AN EVALUATION OF THE USEFULNESS OF RODBARD'S SPHYGMOMANOMETRIC METHOD IN CARDIOVASCULAR EPIDEMIOLOGY

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AN EVALUATION OF THE USEFULNESS OF RODBARD'S SPHYGMOMANOMETRIC METHOD IN CARDIOVASCULAR EPIDEMIOLOGY

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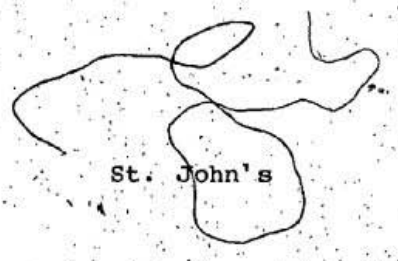

St. John's Newfoundland

ABSTRACT

The purpose of this study was to test the hypothesis that Rodbard's method of noninvasively determining the anacrotic slope of the brachial artery pressure pulse wave is useful in cardiovascular epidemiology.

The materials were the raw records obtained for two groups of subjects aged 55 years living in Göteborg in 1969/70, and the cardiovascular disease information registered for these subjects in the following ten years. The method of checking on the hypothesis was to determine if there was a significant relationship between any of the eleven variables used to quantify the anacrotic slope obtained for each subject and his cardiovascular history in the follow-up period. Because an understanding of the physiological mechanisms was essential for the correct interpretation of any significant results, these mechanisms were evaluated by first submitting the variables to factor analysis and covariance analysis.

The means and the factor score coefficients of the variables were not found to be related to the development of cardiovascular disease in the follow-up period. However, a significant relationship was found between one pair of variables in combination (systolic pressure and the gradient of the initial, linear portion of the anacrotic slope) and the

subject's risk of experiencing a stroke in the follow-up period.

It was concluded that Rodbard's method has the potential to be useful in cardiovascular epidemiology because one member of the pair of variables determined to be of value (the gradient of the initial, linear portion of the anacrotic slope) can be easily obtained only by Rodbard's method.

Two important additional conclusions arose from the use of factor analysis and covariance analysis: it is possible to estimate peripheral resistance noninvasively where systolic pressure and the gradient of the initial, linear portion of the anacrotic slope are known, and it is not necessary to correct the variables for differences in heart rate.

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ABBREVIATIONS AND DEFINITIONS

BMDP Biomedical Data Processing Manual program

c pulse wave velocity (m/sec)

Cardiac contractility: the performance of the heart as a whole, eg as measured by the rate of pressure rise in the ventricle during the isovolumetric contraction period

D duration of the anacrotic slope (msec), one of the Rodbard variables

E Young's elastic modulus, ie the relationship between stress and strain for the arterial wall, in the longitudinal direction (dyn/cm^2)

G gradient of the initial, linear portion of the anacrotic slope (mmHg/sec), one of the Rodbard variables

h arterial wall thickness (cm)

LT duration of the initial, linear portion of the anacrotic slope (msec), one of the Rodbard variables

LVET time elapsing between the opening and the closing of the aortic valves (msec), a systolic time interval

NA area measurement related to the nonlinear portion of the anacrotic slope (mmHg·msec), one of the Rodbard variables

NP amount of nonlinear pressure increase of the anacrotic slope (mmHg), one of the Rodbard variables

NT duration of the nonlinear portion of the anacrotic slope (msec), one of the Rodbard variables

P probability

PEP time elapsing between the Q wave of the electrocardiogram and the opening of the aortic valves (msec), a systolic time interval

Physiological mechanism: any physiological process or property capable of producing a physiological change

PP pulse pressure (mmHg)

R radius of arterial lumen (cm)

r simple correlation coefficient

RKD time elapsing between the R wave of the electrocardiogram and the arrival of the foot of the arterial pressure pulse wave at the brachial artery under the cuff (msec)

Rodbard variables: the seven variables used in this thesis which are only available noninvasively through the use of Rodbard's method

RR cardiac cycle length (msec)

SP systolic pressure (mmHg)

QKD time elapsing between the Q wave of the electrocardiogram and the arrival of the foot of the arterial pressure pulse wave at the brachial artery under the cuff (msec), one of the Rodbard variables

QKS time elapsing between the Q wave of the electrocardiogram and the arrival of the peak of the arterial pressure pulse wave at the brachial artery under the cuff (msec), a Rodbard variable used with QKD to calculate D

ρ blood density (gm/cm^3)

INTRODUCTION

The usual indirect auscultatory method of determining blood pressure (Korotkoff, 1905) has been modified by various researchers to record simultaneously the Korotkoff sounds, brachial cuff pressure, and the electrocardiographic tracings on a three-channel recorder. From the records thus obtained, the time interval from the onset of the QRS complex to the arrival of the arterial pulse at the brachial cuff can be measured. This time interval varies with the pressure in the cuff, being longest for the first sound heard as the cuff pressure falls (systolic pressure) and shortest for the last sound heard (diastolic pressure). These two time intervals are generally designated QKS and QKD respectively. All the time intervals and cuff pressures between QKS and QKD can be used to construct a graph of the anacrotic slope of the brachial artery pressure pulse wave (see Figure 1). This simple, noninvasive method of constructing the anacrotic slope will subsequently be referred to as "Rodbard's method" both for the sake of clarity and conciseness and because, in searching the literature, it became obvious that the name of Simon Rodbard (1911-75) was intimately associated with its development. His publications incorporating this method date from 1952 until 1979, and the term "Rodbard's method" was first used by Geddes, Knight, Posey, and Sutherland (1968).

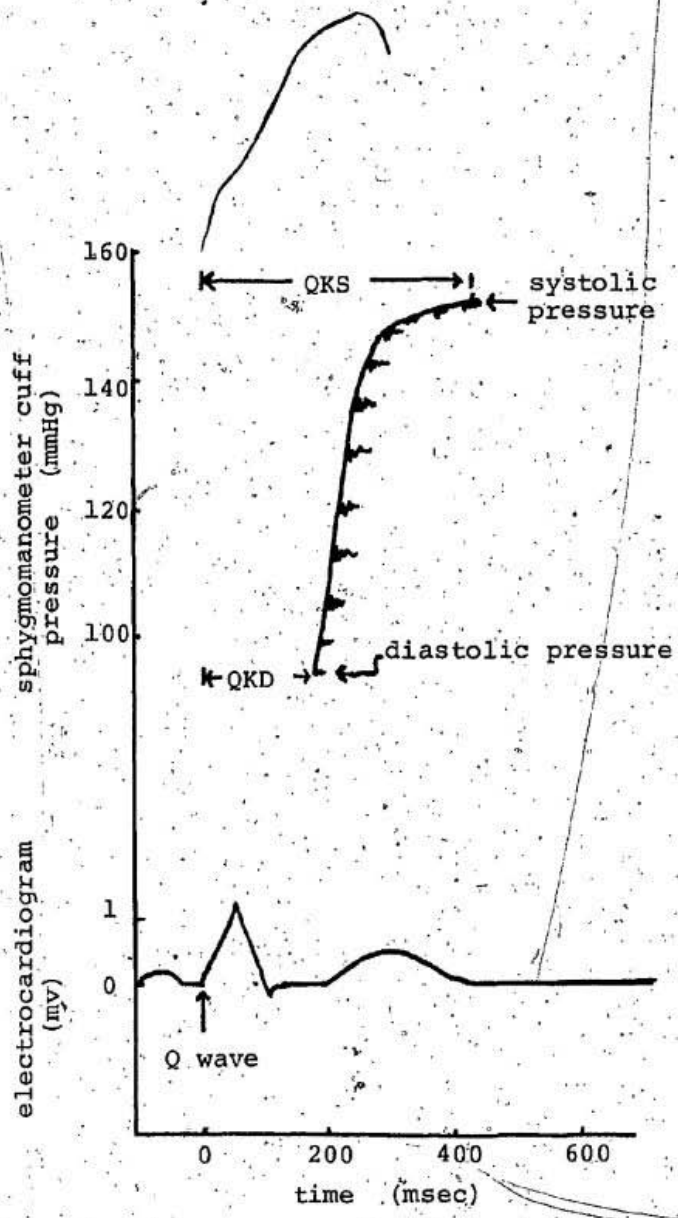


Figure 1. A graph of all QK time intervals between QKS and QKD plotted against the pressure in the sphygmomanometer cuff when each sound was heard. The appearance of the Korotkoff tracings is indicated.

The purpose of this study was to test the hypothesis that Rodbard's method of noninvasively determining the anacrotic slope of the brachial artery pressure pulse wave is useful in cardiovascular epidemiology.

The materials were the raw records obtained for two groups of subjects aged 55 years and living in Göteborg in 1969/70, and the cardiovascular disease information registered for these subjects in the following ten years. The method of checking the hypothesis was to determine if there was a significant relationship between any of the eleven variables used to quantify the anacrotic slope obtained for each subject and his cardiovascular history in the follow-up period. The results and discussion of this research are presented in Chapter IV.

Because an understanding of the physiological mechanisms was essential for the correct interpretation of the results these mechanisms were determined from the literature (Chapter I) and evaluated where possible by first submitting the variables to factor and covariance analysis. The results and discussion of this research are presented in Chapter III.

CHAPTER I

RODBARD'S METHOD: ITS PHYSIOLOGICAL BASES AND ITS POSSIBLE USEFULNESS IN EVALUATING BLOOD FLOW AND PREDICTING CARDIOVASCULAR HEALTH AS DETERMINED FROM THE LITERATURE

SECTION 1

An examination of the validity of Rodbard's method

Rodbard, Rubinstein, and Rosenblum (1957) presented the details of this method, which previously had been available only as an abstract (Rodbard and Rubinstein, 1952). The Korotkoff sounds were picked up with a microphone and recorded simultaneously with an electrocardiographic tracing, on which cuff pressure was indicated manually by marking the cuff pressure on the record at 10 mmHg intervals. A graph was then plotted of the sphygmomanometer cuff pressure as a function of the time interval from the Q wave of the electrocardiographic record until the onset of the Korotkoff sounds. A number of consecutive pulses were required to construct the graph. Rodbard et al (1957) used the abbreviations QKS and QKD to describe respectively the time intervals of the first and last Korotkoff sounds heard as cuff pressure declined.

