value of pulse rate}}, \text{ (Fig. 76).}$$

The four discriminant analyses show that the results will not be better if the zero time blood pressure and heart rate are calculated. As far as listing is concerned, there is no improvement if the isoprenaline-induced changes

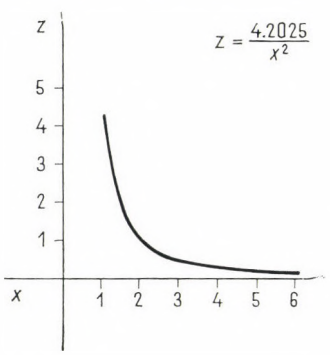

Fig. 76. x and z-based separating functions obtained by logarithmic discriminant analysis. If the point determined by values x and z (representing an individual under investigation) is located on the right side of the coordinate, the individual is mathematically 'healthy', if it is located on the left side, he is mathematically 'ill'. For symbols see Fig. 78

of the systolic and mean blood pressure are considered. The changes found in connection with these parameters show no regularities. It is not worthwhile using these tabulations.

At the same time the question emerges whether it is worth using later on the advantages of the calculation mentioned on p. 172, namely the results of the changes of systolic blood pressure, to avoid 'erroneous' listing.

*

Linear logarithmic discriminant analyses were carried out with the aim to separate patients with and without heart disease. For this calculation (*i*) the maximal increase in the dC/dt, (*ii*) the rest pulse rate, (*iii*) the increase of the pulse rate after 5 μg isoprenaline were used.

Groups with and without heart disease were compared, the patients having an identical zero time blood pressure. Subgroups were formed on the basis of the reactions provoked by isoprenaline:

a. The change in mean blood pressure is greater than 10 mm Hg.
b. The change in systolic blood pressure is greater than 10 mm Hg.
c. Disregarding subgroups *a* and *b*.
d. Without considering zero time blood pressure, in this way all patients with and without heart disease being compared.

These investigations reveal that for the characterization of the heart's condition, of the three parameters, the max dC/dt and the changes in heart rate provide the best guide. In the function used for separation, the max dC/dt is present in square value.

The analysis mentioned in *d* proved to be the most informative. On this basis of the clinically 'healthy' group ($n = 149$) 137 (92 per cent) showed concordant and 12 (8 per cent) discordant results by mathematical listing. Of 47 the clinically proved cardiac cases 34 (72 per cent) showed concordant and 13 (28 per cent) discordant results.

DISCRIMINANT ANALYSES CONSIDERING THE CHANGES OF max dC/dt, SYSTOLIC BLOOD PRESSURE AND PULSE RATE

Previous studies indicated that the application of the changes in systolic pressure (y) could be helpful. Therefore programs were designed in which this factor was also used as discriminant parameter besides max dC/dt (x) and heart rate (z).

In programs A the discriminant function discussed earlier was used with three variables (Chapter 9, p. 218). In other words, the combinations of the logarithms of max dC/dt, systolic pressure and change of pulse rate were sought which give the best means of separating the 'healthy' and 'non-healthy' groups.

In programs B the linear changes of the same parameters were used. Table 13 shows that the logarithmic transformation of the changes in programs A gives a slightly better chance for separation.

Programs A and B and the subsequent programs have been prepared in two variants. The first variant (A_1 and B_1) according to the accepted view in the literature of the discriminant analysis presupposes that in the groups to be separated the standard deviation of the discriminant variables and

TABLE 13

Comparison of discriminatory statistics for programs A to J

Program	Chances of forecast in clinically healthy and cardiac groups				Hit probability		Significance of the deviation from overlapping	F Mahalanobis' to D^2
A_1	9.4	90.6	76.6	23.4	83.6	16.4	$9.67 \cdot 10^{-15}$	27.2
A_2	10.7	89.3	76.6	23.4	82.9	17.1	$3.46 \cdot 10^{-14}$	
B_1	14.1	85.9	76.6	23.4	81.3	18.7	$7.52 \cdot 10^{-13}$	18.6
B_2	17.1	82.6	76.6	23.4	79.6	20.4	$1.39 \cdot 10^{-11}$	
C_1	10.7	89.3	83.0	17.0	86.1	13.9	$6.37 \cdot 10^{-17}$	14.5
C_2	10.1	89.0	80.9	19.1	85.4	14.6	$2.82 \cdot 10^{-16}$	
D_1	10.7	89.3	83.0	17.0	86.1	13.9	$6.37 \cdot 10^{-17}$	14.8
D_2	14.1	85.9	80.9	19.1	83.4	16.6	$1.48 \cdot 10^{-14}$	
E_1	10.7	89.3	83.0	17.0	86.1	13.9	$6.37 \cdot 10^{-17}$	22.0
E_2	13.4	86.6	83.0	17.0	84.8	15.2	$9.67 \cdot 10^{-16}$	
F_1	12.1	87.9	83.0	17.0	85.4	14.6	$2.51 \cdot 10^{-16}$	43.0
F_2	13.4	86.6	83.3	17.0	84.8	15.2	$9.67 \cdot 10^{-16}$	
G_1	9.4	90.6	74.5	25.5	82.5	17.5	$7.23 \cdot 10^{-14}$	39.9
G_2	10.7	89.3	74.5	25.5	81.9	18.1	$2.49 \cdot 10^{-13}$	
H_1	13.4	86.6	83.0	17.0	84.8	15.2	$9.67 \cdot 10^{-16}$	66.6
H_2	13.4	86.6	83.0	17.0	84.8	15.2	$9.67 \cdot 10^{-16}$	
I_1	11.4	88.6	76.6	23.4	82.6	17.4	$6.50 \cdot 10^{-14}$	39.1
I_2	12.1	87.9	76.6	23.4	82.3	17.7	$1.21 \cdot 10^{-13}$	
J_1	11.4	88.6	76.6	23.4	82.6	17.4	$6.50 \cdot 10^{-14}$	39.1
J_2	12.1	87.9	76.6	23.4	82.3	17.7	$1.21 \cdot 10^{-13}$	

the correlations existing between them, are identical. Since this presupposition is usually not valid, in the second variant (A_2 and B_2) discriminant analyses were performed with arbitrary standard deviations and correlation coefficients.

It was found (pp. 164–73) that the weight of the variables in calculations A and B was not uniformly apparent, in programs C and D an attempt was made to improve it by using quadratic discriminant analysis. Since there is not much difference between logarithmic or non-logarithmic values and the calculations with the power of logarithm seemed unrealistic, in programs C the figures were applied showing the changes in the parameters without logarithmic transformation. Eventually, from these data a quadratic discriminant function was formed. In programs D the square roots of the variables were used to form a mixed quadratic discriminant function. Thus, a comparison of programs C and D provides a means for studying the effect of the transformation of the variables. In Table 13 it can be seen that there is no difference between the results of programs C and D. Hence, the structure of the function is of a greater importance than the magnitude of the exponent in the single terms. Our previous results, and the aim that the separating function should be as simple as possible, inspired the idea of leaving out the terms yielding only scanty information of the, original quadratic discriminant functions. So program E was produced, the essence of this being a selection, i.e. from programs C_1 and C_2 only the most informative terms (see Tables 14*a–p*) were kept. In C_1 the x and x^2, in C_2 the x and xy are the most important terms.

(In programs C, D and E, as in programs A and B the first variant presupposes identical, the second any standard deviations and correlations. The same is valid for programs F, G, H, I, and J, too.)

Therefore, a function with three variables was created, in which x, x^2 and xy yielded by the previous functions take part themselves multiplied by z. In this attempt xyz and x^2z are new terms. The xyz corresponds well to the results of program A_1 and the x^2z to the final conclusions of the discriminant analysis described on pp. 164–73. In Table 13 it can be seen that discriminant analyses C_1, D_1, E_1 give equally optimal results from the point of view of forecast and hit, and in respect of the significant deviation from overlap. These are identical not only mathematically but in view of individual judgment (diagnosis) as well.

Note that 'hit probability' is not identical with the agreement percentage (Fig. 80), but is the common average of concordanes (Table 13) attaching higher weights to discordances in smaller groups.

TABLE 14

Discriminant analysis

TABLE 14*a*

Means of groups

Group No.	*A*	*B*
1	2.534	1.794
2	3.018	2.018
3	6.868	3.862
4	3.487	2.281
5	4.165	2.583
6	9.478	4.929

TABLE 14*b*

MS and F values of variance analyses for single properties

FACTOR	TOTAL	BETWEEN POPULATIONS	WITHIN POPULATIONS	*F*
DF	195	1	194	
1. MS		19.5711	0.4834	48.49
2. MS		35.7892	0.7331	48.82
3. MS		335.6817	17.2388	19.47
4. MS		51.9026	1.2845	40.41
5. MS		89.4962	2.0267	44.16
6. MS		739.5891	36.1738	20.45

TABLE 14*c*

Frequency distribution of property 1

	A	*B*
0.96 – 1.12	0	2
1.13 – 1.30	0	5
1.31 – 1.47	4	8
1.48 – 1.64	2	6
1.65 – 1.82	9	12
1.82 – 1.99	6	3
2.88 – 2.16	21	3
2.17 – 2.34	30	4
2.35 – 2.51	15	0

(TABLE 14*c* cont.)

	A	*B*
2.52 – 2.69	9	0
2.70 – 2.86	16	2
2.87 – 3.03	15	0
3.84 – 3.21	3	0
3.22 – 3.38	3	0
3.39 – 3.55	5	0
3.56 – 3.73	1	0
3.74 – 3.90	1	0
3.91 – 4.08	4	0
4.09 – 4.25	2	0
4.26 – 4.42	1	0
4.43 – 4.60	1	0
4.61 – 4.77	0	0
4.78 – 4.95	0	1
4.96 – 5.12	0	1
5.13 – 5.29	0	0
5.30 – 5.47	0	0
5.48 – 5.64	1	0

TABLE 14*d*

Frequency distribution of property 2

	A	*B*
0.82 – 1.82	0	1
1.03 – 1.23	0	3
1.24 – 1.45	1	7
1.46 – 1.66	3	5
1.67 – 1.88	3	9
1.89 – 2.09	6	9
2.10 – 2.30	10	3
2.31 – 2.52	19	2
2.53 – 2.73	19	2
2.74 – 2.95	19	3
2.96 – 3.18	15	0
3.17 – 3.37	18	0
3.38 – 3.59	8	1
3.60 – 3.80	3	0
3.81 – 4.02	6	0
4.82 – 4.23	9	0
4.24 – 4.44	1	0
4.45 – 4.66	2	0
4.67 – 4.87	2	1
4.88 – 5.09	1	0
5.10 – 5.30	2	0

(TABLE 14*d* cont.)

	A	*B*
5.31 – 5.51	1	0
5.52 – 5.73	0	0
5.74 – 5.94	0	1
5.95 – 6,16	0	0
6.17 – 6.37	0	0
6.38 – 6.59	0	0
6.60 – 6.80	0	0
6.81 – 7.01	1	0

TABLE 14*e*

Frequency distribution of property 3

	A	*B*
0.16 – 1.18	0	2
1.19 – 2.22	4	13
2.23 – 3.26	11	13
3.27 – 4.30	15	6
4.31 – 5.34	37	2
5.35 – 6.37	20	2
6.30 – 7.41	15	1
7.42 – 8.45	15	1
7.42 – 8.45	15	1
8.46 – 9.49	10	0
9.50 – 10.52	3	1
10.53 – 11.56	5	0
11.57 – 12.65	3	0
12.61 – 13.64	1	0
13.65 – 14.68	0	0
14.69 – 15.71	1	0
15.72 – 16.75	4	0
16.76 – 17.79	1	0
17.80 – 18.83	2	0
18.84 – 19.87	0	0
19.88 – 20.90	1	0
20.91 – 21.94	0	0
21.95 – 22.98	0	0
22.99 – 24.02	0	1
24.03 – 25.06	0	1
25.07 – 26.09	0	0
26.10 – 27.13	0	0
27.14 – 28.17	0	0
28.18 – 29.21	0	0
29.22 – 30.25	0	0
30.26 – 31.28	1	0

TABLE 14*f*

Frequency distribution of property 4

	A	*B*
0.91 – 1.18	0	4
1.19 – 1.47	1	2
1.48 – 1.75	3	7
1.76 – 2.03	7	9
2.14 – 2.32	5	10
2.33 – 2.60	14	8
2.61 – 2.88	15	2
2.89 – 3.17	18	0
3.18 – 3.45	23	1
3.46 – 3.73	12	1
3.74 – 4.82	16	0
4.03 – 4.30	10	0
4.31 – 4.58	4	8
4.59 – 4.87	3	0
4.88 – 5.15	4	1
5.16 – 5.43	3	0
5.44 – 5.72	4	1
5.73 – 6.00	1	0
6.01 – 6.28	3	0
6.29 – 6.57	1	0
6.58 – 6.85	0	0
6.86 – 7.13	1	0
7.14 – 7.42	0	0
7.43 – 7.70	0	0
7.71 – 7.98	0	1
7.99 – 8.27	1	0

TABLE 14*g*

Frequency distribution of property 5

	A	*B*
0.89 – 1.24	0	5
1.25 – 1.59	1	2
1.60 – 1.95	2	8
1.96 – 2.31	6	8
2.32 – 2.66	7	12
2.67 – 3.02	11	4
3.03 – 3.37	20	1
3.38 – 3.73	10	2
3.74 – 4.09	24	2
4.10 – 4.44	18	0
4.45 – 4.80	12	0

(TABLE 14*g* cont.)