To determine if the graph reproduced the anacrotic slope of the brachial pressure wave, intra-arterial blood

pressure recordings were made in the brachial artery distal to the cuff (Rodbard et al, 1957). It was noted that the onset of the intra-arterial pressure distal to the cuff and the first Korotkoff sound coincided, and also that the anacrotic slope constructed from the Korotkoff measurements yielded a curve with the same contour as that obtained from the intra-arterial pressure measurements recorded proximal to the cuff.

a. An examination of the validity of Rodbard's method by comparing it with intra-arterial pressure measurements

Further validation of Rodbard's method by comparing it with intra-arterial pressure measurements was reported by Mastropaolo, Stamler, Berkson, Wessel, and Jackson (1964); London and London (1967), and Geddes et al (1968). Mastropaolo et al (1964) found that Rodbard's method underestimated intra-arterial systolic pressure measurements by 4 ± 3 mmHg, but was significantly less fallible than the usual auscultatory method. London and London (1967) concluded that Rodbard's method was clinically reliable, because, although it underestimated intra-arterial systolic pressure (phase I), it did so by only 2 mmHg. They found the last Korotkoff sound (phase V) overestimated intra-arterial diastolic pressure by 4-10 mmHg, a smaller error than that obtained when muffling (phase IV) was used to determine diastolic pressure. Muffling was found to

overestimate intra-arterial diastolic pressure by 12-20 mmHg, and to be absent in a large proportion of the measurements. Like Rodbard et al (1957), London and London (1967) also concluded that the Korotkoff sounds were chronologically related to the shape of the ascending pressure wave front. However, Geddes et al (1968) found that the rate of pressure rise determined by Rodbard's method was slightly less than that determined from their intra-arterial pressure records. The best agreement was obtained when the cardiovascular system was stable, ie, when no arrhythmias were present, and when the intra-arterial pressure record showed minimal respiratory variations.

The validity and usefulness of the auscultatory method of blood pressure measurement is well established although inaccuracies have been found during and after exercise (Henschel, Dela Vega, and Taylor, 1954). London and London (1967) reported that occasionally there were greater discrepancies than expected between intra-arterial pressure and cuff pressure at the first Korotkoff sound: intra-arterial pressure was as much as 20 mmHg higher than cuff pressure. Because little detail was given about their subjects or the blood pressure levels measured, no definite conclusions can be drawn from this paper. Perhaps the error was related to the level of systolic pressure. From graphs presented by Van Bergen, Weatherhead, Treolar, Dobkin, and Buckley (1954) it appears that the discrepancy between

direct and indirect systolic pressure was greater when systolic pressure was higher. This discrepancy can be estimated by taking values directly from their graph. The intra-arterial systolic pressure was underestimated by 20 mmHg when intra-arterial systolic pressure was 190 mmHg; by 16 mmHg when intra-arterial pressure was 160 mmHg; and by 10 mmHg when intra-arterial pressure was 120 mmHg. A similar relationship between intra-arterial systolic pressure and the size of the difference between direct and indirect systolic pressure measurements was also reported by Roman, Henry, and Meehan (1965) and Breit and O'Rourke (1974). Roman et al (1965) found that the mean systolic error was 17 ± 14 mmHg, when intra-arterial systolic pressure was above 190 mmHg; 9.5 ± 8 mmHg when intra-arterial systolic pressure was 170-190 mmHg; 8 ± 7 mmHg when intra-arterial systolic pressure was 150-170 mmHg; and 4 ± 2 mmHg when intra-arterial systolic pressure was less than 150 mmHg. The mean error for systolic pressures up to 150 mmHg was similar to that found by Mastropaolo et al (1964), by London and London (1967), and Geddes et al (1968). Breit and O'Rourke (1974) obtained a significant correlation ($r = .56$, $P<.002$) between the height of the intra-arterial systolic pressure and the degree of accuracy involved in measuring systolic pressure by Rodbard's method. They found that the accuracy of Rodbard's method was greatest for systolic pressures of 110-120 mmHg and that above these pressures readings became progressively less accurate. It is possible

to suggest two reasons for the larger errors found at high systolic pressures:

1) If the Korotkoff sounds are caused by wall movements associated with the increase in arterial diameter (see subsection c, pp. 13-17), the relationship between the size of the discrepancy between the two methods and systolic pressure may be due to the non-linear elastic properties of the arterial walls. At high systolic pressures wall movements may be small because of the high wall tension, with the result that no sounds are heard.

2) If, as seems likely, wave reflection is important in determining the shape of the anacrotic slope, then the presence of the inflated cuff may also be a factor responsible for the discrepancy between the two methods (see p 99).

A similar relationship between intra-arterial diastolic pressure and the size of the difference between direct and indirect diastolic pressure measurements was not found. Indirect diastolic pressure consistently overestimated intra-arterial diastolic pressure as follows: 3 ± 2 mmHg (Mastropaolo et al, 1964), 5.0 ± 2.9 mmHg (Roman et al, 1965), and 6.70 ± 6.88 mmHg (Breit and O'Rourke, 1974). In a sophisticated approach to the Korotkoff sounds at diastole, Anliker and Raman (1966) determined the factors affecting the accuracy of auscultation, first by using an experimental model to develop equations, and then by substituting the physiological properties of the brachial artery into these equations. They found that the indirect

diastolic pressure was always higher than the intra-arterial diastolic pressure; and that an increase in the ratio of brachial wall thickness to internal diameter, an increase in the brachial wall mass (wall density times wall thickness), and an increase in Young's modulus (which indicates a decrease in arterial compliance) all increased the overestimate of intra-arterial diastolic pressure. In addition, the authors determined that there was an optimum cuff size below which the indirect error increased and above which there was no noticeable effect upon the size of the indirect error. It is unfortunate that a similar mathematical model is not available to determine factors affecting the accuracy of indirect systolic pressure measurements.

To summarize: The anacrotic slope of the brachial arterial pressure wave as constructed by Rodbard's method is closely related to the intra-arterial pressure wave. However, there is evidence that it rises more gradually than the intra-arterial pressure wave, overestimates diastolic pressure, and underestimates systolic pressure. The extent to which systolic pressure is underestimated is related to the level of systolic pressure, but the reason for this is not certain. The extent to which diastolic pressure is overestimated was found to increase where Young's modulus, arterial wall mass, or the ratio of wall thickness to internal diameter of the brachial artery were increased, or

where the size of the sphygmomanometric cuff was less than optimum.

b. An examination of the validity of Rodbard's method by comparing it with auscultatory arterial pressure measurements

Recording the Korotkoff sounds and sphygmomanometer cuff pressures has formed the basis of automatic blood pressure measurement devices, developed to reduce subjective measurement errors. These devices were usually designed to pick up the sounds audible through a stethoscope, and were validated by a comparison of the systolic and diastolic pressures measured by the devices with those measured by auscultation. In validating these devices, aspects of Rodbard's method were also validated, because Rodbard's method determines systolic pressure (phase I) and diastolic pressure (phase V) in the same way.

Currens, Brownell, and Aronow (1957) found that their recording device gave mean systolic pressures 2 mmHg higher and mean diastolic pressures 4 mmHg lower than auscultation. These values were similar to those found by Zuidema, Edelberg, and Salzman (1956), Edinger and Spring (1963), and Mastropaolo et al (1964).

The use of Korotkoff sounds as the basis of automatic blood pressure measurement devices led to research into the character of the Korotkoff sounds. A review of this topic was included in a paper by Maurer and Noordergraaf (1976),

who found three characteristic frequency changes during blood pressure measurement. At phase I there was an increase in amplitude in the range of 20-70 cps, at phase IV there was a decrease in amplitude in the range of 60-300 cps, and at phase V there was a decrease in amplitude in the range of 40-300 cps. These changes are similar to those reported by McCutcheon, Baker, and Wiederhielm (1969) and by Golden, Wolthuis, Hoffler, and Gowen (1974). McCutcheon et al (1969) found an increase in amplitude in the range of 60-180 cps at phase I, and a decrease in this same range at phase IV. Golden et al (1974) found an increase in amplitude between 18-26 cps at phase I, and a decrease between 40-60 cps at phase V. These differences in the frequency composition of the Korotkoff sounds were probably due to their variability from subject to subject and sound recorder to sound recorder. Differences within the same subjects from time to time have also been found: the amplitudes of the higher frequencies were increased in intensity by exercise (Ware and Anderson, 1966), and decreased during cardiovascular shock (Whitcher et al, 1967).

Whitcher, Smith, Cole, Mantey, Weaver, Huntingdon, and Dixon (1967) found that in two normal subjects 90.2% of the energy of the Korotkoff sounds was below 32 cps and 68% of the energy was below 8 cps. This preponderance of inaudible sound was even greater in a hypotensive postoperative patient, where 99% of the energy of the Korotkoff sounds was

below 8 cps. Maurer and Noordergraaf (1976) found that more than 90% of the energy of the Korotkoff sounds was present at frequencies less than 25 cps, and insisted that this low frequency sound must be filtered out if the small changes occurring at phases IV and V were to be detected. As a result of their frequency studies these authors used a 50-160 cps filter in their automatic recorder to detect phases I, IV, and V of the Korotkoff sounds. With this filter, phase I was correctly identified in 97% of the measurements when compared with independent auscultatory measurements, phase V in 94% of the measurements, and phase IV in 55% of the measurements. The criterion for a correct reading was that the discrepancy was 5 mmHg or less. When the filter was changed to 40-140 cps, agreement between the machine and the independent auscultatory measurements was reduced. Phase I was correctly identified in only 65% of the measurements, phase V in 67% of the measurements, and no reliable results were obtained for phase IV.

To summarize: Both automatic blood pressure measurement devices and Rodbard's method rely on the efficient detection of those Korotkoff sounds which are in the audible range. Detection was found to be most efficient when low frequency sounds were filtered out with a 50-160 cps filter. Systolic and diastolic blood pressures measured with recording devices were found to be closely correlated with auscultatory values obtained by trained observers.

As Rodbard's method determines phases I and V in the same way as automatic blood pressure measurement devices, the validation of these devices also validates Rodbard's method as a method for determining blood pressure indirectly.

c. An examination of the validity of Rodbard's method by considering the causes of the Korotkoff sounds

A knowledge of the causes of the Korotkoff sounds is essential to an understanding of the nature of the slope produced by Rodbard's method.

McCutcheon and Rushmer (1967) isolated two components of the Korotkoff sounds: the first was a sharp tapping noise which was nonspecific and could be imitated by tapping the skin of the arm, and the second was a low-amplitude jet noise or compression murmur which was present throughout but tended to be masked until phase IV by the first component. The authors used the onset of the first component to identify phase I (systolic pressure), its disappearance to identify phase IV, and a marked decrease in the second component to identify phase V (diastolic pressure).

To investigate the causes of the Korotkoff sounds they placed Doppler flow meters over the brachial artery 2 cm proximal to the sphygmomanometer cuff and also under the cuff. They compared the output of the flow meters with the Korotkoff sounds produced during deflation of the cuff. The proximal flow meter signal changed only slightly, but the cuff flow meter signal changed markedly. At phase I the

cuff flow meter produced a sharp spike which remained while cuff pressure continued to fall, until at phase IV it disappeared. In addition, as the cuff pressure fell below systolic pressure the remaining portion of the cuff flow meter signal increased until, allowing a slight delay for transmission time, it resembled the proximal flow meter signal. Tall signal spikes from Doppler flow meters are produced by low velocity displacement of surfaces such as arterial walls and the intervening fascial planes. The appearance of the spike at phase I and its disappearance at phase IV coincided with the appearance and disappearance of the first component of the Korotkoff sounds. From this the authors concluded that the first component of the Korotkoff sounds is associated with sudden, transient wall movements produced by the advancing slope of the blood velocity wave.