	A	*B*
4.81 — 5.15	8	1
5.16 — 5.51	5	0
5.52 — 5.87	7	0
5.88 — 6.22	6	0
6.23 — 6.58	2	0
6.59 — 6.93	0	0
6.94 — 7.29	5	1
7.30 — 7.64	3	0
7.65 — 8.00	0	0
8.81 — 8.36	1	0
8.37 — 8.71	0	0
8.72 — 9.07	0	0
9.08 — 9.42	0	1
9.43 — 9.78	0	0
9.79 — 10.14	1	0

TABLE 14*h*

Frequency distribution of property 6

	A	*B*
— 0.38 — 1.19	0	2
1.20 — 2.69	3	15
2.70 — 4.20	9	17
4.21 — 5.70	21	7
5.71 — 7.20	33	1
7.21 — 8.71	22	1
8.72 — 10.21	15	1
10.22 — 11.71	13	0
11.72 — 13.22	7	0
13.23 — 14.72	5	0
14.73 — 16.23	5	1
16.24 — 17.73	2	0
17.74 — 19.23	1	0
19.24 — 20.74	3	0
20.75 — 22.24	5	0
22.25 — 23.74	1	0
23.75 — 25.25	1	1
25.26 — 26.75	0	0
26.76 — 28.25	1	0
28.26 — 29.76	1	0
29.77 — 31.26	0	0
31.27 — 32.76	0	0
32.77 — 34.27	0	0
34.28 — 35.77	0	0
35.78 — 37.28	0	0

(TABLE 14*h* cont.)

	A	*B*
37.29—38.78	0	0
38.79—48.28	0	1
40.29—41.79	0	0
41.80—43.29	0	0
43.30—44.79	1	0

TABLE 14*i*

Discriminant coefficients (lambdas)

1.	0.000707
2.	0.044068
3.	—0.006365
4.	0.039690
5.	—0.027251
6.	—0.002079

TABLE 14*j*

Frequency distribution of *Z* values

	A	*B*
469— 501	0	1
502— 533	0	1
534— 566	0	3
567— 598	0	1
599— 631	1	2
632— 664	1	4
665— 696	2	5
697— 729	3	3
730— 761	2	2
762— 794	1	11
795— 827	6	5
828— 859	10	1
860— 892	8	8
893— 924	24	4
925— 957	20	2
958— 990	19	2
991—1022	25	0
1023—1055	21	0
1056—1087	4	0
1088—1120	2	0

TABLE 14*k*

Multiplied Z values in growing order

MULTIPLIER = 10 000

IDENTIFIER	$Z1$	$Z2$
0623		492
0407		501
0564		535
0626		553
0628		557
1175		589
0620		601
0451	622	
0383		630
0020	634	
0846		642
0621		649
0622		649
0514		657
0891	670	
1355		674
0381	677	
1333		679
1364		681
0402		691
1331		698
0508	703	
0624		716
0003	722	
1301		723
0001	725	
1303		734
0761	752	
0390	754	
0055		758
0629		762
0684		764
1249		767
0437		774
0529		774
1178		781
1199		781
1214		782
1201		783
0853		786
1262		789

(TABLE 14*k* cont.)

MULTIPLIER = 10 000

IDENTIFIER	*Z*1	*Z*2
0445	789	
1229		795
0848	797	
0928	799	
1366		802
0343		806
0962	809	
0962	809	
0375	809	
1250		811
0807		817
0991	825	
1001	826	
1275		831
8518	831	
0512	833	
0352	843	
0978	847	
0492	848	
0486	848	
0565	852	
0821	853	
0519	853	
0509	856	
0888	862	
0903	865	
0530	878	
0934	880	
0485	887	
0793	887	
0989	888	
0844	889	
0344		894
0877	895	
0857	895	
0017	895	
1191		897
0875	897	
0855	899	
0869	899	
0879	902	
0883	903	
0523	903	

(TABLE 14*k* cont.)

MULTIPLIER = 10 000

IDENTIFIER	*Z*1	*Z*2
0873	904	
0974	907	
1180		907
0969	907	
0833	910	
0977	911	
0380	911	
0606		915
0913	918	
0465	918	
0865	919	
0885	922	
0361	922	
0361	922	
0830	924	
0379	924	
0825	924	
0487	924	
0881	926	
1309		926
0662	926	
0353	927	
0439	928	
0861	929	
0409	929	
0859	931	
0942	931	
0520	934	
0897	935	
0349	936	
0392		940
0068	941	
0068	941	
0790	943	
0871	943	
0818	944	
0806	948	
0359	951	
0489	952	
0434	952	
0812	955	
0863	957	
0404	958	

(TABLE 14*k* cont.)

MULTIPLIER = 10 000

IDENTIFIER	*Z*1	*Z*2
0985	958	
0354	961	
0804	961	
0919	965	
0456	968	
0002	970	
0922	971	
0971	973	
0348	975	
0840	978	
0562	979	
0495	985	
0965	981	
1357		982
0552	984	
0815	985	
0799	987	
0828		988
0059	988	
0403	991	
0836	991	
0360	992	
0525	994	
0405	995	
0372	997	
0355	998	
0597	998	
0910	999	
0400	999	
0550	1002	
0838	1004	
0341	1005	
0356	1008	
0916	1011	
0394	1012	
0365	1014	
0979	1016	
0776	1016	
0515	1017	
0345	1018	
0550	1019	
0362	1019	
0809	1028	

(TABLE 14*k* cont.)

MULTIPLIER = 10 000

INDENTIFIER	Z1	Z2
0038	1023	
0449	1024	
0012	1024	
0030	1028	
0061	1030	
0014	1031	
0541	1033	
0503	1036	
0358	1036	
0545	1036	
0369	1036	
0758	1037	
0460	1038	
0669	1040	
0900	1040	
0497	1041	
0869	1046	
0572	1048	
0397	1050	
0507	1052	
0983	1052	
0850	1057	
0493	1061	
0466	1063	
0466	1063	
0342	1070	
0419	1096	
0500	1106	
	GROUP MEANS	
	939	743

TABLE 14*l*

Forecast and hit statistics

CHANCES OF FORECAST				DISCRIMINANT THRESHOLD	HIT AND ERROR PERCENTAGE		SIGNIFICANCE OF THE DEVIATION FROM OVERLAP
10.7	89.3	83.0	17.0	828	86.1	13.9	$6.370 \cdot 10^{-17}$

TABLE 14*m*

Variance analysis of the Z values

FACTOR	SS	DF	MS	F
TOTAL		195		
BETWEEN POPULATIONS	0.01364	6	0.0022726	21.93
WITHIN POPULATIONS	0.01954	189	0.0001034	

PERCENTUAL REDUCTION OF D^2
WHEN OMITTING SINGLE VARIABLES

1. 0.00
2. 3.58
3. 3.36
4. 3.36
5. 2.50
6. 0.86

TABLE 14*n*

Decomposition of the generalized distance D^2 into effects of single and paired variables

COMPONENT	DETERMINATION COEFFICIENTS	
	ABSOLUTE	RELATIVE
B_1^2	0.0000	0.002
B_2^2	0.2762	14.139
B_3^2	0.1355	6.935
B_4^2	0.3790	19.402
B_5^2	0.2920	14.946
B_6^2	0.0303	1.553
$2B_1\ B_2\ R_{12}$	0.0068	− 0.347
$2B_1\ B_3\ R_{13}$	−0.0049	−0.253
$2B_1\ B_4\ R_{14}$	0.0074	0.381
$2B_1\ B_5\ R_{15}$	−0.0061	−0.311
$2B_1\ B_6\ R_{16}$	−0.0023	−0.115
$2B_2\ B_3\ R_{23}$	−0.3563	−18.240
$2B_2\ B_4\ R_{24}$	0.5635	28.819
$2B_2\ B_5\ R_{25}$	−0.5109	−26.155
$2B_2\ B_6\ R_{26}$	−0.1667	−8.534
$2B_3\ B_4\ R_{34}$	−0.3902	−19.976
$2B_3\ B_5\ R_{35}$	0.3178	16.270
$2B_3\ B_6\ R_{36}$	0.1237	6.330
$2B_4\ B_5\ R_{45}$	−0.6405	−32.787
$2B_4\ B_6\ R_{46}$	−0.2037	−10.428
$2B_5\ B_6\ R_{56}$	0.1695	8.675
TOTAL (D^2)	0.0195	1.000

TABLE 14*o*

Effect of the variables on shaping the D^2 generalized distance

PROPERTY	PERCENTUAL CONTRIBUTION B^2/D^2 (DIRECT)	+	$\sum B_i B_j R_{ij}/D^2$ (INDIRECT)	=	H (TOTAL)
1.	0.240		2.437		2.677
2.	1413.865		−1188.100		225.765
3.	693.550		−793.417		−99.867
4.	1940.204		−1699.590		240.614
5.	1494.614		−1715.387		−220.773
6.	155.252		−203.668		−48.416

TABLE 14*p*

Correlation matrix of the differences of the means

1.000	0.942	0.980	0.883	0.821	0.946
0.942	1.000	0.921	0.870	0.900	0.911
0.980	0.921	1.000	0.861	0.799	0.964
0.883	0.870	0.861	1.000	0.963	0.950
0.821	0.900	0.799	0.963	1.000	0.900
0.946	0.911	0.964	0.950	0.900	1.000

The construction of the separating function was suggested on the basis of E_1 analysis (Table 14*a–p*). This is simpler than the others, has a smaller number of terms, the F value being slightly more significant. The result is considered the 'best mathematical' diagnosis and it is compared with the clinical observation. As a final result of 172 cases 87.7 per cent concordance was found between the mathematical calculation and clinical diagnosis and discordance in 24 cases, i.e. 12.3 per cent. Of the individuals considered healthy the results agreed in 89.3 per cent and disagreed in 10.7 per cent. Of patients regarded as having heart disease in 83 per cent the agreement was good, while in 17 per cent it was bad (see Tables 13 and 15, Fig. 80).

Program E_1, and, similarly programs A to J, contain numerous results which enhance sophisticated evaluation. These yield in every case the evaluation of functions of one or more of these three relative changes (e.g. x^2 or xyz). These are the functions which were sought by linear discriminant analysis as being the best of the linear combinations. These are treated by the program as 'discriminant properties'. The frequency distributions of these properties are given.

According to the properties, the variance analysis compares the variances (the squares of the standard deviations) inside and outside the groups. The quotient of these two is the F value, which is identical with the square

of the t value, existing between the two groups. The contribution of the single properties to the discrimination – more precisely the shaping of the between-group distance D^2 – is analysed in three different ways. This analysis and the calculations for chances of the forecast can be found in Chapter 9. Here, only the methods suitable for examining the discriminating power of the properties are enumerated.

a. D^2 is split into the effects of single variables and variable-pairs.

b. From these equally distributing the effect of the pairs D^2 is divided into the total effect of the variables.

c. The percentage is given with which the D^2 would diminish if the single variables (properties) were deleted.

The dividing function:

$$7xy - x^2 + 6xz - 5xyz = 13.0175.$$

This means that if

$$7xy - x^2 + 6xz - 5xyz > 13.0175$$

TABLE 15

Skeletal comparison of the three most important discriminant analyses

Discriminant analysis	Clinical diagnosis				Hit probability		Significance of hit probability and deviation from the overlapping	F to Mahalanobis' D^2
	healthy 149		cardiac patients 47					
	concordant %	discordant %	concordant %	discordant %				
Using the relative changes of max dC/dt (x) and heart rate (z) (preliminary program)	91.9	8.1	72.3	27.7	82.1	17.9	$1.51 \cdot 10^{-13}$	24.1
Using the relative changes of max dC/dt (x) and systolic pressure (y) (Program H_1)	86.6	13.3	83.3	17.0	84.8	15.2	$9.67 \cdot 10^{-16}$	66.6
Using the relative changes of dC/dt (x), systolic pressure (y) and heart rate (z) (Program E_1)	89.3	10.7	83.3	17.0	86.1	13.9	$6.37 \cdot 10^{-17}$	14.5

on the basis of 'mathematical diagnosis' the investigated person was listed as 'healthy'.

However, if

$$7xy - x^2 + 6xz - 5xyz \leq 13.0175$$

the individual is considered having heart disease.

Figures 77 and 78 were prepared with the help of this function. In these figures the changes of max dC/dt are shown on the x axis, in linear scale, the maximal value obtained after 5 μg isoprenaline being divided by the zero time value. On the y axis the changes in systolic pressure are given. Z is the relative change of the pulse rate. The Zs were increased from 0.8 to 2.0 by 0.05 and 0.1, resp. and substituted by constants. This procedure yielded reduced 2-variable equations and several curves.

Figure 77 shows them from $x = 0$ to $x = +10$ and from $y = -10$ to $y = +10$. If the value of z is less than 1.4, the corresponding hyperbolas at the beginning have a downward trend, if z is greater than 1.4, the trend is upward. In case $z = 1.4$ as a special case of the hyperbola, there are two vertical lines. The real hyperbolas (except if $z = 1.4$) have an extreme value of around 3.6, exactly the square root of 13.0175. This means the minimum if the z values are below 1.4 and the maximum if the values are above 1.4. These extreme values and the reclinings of the curves do not cause any difficulty since the range is narrower than the one which is dealt with. Consequently, the parts of the curve are given which are between $x = 0.8$ to $x = 3.2$ and $y = 0.8$ to $y = 1.5$, and which can be found in the oblong of Fig. 77 being presented in an enlarged form in Fig. 78.

This figure seems highly suitable for graphic discrimination. The change in the pulse rate of the individual (z), the change of max dC/dt (x) and the change in systolic blood pressure (y) should be measured. The x and y coordinates determine one point in Fig. 78. If this lies on the right of the corresponding z_n the individual is 'mathematically healthy', if it lies on the left, he can be regarded as a 'cardiac patient'.

The figure shows the characteristic features of the discriminant function, namely that all the curves cross 2 points, determined by coordinates $y = 1.2$ and $x = 2.05$ and $y = 1.2$ and $x = 6.35$.

The possible values appearing in the range of the measurements are presented in Fig. 78. In this figure $y = 1.2$ and $x = 2.05$ occupy a central position, whereas the other intersection lies outside the range. If values $y = 1.2$ and $x = 2.05$ and $z = 1.4$ (where the hyperbola has its border line,

it appears as a straight line, its convexity turning) are regarded as 'critical' values, the following statement can be made as to the three parameters:

1. If $x = 2.05$ the individual is healthy only if $y < 1.2$ and coincidentally $z > 1.4$ or, if $y > 1.2$ and, at the same time, $z < 1.4$.
2. If $y = 1.2$, the individual is healthy only if $x < 2.05$ and, at the same time, $z > 1.4$, or, if $x > 2.05$ and at the same time $z > 1.4$.
3. If $z = 1.4$ the individual is healthy only if $x > 2.05$.

The statements outlined in 1 and 2 mean that in cases where neither max dC/dt, nor the change of systolic pressure unquestionably indicates

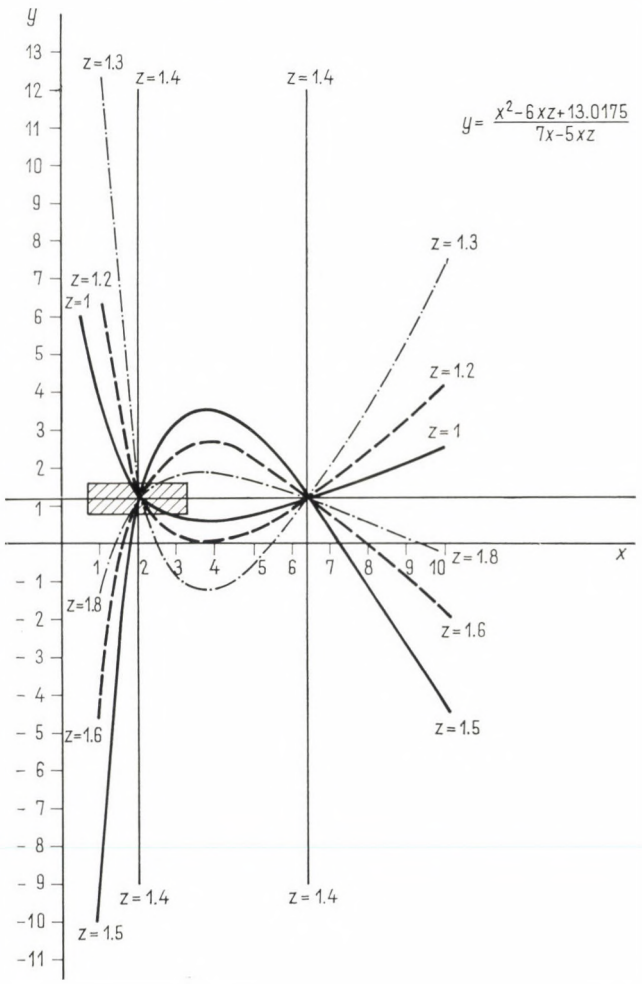

Fig. 77. A separating function with three variables (z, x, y) obtained by discriminant analysis by various fixations of z, gives graphically a pile of hyperbolas. The curves are convex from below, if $z < 1.4$, in case $z = 1.4$, $x_1 = 2.05$ and $x_2 = 6.35$, there is no hyperbola, only two vertical lines. If $z > 1.4$ the hyperbola is convex from above. Each curve goes through points $y = 1.2$ and $x_1 = 2.05$ and $y = 1.2$ and $x_2 = 6.35$. The part of the curve enclosed by coordinates $x = 0.8$ to $x = 3.2$ and $y = 0.8$ to $y = 1.6$ can be seen enlarged in Fig. 78. The values obtained by measurements usually fall into this sphere. For explanation of x and z see Fig. 76; $y =$ the ratio of the change of blood pressure calculated in a similar way

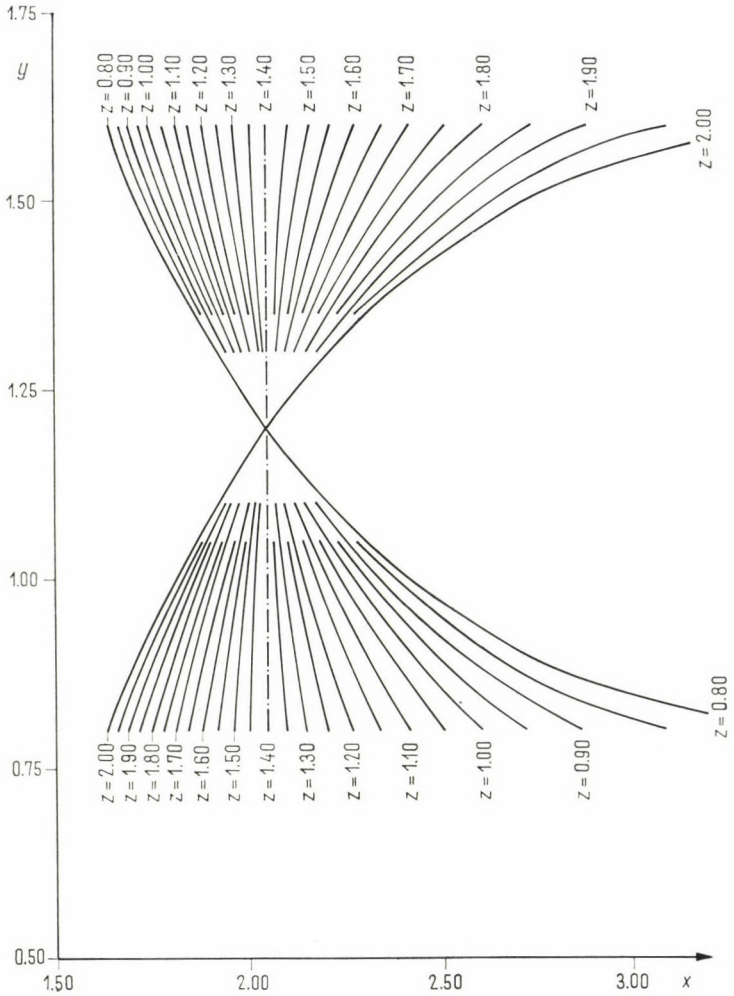

Fig. 78. Nomogram constructed for 'graphic diagnosis' (see also Fig. 77). If points determined in the co-ordinate system by recorded x and y values are located on the right of the hyperbola belonging to the recorded z value, according to the 'graphic diagnosis' the individual is healthy. If it is on the left, the individual is 'mathematically cardiac patient'

$$x = \frac{\text{the greatest max } dC/dt \text{ after 5 } \mu g \text{ isoprenaline}}{\text{zero time max } dC/dt};$$

y = systolic pressure ratio for the above times; z = pulse frequency ratio calculated similarly

either healthy or pathological heart function, the healthy heart can be recognized by the fact that one of the two additional parameters shows a greater change, and the other one shows a smaller change than that of the critical value. This elucidates our statement made on p. 151 about the 'relatively independent' regulation of the parameters. There it has been demonstrated that in case of heart disease the distinctive feature is the weak regulation of the parameters, as has been confirmed by this part of the study, too, and being valid in such cases where one of the parameters has a 'critical' value. Cases in which with the 'critical' reaction of one parameter the other two parameters react strongly and above the critical values are also regarded as pathological. Beside the conspicuous 'critical' values there are cases in which more parameters have a 'strong' reaction, the x and y points measured lie on the left side of the z curve, i.e. in the 'pathological' range ! Such observations were made mostly in young non-sclerotic cardiac patients (valvular defects) attributed to a mechanism of overcompensation.

The statement made in point 3 on p. 145 confirms the prominent role of the derivative. The regulation of the contractility independently of the systolic pressure is in itself a characteristic feature of the healthy heart.

In connection with nomograms with more curves in Fig. 78 it should be added that when the points of the individuals under investigation are considered, it is possible to make a numerical or graphical interpolation between two neighbouring curves.

Within the framework of the calculations of programs F–J, the supposition has been investigated whether one could discriminate by using only the max dC/dt and systolic pressure, i.e. by disregarding the pulse rate. Programs F are directed to find the best linear combination for the separation of the changes of max dC/dt and systolic blood pressure. As it can be seen in Table 13, in the patients clinically found 'cardiac patients', the forecast is as good as with the previous methods. However, among the persons found clinically 'healthy', there are more 'erroneously sick'. Programs G evaluate the discriminant combination of the logarithms of the changes of max dC/dt and systolic blood pressure. According to Table 13, the mathematical judgement clinically healthy people is as good as in the case of the E programs, nevertheless, the logarithmic evaluation of the clinically diagnosed cardiac patients does not yield good result. After having obtained some information on the usefulness of the most simple discriminant function of the two parameters, within programs H, it has been studied whether it is an improvement if corresponding to programs C rough ratios are used for the two parameters. H_1 and H_2 as well as E_2 and F_2 have given identical results. Hence and from the fact that program H_1 yielded the highest F values (see also Table 13),

this program is considered the most satisfactory in view of discrimination among the combinations using two parameters, i.e. disregarding the pulse rate (Fig. 79).

Programs *I* investigate whether the changes of the max-derivative (x) and those of the systolic pressure could be used in themselves instead of combinations as criteria for the separation of healthy and cardiac groups. The precondition of 'healthiness' should have been the high values of x and xy. This experiment was, however, not profitable. It did not help when within programs *J* the changes of the pulse rate were involved in the form of z, xz and xyz (Table 13). This supports the previous suggestion that the combination of three parameters is the best approach.

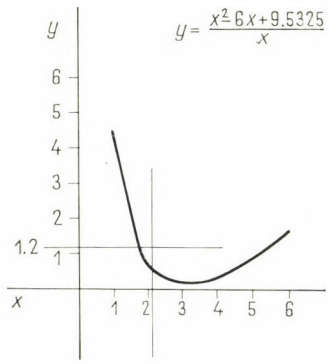

Fig. 79. Separating function yielded by discriminant analyses for pairs of individual x and y values. If a point defined by someone's x and y recordings falls to the right-hand side of the curve, the mathematical diagnosis is 'healthy', for the left-hand side, it is 'ill'

$$x = \frac{\text{highest value of max } dC/dt \text{ after 5 } \mu\text{g isoprenaline;}}{\text{rest value of max } dC/dt};$$

y = similarly calculated change ratio of systolic pressure

In Table 15 the best separation was compared, by using x and z (see p. 174), with the presently found best method using values x and y, and then with the best forms using three parameters (x, y and z). The combination of x and z has given very good concordance if healthy individuals were investigated, however, there is no good conformity in the case of 'cardiac patients'. The x, y combination improves the judgement on 'cardiac patients', but is less efficient in recognizing healthy people. The x, y, z triple combination comes the nearest to the clinical diagnosis. Although it is less efficient in recognizing the 'healthy', but among the 'erroneously sick' patients there are cases in which the mathematical approach could be more realistic (see pp. 197–202).