On the other hand, Mastropaolo et al (1964), London and London (1967), and Geddes et al (1968) inasmuch as they compared the slope produced by Rodbard's method with intra-arterial pressure measurements, would appear to have attributed the production of the first component of the Korotkoff sounds to the advancing slope of the pressure pulse wave.

The blood velocity wave, the pressure pulse wave, and the diameter pulse wave are not the same (Dontas and Cottas, 1962; Mills, Gabe, Gault, Mason, Ross, Braunwald, Shillingford, 1970; and McDonald, 1974, pp 118-119). The blood velocity wave is the pulse wave measured as blood flow

in cm/sec, the pressure pulse wave is the pulse wave measured in mmHg, and the diameter pulse wave is the pulse wave measured as the percentage increase of arterial diameter (see Figure 2). The blood velocity wave arrives later than the pressure pulse wave, peaks before the pressure pulse wave, and decreases while the pressure pulse wave is still rising. It is unlikely that the blood velocity wave is reproduced by Rodbard's method, because the blood velocity wave has already peaked and is falling when the pressure pulse wave is still rising. However, pulsatile changes in the diameter of the artery could produce the transient wall movements observed by McCutcheon and Rushmer (1967): only minor differences exist between the pressure pulse wave and the diameter pulse wave, and the differences that do exist can readily be explained in terms of non-linear elasticity and viscosity (O'Rourke, 1971). As intra-arterial pressure increases the diameter change per mmHg decreases (Steele, 1937; Cox, 1979), so that, depending upon the elastic properties of the arteries, wall movements would be expected to decrease and perhaps cease altogether as systolic pressure rises.

Dontas and Cottas (1961) compared the diameter pulse wave with the pressure pulse wave in the brachial artery of young human subjects and found that they were very similar: the foot of the pressure pulse wave arrived 10.4 ± 12.7 msec later than the foot of the diameter pulse wave, although the pressure pulse wave increased more quickly than

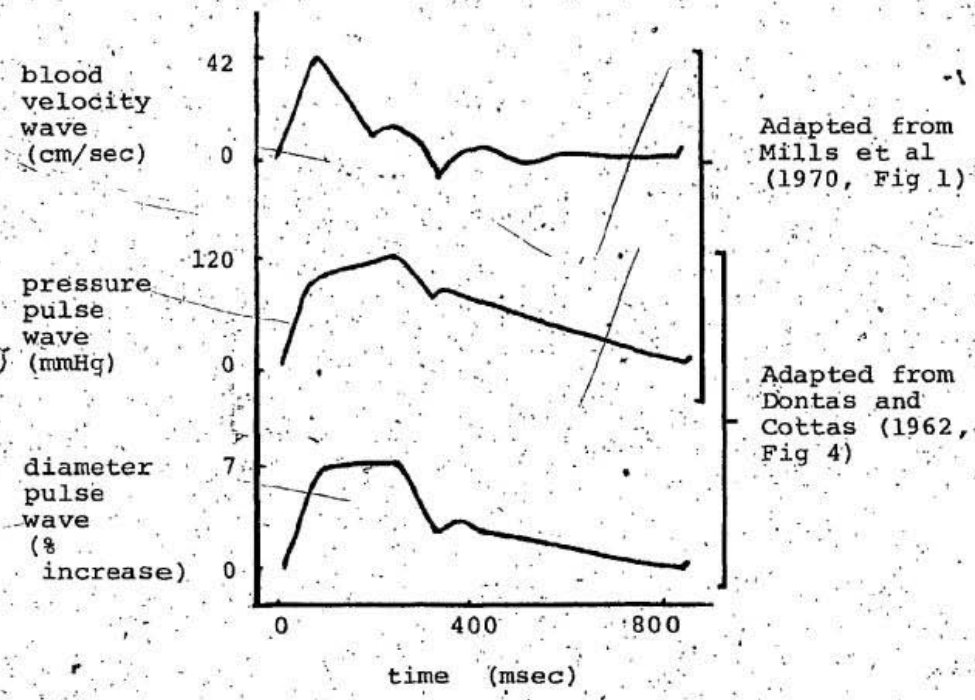


Figure 2. Blood velocity wave, pressure pulse wave, and diameter pulse wave as they might look if they were recorded simultaneously from the brachial artery of a man aged fifty-six years.

the diameter pulse wave. If the first component of the Korotkoff sounds is produced by wall movements caused by the diameter pulse wave, then the slope produced by Rodbard's method is most likely that of the diameter pulse wave rather than that of the pressure pulse wave. If this conclusion is correct, it explains why Geddes et al (1968) found that the rate of pressure rise determined by Rodbard's method was slightly less than that determined from their intra-arterial records. It also explains why there was a highly significant correlation ($r = .56$, $P<.002$) between the height of the intra-arterial systolic pressure and the degree of accuracy involved in measuring systolic pressure by auscultation or by Rodbard's method (Breit and O'Rourke, 1974; see also Van Bergen et al, 1954; and Roman et al, 1965). From the foregoing it would seem likely that the first component of the Korotkoff sounds isolated by McCutcheon and Rushmer (1967) is associated with sudden, transient wall movements produced not by the advancing slope of the blood velocity wave as the authors tentatively suggested, but rather by the diameter pulse wave.

The second component, ie, the low amplitude jet noise heard between phases IV and V, is probably produced by a different mechanism because the amount of displacement of the arterial wall by the cuff is minimal between phases IV and V. McCutcheon and Rushmer (1967) suggested that this second component is due to disturbances in the blood as it

flows under the cuff, and indeed Anliker and Raman (1966) found that the mere presence of the cuff was responsible for the audible nature of the disturbances in the blood at this stage because it so destabilized the artery that previously inaudible disturbances were amplified into the audible range. Thus it is possible that the low amplitude jet noise is produced by the sudden acceleration and deceleration of the velocity flow wave as it passes through the destabilized artery. Rodbard and Saiki (1953), using an experimental model, recorded the audible vibrations of the simulated arterial wall for different fluid velocities and cuff pressures, and explained these vibrations in terms of Bernoulli's principle: when either lateral pressure or velocity increases the other must decline by an equivalent amount. To apply this to the actual arterial wall: when the velocity of blood flow increases, lateral pressure decreases so that the arterial wall can be expected to move inwards; and when velocity of blood flow decreases, lateral pressure increases so that the arterial wall can be expected to move outwards. This provides a likely explanation of the wall vibration caused by the sudden acceleration and deceleration of the velocity flow wave, and indeed Rodbard (1953) and Rodbard et al (1957), while recording the Korotkoff sounds in human subjects, found a direct relationship between blood flow and the duration and intensity of the second component of the Korotkoff sounds: reducing flow

to an arm by tightening a tourniquet distal to the sphygmomanometer cuff reduced the duration and intensity; and increasing flow by producing a reactive hyperemia in the same arm increased the duration and intensity. Rodbard and Margolis (1956) found a direct relationship between cardiac cycle lengths in the 400-600 msec range and the duration and intensity of the second component of the Korotkoff sounds. Using a constant cuff pressure of 100 mmHg, they found that in seven patients whose cardiac cycle lengths changed spontaneously because of atrial fibrillation the duration and intensity were greatest when the previous cycle lengths were longest, and least when the previous cycle lengths were shortest. It should be noted that the above changes in cardiac cycle length would be expected to change blood flow, and thus the findings of Rodbard and Margolis (1956) would appear to be compatible with those of Rodbard (1953) and Rodbard et al (1957). The changes in flow in these three papers probably involved increases in both the blood velocity wave and the diameter pulse wave, and it is unfortunate that neither of these pulse waves was measured in any of the papers.

To summarize: Korotkoff sounds are probably caused by disturbances in the blood itself and by arterial wall movements produced by the diameter pulse wave, nonlaminar flow in the artery, and the interrelationship of the velocity flow wave and lateral pressure.

It is suggested that the first component of the Korotkoff sounds, that heard between phases I and IV, is produced by wall movements caused by the diameter pulse wave, and that the slope constructed by Rodbard's method at this stage is that of the diameter pulse wave rather than that of the pressure pulse wave. This would explain the highly significant correlation between the level of intra-arterial systolic pressure and the size of the discrepancy between the systolic pressure values measured intra-arterially and those measured by auscultation.

It is further suggested that the second component of the Korotkoff sounds, that heard best between phases IV and V, is largely produced by wall movements caused by the sudden acceleration and deceleration of the blood velocity wave, and that the slope constructed by Rodbard's method at this stage is that of the blood velocity wave. It was found that the mere presence of the cuff was responsible for the audible nature of the disturbances in the blood or arterial wall at this stage, because it so destabilized the artery that previously inaudible disturbances were amplified into the audible range.

If it is true that the Korotkoff sounds are produced by wall movements caused by the diameter pulse wave and the velocity flow wave, variations in the Korotkoff sounds can be expected to result from variations in the strength of these two waves between subjects and within the same

subjects from time to time. Within the same subjects marked variations in frequencies and intensities have been found to be associated with exercise and cardiovascular shock, and marked variations in intensity and duration have been found after manoeuvres expected to modify blood flow under the sphygmomanometer cuff. Little investigation has been done into the variations in frequencies, intensities, and duration between subjects, even though such research might yield information useful to the clinician.

Because the diameter pulse wave is closely related to the intra-arterial pressure pulse wave it will be assumed in this thesis that the slope constructed by Rodbard's method adequately approximates the anacrotic slope of the intra-arterial pressure pulse wave. This assumption is appropriate to an epidemiological study where most of the comparisons are made with auscultatory and not with intra-arterial pressure measurements.

SECTION 2

QKD

Basically Rodbard's method provides two pieces of information. The first of these is QKD, which is a numerical value for the time elapsing between the Q wave of the electrocardiograph and the arrival of the foot of the arterial pressure pulse wave at the brachial artery under

the cuff. The second and more complex piece of information is the shape of the anacrotic slope of the pressure pulse wave, which will be considered in Section 3 after the factors affecting QKD have been investigated.

QKD is a complex time interval. It can be considered as being made up of two components: the pre-ejection period of the cardiac cycle, and pulse wave transmission time, ie, the time taken for the foot of the pressure pulse wave to travel from the ascending aorta to the brachial artery. An understanding of the nature of both of these components is essential to a proper understanding of the nature of QKD. Pre-ejection period and pulse wave transmission time will be considered separately, with particular reference to the factors affecting them and their usefulness as predictors of cardiovascular disease. The changes in QKD reported in the literature will then be examined to see the extent to which the factors which affect its two components also affect QKD, and the extent to which QKD itself is useful as a predictor of cardiovascular disease.

a. The factors affecting pre-ejection period

Pre-ejection period is also a composite of two time intervals: electromechanical delay, and isovolumetric contraction time. Electromechanical delay is the time elapsing between the Q wave of the electrocardiograph and the onset of mechanical contraction. It includes the time

taken for the ventricular muscle to be completely depolarized and also the time taken for the myofibrils to stretch the elastic components of the heart up to the point where pressure begins to rise and the mitral valve closes. Isovolumetric contraction time is the time taken to raise ventricular pressure from ventricular end-diastolic pressure to aortic diastolic pressure. Most of the changes in pre-ejection period are due to changes in isovolumetric contraction time (Metzger, Chough, Kroetz, and Leonard, 1970; Martin, Shaver, Thompson, Reddy, and Leonard, 1971; McConahay, Martin, and Cheitlin, 1972; Spodick and Quarry-Pigott, 1973). As Rodbard's method does not distinguish between electromechanical delay and isovolumetric contraction time it is necessary in this thesis to combine these two intervals and treat pre-ejection period as a unit. An indication of the duration of pre-ejection period for groups of normal subjects resting supine is provided by Table 1.

1. Cardiac contractility

Cardiac contractility is the chief factor affecting pre-ejection period. Any factor which increases cardiac contractility decreases pre-ejection period, and vice versa (Tavel, 1978, pp 189-92). This was seen by, among others, Martin et al (1971), Talley et al (1971), and McConahay et al (1972), who used the rate of rise of ventricular pressure as their measure of cardiac contractility. Where cardiac

Table 1. The duration of pre-ejection period in seven groups of normal subjects at rest in the supine position.

Authors	Pre-ejection Period (msec)	Standard Deviation	Number of Subjects
Harris et al, 1967	105	14	49
Amidi et al, 1968	103	16	10
Fabian et al, 1972	100	13	50
Shaw et al, 1973	99	15	218
Spodick et al, 1973	109	16	10
Cokkinos et al, 1976	107	9	26
Wikstrand et al, 1978	104	13	54

contractility is altered by factors which influence or imitate the inotropic action of the sympathetic nervous system, pre-ejection period is also altered. For example: pre-ejection period decreased 30 msec ($P<.001$) during exercise (Spodick et al, 1973; Van der Hoeven, Clerens, Donders, Beneken, and Vonk, 1977), decreased 30 msec ($P<.001$) with the administration of epinephrine (Harris, Schoenfeld, and Weissler, 1967), and increased 10-24 msec ($P<.05$) with the administration of the β-blocking drug, propranolol (Harris et al, 1967; Roland, Safar, Lelguen, Aboras, Weiss, and Milliez, 1977). In addition, where cardiac contractility is altered by factors which influence the myocardial metabolism directly, pre-ejection period is also altered. For example: pre-ejection period was found to be 25 msec ($P<.001$) shorter in hyperthyroid subjects and 40 msec ($P<.005$) longer in hypothyroid subjects than it was in the normal controls (Amidi, Leon, DeGroot, Kroetz, and Leonard, 1968).

2. Ventricular end-diastolic pressure and volume

The relationship between pre-ejection period and ventricular end-diastolic pressure and volume is not as well established as that between pre-ejection period and cardiac contractility. Within subjects with cardiac disease a positive correlation may exist as compared with healthy subjects where the correlation is negative. Talley et al (1971) found that within dogs an inverse relationship

existed between pre-ejection period and ventricular end-diastolic pressure. Similarly Spodick et al (1973) found pre-ejection period was 109±16.2 msec in ten healthy human subjects in the supine position (where end-diastolic pressure and volume are maximum) and 127±17.7 msec in the same subjects in the upright position (where end-diastolic pressure and volume are reduced). The probable explanation of this inverse relationship is that pre-ejection period is lengthened when end-diastolic pressure and volume are reduced because it takes longer for the myofibrils to stretch the elastic components of the heart when they are under reduced tension. Quite the opposite relationship was found by Garrard, Weissler, and Dodge (1970), who obtained a significant positive correlation ($r = .56$, $P<.001$) between pre-ejection period and ventricular end-diastolic volume in a group of sixty-eight patients with a wide variety of cardiac conditions. That the relationship between pre-ejection period and end-diastolic pressure and volume in patients with cardiac disease is opposite to that found in healthy subjects is probably due to the relationship that exists between the degree of heart failure and both the rate of ventricular pressure rise and end-diastolic volume.

3. Diastolic pressure

A small but significant relationship between pre-ejection period and aortic diastolic pressure was found in

dogs by Talley et al (1971) and in comparisons between nine hypertensive human subjects, with diastolic pressures of 90-135 mmHg by Shaw, Rothbaum, Angell, and Shock (1973). However, no relationship was found in comparisons between normotensive human subjects with diastolic pressures of less than 90 mmHg (Montoye, Willis, Howard, and Keller, 1971; Shaw et al, 1973).

4. Heart rate

Heart rate has been considered to be an important factor affecting pre-ejection period, and it has been customary in comparisons between individuals to correct pre-ejection period for differences in heart rate (Shaw et al, 1973; Meng, Hollander, Liebsen, Teran, Barresi, and Lurie, 1975; Ghose, Mitra, and Chhetri, 1976; Cokkinos, Theimonas, Demopoulos, Haralambak, Tsartsalis, and Gardikas, 1976; Sykes, Wright, Malins, and Pentecost, 1977). Usually these corrections are based on regression equations published by Weissler, Harris, and Schoenfeld (1968). However, although these authors provided significant ($P<.005$) regression equations for pre-ejection period and other systolic time intervals, they did not give correlation coefficients and so it is difficult to estimate the amount of variation explained by heart rate. Weissler was one of three co-authors of a paper (Garrard et al, 1970) in which correlation coefficients as low as $r = .31$ were reported to be significant ($P<.001$). Correlations of $r = .3$ are

considered to explain only approximately nine per cent of variation, and therefore it is doubtful if the data provided by Weissler et al (1968) justify the correction of pre-ejection period for heart rate.

An indication of the degree of correlation of pre-ejection period and heart rate in comparisons between individuals at rest is provided in Table 2. It is doubtful whether these low levels of correlation justify the correction of pre-ejection period for differences in heart rate.

Intuitively, pre-ejection period and heart rate are expected to be inversely correlated because of the known inotropic and chronotropic effects of the sympathetic nervous system, which are particularly evident when sympathetic function has been stimulated by exercise or mimicked by medication. Certainly, in comparisons within the same individuals Van der Hoeven et al (1977) obtained a high degree of correlation ($r = -.97$) between pre-ejection period and heart rate when changes in heart rate were produced by gradually increasing exercise work loads. However, significant correlation of these two variables measured within the same individuals does not justify correction of pre-ejection period for heart rate in comparisons between individuals at rest, because, as was pointed out by Abboud (1979), activation of sympathetic efferent activity in resting individuals is non-uniform.

Table 2. The correlation and significance of the association between pre-ejection period and heart rate in six groups of normal subjects at rest in the supine position.

Authors and (where provided) Regression Equations	Correlation Coefficient	Level of Significance	Age (years)	Number of Subjects
Weissler et al, 1968 PEP = 131 - 0.4 HR	?	P<.005	19-65	121
Montoye et al, 1971 PEP = 114.5 - 0.39 HR	- .28	P<.005	40-49	151
Fabian et al, 1972 PEP = 126 - 0.34 HR	- .3	P<.05	18-79	50
Shaw et al, 1973 PEP = 136 - 0.56 HR	- .42	P<.001	20-89	218
Wikstrand et al, 1978				
Normotensive subjects	0	-	50	36
Hypertensive subjects	- .52	P<.05	50	18

HR: heart rate
PEP: pre-ejection period

Talley et al (1971) suggested that correlation of pre-ejection period and heart rate was due to adrenergic stimulation and that changes in heart rate alone did not result in changes in pre-ejection period. Harris et al (1967), Talley et al (1971), and Cokkinos et al (1976) all found that changes in heart rate produced by administration of atropine or by atrial pacing did not result in changes in the pre-ejection period even when heart rate was markedly altered. Therefore it is likely that the level of correlation of pre-ejection period and heart rate that was found in comparisons between individuals at rest (see Table 2, p 29) was not caused by changes in heart rate but rather by sympathetic activation above the basal level. For example, the low levels of correlation found by Montoye et al (1971), Fabian, Epstein, Coulshed (1972) and Shaw et al (1973) probably resulted from sympathetic activation triggered by the unfamiliar environment of the tests, fasting, etc, while the higher level of correlation found by Wikstrand, Berglund, Wilhelmsen, and Wallentin (1978) in his hypertensive as opposed to his normotensive subjects probably resulted from the high level of sympathetic activity that is present in a small proportion of hypertensives.

Because the levels of correlation of pre-ejection period and heart rate in comparisons between individuals at rest are low and because heart rate per se does not appear to affect pre-ejection period, this author is not convinced

that the automatic correction of pre-ejection period for heart rate is justified.

This is in contrast to the automatic correction of another systolic time interval, left ventricular ejection time, for differences in heart rate. This correction can be justified because:

1) the level of correlation between left ventricular ejection time and heart rate in comparisons between individuals is high (eg, Wikstrand et al [1978] found a correlation of $r = -.79$, $P<.001$), and

2) an explanation of the underlying mechanism producing this correlation has been provided by O'Rourke (1970), who found that, because left ventricular ejection time was affected by the harmonic composition of the pulse wave (see this thesis pp 79-82) which in turn was affected by heart rate and/or cardiac contractility, changes in heart rate alone, regardless of cause, are capable of producing changes in left ventricular ejection time.

5. Age and disease

Pre-ejection period has been found to change with age. It increases markedly in children up to age fifteen (Spitaels, Arbogast, Fouron, and Davignon, 1974); and small increases of 4 msec per decade were found in adults up to age sixty, after which it was found to decrease (Simonson and Nakagawa, 1960; Montoye et al, 1971; Shaw et al, 1973).

Van der Hoeven et al (1977) found that pre-ejection period was 9 msec longer for a group of subjects aged forty-one to sixty-six years than it was for a group aged twenty-one to thirty-eight years.

As with other systolic time intervals, significant correlations have been found between pre-ejection period and certain invasively measured indices of cardiac function, eg cardiac index, stroke index, venous pressure, and total peripheral resistance (Weissler et al, 1968; Weissler, Harris, and Schoenfeld, 1969; Garrard et al, 1970; Martin et al, 1971; McDonald and Hobson, 1974; Meng et al, 1975). However the discriminatory value of systolic time intervals to detect cardiac impairment is poor because their sensitivity and specificity are too low (McConahay et al, 1972; Parker and Just, 1974; Wikstrand et al, 1978). Tavel (1978, pp 201-02), while agreeing in the main with the findings of these last authors, nevertheless found that pre-ejection periods longer than 120 msec in combination with values of 0.5 or more for the ratio of pre-ejection period to left ventricular ejection time were associated with profound myocardial disease and thus were useful in assessing the value of surgery for patients with mitral regurgitation. Benchimol (1977, p 367) attached very little importance to the measurement of systolic time intervals, especially pre-ejection period, as a noninvasive technique available to the cardiologist. However, he did conclude that the ratio

of pre-ejection period to left ventricular ejection time appeared to be correlated with the degree to which stroke volume or left ventricular function was impaired. Thus it would appear that pre-ejection period alone, although it is prolonged in profound myocardial disease, lacks the sensitivity and specificity required to be useful as a screening measurement for cardiovascular disease.