The two-parameter discriminants have higher F values, still the three-parameter (x, y and z) discriminations are considered an optimal method of calculation. This is so because of better hit probability and of the greater mathematical significance.

From the methods discussed above the triple combination of the scalar

change (quotient of change) of the max dC/dt, systolic blood pressure and pulse rate is regarded as the best.

The corresponding function is

$$7xy - x^2 + 6xz - 5xyz = 13.0175.$$

This is the function recommended for use. For 'graphical diagnosis' the nomogram constructed by using this function is recommended.

*

The discriminant analysis using the double combination of max dC/dt (x) and the pulse rate (z) was discussed on p. 174. Now a triple combination was applied, i.e. the change in systolic blood pressure (y) also being included, and the three elements were used for discrimination. In some serial investigations it was also studied whether by omitting z (pulse rate), the use of only two parameters, max dC/dt (x) and blood pressure (y), would suffice for separation between healthy and non-healthy groups.

For using a triple combination the following function was found the best:

$$7xy - x^2 + 6xz - 5xyz = 13.0175.$$

By applying this equation there was 87.7 per cent concordance between the clinical diagnosis and the mathematical forecast, and 12.3 per cent discordance (see also pp. 197–202).

The mathematical analysis revealed that simultaneous excessive modification of the parameters in both directions (vigorous or sluggish) may indicate some disease.

The constructed nomogram seems to be suitable for 'graphic diagnosis', i.e. for reading the results after locating the place of the values on the coordinate.

COMPARISON OF THE RESULTS OF THE MATHEMATICAL ANALYSIS WITH THE CLINICAL PICTURE

In the preceding sections the comparison has been made by matching the serial numbers of the individuals, previously grouped and the preliminary judgement with the results obtained by various mathematical discriminant analyses. In this Section those cases are examined where deviation was seen between the two approaches. The patients were identified according to their serial numbers and our conjecture was evaluated on the basis of their case history, i.e. they were compared with the forecasts of the mathematical diagnosis and it was considered whether in some cases the

latter was more reliable. At a later stage sampling material of the whole was carried out with various techniques in order to make the study representative. The comparison mentioned above was extended to these cases as well.

According to the discriminant analysis (see p. 174) on the effect of 5 μg isoprenaline from 149 individuals previously (clinically) considered 'healthy', the mathematical analysis found 12 (8 per cent) as 'erroneously sick'. This result was obtained from that part of the study where the grouping of patients according to the blood pressure at rest and the changes of systolic and mean blood pressure after administration of 5 μg isoprenaline were disregarded. However, when considering those analyses where the latter were also taken account of, it was found that from the 12 'erroneously' ordered cases at least 8 cases were similarly judged by at least three discriminant analyses. On the basis of this comparison, only the discriminant analysis mentioned on p. 174 was used. Of 47 individuals, clinically diagnosed cardiac patients, the combined mathematical discriminant analysis judged 13 individuals to be healthy (in the discriminant analysis the groupings according to blood pressure at rest, changes in systolic and mean blood pressure were not used). Taking into account also the latter parameters, there were at least 9 out of 13 cases in which the same individuals turned out to be 'erroneously healthy' on the basis of at least three types of discriminant analyses.

The next step has been described on pp. 175–97. The discriminant analyses based on the changes of max dC/dt, systolic blood pressure and heart rate yielded the following results. By considering one of these elements according to the mathematical analysis, of 196 cases there was a concordance in 172 (87.7 per cent) and discordance in 24 (12.3 per cent). Clinically, the concordance in the healthy cases was 89.3 per cent and the discordance 10.7 per cent. The patients clinically diagnosed to have heart disease showed 83 per cent concordance and 17 per cent discordance (Fig. 80).

The individual cases in which the mathematical diagnosis deviated from the clinical prediction, i.e. which were clinically diagnosed as 'non-cardiac patients' and mathematically judged as 'erroneously sick', are listed below.

1. R. L.	male, 46 years	hypertension
3. F. L.	male, 56 years	state after pneumonia
20. M. L.	male, 67 years	state after cholecystectomy
375. S. J.	male, 37 years	hypertension, adiposity
390. N. I.	female, 44 years	diabetes (88 kg-m, 170 cm)
		State after pneumonia
		ECG: flat t were

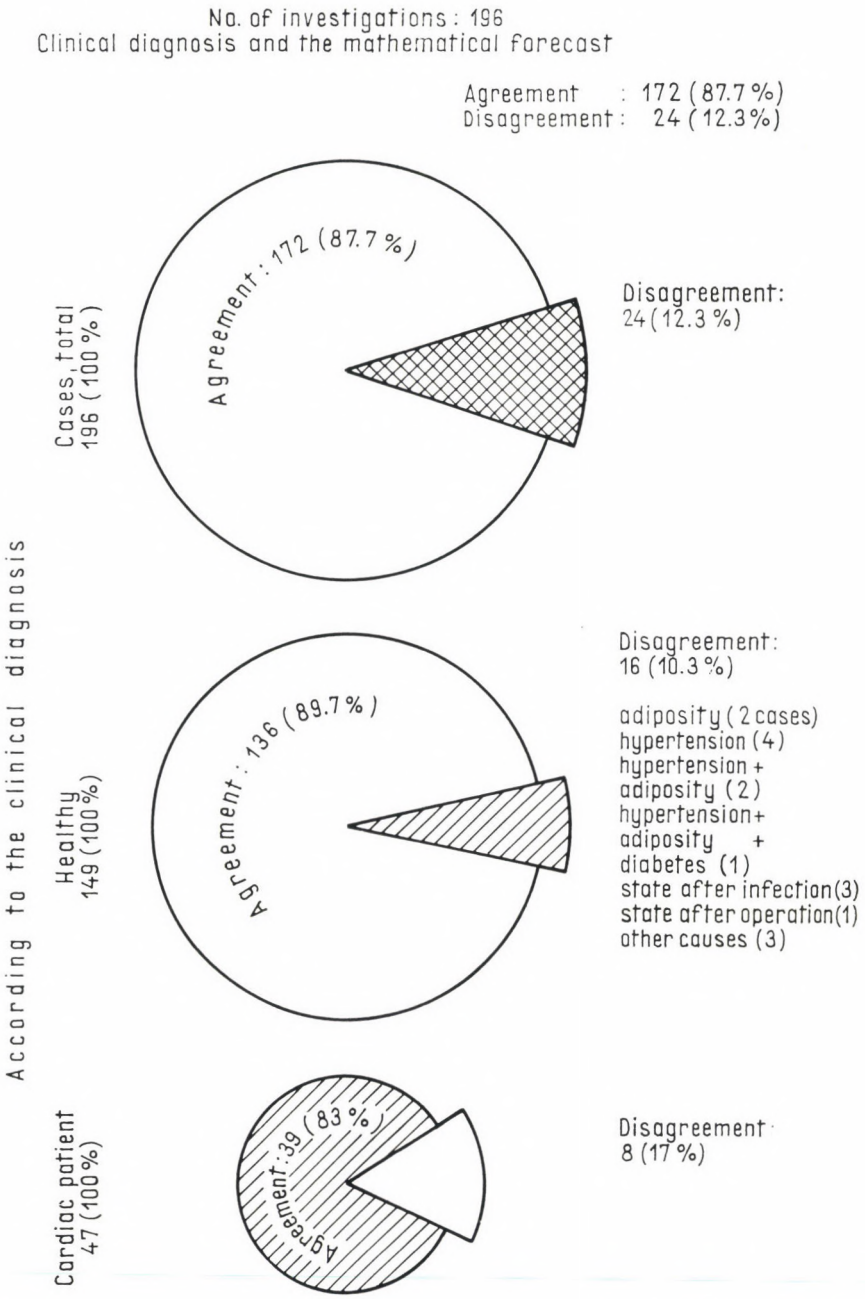

Fig. 80. The results of the authors' discriminant analyses (see Figs 77 and 78). It is assumed that among individuals diagnosed clinically 'healthy', the mathematical analysis revealed some latent cardiac cases

445. N. J.	female, 72 years	adiposity (89 kg-m, 165 cm)
451. S. J.	male, 22 years	chronic gastritis
508. M. I.	female, 50 years	adiposity (75 kg-m, 148 cm)
761. B. P.	male, 50 years	hypertension, adiposity (97 kg-m, 170 cm)
848. K. I.	male, 60 years	hypertension
891. K. A.	male, 56 years	hypertension
928. H. J.	female, 48 years	hypertension, adiposity (90 kg-m, 165 cm)
962. S. S.	male, 57 years	diabetes mellitus
991. B. H.	male, 53 years	hypertension
1001. P. F.	male, 50 years	duodenal ulcer

It seems probable that in cases with obesity the patients show similar reactions to those with congestive cardiac failure, and they may have the symptoms of latent cardiac failure, respectively. This is particularly so in cases with obesity + hypertension. It can be surmised that in our hypertensive patients with systolic pressures often above 200 mm Hg and diastolic pressures above 100–120 mm Hg, there was an additional latent cardiac disease. This may be valid in elderly patients, and there is some uncertainty in the case of younger ones as well. Infectious diseases and the recovery state after operations may imitate cardiac failure, moreover, this may not be an imitation but an effective failure as well. By evaluating our findings it can be stated that mathematical analyses in some cases are better indicators of cardiac disease than the clinical diagnosis.

In consequence of the mathematical analysis, the following patients were transferred from the group of 'clinically sick' to that of 'erroneously healthy'.

344. H. J.	male, 70 years	sclerotic cardiopathy, congestive failure, II
392. G. M.	male, 49 years	sclerotic cardiomyopathy, congestive failure, I
606. G. T.	male, 67 years	polycythaemia, sclerotic heart disease, congestive failure, II
828. K. J.	male, 60 years	sclerotic and pulmonal heart disease, congestive failure, I

1180. T. J.	female, 65 years	adiposity, sclerotic heart disease, congestive failure, I
1191. B. J.	male, 55 years	sclerotic heart disease, congestive failure, I
1309. G. J.	female, 45 years	sclerotic heart disease, congestive failure, I
1357. O. O.	female, 64 years	state after myocardial infarction (4 years ago), congestive failure, I

None of the patients had severe congestive failure, they were borderline cases. It can be assumed that the regulation of the cardiac function of these patients is similar to that of healthy individuals.

In examining the causes of the latent circulatory insufficiency it appears that obesity is often a precipitating factor. Therefore, we have selected the numbers of individuals having a body weight higher than 79 kg.

Group I	379.	86 kg	
	493.	100 kg	
	821.	80 kg	
	830.	80 kg	
Group II	367.	89 kg	(diabetes)
	375. +	86 kg	(diabetes)
	445. +	89 kg	
Group III	903.	93 kg	
	928. +	90 kg	
	508. +	75 kg	(145 cm)
Group IV	761. +	97 kg	

These results show that among 11 individuals with increased body weight haemodynamic reactions from which the existence of latent cardiac failure can be inferred were found in 5. These cases are marked with +.

In order to control the method, cases were picked out and results of the clinical and mathematical analyses were repeatedly compared. A good agreement was found between these two approaches.

*

Cases were re-examined which were listed 'erroneously' according to mathematical methods. Among the 'erroneously sick' individuals, 5 had an overweight, in 2, in addition, hypertension also occurred, and in 1 case, obesity, diabetes and hypertension were jointly present. Four individuals with normal weight had hypertension, in 3 cases there was a postinfective and in another a postoperative state. It can be assumed that in some of these cases the mathematical analysis better characterized the condition of the circulation and indicated a heart failure which clinically was not yet significant.

The 'erroneously healthy' individuals were usually less severely affected clinically.

The 80 to 90 per cent concordance between the mathematical and the clinical approaches confirms the usability of the mathematical method all the more, because the 'mathematical diagnosis' may call attention to cardiac failures being not apparent clinically.

A DISCUSSION OF COMPUTER RESULTS CONCERNING VARIOUS CARDIAC STATES

Computers are now being used very much in medicine, having manifold applications (Schmitt 1962, Geselowitz 1962, Leedley 1965, Bohus 1968, Kalmár 1969, Wallace and Rosati 1973, Monos 1973, Horváth 1974, Swatzell et al. 1973, McPherson et al. 1972). Some examples may be enumerated, however, with no intention of providing a complete picture. The computer is highly useful in cases where conclusions need to be drawn from a great number of data. It is suitable for preparing statistics on patient-turnover, health insurance and morbidity. By using a suitable code-system, it is possible to store data on patients, e.g. case history, findings and course of the disease. This information is provided in an easily accessible form. It can be used with good results in health administration. It facilitates the statistical analysis of numerical data. The results obtained in automated laboratories can be computerized (Rappaport et al. 1967).

Part of the tasks to which the computer is being or can be applied, could be resolved by simpler means. Nevertheless, its use is justified by the speed with which it works and by its saving manpower. Computers can be programmed to 'learn' medical textbooks. Data fed into the computers enable them to make diagnosis. In addition, they often tell us about the missing data which may be needed for making further assessment. They may help to resolve complicated problems (Levendel and Fenyő 1961). Rushmer (1962) writes about their use in physiology. Computerization enhances the

listing of medical literature which has grown tremendously (Németh-Csóka 1968). It is a help in rehabilitation, namely by helping the blind in reading (Sterling 1967). It is being used in cardiology, too. Digital and analog circulatory models can be prepared. Models can be constructed on various pathological states and on theoretical or planned medical intervention in these states (Clynes 1962, Boom and Noordergraaf 1963, Noordergraaf et al. 1963, Westerhof et al. 1969, Szűcs and Monos 1970, Szűcs et al. 1970, 1972, 1973, 1975, Noordergraaf 1972, 1973, Starr et al. 1973, Koch 1964, Pater and Berg 1964, Eckermann et al. 1969, Ficsor et al. 1975, Newgard 1963, Simmons et al. 1967, Naszlady and Kiss 1969, 1974 and Kiss and Naszlady 1969). It can be utilized for the rapid determination of cardiac output (Cooper et al. 1963, Benchimol et al. 1966, Maronde et al. 1968, Bánsági et al. 1971).

There is a great deal of literature on computerized interpretation of the ECG (Rikli et al. 1961, Tolles et al. 1961, Caceres 1962, Caceres et al. 1962, Pipberger 1962, Steinberg et al. 1962, Levine 1965, Smith and Wherry 1966, Attinger 1967, Walker 1967, Gillmann 1968, Ghyczy et al. 1971, Battistig et al. 1971, Bak et al. 1971, Antalóczy 1972, Kenedi et al. 1972, Pipberger and Cornfield 1973, Antalóczy et al. 1974*a*, *b*, Bailey et al. 1974*a–c*, Monro et al. 1974).

Steinberg et al. (1961) studied simultaneously the data on ECG, PCG, BCG and apex cardiogram. They obtained data relating to the heights of certain points and marked their position on the time axis. In this way the findings of healthy individuals and patients with aortic valve disease differed from those with hypertension.

Simmons et al. (1967) conceived a method for the interpretation of peripheral vascular tracings by computer. Freis et al. (1966) carried out this on the carotid tracing, and compared the means of the data obtained by this method in various groups. The waves of the curve alter with age: in elderly individuals, the maximum moves nearer to the second systolic wave and the height of the incisura increases. The curves of hypertensives are similar to those found in old age. There is a similar effect after drugs which raise blood pressure, whereas the administration of amylnitrite, trimetaphan and isoprenaline has an opposite effect. These observations agree with ours.

Cardiac catheterization data (Harrison et al. 1971, Blackburn et al. 1974), the structure of the heart sounds (Adolph et al. 1970, Frome and Frederickson 1974, Kozmann et al. 1974, Tuinstra 1974), systolic time intervals (Swatzell et al. 1973, Zoneraich et al. 1974) can be analysed by computer.

We could not find publications concerning computer analysis of changes in circulatory dynamics due to isoprenaline (and other drugs and loadings,

respectively), and measured by 'noninvasive' complex means. This part of our work can be regarded as the presentation of new data (Simonyi et al. 1972*b*, *e*, 1973, 1974*a*, *b*, Simonyi and Fischer 1972, Fischer and Simonyi 1972, Fischer et al. 1972*a*).

The aim of our study was to characterize the human circulation under physiological as well as pathological conditions. In order to achieve this (*i*) the circulation of the individual was checked at various points to simultaneously study the role of central and peripheral factors; (*ii*) many points of the (central) carotid curve, particularly those of biological significance, were processed; (*iii*) the state of rest and the changes after loading with various doses of isoprenaline were interpreted; (*iv*) groups with a sufficient number of patients were studied. The groups contained healthy individuals, patients with circulatory disorders, with damage of the myocardium and with combination of the latter two. The results obtained on the circulation in these groups were compared.

To achieve our aim it was necessary to apply a method (*i*) which was not troublesome to the patient; (*ii*) which was suitable for obtaining enough data for statistical analysis; (*iii*) which provided quantitative and fairly accurate data; (*iv*) which did not require complicated equipment; (*v*) which allowed the measurement of parameters having physiological and pathophysiological significance.

In our opinion, the noninvasive but complex method described here has fulfilled these conditions. This raises the hope that after appropriate assembly, the obtained responses could be used for answering clinical questions.

The main object of this study was to characterize the heart's condition on the basis of mathematical processing of suitable parameters. Apart from the question of 'healthy' or 'insufficient' cardiac function, the peripheral circulation was also an objective of this study.

To achieve this aim we had to (*i*) unify the techniques applied; (*ii*) form groups with suitable numbers comparable as to cardiac involvement. (*iii*) Furthermore the parameters had to be given in figures, in other words we digitized them for making them apt to put on punched tape for computer processing. (*iv*) A computer program had to be worked out to exclude errors made by transcription and/or punching. (*v*) From the parameters fed directly into the computer combined indicators had to be created by simple means, being usable to carry out more computations. (*vi*) It was necessary to make a schedule of the logics of the mathematical processing, and its 'software', i.e. the order hierarchy and the character of the program of statistical appraisal had to be decided. (*vii*) It was necessary to compare the stages of mathematical processing with physiological and pathophysio-

logical facts. (*viii*) On the basis of the appraisal a schedule was made for the forthcoming clinical and mathematical calculations. (*ix*) The information obtained had to be summarized with regard to the practical use. (*x*) Considering the experience gained, the trend of our further investigation was decided.

The sequence of thoughts of processing is shown in Fig. 81.

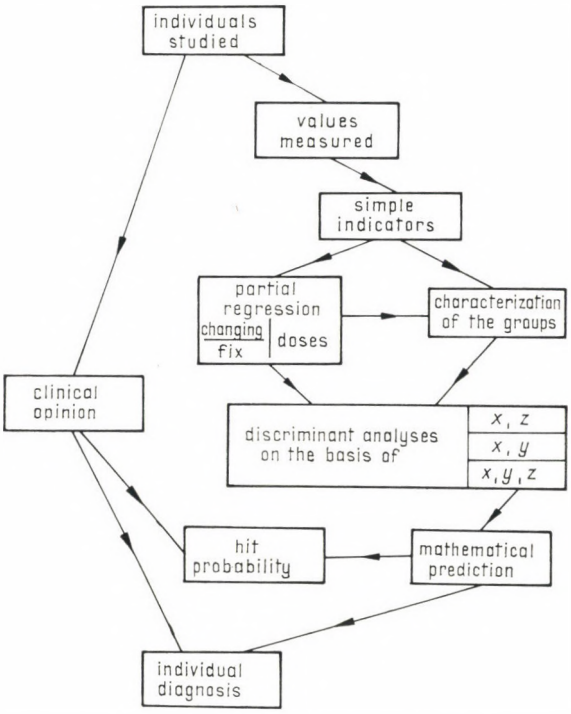

Fig. 81. Block diagram of the mathematical-biometrical analysis

There are various methods available for digital conversion. (*i*) To denote the figures representing the values of the heights of the curve at various and suitable intervals. (*ii*) To mark out single (selected) points. In both cases the coordinates of the points give numerical values. Theoretically, it is possible to use automatic or semi-automatic method. In the latter case an equipment should be employed which senses the selected points putting these points on a punch tape with manual direction. In the former case an equipment is needed which is able to use analog/digital converter and records the data. This solves the problem of recording points with a suitable

frequency. However, the selection of characteristic points can only be done by computer programming. Similarly, programming is necessary to sort out the artefacts appearing on the curve; for this the manual method has been used. The main disadvantage of this method lies in the fact that it is rather laborious. Nevertheless, it was possible to pinpoint by it the biologically characteristic points, and screen the artefacts.

With the computer analysis the ranges of the single indicators were considered and in some cases it was feasible to give the regularity of the magnitude. This control program sorted out presumably the rough errors and made it possible to carry out corrections.

An account of the parameters produced by simple means has already been given earlier. Our observations on the arterial mean pressure can be used without embedding them in the whole of this work.

Having finished this preparatory work, partial logarithmic regression calculations were chosen as a first step of the further mathematical processing. At the first stage the influence of varying the dose of isoprenaline was considered. Later those groups were examined in which the dose of isoprenaline was constant, i.e. 5 μg. (For these studies see p. 105, where reasons were given to explain why it was advantageous to use logarithmic calculations.)

The partial logarithmic regression function is based on the changes of the logarithm of max dC/dt as a dependent variable, since this parameter was regarded as a first-rate characteristic consequent to changes caused by loadings. The equation of the regression function is a simple equation of which the independent variables are (*i*) the logarithms of the changing rates of the other parameters, and (*ii*) in case of changing doses the logarithm of the dose. The partial regression gives the simple expression of the independent variables, by which the logarithmic changes of the max dC/dt can be approximated so that from this approximation the logarithmic values computed from the real derivatives have the least standard deviation. Accordingly, the regression coefficients of the independent single variables can be regarded as the weights of these parameters in the formation of the changes of max dC/dt. Our results confirm that this method being widely used in studies of biological actions (Draper and Smith 1967) is usable. In our opinion, the interpretation of (*i*) the regression coefficients yielded by our program named partial logarithmic regression and (*ii*) the other computed indicators provided a basis for working out further programs. Our investigations, in which one variable was the dose of isoprenaline used, proved that there is a strong correlation between the magnitude of the dose and the effect. This was indicated most sensitively by the change in

the max dC/dt. This means that it is the most sensitive indicator for studying dose–effect relations in clinicopharmacology in case of isoprenaline-like drugs producing positive inotropic effects. There is a strong negative correlation between the changes of ejection time and heart rate, which justifies that in subsequent studies only one of them was applied.

The partial logarithmic regression analyses using fixed doses have given a better insight into the regulation of circulation of the single disease groups.

It is characteristic of healthy individuals that the parameters related to the cardiac contractility, peripheral regulation and heart rate (except the negative correlation between heart rate and ejection time) vary independently and markedly. The correlations found in patients' groups corresponded well to the known pathomechanism of the disease found by clinical observations, moreover, they supplement these observations. In hyperkinetics the calculations confirmed the view that the decrease in peripheral resistance has an important role in the regulation of cardiac contractility. In less severe hypertensive patients, such findings occurred which suggest that the increased systolic output and the change of the peripheral regulation both contribute to the development of the disease. In more severe hypertension, the mathematical analysis reveals the character of the 'resistance' hypertension.

In the heart disease group the mathematical analysis discloses not only a slower reaction of the parameters but, in addition, it shows that their independence becomes restricted so that links are formed between them, and the number of links increases if heart disease (cardiac muscle dysfunction) and hypertension co-exist. In this latter case the regulation of changes in most of the parameters is more strongly dependent on the control of the heart rate.

In our opinion, the findings yielded by the partial regression analyses may have provided much new and interesting information.

These studies provided the necessary basis for further steps and for the use of discriminant analyses.

The discriminant analysis is a suitable method enabling us to separate the groups by using appropriate combinations of properties. This method was applied because it provides equation-like results, and in our case it is apt to distinguish between healthy subjects and individuals with heart disease. For practical purposes this method was considered more suitable, contrary to the procedure followed by other investigators, according to which the algorithms 'learn' the data of the new individual, but to express results with the latter a computer is needed. The linear discriminant analysis

yields linear combination of the values which are the most appropriate to separate the groups. This means that if the simple expression provided by the analysis was marked by *Z*-alpha, above a carefully selected *Z*-alpha threshold those values can be found which denote subjects free of heart disease, and below are those which denote patients with cardiac disease. The discriminant analysis which, in principle, was constructed for variables with normal distribution having a simple (linear) relation, became a method frequently used for biomedical statistical evaluation, because in quite a number of cases it was useful in separating the groups (Rahlfs 1971, Dickson and Brown 1970).