To summarize: The pre-ejection period component of QKD is affected by cardiac contractility, with which it is inversely correlated. Cardiac contractility may be altered indirectly by factors (such as exercise and propranolol) which affect the inotropic activity of the sympathetic nervous system, or directly by factors (such as the thyroid hormones) which affect the myocardial cells. Pre-ejection period is also influenced by ventricular end-diastolic volume, which may be altered by a change of body position or by cardiovascular disease. Pre-ejection period is affected by aortic diastolic pressure, as was seen in animal experiments and in a small group of hypertensive human subjects.

Pre-ejection period does not appear to be affected by heart rate when cardiac contractility is unchanged, and the low level of correlation between pre-ejection period and heart rate in comparisons between resting individuals relies upon the correlation of the inotropic and the chronotropic

effects of the sympathetic nervous system when it is stimulated above its basal level.

Pre-ejection period increases markedly in children up to age fifteen years, and more gradually in adults up to age sixty years, after which it decreases.

While pre-ejection period is correlated with invasively measured indices of cardiac function and is prolonged in profound myocardial disease, it lacks the required sensitivity and specificity to be useful as a tool to screen populations for cardiovascular disease.

b. The factors affecting pulse wave transmission time

Pulse wave transmission time depends upon pulse wave velocity and arterial length (the distance travelled by the pressure pulse from the aortic valves to the brachial artery under the cuff).

1. Pulse wave velocity

Pulse wave velocity can be estimated by the Moens-Korteweg equation: $c = (Eh/2R\rho)^{1/2}$ where c is pulse wave velocity, E is Young's modulus for the artery, h is its wall thickness, R is its internal radius, and ρ is the density of the blood (McDonald, 1974, pp 253-55). This equation indicates the factors which have the potential to influence pulse wave velocity: Young's modulus, the ratio of the thickness of the arterial wall to its internal diameter, and blood density.

It is to be noted that neither blood flow velocity nor heart rate are in this list. In theory, blood flow velocity should be added to the Moens-Korteweg equation because this equation was designed to apply to a static fluid only. However, in fact, mean blood flow velocity is small (0.15-0.25 m/sec) when compared with mean pulse wave velocity (4.0-8.0 m/sec) and so it is generally ignored as a factor affecting pulse wave velocity (McDonald, 1974, pp 404-06). Heart rate, which was not included in the Moens-Korteweg equation, has been considered to be a possible factor affecting pulse wave velocity, but it has been determined experimentally that it has no influence (Anliker, Histand, and Ogden, 1968; Eliakim, Sapoznikov, and Weinman, 1971).

Blood density, although it is represented in the Moens-Korteweg equation, can be disregarded as a factor producing variation in pulse wave velocity, because it remains so constant in vivo. Van Slyke, Phillips, Dole, Hamilton, Archibald, and Plazin (1950) found that for a group of twenty normal men, the mean specific gravity of whole blood was 1.0595 ± 0.0021 and the range was 1.0568-1.0635; and that even for a group of forty-seven hospital patients including fourteen with hematocrits of less than 30% (a condition associated with low specific gravity of the blood), the range of specific gravity was 1.0289-1.0640. If all the other factors in the Moens-Korteweg equation remain constant, the change in pulse wave velocity, using the most

extreme range of specific gravity given by Van Slyke et al (1950), would be only 0.15 m/sec. This is too small in comparison with the level of variation in pulse wave velocity to be significant.

Thus, in vivo, Young's modulus and the ratio of the thickness of the arterial wall to its internal diameter remain the two factors of the Moens-Korteweg equation which have the potential to influence pulse wave velocity. However, both these factors are themselves influenced by the location of the artery, the age of the subject, intra-arterial pressure, smooth muscle tone, and arterial disease. Because this thesis is more concerned with this latter set of factors, their effect on pulse wave velocity will now be considered seriatim. Where appropriate, reference will be made to Young's modulus and the ratio of arterial wall thickness to its internal diameter.

i. Location of the artery

Pulse wave velocity depends upon the location of the artery over which it is travelling. One reason for this is that Young's modulus of the arterial wall increases with distance from the heart (McDonald, 1974, p 277) because of changes in arterial composition (ie the relative amounts of elastin, collagen, and smooth muscle [McDonald, 1974, pp 262-266]), and arterial structure (ie the proportion of collagen fibres actually supporting wall stress at a given

pressure [Cox, 1979]). Another reason why pulse wave velocity depends upon the location of the artery is that the ratio of the thickness of the arterial wall to its internal diameter would appear also to increase with distance from the heart (Learoyd and Taylor, 1966).

As is to be expected from the increase in Young's modulus and the ratio of the thickness of the arterial wall to its internal diameter, pulse wave velocity also increases with distance from the heart. This can be seen in Table 3.

ii. Age

The subject's age was found to be the most important factor affecting pulse wave velocity in human subjects (Haynes, Ellis, and Weiss, 1936; Steele, 1937; Simonson and Nakagawa, 1960; Schimmler, 1966; Eliakim et al, 1971; Della Corte, Locchi, Spinelli, and Scarpelli, 1979; Hasegawa and Rodbard, 1979). Pulse wave velocity increases 0.28-0.72 m/sec for each ten years of age between twenty and sixty years, and 0.8-0.9 m/sec after fifty-five years (Della Corte et al, 1979).

This increase in pulse wave velocity with age is caused by the parallel increase with age of Young's modulus of the arteries, intra-arterial pressure, and the ratio of the thickness of the arterial wall to its internal diameter. The most important of these is the increase of Young's

Table 3. Pulse wave velocity values for several canine and human arteries determined by a variety of authors.

Authors	Arteries Involved	Pulse Wave Velocity (m/sec)
SINGLE ARTERIES		
Canine Values		
McDonald, 1968	Thoracic Aorta	4.46
	Abdominal Aorta	5.96
	Carotid	7.35
	Iliac	6.99
	Femoral	9.93
	Tibial	13.39
Human Values		
*Learoyd and Taylor, 1966	Thoracic Aorta	5.8-8.0
*Learoyd and Taylor, 1966	Abdominal Aorta	5.5-8.0
De Monchy and Van der Hoeven, 1976		4.5
*Bramwell et al, 1923	Carotid	8-12
*Learoyd and Taylor, 1966	Iliac	7-8
*Kapal et al, 1951	Femoral	8
*Learoyd and Taylor, 1968		13-18
MULTIPLE ARTERIES		
Human Values		
*Fulton and McSwiney, 1930	Carotid to Brachial	4.7
*Hickson and McSwiney, 1925	Carotid to Radial	5-6
*Hemingway et al, 1928		6
*Hallock, 1934		6-7
*Wezler and Boger, 1936		7.5-9.0
Woolam et al, 1962		6.5-9.0
Gunn et al, 1965		6.75-9.8
De Monchy and Van der Hoeven, 1976	Axillary to Radial	10
*Bazett and Dryer, 1922	Brachial to Radial	8.5-7.0
*Fulton and McSwiney, 1930		8.7
Kroeker and Wood, 1955		11-14
Simonson and Nakagawa, 1960	Aortic to Femoral	6.73
*Bazett and Dryer, 1922	Femoral to Dorsalpedis	9
*Bazett et al, 1935		8.8
Cachovan et al, 1968		9.48
Eliakim et al, 1971		9.4-10.2
De Monchy and Van der Hoeven, 1976		7.5

Note: Pulse wave values obtained by authors marked with an asterisk are reproduced from a table collated by McDonald (1974, p 418) and they are not included in the list of references accompanying this thesis.

modulus with age. Bader (1967) found that Young's modulus was four times greater in a group of subjects aged eighty-five years than it was in a group aged twenty years. As can be seen from the Moens-Korteweg equation, if all other factors remain constant a four-fold increase in Young's modulus would double pulse wave velocity.

The second reason for the increase of pulse wave velocity with age is the increase in intra-arterial pressure with age. Della Corte et al (1979), using multiple regression analysis, found that the correlation of the increase of pulse wave velocity with the increase of age was $r = .691$ ($P<.001$) while the correlation of the increase of pulse wave velocity with the increase of intra-arterial pressure was $r = .392$ ($P<.01$). Pulse wave velocity increased 0.585 ± 0.087 m/sec for each ten years of age, and 0.177 ± 0.059 m/sec for each 10 mmHg.

The third reason for the increase of pulse wave velocity with age is the increase with age of the ratio of the thickness of the arterial wall to its internal diameter. Learoyd and Taylor (1966) found that this ratio was twice as great in the arteries of a group of subjects aged thirty-six to fifty-two years as it was in the arteries of a group aged eleven to twenty years. As can be seen from the Moens-Korteweg equation, if all other factors remain constant a two-fold increase of the ratio of the thickness of the

arterial wall to its internal diameter would increase pulse wave velocity by forty percent.

iii. Intra-arterial pressure

Pulse wave velocity increases with rising intra-arterial pressure, because, as was reported by McDonald (1974, p 268), rising intra-arterial pressure produces an increase in Young's modulus. However, rising intra-arterial pressure also produces a decrease in the ratio of the thickness of the arterial wall to its internal diameter (Learoyd and Taylor, 1966; Folkow, 1978a), which tends to oppose the increase in pulse wave velocity caused by the increase in Young's modulus.

The four components of intra-arterial pressure (systolic pressure, diastolic pressure, pulse pressure, and mean arterial pressure) have all been tested to determine their effect upon pulse wave velocity. Steele (1937) established that diastolic pressure was the only component of intra-arterial pressure which affected pulse wave velocity. In canine experiments he altered systolic pressure and diastolic pressure independently by opening arterio-venous shunts, by clamping the aorta, and finally by cutting the aortic valve. By these procedures he showed that within the individual dogs pulse wave velocity was affected by diastolic pressure and not by systolic pressure, pulse pressure, or mean arterial pressure. Steele (1937); Kraner,

Ogden, and McPherson (1959); Woolam, Schnur, Vallbona, and Hoff (1962) and Hasegawa and Rodbard (1979) found that within human subjects also diastolic pressure was important in determining pulse wave velocity.

Many authors, however, regard mean arterial pressure as the aspect of intra-arterial pressure which determines pulse wave velocity within individual subjects (Cachovan, Linhart, and Prerovsky, 1968; Brew and Fitzgerald, 1976; Steptoe, Smulyan, and Gribbin, 1976; Della Corte et al, 1979). This apparent divergence of opinion can be reconciled by bearing in mind that mean arterial pressure is based largely on diastolic pressure: it is usually calculated as being diastolic pressure plus one third of the pulse pressure, which itself is correlated with diastolic pressure.

However, when comparisons are made between individuals the relationship between diastolic pressure and pulse wave velocity is confounded. For example, Simonson et al (1955) obtained a significant correlation between individuals only in their hypertensive group ($P<.05$) and not in their normotensive group (see also Steele, 1937). The confounding of the relationship between diastolic pressure and pulse wave velocity is probably due to differences in arterial properties between individuals. Such differences were found to exist with respect to Young's modulus (Learoyd and Taylor, 1966) and the ratio of the thickness of the arterial wall to its internal diameter (Cox, 1979). For example, the latter

author found that when intra-arterial pressure was 100 mmHg the wall thickness of the carotid arteries was 45% larger and the internal diameter was 11.5% smaller in a group of ten-week-old spontaneously hypertensive rats than they were in a group of ten-week-old Wistar rats. That Steele (1937) and Simonson, Koff, Keys, and Minckler (1955) obtained a correlation between diastolic pressure and pulse wave velocity between individuals in their hypertensive groups and not between individuals in their normotensive groups is probably to be explained by the fact that the range of diastolic pressure was greater among the hypertensives, and the fact that, as was found by Learoyd and Taylor (1966) and Brew and Fitzgerald (1976), Young's modulus increases exponentially as a function of pressure and therefore the increase in pulse wave velocity for a unit increase in pressure is greater in the hypertensives.

iv. Smooth muscle tone

McDonald (1974, pp 406-07) found that in the canine aorta, pulse wave velocity increased when smooth muscle tone was increased by the infusion of norepinephrine, and intra-arterial pressure was kept constant. This increase in pulse wave velocity is what is to be expected because Young's modulus of smooth muscle increases with contraction from 0.0 dyne/cm^2 to 3.0 x 10^6 dyne/cm^2 (McDonald, 1974, p 264), and because the ratio of the thickness of the

arterial wall to its internal diameter also increases with contraction (Folkow, 1978).

The extent of the change in pulse wave velocity which results from a change in smooth muscle tone can only be guessed at because there is no suitable method of measuring smooth muscle tone. However, some idea of the magnitude of the change in pulse wave velocity resulting from a change in smooth muscle tone can perhaps be gained from Kroeker and Wood (1955). The unexpected decrease in human brachio-radial pulse wave velocity (from 12.5 m/sec to 11.0 m/sec) which these authors found when diastolic pressure was increased after exercise, may be attributed to a decrease in smooth muscle tone. The unexpected increase (from 12.5 m/sec to 14.1 m/sec) which they found when diastolic pressure was increased by only 2 mmHg during a seventy degree head-up tilt, may be attributed to an increase in smooth muscle tone.

v. Disease

Pulse wave velocity was found to be a poor indicator of cardiovascular disease (Haynes et al, 1936; Eliakim et al, 1971). While it was found to be increased in hypertension (Haynes et al, 1936; Steele, 1937; Simonson et al, 1955; Cachovan et al, 1968), Steele (1937) found no difference after correcting for age and diastolic pressure, and McLean, Clason, and Stoughton (1964) and Eliakim et al (1971) found

no significant increase in pulse wave velocity in hypertensive subjects under sixty years of age.

Pulse wave velocity was found to be consistently decreased in patients having advanced peripheral vascular disease, but no consistent change was found with arteriosclerosis (Simonson et al, 1955; Eliakim et al, 1971), even when calcification was clearly seen in X-ray pictures (Haynes et al, 1936).

In view of the lack of a consistent relationship between pulse wave velocity and disease, it is unlikely that pulse wave velocity will be a useful screening measurement for cardiovascular disease with the possible exception of advanced peripheral vascular disease.

2. Arterial length

Arterial length has the potential to be an important factor where comparisons are made between individuals, especially where significant differences in body size are present. Although arterial length in children has been found to be highly correlated both with pulse wave transmission time ($r = .97$; DeMonchy and Van der Hoeven, 1976) and with QKD ($r = .86$; Bereu, Haupt, Johnsonbaugh, and Rodbard, 1979), this variable has been ignored as a factor affecting the pulse wave transmission time component of QKD in adults.

To summarize: Brachial pulse wave transmission time depends upon pulse wave velocity and the length of the arterial segment travelled by the pressure pulse wave.

Pulse wave velocity is affected most by changes in Young's modulus and the ratio of the thickness of the arterial wall to its internal diameter, which are both influenced, in turn, by location of the artery, age of the subject, intra-arterial pressure, smooth muscle tone, and arterial disease. The effect upon pulse wave velocity of the density and the mean velocity of flow of blood is small enough to be ignored, and heart rate has no effect upon pulse wave velocity.

Pulse wave velocity

1) increases with distance from the heart and with age, because Young's modulus and the ratio of the thickness of the arterial wall to its internal diameter increase with distance from the heart and with age;

2) increases with rising intra-arterial diastolic pressure because rising diastolic pressure produces an increase in Young's modulus. The increase in pulse wave velocity is somewhat less than would be expected from the increase in Young's modulus because rising diastolic pressure decreases the ratio of the thickness of the arterial wall to its internal diameter. When comparisons are made between individuals the correlation of pulse wave velocity and

diastolic pressure is confounded by the differences which exist between individuals with respect to Young's modulus and the ratio of the thickness of the arterial wall to its internal diameter;

3) increases with an increase in smooth muscle tone because the contraction of smooth muscle increases Young's modulus and the ratio of the thickness of the arterial wall to its internal diameter;

4) decreases with advanced peripheral vascular disease. (No consistent change in pulse wave velocity has been found to be associated with hypertension or arteriosclerosis when pulse wave velocity is first corrected for the age and diastolic pressure of the subject.)

Although significant correlation between brachial pulse wave transmission time and arterial length has been found in comparisons between children, arterial length has been ignored as a factor influencing the pulse wave transmission time component of QKD in comparisons between adults.

c. The factors affecting QKD

It is often difficult to identify the factors affecting QKD in a given experimental procedure, because the two components of QKD, pre-ejection period and pulse wave transmission time, can shorten or lengthen independently, and because often more than one factor is involved. Factors

affecting these two components, and the nature of the responses, are summarized in Table 4.

The difficulty of identifying the factors affecting QKD in a given experimental procedure is exacerbated by the fact that information required for this purpose is not present in much of the literature. In addition to the understandable absence of numerical values for cardiac contractility, end-diastolic volume, and smooth muscle tone, even diastolic pressures are often omitted, and in the earlier papers there is a lack of even the most rudimentary statistical analysis. In spite of all these difficulties, an attempt has been made to identify and evaluate the relative importance of the factors most likely to be responsible for the changes in QKD reported in the literature and to classify the papers accordingly.

1. Comparisons within the individual

i. End-diastolic volume and diastolic pressure

Both end-diastolic volume and diastolic pressure are probably important factors in the changes in QKD reported by Rodbard and Margolis (1956). This paper, which is concerned with the relationship between QKD and cardiac cycle length in seven patients whose cardiac cycles changed spontaneously because of atrial fibrillation, provides a good example of the difficulties encountered in attempting to identify and evaluate the relative importance of the

Table 4. Factors affecting the two components of QKD (ie pre-ejection period and pulse wave transmission time) with an indication of the size and direction of the responses.

Factor Producing the Change	Pre-ejection Period (msec)	Pulse Wave Transmission Time (msec)
Comparisons within the individual		
Increased end-diastolic volume (after assuming horizontal position)	--	0
Increased diastolic pressure	+	--
Increased cardiac contractility (after exercise or epinephrine)	---	0
Decreased cardiac contractility (after propranolol)	++	0
Increased smooth muscle tone	0	-
Comparisons between individuals		
Increased arterial length (body height)	0	+
Increased age <15 years	++	-
20-55 years	+	-
>56 years	-	-
Hyperthyroidism	--	?
Hypothyroidism	+++	?
Profound myocardial disease	++	0
Advanced peripheral vascular disease	0	+

N.B. Symbols indicate the size of the responses recorded in sections IIa and IIb of this thesis:

+ = <15 msec increase - = <15 msec decrease
++ = 16-24 msec increase -- = 16-25 msec decrease
+++ = >26 msec increase --- = >26 msec decrease

factors responsible for the changes in QKD reported in the literature. The authors found that QKD was related to the length of the preceding cardiac cycle, being longest (240 msec) for the shortest cycles that allowed measurement of QKD, and shortest (140 msec) for the longest cycles. Unfortunately, although diastolic pressure is known to fluctuate markedly in atrial fibrillation, the 20 mmHg fluctuations presented in graphs for only four of the seven patients were the only measurements of changes in diastolic pressure available in the paper. Consequently, it is difficult to evaluate, for example, the relative importance of diastolic pressure and end-diastolic volume as factors causing the increase in QKD as cardiac cycle length decreases. (In atrial fibrillation diastolic pressure and end-diastolic volume are both reduced where cardiac cycle length is short). Using information supplied by Steele (1937), Steptoe et al (1976), and Hasegawa and Rodbard (1979), it is possible to estimate that a 20 mmHg fluctuation in diastolic pressure produces a change in pulse wave velocity of 1-2 m/sec and thus a change of 10-20 msec in the pulse wave transmission time component of QKD. This 10-20 msec interval will affect the length of the ensuing QKD. To obtain the amount of fluctuation in the pre-ejection period component of QKD which results from a fluctuation in end-diastolic volume it is necessary to correct QKD for the diastolic pressure prevailing at the time the QKD was

determined. This is impossible from the data presented in the paper because no diastolic pressure measurements were given for the QKD values provided. However, the 10-20 msec change in pulse wave transmission time calculated by the present author from the 20 mmHg fluctuations in diastolic pressure presented in the graphs are small compared to the 100 msec fluctuation in QKD reported in the paper, which would suggest that in atrial fibrillation changes in the pre-ejection period component due to fluctuations in end-diastolic volume have a much greater influence on QKD than do the changes in the pulse wave transmission time component due to the 20 mmHg fluctuations in diastolic pressure.

Another experimental model where end-diastolic volume may be the chief factor responsible for the change in QKD is one in which the subject is tilted from a supine to a standing position. End-diastolic volume is normally maximum when the individual is resting supine and reduced when he is resting in the upright position. Kroeker and Wood (1955) used the R wave of the electrocardiograph record for their reference point, and so their values are smaller than QKD by an amount equal to the QR interval. They obtained RKD values of 147 msec for subjects in the supine position and 165 msec after tilting them to a 70 degree head-up position. A change in pulse wave transmission time can be eliminated as a factor responsible for the change in RKD, because the

authors simultaneously measured pulse wave transmission time from the aorta to the brachial artery with intra-arterial catheters and found that it decreased by only 2 msec (which is clearly too small to be significant). Thus the increase, on tilting, of 18 msec in RKD was most probably due to an increase in the pre-ejection period component caused by the decrease in end-diastolic volume. Unfortunately, no statistical analysis was presented by the authors, and so this 18 msec change may not be significant. However, a similar increase on tilting was found by Miyahara and Rodbard (1961), and Hasegawa and Rodbard (1979). Miyahara and Rodbard (1961) found that QKD was 201 msec for subjects in the supine position and 230 msec after tilting them to a 75 degree head-up position. Again, this 29 msec increase in QKD was most probably due to a decrease in end-diastolic volume and its effect upon the pre-ejection period component of QKD. Support for this theory is to be found in the following:

1) When an anti-gravity G-suit was inflated prior to the tilt, there was no increase in QKD with tilting. This is to be expected because the decrease in end-diastolic volume resulting from the normal redistribution of blood away from the heart would be prevented by the positive pressure of the suit upon the abdomen and legs. (When the air pressure in the G-suit was lowered to atmospheric levels, QKD again increased.)