The method yields a discriminant equation with high reliability if a large number of measurements suitably performed are available. Using these principles and the graphs constructed accordingly a differential diagnostic method was obtained working with a small probability of error. This enabled the interpretation of the newer cases without using the computer.

Several discriminant analyses were applied (see Chapter 8, pp. 164–75). Eventually, it was concluded that the combined analysis without grouping the cases would be used. In this analysis the two patient groups to be separated are different in the sense that one is considered clinically healthy and the other sick. By this method in 92 per cent of the investigated healthy individuals the result obtained mathematically was the same as it had been predicted clinically. In those with clinically diagnosed heart disease, the agreement between clinical assessment and mathematical prediction was 72 per cent.

In the procedure described on pp. 175–97, in an ideal case the concordance was 87.7 per cent and the discordance 12.3 per cent. For differentiation, in the latter, three parameters were used, i.e. the changes in the max dC/dt, systolic blood pressure and heart rate. With this method, in the clinically healthy group, there was an 89.3 per cent concordance and 10.7 per cent discordance. In the clinically sick group these figures were 83 per cent and 17 per cent. Based on this experience graphs were constructed, in an attempt to derive separate curves for healthy individuals and for those with cardiac disease. One of these graphs used changes in the max dC/dt and the systolic blood pressure (Fig. 79), and the other included the changes in heart rate (Figs 77 and 78). Thus it was possible to put the changes in the parameters due to 5 μg isoprenaline directly on the abscissa and the ordinate and without using a computer to determine whether the points defined by the coordinates represented a 'healthy' or a 'sick' person.

Having re-examined the cases clinically it was thought that the error was not always due to the defect in mathematical analysis, particularly this

was so with the 'mistaken cardiac patients'. In fact, the analysis called our attention to cases with heart failure clinically not obvious.

There are no absolute methods in biology or medical sciences. Every method has its shortcomings, biological and mathematical techniques alike. An error around 15% can be considered acceptable or even very good indeed.

At the end of our investigations it can be hoped that with the applied 'noninvasive' method and with a new mathematical approach it has succeeded to obtain a better insight into the regulation of the circulation in healthy individuals, in essential hyperkinetic heart syndrome, in hypertension as well as in cardiac failure. At the same time it was possible to differentiate between 'healthy' and 'non-healthy' individuals by using suitable parameters and mathematical analysis.

CHAPTER 9

METHODS AND EQUATIONS OF THE MATHEMATICAL CALCULATIONS

All the mathematical-statistical methods applied in this study occur in both the partial regression analysis and discriminant analysis. Therefore, the interpretation of the methods and equations is explained within the scope of these two procedures. Mechanical processing is dealt with only in brief. The mathematics of the discriminant analyses (see also Fischer et al. 1974), the processes and equations connected with it, and the logic of the succession of the analyses are discussed on p. 218.

The partial logarithmic regression analysis, the interpretation of the calculation and results can be found in Chapter 6. In Chapter 9 only the principles will be outlined.

Mean (arithmetical mean, $\bar{x}$). The value is calculated in the usual way, by dividing the sum of the data concerned (Σx) by the number of individuals. The calculation of the means often occurs in our study, thus in the basic tabulation, and in the mechanical tabulation used in the discriminant analysis. In the partial logarithmic regression calculation the changes due to the effect of drug, expressed in quotient, are represented as means of their natural logarithms. For example, if within one patient group the value is denoted by x, which is obtained in an individual by dividing the derived peak value of the carotid derivative pressure after isoprenaline load by the peak of the zero time derivative, and the natural logarithm of this quotient is taken, x is the value being called the mean of the logarithmic max dC/dt change of the group. The calculation with logarithms (logarithmic transformation) is justified because it creates a symmetrical distribution of the parameters within the group, moreover, because the correlation between the parameters moves thus closer to the more lucid and mathematically comprehensible linear correlation describable by a straight line. Therefore, if these logarithmic means are retransformed to the original scale, i.e. the figures are searched for in the logarithmic table, the set of individual changes is characterized not by arithmetical but by geometrical means. By this the trend of the change present in the single group has been characterized more realistically. By computing the means a figure has to be obtained repre-

senting the centre of the group with all the values within the group being located around this figure. These single figures display clearly and with a minimum of bias the differences between the groups to be compared.

Standard deviation (s). The use of this value is similar to that of the mean. The standard deviation (scatter) denotes the mean deviation of the individual values from their own means, and thus it can be applied for characterizing the individual variability within the group. This variability could be measured in other ways, for instance, with the difference between the highest and the lowest value, furthermore biological, technical, systematical and fortuitous components can bias it. The standard deviation, however, forms a natural counterpart with the mean in a sense that it gives the most common information on the numerical fluctuations of complex effects the 'mean' behaviour of which is expressed by the average.

The standard deviation can be computed as

$$s = \sqrt{\frac{\Sigma (x - \bar{x})^2}{n - 1}}$$

where x denotes the individual data, $\bar{x}$ the mean, and n the number of cases.

It is logical, and can also be seen from the formula that if we transform the individual data (e. g. by using the logarithms as it has been mentioned above) the standard deviations must be calculated, similarly to the average, from the transformed data. A symmetrical type of variation (i. e. one fluctuating in the same manner on both sides of the average) can be interpreted by imagining that all multiple values of the standard deviation added to or subtracted from the mean as upper or lower limits newly formed, enclose the same number of cases. If the distribution of the data is described by the well-known bell-shaped Gaussian normal distribution, about one-third of the cases to be found between the mean minus standard deviation ($\bar{x} - s$), and the mean ($\bar{x}$) can be expected. At the same time, however, the same number can be expected between $\bar{x}$ and $\bar{x} + s$. Similar numbers can be expected with other real percentages, if instead of the standard deviation its half or its double value, etc. is added to or subtracted from the mean. In cases of similar distributions, in other words, if the so-called 'density curves' generated by the frequency distribution, differ from each other in a way that by pulling apart or by pressing together the one or the other can be obtained, then the greater standard deviation can be regarded as expressing the smaller variability. By squaring the individual deviations from the mean and taking the square root of their sum divided by $n - 1$ as indicated by the formula, it can be seen that if, e.g. all the data

are double of those of another group, the value of s will be the double of the former, too. To achieve this, it is not necessary to double the number of data, it suffices if these are located twice as sparsely, i.e. more variably around the mean, since the $x - \bar{x}$ values will become hereby twice as great. In accordance with the foregoing, if the standard deviations, which can be called variability indicators, are computed from transformed (logarithmic) data and if in the latter the distribution is asymmetric, the previously mentioned properties are valid for the logarithms of the data. Therefore, if the standard deviation has to be interpreted in its original scale (in terms of mathematics retransformation is performed), the symmetrical interpretation outlined above will not be valid, but it can be suitably modified. In case of logarithm it means that the retransformed value of the standard deviation (e^s) or that of the double standard deviation (e^{2s}), etc. will yield a figure by which dividing the retransformed arithmetical mean ($e^{\bar{x}}$) or multiplying it respectively, roughly an identical number of cases can be expected between this value and the former mean.

Correlation coefficients (r). These are the indices showing correlations between various variables (properties, parameters). The best known version is Pearson's correlation index, also used in our work. This is computed by dividing the combined variability of the two variables (x, y), the so-called covariance

$$s_{x,y} = \frac{\Sigma (x - \bar{x}) \cdot (y - \bar{y})}{n - 1}$$

by the product of standard deviations expressing the separate variability of the two variables

$$r = \frac{s_{xy}}{s_x s_y} .$$

The correlation coefficient can be visualized as the angle or more exactly as the cosine of the angle (in the n dimensional space) formed by the vectors composed of the $x_1, x_2, \ldots, x_n$ and $y_1, y_2, \ldots, y_n$ observed values. Accordingly, the value of r can range from -1 to $+1$. A positive correlation coefficient means that the changes of the two parameters are unidirectional, the negative r means that the changes have an opposite trend. A value around zero means the lack of correlation. It must be mentioned that this interpretation of the r value can be baseless in some bad cases, and it is the more acceptable the better it can be expressed by the direct correlation of the variables, i. e. the more 'linear' is the connection between them. The linear connection means that the values of one of the variables shifted by a suitable constant and by pulling apart or pressing together the scale

of the variable with a suitable proportionality, with smaller or greater standard deviation, a value near to the other variable is obtained. (The angle of the 'observation vectors' of the two properties will be characteristic for the trend and intensity of their unidirectional change. This is not so, if the components of the vectors, i.e. the related observed values of the two properties in some dimensions, in our case in some of our examined individuals are correlated in a different manner than in the other dimensions, in our case in the other part of the patients.) If the type of correlation between the variables is strictly curvilinear, which manifests itself by the fact that between the points determined by the pairs of properties on the coordinate plane only a curved line can de drawn which is far from being straight, the r values reveal a strong bias. The equation of the covariance shows that in an extreme case, for instance, if the correlation is characterized by a semicircle, the value of r will be close to zero with the values being located near to the semicircle. It is worth considering this point in detail because the measurement of intensity of interdependence between the variables is a very difficult problem of mathematical statistics, the interpretation of the results being a stringent task. It is unavoidable, therefore, as it has been attempted in this work, to use the appropriately selected function (logarithm) instead of the variable itself. The correlation of the new variables obtained in this way should practically be linear, offering a real chance for measuring the strength of their correlation and for comparing the relational strength of the single pairs.

In order to examine more variables, the presentation of the correlation coefficients is obligatorily done in the matrix form. In this square scheme the figures found at the intersection of columns and rows express the r values of two variables with the corresponding serial number. As the single variables have a perfect linear correlation with themselves, the main diagonal of the matrix contains mere values of 1.0000. At the symmetrical places with regard to the main diagonal the same numbers can be seen, since they give the correlation of the same two variables. It must be noted that the matrices formed from the covariance (covariance matrices) have similar properties as the correlation matrix. It could be seen from the equation that the self-covariance of any variable is equal to the squared standard deviation of the variable (so-called variance), therefore the main diagonal of the covariance matrix contains the variances. The covariance matrix is also symmetrical with respect to the main diagonal, because the covariance of y with any x variable is the same as that of y with x.

Partial correlation coefficient. It describes the correlation of two parameters (in our case the correlation of the logarithmic changes of max dC/dt with

the column concerned) by neglecting the effect of the other variables. Similar rules are valid for this index as far as value, sign and reality are concerned as in the case of a simple correlation coefficient. This index was used in our study only as a control for the validity of the correlations, and the formula is fairly complicated, so it is not discussed here in detail. The partial correlation coefficient of the changes of max dC/dt with itself is -1.

Regression coefficients (*regression constant*, a, *regression coefficients*, b_1, ...). In this study regression was always computed in order to describe the correlations, with a suitable selection of the indices, by a simple equation:

$$y = a + b_1 x_1 + b_2 x_2 + \ldots b_k x_k.$$

If there is only one independent and one dependent variable, then

$$y = a + bx$$

(this is the equation of the straight line). The coefficients which best describe the correlation can be determined that way by substituting on the right side of the equation the actual values of the independent variables. The standard deviation of the dependent variable y, around the estimated value of y (linear combination), should be the smallest. The regression coefficients have the following form if there are two variables:

$$b = \frac{\Sigma (x - \bar{x}) \cdot (y - \bar{y})}{\Sigma (x - \bar{x})^2},$$

$$a = \bar{y} - b\bar{x}.$$

Hence, the regression coefficient b is related to the correlation coefficient r, as the standard deviation of y to the standard deviation of the x variable. As far as the sign of b is concerned, the rules are the same as in the case of correlation coefficients. The equation of a reveals that the regression line crosses the point determined by the averages. The regression coefficient a is also called 'intercept' and the coefficient b 'slope'. In Table 11, the partial regression coefficients with more variables are listed in the following order: a, b_1, b_2, etc. under the name of 'regression parameters'.

The regression equation makes possible that using the independent variables (in our case: the rest values and the values after exercise), the changes of the values of the dependent variable can be forecast (in our case: max dC/dt). The 'prominent' role of dependent variable has been given to the latter because the carotid derivative is the primary methodical basis of this study. The question was to decide in mathematical terms to what extent

the modification of this index after isoprenaline administration was influenced dy the behaviour of other haemodynamical parameters. Later, tests were carried out for checking the correlation and the significance of the regression coefficients. These exercises and the study of the correlations, together with the significance tests (see later), enabled the selection of the most suitable parameters, apart from max dC/dt, for the characterization of the heart's condition.