2) Patients with previous or present congestive heart failure did not show the expected increase in QKD on tilting. Again this is to be expected because such patients, having chronically high venous pressure and increased end-diastolic volume, may be unable to show the expected decrease in end-diastolic volume and the resulting increase in QKD. Changes in diastolic pressure and smooth muscle tone can both be eliminated as factors responsible for the 29 msec increase in QKD on tilting shown by the normal subjects, because both would be expected to cause, if anything, a decrease in QKD on tilting. Hasegawa and Rodbard (1979) obtained a 16 msec ($P<.05$) increase in QKD when their subjects were tilted to a 90 degree head-up position. Again, end-diastolic volume would appear to be the most likely factor responsible for the increase in QKD, because the 6.4 mmHg ($P<.05$) increase in diastolic pressure on tilting reported by the authors would be expected to cause a decrease, and not an increase, in QKD.

ii. Cardiac contractility

Although end-diastolic volume was probably the most important factor in the changes in QKD in the atrial fibrillation and postural studies, it is unlikely to be important in the following studies where all the measurements were made in the supine position at physiological heart rates. This is because end-diastolic volume is

maximum in the supine position, and diastolic filling time has an adequate reserve at physiological heart rates.

Changes in cardiac contractility and hence pre-ejection period can be produced by changes in the level of activity of the sympathetic nervous system supplying the left ventricle. The latter changes are produced by changing the amount of physical exercise or by administering drugs which mimic or block the action of the sympathetic nervous system.

Rodbard et al (1957) found that QKD, measured supine, had been reduced by 30 msec after two minutes of vigorous hopping, and Wassermil and Rodbard (1968) found that QKD had been reduced by 60 msec after the standard Masters two-step exercise. Inagaki, Wassermil, and Rodbard (1976) found that the mean QKD of sixteen subjects resting supine was 205 msec, and that immediately after four minutes of treadmill walking at 4 km/hr on a 10% incline, the mean QKD, again measured in the supine position, had been reduced by 60 msec. These reductions in QKD were probably due to an increase in cardiac contractility (and hence a decrease in the pre-ejection period component of QKD) known to occur with exercise. It is unlikely that reductions in QKD were due to a change in the pulse wave transmission time component of QKD because smooth muscle tone was probably reduced during the period of high systolic pressure immediately following the exercise, and Rodbard et al (1957) and Inagaki

et al (1976) reported that the changes in diastolic pressure were "minimal".

A reduction in QKD is also produced by drugs which mimic an increase in sympathetic nervous stimulation. Rodbard et al (1957) found that 0.03 mg of epinephrine injected intravenously reduced QKD by 40 msec. As it would seem from their graph that the epinephrine had no effect on diastolic pressure (which is indeed what one would expect), the shortening of QKD was most likely due to an increase in cardiac contractility. Unfortunately, the results of this experiment lack the support of statistical analysis. The same can be said of the paper by Henderson, Rodbard, and Morse (1972), who found that an injection of 1 mg of the beta-blocker propranolol promptly prolonged QKD from 220 msec to 250 msec, and that an additional 1 mg of propranolol prolonged QKD still further to 270 msec. Keller and Rodbard (1971) found that 40 mg of propranolol administered orally prolonged their QKD control value (212 ± 8 msec) by 31 ± 5 msec ($P<.01$) in twenty young adults. The decrease in QKD in response to epinephrine was most probably due to its known positive inotropic effect, and the increase in QKD in response to propranolol, a negative inotropic agent, supports this conclusion.

Changes in cardiac contractility and hence pre-ejection period can also be produced by administering drugs which affect the myocardial cells directly. Greco, Brereton, and

David Rodbard (1976) found that in eighty-nine subjects QKD had been increased by 13-24 msec two to three weeks after the infusion of adriamycin, which depresses myocardial function and which, administered in excess, can eventually cause overt heart failure. It is likely that at least a proportion of this increase in QKD resulted from the decreased cardiac contractility, and hence the increased pre-ejection period, which is expected to result from the myocardial toxicity of adriamycin. (This theory is supported by the fact that one of the patients, who died as a result of severe congestive heart failure, showed at autopsy marked fragmentation and edema of the myocardium, and also disruption of the mitochondria and myofibrils, all of which have been associated with adriamycin toxicity.) However, as the authors gave no diastolic pressures and did not refer to the effects of adriamycin toxicity upon smooth muscle tone, it is impossible to rule out a change in pulse wave transmission time as a factor in the increased QKD values reported by the authors.

The thyroid hormones are known to produce an increase in cardiac contractility and hence a decrease in the pre-ejection period component of QKD by directly affecting the myocardium (Amidi et al, 1968; Parisi, Hamilton, Thomas, and Mazzaferri, 1974). Rodbard and Kramer (1966), in a clinical study of four hypothyroid patients, found an unusually long mean QKD value of 270 msec. After three or more months of

thyroid medication, the mean QKD fell to 200 msec, which is within the normal range. In addition to an increase in cardiac contractility, increased diastolic pressure, and changes in smooth muscle tone and arterial structure may have contributed to this reduction. Of these four factors it is possible to estimate the contribution of only diastolic pressure, and then only in the case of the two patients for whom diastolic pressures were given. In both it increased by approximately 20 mmHg and such an increase can be expected to shorten the pulse wave transmission time component of QKD by <20 msec. Since QKD was reduced by 110 msec in these two patients, the difference between these two figures (ie 90 msec) is the change in QKD estimated to have been produced by increased cardiac contractility and changes in smooth muscle tone and arterial structure. Increased cardiac contractility can be seen to have been at work from the steeper arterial slopes which followed the thyroid medication; and, intuitively, cardiac contractility would seem to have been the most important factor in the reduction of QKD reported by these authors. Young, Van Herle, and Rodbard (1976) similarly found unusually long QKD values (>260 msec) in three hypothyroid patients, and an unusually short mean QKD value (137±15.6 msec) in ten hyperthyroid patients. With treatment, these QKD values returned to the normal range. Again the major factor contributing to these changes in QKD is most likely to have been cardiac contractility.

iii. Electromechanical delay

In the experiments discussed thus far in this subsection (pp. 46-56), changes in the duration of the electromechanical delay portion of pre-ejection period probably did not contribute to the changes in QKD. The same cannot be said for experiments where QKD values were obtained in the presence of left bundle-branch block or epicardial pacing of the heart. Libanoff and Rodbard (1967) found that when left bundle-branch block was present, QKD was increased by 90 msec, 60 msec, and 80 msec respectively in three patients with arteriosclerosis and coronary heart disease; and by 50 msec and 60 msec respectively in two patients with subaortic muscular stenosis. These increases in QKD were probably due to the fact that when the wave of depolarization travels over unspecialized cardiac fibres as a result of left bundle-branch block its velocity is much slower than if it had travelled the normal route along the bundle of His and the Purkinje network. (An additional but weaker factor which may contribute to the prolongation of QKD in the presence of left bundle-branch block is that cardiac contractility may be reduced by the less efficient synchronization of the myocardial fibres which results when the wave of depolarization does not travel the normal route.) Hasegawa and Rodbard (1976) found that when epicardial pacemakers were used to pace the hearts of sixteen patients with third degree atrioventricular block,

QKD was increased by 94 msec. That the time from the Q wave of the electrocardiograph to the first heart sound was also increased by 90 msec indicates that the increase in QKD with an epicardial pacemaker occurred in the electromechanical delay portion of the pre-ejection period. Because the wave of depolarization produced by an epicardial pacemaker also travels over unspecialized cardiac fibres, these results support the conclusion that the increase in QKD found in the presence of left bundle-branch block is also due to an increase in the electromechanical delay portion of the pre-ejection period.

2. Comparisons between individuals

Where comparisons are made between individuals the number of factors capable of influencing QKD is increased. In addition to the factors already reviewed in the immediately preceding subsection, age, arterial length and structure, and the presence or absence of cardiovascular and hormonal disease should be taken into account. However, with the exception of age and disease, these factors have been neglected.

To evaluate abnormal QKD values, it is essential first to establish the normal range of this variable, which can be done by collating the findings of various researchers in this field. Their values for normal subjects resting supine are given in Table 5, which also includes the age of the

Table 5. The duration of QKD in nine groups of normal subjects at rest in the supine position.

Authors	QKD (msec)	Standard Deviation (msec)	Number of Subjects	Age (years)
Rodbard et al, 1957	210	-	24	-
Miyahara and Rodbard, 1961	207	-	14	-
David Robard et al, 1967	210	12 or 17	80	19-59
Fujita et al, 1967	210	19	23	23-70
Libanoff and Rodbard, 1967	195	18	103	30-89
Keller and Rodbard, 1971	212	8	20	'young'
Da Costa et al, 1973	214	18	40	20-49
Inagaki et al, 1976	205	13	16	18-61
Hasegawa and Rodbard, 1979	204	24	48	15-75

subjects where available, as age has an important influence on QKD. As can be seen, mean QKD values ranged from 195-214 msec with standard deviations of 8-24 msec.

i. Age

Murata et al (1976) found age to be a significant factor affecting QKD, as can be seen in Table 6. Using the QKD values obtained from the males and females aged twenty to twenty-nine years as their basis of comparison, they found the QKD values to be significantly shorter ($P<.01$) for the males and females aged six to nineteen years, for the males aged fifty to seventy-nine years, and for the females aged sixty to seventy-nine years. With the exception of the group aged fifty to fifty-nine years, they found no significant difference in QKD values obtained from males and females. The shortening of QKD in the males after age fifty years and the females after age sixty was most probably due to a reduction in pulse wave transmission time caused by an increase in pulse wave velocity with age, (this thesis pp 37-39) whereas the shortening of QKD in both males and females below age twenty was most probably due to a reduction in pulse wave transmission time caused by shorter height and hence shorter arterial length. A reduction in pre-ejection period may also have contributed to this shortening of QKD (see this dissertation, pp 31-32).

Table 6. The duration of QKD in males and females at rest in the supine position, classified into eight groups according to age, compiled from Murata et al (1976).