In Tables 10 and 11, there are two basic forms for the calculation of the partial logarithmic regression. The results obtained by these methods described above revealed that the regression analysis of the the experiments using 5 μg (fixed dose) isoprenaline is, as far as interpretation is concerned, superior to the experiments carried out with changing doses of isoprenaline.

F test. This is a mathematical-statistical method based on the quotient of two variances:

$$F = \frac{s_2^2}{s_1^2}.$$

The computation of the F value was done (in the course of the partial logarithmic regression calculations) from the standard deviations of the regression of y on x, thus characterizing the strength of the regression relation. In this case, the F test table is used to find the probability—assuming no correlation between the dependent variable and the independent ones—of attaining the actual F value by calculation from data (significance level). By using the F test, it was also possible to evaluate the relation of the standard deviation within and among the various diagnostic groups (see D^2).

It is worth mentioning that the significance tests are often not interpreted correctly. Let us consider test statistics (in our case the F values) based on our experimental data. In the statistical tables the values of the test statistics correspond to a certain probability, the so-called p value. (So in the F tables the critical values are found belonging to the p values and corresponding to the degrees of freedom of the numerator and the denominator.) It would be erroneous to say that if by calculating the real value of the test statistics the critical F is obtained, this gives the probability of the two options (there is *no*, or there *is* a correlation), because if $p = 0.05$, the probability of the first option (no correlation) is 0.05, i.e. 5 per cent and that of the second (existing correlation) is 0.95, i.e. 95 per cent. In fact, it is logically impossible for us to form an opinion on the above probabilities. For doing so it would be necessary to know the chance of realization of that very possibility ('there *is* a correlation'), about which we are seeking information only

now. The correct interpretation is as follows: the p value is the probability of our test statistics reaching the critical level provided the starting option ('no correlation') is valid. The starting hypothesis ('null hypothesis') in our system has a fixed position, and knowing the distribution of the data, the probabilities belonging to the various F values can be computed. Therefore, if the significance probability is 0.05, the complementary figure 0.95 (contrary to the erroneous interpretation) does not say anything about the counter-hypothesis. It just reveals that if the null hypothesis is valid the test statistics does not reach the critical level by 0.95 probability. The validity of the counter-hypothesis can be inferred from indirect data. If the value of p is fairly small, i.e. if the null hypothesis is valid, the '$1 - p$' value has to be large enough that our test statistics should not attain the critical level, while in our case it attained it. If the null hypothesis is maintained, the realization of a highly improbable event has to be stated. Therefore it is discarded and the counter-hypothesis is chosen. This reasoning, appearing earlier several times, had to be repeated because the erroneous interpretation of significance mentioned above causes mechanical utilization of the data without proper professional control. The results of the statistical tests are considered landmarks for orientation, which cannot be interpreted either by themselves or by their numerical values but only in the context of our biological and mathematical knowledge. The reader is requested to evaluate test statistics and significances in our work with this thought in mind.

t test (*Student test*). It is based on the value of t which is the quotient of the mean of the quantity investigated and the standard error of this mean.

At the computation of the partial regression the slope of the regression was related to its own standard error. In case of two variables the equation of t is as follows:

$$t = \frac{r\sqrt{n-2}}{\sqrt{1-r^2}},$$

where r is the correlation coefficient, n is the number of cases. This formula was used to calculate the significance of the regression coefficient. The significance of the change or the significance between similar data of two groups were calculated by Student's one- or two-sample t test.

$$t = \frac{\bar{x}\sqrt{n}}{s}, \qquad t = (\bar{x} - \bar{y}) \frac{\sqrt{\frac{n_x n_y}{n_x + n_y}}}{S}.$$

Here x, y are the arithmetic means, n is the corresponding number of cases,

S, in case of one-sample test, is the standard deviation and in two-sample test, the common standard deviation.

$$S = \sqrt{\frac{(x - \bar{x})^2 + (y - \bar{y})^2}{n_x + n_y - 2}}.$$

The $n-2$ occurring at the calculation of significance of the regression coefficient the $n - 1$ in the formula of standard deviation at the on-esample t test and $n_x + n_y - 2$ at the equation of the two-sample t test are the degrees of freedom. The degrees of freedom tell us how many data can be freely observed, i.e. their value is not fully determined. In case of simple linear regression the equation of the straight line is dealt with, which is determined by two data (intercept, slope), therefore from n dependent variables only $n - 2$ data can be given without restriction to a given straight line and added to given independent variables, since the two other points have already been determined by the two correlations mentioned in the part of this study dealing with regression coefficients and based on observed data. This can also be seen at the calculation of one-sample t test. Only $n - 1$ data can be freely selected for the standard deviation. One point, the mean ($\bar{x}$) is given, with the values of scattering being located around this figure. The same principle is valid for the two-sample t test, where $n_x - 1$ data can be freely selected around $\bar{x}$ and $n_y - 1$ around $\bar{y}$, so altogether $n_x + n_y - 2$. The degree of freedom means that the variable can be considered the summation of the squares of such a number of independent normal variables. It belongs to the determination of the probability distribution of the t test statistics, in other words, to the determination of what probability is to be expected for the frequency of certain values provided that the null hypothesis holds. The probability values are to be taken from the t-table with regard to the degree of freedom.

In the F statistics, both the numerator and the denominator contain an s^2 quantity, therefore the F table has been made with two types of degree of freedom, one for the numerator and the other for the denominator. This takes two dimensions, so the p values can be found in the headings of the tables.

In the first part of this chapter the standard error of the mean has been mentioned. The meaning of this is as follows. It should be known how reliable this value is, how it can be expected, in eventual subsequent observations, to be near to its present value. Answers may be found for the correlation t test with the following definition:

$$\sqrt{\frac{1 - r^2}{n - 2}}$$

for the one-sample t-test:

$$\frac{s}{\sqrt{n}}$$

and for the two-sample t-test:

$$S \sqrt{\frac{n_x + n_y}{n_x n_y}}.$$

The latter two are usually called standard error of the mean (standard error) and standard error of the mean difference. It is also customary to use this as a measure for the reproducibility and to write it down either separately or next to the mean with $\pm$ sign.

The significance of these values is the same as for the standard deviation. For instance, by considering the standard error of the mean the variability of the mean of similar observation sets with n data can be characterized, just like by increasing or decreasing the standard deviation, values with different variability are thought of.

Significance probability (p). As has been said when dealing with the F test, this is a probability with the assumption that the 'null hypothesis' (no change, no difference, no correlation, etc.) holds. Its value gives the chance for reaching the figures obtained by the test statistics (F, t, etc). The traditional line is followed and generally the existence of a relevant effect (change, difference) is assumed if p is less than 0.05, i. e. lower than the 5 per cent significance threshold. However, the p values are rather considered guide lines for a better interpretation of our results.

SOME CONCEPTS AND NOTATIONS OF THE DISCRIMINANT ANALYSIS

Computations performed by this method can be found in Chapter 6, and are best illustrated by Tables 14*a–p*. This time we are presenting briefly the elements of the method.

Matrix of sums of products (*of deviations*. This is the matrix of $SP = \Sigma(x - \bar{x})(y - \bar{y})$. In the main axis are the $SQ = (x - \bar{x})^2$ deviation square sums. S_1 matrix contains the sums of Group 1, matrix S_2 those of Group 2, and S contains the total sum, i. e. the sum of the corresponding figures of the two matrices. These matrices, similarly to those of correlation matrices, are symmetrical. The discriminant analysis described on p. 165 of Chapter 8 looks for such a linear combination of the variables which

should have a maximal two-sample t between the two groups. The method of the discriminant analysis, similarly to the calculation of the common standard deviation of the two-sample t-test computes a common matrix (S) from matrices S_1 and S_2.

Discriminant 'weights' (*lambdas*). These are the coefficients of the single variables in the previously mentioned linear combinations.

If the optimal combinations for three variables are:

$$\Lambda_x x + \Lambda_y y + \Lambda_z z$$

and x, y and z represent logarithmic changes (natural, e-base logarithm) the power functions are:

$$\left(\frac{X_{\max}}{X_0}\right)^{\Lambda_x} \left(\frac{Y_{\max}}{Y_0}\right)^{\Lambda_y} \left(\frac{Z_{\max}}{Z_0}\right)^{\Lambda_z}$$

where max denotes the maximum derivative and 0 is the zero time.

The individual weight of the single variable is expressed more realistically by the so-called 'standardized' discriminant weights: $\lambda \sqrt{SQ}$. The SQ values are the elements of the diagonal line of the S matrix, for instance, for the second variable it can be found at the crossing point of the second column and the second row.

Diagnostic scores (*Z alphas*, Z_α). The realizations of the mentioned linear combination on the material observed. If $\alpha = 1$ (in our case the healthy group), for three variables

$$Z_1 = \lambda_x x + \lambda_y y + \lambda_z z$$

x, y and z are interacting variables (logarithmic changes) in the same individual. If $\alpha = 2$ (in our case Group 2, clinically diagnosed as cardiac patients), for the individuals of the group:

$$Z_2 = \lambda_x x + \lambda_y y + \lambda_z z$$

with the same lambda values, but—if the separation of the groups was successful—with a different range (in our case it is lower).

Mahalanobis' D^2 statistics ('*generalized distance*'). It expresses the segregation of the groups realized by discriminant analysis. With the value of D^2 the standard deviation of the Z figures inside the group can be characterized

$$S_z = \frac{D}{\sqrt{n_1 + n_2 - 2}}$$

(the value of the latter is between S_{Z_1} and S_{Z_2} group standard deviations, printed in lower lines of Table 11). The Mahalanobis statistic is specific for

the standard deviation of the Z_α figures within one group and between the groups. Therefore, value F can be directly calculated and the significance of the segregation can be evaluated (see F test).

Discriminant threshold (Z_0). This is a critical value of the Z_α combination which must be exceeded by the diagnostic scores to enable the listing of the individual in Group 1. This is necessary to preserve the validity of the principle that the sum of the probabilities of 'erroneous' listing (that of the two different listings) should be minimal.

Chances of prediction of the discriminant analysis. These are the proportions of percentages of the 'correct' and 'erroneous' listing using the discriminant analysis for segregation. The formulas are

$$\frac{100\,n(Z > Z_0)}{n_1} \quad \text{and} \quad \frac{100\,n(Z_1 \leq Z_0)}{n_1}$$

respectively

$$\frac{100\,n(Z_2 \leq Z_0)}{n_2} \quad \text{and} \quad \frac{100\,n(Z_2 > Z_0)}{n_2}$$

where n is the number of cases.

In our study the probability of listing individuals as 'correctly healthy', 'erroneously healthy', 'correctly ill' and 'erroneously ill' can be estimated with these figures.

Significance probability of the deviation from overlap. This is the probability which can be calculated from the difference between the similar predictions given to the individuals of the two groups, in our case between chance 1 correctly 'healthy' and 4 erroneously 'healthy' or 2 correctly 'ill' and 3 erroneously 'ill'. This is not characteristic for the standard deviation between and inside the two groups (contrary the F test calculated from D^2). This indicates statistical safety of the distinction, in other words deviation from the overlap in the two diagnostic groups (Z_1 and Z_2). Thus it gives a more direct information about the efficiency of the discriminant analysis and mathematical processing.

The structure of further discriminant analyses. In the course of our study the changes of the max dC/dt, systolic blood pressure and pulse rate and their functions were selected to distinguish between healthy and cardiac individuals. This separation means that using the suitable functions of the parameters by means of the discriminant analysis linear combination of the functions is chosen, providing numerical values so that one of them is a threshold. Individuals having figures below this threshold are cardiac patients and those above it are mathematically 'healthy'.

For this purpose the discriminant functions prepared in programs A–J have been constructed with a unified method. With some indices and criteria it was possible to construct the basic functions and combinations of these functions suitable for discrimination.

At this point an account will be given on the sequence of discriminant analyses, primarily for the reader interested in mathematics. The processing was made in the Computer and Automation Institute, using a CDC-3300 computer of the Hungarian Academy of Sciences. ALGOL language was used for the programming, for the matrix procedures FORTRAN was also used.

The general properties of the programs are as follows.

1. The linear discriminant analysis was made parallel, using two separate optimum criteria.

(*a*) It is a traditional criterion of the discriminant analysis that seeks for such a linear combination of the given basic functions, which maximizes the Student's two-sample t values between the two main groups (healthy and cardiac patient). This corresponds to the hypothesis accepted in the mathematical–statistical literature that the standard deviations of the discriminating variables (basic functions) and the correlation coefficients expressing the link between the variables are identical in the basic populations of both groups; the variation of the actual figures is fortuitous. In this case, the discriminant analysis is based on the covariance matrix within the groups. The elements of the latter are identical with those of the two-sample t test and can be calculated using the following equation:

$$a_{ij} = cov\,(x_i, x_j) = \frac{\Sigma(x_{1i} - \bar{x}_{1i})\,(x_{1j} - \bar{x}_{1j}) + \Sigma(x_{2i} - \bar{x}_{2i})\,(x_{2j} - \bar{x}_{2j})}{n-1} .$$

By the inverse of this matrix the discriminant coefficients are formed:

$$\lambda_i = \sum_j a_{ij}^{(-1)}\,(\bar{x}_{ij} - \bar{x}_{2j}) .$$

The weights of the single variables, by elimination of the influence of the various scales, are expressed as 'standard' discriminant coefficients:

$$\lambda_i' = \lambda_i \sqrt{SQ_i} .$$

The same inverse matrix yields the expression

$$D^2 = \sum_i \sum_j a_{ij}^{(-1)}\,(\bar{x}_{1i} - \bar{x}_{2i})\,(\bar{x}_{1j} - \bar{x}_{2i})$$

which is quadratic in the basic variables. The value of this 'generalized distance' according to Mahalanobis (D^2) is:

$$D^2 = \bar{Z}_1 - \bar{Z}_2$$

where Z_1 and Z_2 donete the individual values of the discriminant function, in other words the so-called 'diagnostic scores'.

The computation yields an optimum, which beside the supposition of the normal distribution of the discriminant variables, in our case presupposes only a rough covariance homogeneity. This means that the bell shape of the frequency distributions of the variables does not differ, however, their location is different. Therefore, in our opinion, the latter presumption can be omitted, and an attempt can be made to produce thus an optimal linear combination, too.

(*b*) The covariance matrices were formulated allowing in the basic populations different standard deviations and correlation coefficients, too. In this formulation, instead of Student's two-sample t value the Behrens–Fisher d value was maximal between the two groups and it was determined by the following formula:

$$d = \frac{Z_1 - Z_2}{\sqrt{s^2_{z_1} + s^2_{z_2}}} .$$

Those parts of the program which deal with the computation of the discriminant analysis were modified, namely the calculations in point (*a*) were carried out as if instead of the original variables they had been made with modified variables obtained by

$$x' = \frac{x}{\sqrt{n_\alpha (n_\alpha - 1)}} .$$

Seemingly, this optimum principle is not necessary because in case of more variables with normal distribution using quadratic discriminant analysis, theoretically an optimum is obtained by various covariance matrices.

Nevertheless, discriminant functions had to be used being lucid and easy to compare and interpret. Therefore, for heteroscedastic cases linear discriminant analysis was used as well.

It should be noted that according to (*a*) the F can be calculated from D^2:

$$F = \frac{n_1 n_2 (n_1 + n_2 - k - 1)}{k(n_1 + n_2)} \cdot D^2.$$

This can be modified using the principles of (*b*):

$$F = \frac{n_1 n_2 \left[\frac{(s^2_{\bar{z}_1} + s^2_{\bar{z}_2})^2}{s^4_{\bar{z}_1}/(n_1 - 1) + s^4_{\bar{z}_2}/(n_2 - 1)} - (k + 1) \right]}{k(n_1 + n_2)} \cdot D^2 .$$

This is a satisfactory approximation, and this statement is supported by the fact that in homoscedastic and in one-sample (comparison with a constant) special cases the exact degrees of freedom are obtained. As a matter of fact, this is a multidimensional generalization of the degree of freedom equation described by Welch for the Behrens–Fisher case.

The interpretation of the basic functions is based on the results obtained by the calculations according to (*a*) and (*b*). These have also pointed to the new functions to be applied.

2. The chances of prediction are calculated and appraised as regards the two groups of patients.

The programs give the diagnostic scores (figures) as to the results of discriminant analysis by the use of one-fourth of the standard deviation of the frequency distribution of the original variables ('properties', like x, y and z) as a group distance. Furthermore, this was also enhanced by the interpretation of the variance analysis of the deviations between the groups.

On the left side of the tables, next to the identification numbers of the individuals, are the products of values yielded by the equation:

$$\pm \text{num} \log \left\{ \begin{matrix} \text{integer} \\ \text{part of} \end{matrix} \left[3 - \log \left(\frac{\sqrt{|\min(z)|} + \sqrt{|\max(z)|}}{2} \right)^2 \right] \right\} .$$

On the right side the same figures can be found concerning the cardiac patients. The aim of the multiplication is to raise the majority of the figures up to the positive three-digit range.

The separation from the listing of the points is carried out by fixing the 'discriminant threshold', i. e. the number of points below which the individuals are healthy, and above which they are cardiac patients. The threshold was fixed by using the maximum hit probability with regard to the clinical diagnosis. This means that the percentage rate of correct qualification, i. e. qualifying the healthy as 'healthy' and the sick as 'sick' should be maximal.

On the basis of hit probability, a null hypothesis can be examined, which is of course absurd and thus yields a very strong significance, namely whether the probability distributions of the diagnostic scores of the two main clinical

groups are identical or not. This can be performed by the formula based on the theorem of Gnedenko–Korolyuk

$$P\left[\sqrt{\frac{n_1 n_2}{n_1 + n_2}}(F_1 - F_2) < y\right] = 1 - e^{-2y^2}$$

and by its variant applicable to our special case:

$$P(W \geq W_0) = \exp\left[-\frac{n_1 n_2 W_0^2}{5000(n_1 + n_2)}\right]$$

where $\frac{100 + W_0}{2}$ is the maximal hit percentage.

This test used for comparison of probability distributions is simple but remarkably improves the possibilities of checking the 'correctness' of the separations obtained by various discriminant analyses.

By comparing within the programs the F values obtained by the 'variance analysis of the Z values' with that of 'deviation from the overlap', some points should be considered. The F values, or more exactly, the order of magnitude of their significance, indicate the probability of the repetition of an actually observed separation in a hypothetical investigation to be performed later. This probability computation is based on the standard deviation of diagnostic scores within and between the groups. The listing according to the deviation from the overlap, however, gives information about the accuracy of the hit probability (in distribution-free sense), and it is less suited for the prediction of repetition. The consideration of the two rank orders, the simple functions being easy to evaluate, and, in addition, the D^2 analysis provide a good chance for classification of the results of the discriminant analyses and for the selection of the 'best' combinations of functions.

Three types of breakdown are given for the current D^2 values the latter being in functional connection with the maximal t and d values.

(*a*) *The breakdown of the generalized D^2 distance according to variables.* This breakdown enumerates as 'determination coefficients' participating values obtained by breakdown and yielded by discriminant analysis. These values are yielded in absolute and relative rates (with D^2 or unity as sum) in components corresponding to single variables and pairs:

$$\lambda_i'^2 \text{ resp. } 2\lambda_i' \lambda_j' r_{ij}.$$

(*b*) *Effect of variables on the formation of generalized distance D^2.* A table with this heading presents contributions expressed in percentages. In this

respect the variables are examined as to their discriminating power. In the first column there are the squares of the contributions [point (*a*)], in the second column the half sum of the percentage of participation of the single properties obtained according to point (*a*) with that of all the others. Finally (as the sum of the direct and indirect discriminating contributions) the summarized data of the two previous columns are displayed. Consequently, the sum of the H values in the third column is 100.

(*c*) *The percentage decrease of* D^2 *after omission of the single variables.* In this table not the total breakdown of D^2 is presented, but the percentage decrease of its value in case the discriminant analysis had been made by one variable less, i. e. by omission of a specific variable. The computation of these percentage decreases can be performed from the relation for the extension of the symmetrical matrices by one dimension:

$$D_k^2 = D^2 - \frac{\lambda_k^2}{\alpha_{kk}^{(-1)}} = \delta_k D^2.$$

The application of this relation is considered by us useful, in addition to the more suggestive relations mentioned under (*a*) and (*b*), because these 'rates of decreases' have a functional connection with the decrease of the index derived from information theory and related to inter-group discrimination information (Kullback 1962). Based on experience gained by numerous discriminant analyses, it was concluded that the variables which yield not more than 20 per cent of the total amount of discrimination information can be omitted. Since the discrimination informations are linear functions of logarithms of the corresponding D^2, the following equation is the expression of this criterion:

$$\prod_{\delta_i > \delta_0} (\delta_i)^6 \geqq \pi_i \, \delta_i.$$

This has been applied in the present study to emphasize the relevant variables and they will be applied in further studies as well.

Negative components may also occur in decompositions discussed under (*a*) and (*b*). Moreover, this does not disturb the conclusions which can be drawn on the relevance of the single variables, because with the investigation of the homoscedastic and heteroscedastic versions an opinion can be formed, at least as to what versions to apply subsequently.

The logic of the processing, evaluation and sequence of our discriminant analysis programs has been outlined. The actual order of the programs and the characterization of their results are discussed on pp. 175–97. In conclusion of the mathematical part of the study on discriminant analysis the

basic versions are surveyed of which optimal linear combinations were used for the different discriminant analyses.

The discriminant coefficients obtained for the single variables were multiplied, this being made so that the yielded values should be proportional and easy to handle and their relations could be interpreted satisfactorily. In no case was the rounding of the values a disturbing factor in discrimination of the material.

THE SIGNIFICANCE OF COMPUTER PROCESSING

1. In extensive preliminary computations it enhances the appropriate selection of material and parameters. This screening has been mentioned earlier.

2. It helps a great deal in investigations with more variables in computations being difficult to carry out by manual methods. It is simple to carry out linear regression with two variables and the two-sample t test in which there are multiplications with the reciprocal of the standard deviation. A similar but much more complicated task is the production of the inverse matrix as the generalization (with more variables) of the reciprocal values. The aim of this operation is to characterize deviations and correlations by multivariate statistical means, i. e. by the standard deviation corresponding to the variables' connection.

3. Mechanical processing methods were found suitable with little modification, for more variables and by the direct digital working up of analog signs, for automated and wide range interpretation of investigations similar to ours.

4. It is possible to carry out rapid computations, and in addition to the results with primary relevance, less important or marginally important results can be used, completing the information as well. In this context the dispersion coefficient expressing the accuracy of the regression is mentioned, and the total correlation showing the global strength of correlation, further the construction of inverse matrices. These are not discussed in this study. The grouping according to magnitude, particularly in case of Z figures, is highly time consuming. Nevertheless, this grouping, performed by computer processing, gives a chance for control and evaluation. This justifies the introduction of computer processing into cardiological diagnosis. Computer processing is furthermore indispensable for the chain of discriminant analyses (cf. pp. 175–97), and also for finding the optimal discriminating function in further studies.

CHAPTER 10

THE LIMITATIONS OF OUR METHODS. OUR OBJECTIVES

There are no methods with absolute values, so after describing the advantages and practicability of our method an account has to be given of the limitations.

These have various characters. Naturally everything holds for our method which is valid for the 'noninvasive' mechanographic methods in general. Moreover, its usability is limited, there is a hindrance to register a reproducible and estimable tracing on the place of maximal pulsation of the carotid artery. Difficulty may be found in persons having a short and stout neck, and showing a lack of cooperation. It is not always possible to record a technically satisfactory curve in young children. We have no experience with children, nevertheless there are some publications advocating the use of the method in children (Simon et al. 1970, Son 1972).

The method is theoretically not applicable in case there is an obstacle between the intraventricular space and the point of detection (aortic stenosis, valvular stenosis, IHSS).

We have no experience with our method in patients with other valvular failures so we cannot comment on difficulties in those cases.

We think we have not completed our task, it is necessary to add further data with respect to techniques and mathematics. It is necessary to investigate more patients as well.

With regard to technique, our aim is the immediate digitalization of the reaction processing as well as a rapid answer. It cannot be stated for certain which solution is ideal: (*i*) the construction of an analog, so-called object-computer or (*ii*) a continued link with digital universal computer and a fast reply. It is necessary to standardize the place of the application of the carotid sensor.

In addition to drug reaction, for a better practical use, the interpretation of the effect of physical exercise should be worked out. The extension of the circle of parameters used so far is a possibility. From the latter those should be preferably introduced which have already been mentioned in the previous chapters. These are the amplitude changes specific for the pre-ejection phase,

and the tracing of pulsation of an artery located distantly from the heart. However, no computerized processing has been made on the results so far. Investigations should be carried out on the usability of the second derivative of the carotid tracing (Simonyi et al. 1968*a*).

It seems to be necessary to check the applicability of our method in cases of valvular failures.

Some preliminary investigations have been made on the use of our method for pre-operative, intraoperative and postoperative monitoring of patients.

We are planning to extend the clinicopharmacological studies and want to develop further the methodology of computer processing of the data. A part of these has already been completed.

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