	Males		Females	
Age (years)	QKD (msec)	Number of Subjects	QKD (msec)	Number of Subjects
6 - 9	171±10	5	161±10	5
10 - 19	196±18	19	186±16	13
20 - 29	221±14	48	214±17	23
30 - 39	211±14	19	209±10	13
40 - 49	209±14	11	213±20	11
50 - 59	192±10	10	208±27	10
60 - 69	193±20	7	191±14	6
70 - 79	185±14	13	179±14	11

Bereu et al (1979) found that the significant correlation (r = .83) between QKD and age in sixty-three children aged seven months to eighteen years was probably due to the correlation between QKD and height (r = .86) and DeMonchy and Van der Hoeven (1976) found that while pulse wave velocities changed very little with age in children, pulse wave transmission time was highly correlated with height.

ii. Heart rate

Heart rate has been investigated as a factor affecting QKD in both children and adults.

In a group of sixty-three normal children aged seven months to eighteen years, Bereu et al (1979) found that while QKD was highly correlated with both heart rate (r = -.73) and height (r = .86) when these two factors were tested singly, QKD was correlated only with height when the two factors were analysed together by multiple regression, and was not correlated with heart rate when it (QKD) was first corrected for height. QKD and height were strongly correlated (r = .86) because height (and arterial length) and hence the pulse wave transmission time component of QKD increase as children grow older, whereas QKD and heart rate were strongly correlated (r = -.73) solely because of the strong correlation (r = -.99) existing between heart rate and height. From these findings it would appear that in

children the correlation of QKD and heart rate is merely coincidental.

In a group of normal adult subjects aged nineteen to forty years, Da Costa, Da Silva, Ranchard, and Da Costa (1973) found the correlation of QKD and heart rate was $r = -.48$ ($P<.003$) for their forty female subjects aged twenty to forty-nine years, but that there was no significant correlation of QKD and heart rate for their forty male subjects in the same age range. Similar levels of correlation between QKD and heart rate were found by Murata, Yoshitake, Baba, Suga, Yamane, and Shigiya (1976): $r = -.464$ ($P<.01$) for their forty-seven females aged twenty to forty-nine years, and $r = -.239$ ($P<.05$) for their seventy-eight males in the same age range. The pulse wave transmission time component of QKD is not affected by heart rate (this thesis, pp 30-31). Therefore, these levels of correlation between QKD and heart rate found by Da Costa et al (1973) and Murata et al (1976) depend solely upon the correlation of the pre-ejection period component of QKD and heart rate, and this correlation itself depends upon the level of activity of the sympathetic nervous system, which affects both cardiac contractility (and hence the pre-ejection period component of QKD) and heart rate. Thus in adults too it would appear that the correlation of QKD and heart rate is coincidental. This conclusion is supported by the fact that where the level of activity of the sympathetic

nervous system was not affected and the heart rate was changed solely by the use of artificial pacemakers, there was no correlation between QKD and heart rate (Hasegawa and Rodbard, 1976).

iii. Disease

Both thyroid and cardiovascular disease have been investigated as factors affecting QKD.

Rodbard, Fujita, and Rodbard (1967) compared thirty-seven hyperthyroid and ten hypothyroid patients with a control group of eighty euthyroid subjects. The mean QKD for the control group was 210.6 msec, but unfortunately two different values were given for the standard deviation: 12 msec in the table, and 17 msec in the text. The smaller of these was used by the authors to calculate their 95% confidence limits (186 msec and 235 msec). All thirty-seven of the hyperthyroid patients, nine of the ten hypothyroid patients, and one of the eighty euthyroid subjects were outside these limits. However, if, to err on the safe side, the 17 msec standard deviation given in the text is used, the 95% confidence limits would be 177 msec and 245 msec. Between thirty-one and thirty-six of the thirty-seven hyperthyroid patients, nine of the ten hypothyroid patients, and none of the euthyroid subjects would have been outside these wider 95% confidence limits. Whether or not these wider confidence limits are capable of universal application can

be tested to a limited extent by applying them to the data presented in other papers. When this is done, it is found that all twenty-three of the hyperthyroid patients of Fujita, Yoshikawa, Ito, Suzuki, and Rodbard (1967), and all ten of the hyperthyroid patients of Young et al (1976) were below 177 msec. Very few hypothyroid patients have been tested, but three of the four hypothyroid patients of Rodbard and Kramer (1966) and all three of the hypothyroid patients of Young et al (1976) were above 245 msec. There is thus some evidence to suggest that QKD values have a high sensitivity and specificity in detecting thyroid disease. However, the experimental data may be misleading because no marginal cases were included, and age was not considered as a confounding factor. In addition, false positives could result: excitable or hypertensive individuals could be picked up below the confidence limits, and individuals with myocardial disease or peripheral vascular disease could be picked up above the confidence limits. Information from a completely randomized sample of a population is essential before developing this method further as an instrument to screen population groups for thyroid disease.

There are theoretical grounds for regarding QKD as a potential screening tool in a very limited number of cardiovascular disease states: the pre-ejection period component of QKD lengthens in profound myocardial disease (this thesis, p 33), and the pulse wave transmission time

component of QKD lengthens in advanced peripheral vascular disease (this thesis, pp 43-44). However, in both disease states age can be a confounding factor. This is because pulse wave transmission time shortens up to sixty years of age, and both it and pre-ejection period shorten after this age. (Another possible confounding factor in peripheral vascular disease might be excessive sympathetic stimulation of the heart, which would also shorten pre-ejection period.)

Miyahara and Rodbard (1961) found a mean QKD value of 198 msec in eight patients with current congestive heart failure or a history of congestive heart failure. (No standard deviation was given, but the range was 146 msec to 236 msec.) Rodbard and Libanoff (1965) found mean QKD values of 200 ± 10 msec in six patients with mitral regurgitation, 180 ± 30 msec in six patients with subaortic muscular stenosis, 260 ± 30 msec in five patients with mild aortic-valve stenosis, and 280 ± 30 msec in five patients with moderate to severe aortic-valve stenosis. Libanoff and Rodbard (1967) reported mean QKD values of 162 ± 9 msec for eight patients with arteriosclerosis and coronary heart disease, 190 ± 21 msec in seven patients with subaortic muscular stenosis, and 243 msec in three patients with myocardiopathy. The short QKD values in the group with arteriosclerosis and coronary heart disease could have been due primarily to their advanced age

(the mean age was sixty-eight years). However, as the authors were mainly concerned with the effect of left bundle-branch block, they did not consider the effect of aging on QKD. Hasegawa and Rodbard (1976) found a mean QKD value of 206±55 msec in sixteen patients requiring pacemaker implantation.

Because a high proportion of these cardiovascular patients had QKD values within the 177 msec to 245 msec confidence limits used above, QKD values would seem to lack the sensitivity required for screening population groups for cardiovascular disease, especially when it is remembered that if the QKD values had been corrected for age the proportion of patients falling within the confidence limits would probably have been even higher.

(Although QKD has these demonstrable deficiences in comparisons between individuals, it does have certain potential clinical uses in comparisons within individuals: to measure cardiac contractility or cardiac distress in a patient during anesthesia [Henderson et al, 1972; Jackson, 1974; Rodbard, 1975] thyroid medication [Rodbard and Kramer, 1966; Young et al, 1976], beta-blocker medication [Keller and Rodbard, 1971] and adriamycin medication [Greco et al, 1976].)

To summarize: The changes in QKD reported in the literature are compatible with the changes reported to occur

in the two components of QKD under similar experimental conditions.

In comparisons within the individual, QKD shortens as cardiac contractility increases and hence decreases the pre-ejection period component of QKD, lengthens as end-diastolic volume decreases and hence increases the pre-ejection period component of QKD, and shortens as diastolic pressure increases and hence decreases the pulse wave transmission time component of QKD.

In comparisons between individuals QKD increases as children grow in height, mainly because the pulse wave transmission time component increases as arterial length increases, and to a lesser extent because the pre-ejection period component increases in length as children grow older. QKD decreases with age after fifty years in males and after sixty years in females because of a corresponding decrease in both components of QKD. That QKD is correlated with heart rate is probably coincidental in both children and adults: in children the correlation relies upon the very high level of correlation between heart rate and arterial length that exists in children of different ages, and in adults the correlation relies upon the level of activity of the sympathetic nervous system, which is a factor common to both heart rate and cardiac contractility (and hence the pre-ejection period component of QKD).

Marked differences in QKD are found when both hyperthyroid and hypothyroid patients are compared with euthyroid subjects, but marked differences are not found when individuals with cardiovascular disease are compared with normal individuals. (Unfortunately none of these studies used age related controls). QKD would seem to have the potential to be used as a tool to screen populations for thyroid disease but not for cardiovascular disease. It would also seem to have the potential for clinical use within individuals: to monitor the cardiac response to anesthesia and to adriamycin or beta-blocker medication; and to monitor the response of thyroid patients to their treatment.

SECTION 3

The anacrotic slope of the brachial artery pressure pulse wave

The second of the two pieces of information provided by Rodbard's method is the anacrotic slope of the brachial artery pressure pulse wave. The anacrotic (from Greek ana up, krotos striking) slope is the name given to the initial portion of the pressure pulse wave, ie the portion where the arterial pressure rises from diastolic pressure (the point at which QKD is obtained) to systolic pressure (the point at which QKS is obtained).

No universal mathematical formula was found to quantify the shape of the anacrotic slope and thus make possible a direct investigation of the factors affecting it. However, visual examination of the anacrotic slope provided by Rodbard's method suggested that for convenience it could be divided into two portions: an initial, linear portion and a later, nonlinear portion. For the initial, linear portion the following hypothesis was set up: That cardiac contractility is a major factor affecting the gradient of the initial, linear portion of the anacrotic slope. A literature search was carried out to check on this hypothesis, and data were found supporting it. This material is presented in subsection a.

To determine the factors affecting the nonlinear portion a more indirect route had to be used. Mathematical formulae have been used to describe the entire brachial artery pressure pulse wave (O'Rourke and Taylor, 1967). Therefore it was decided to identify, and to determine the mechanisms of, the factors affecting the shape of the entire nonlinear portion of the brachial artery pressure pulse wave, and then to make the hypothesis that these same factors affect the shape of the nonlinear portion of the anacrotic slope and in the same way. However, it was found that in effect the hypothesis had to be expanded to include the duration of the entire anacrotic slope, because the only measurements available in the literature which related to

the shape of the nonlinear portion of the anacrotic slope were measurements of the duration of the entire anacrotic slope. This material is presented in subsection b.

a. Cardiac contractility as a major factor affecting the gradient of the initial, linear portion of the anacrotic slope

If it is true that cardiac contractility is a major factor affecting the gradient of the initial, linear portion of the anacrotic slope then it is essential that 1) the initial rate of pressure rise in the ascending aorta should be found to be directly related to cardiac contractility, and

2) the initial rate of pressure rise in the brachial artery should be found to be directly related to that in the ascending aorta.

When considering the first of these two conditions, it is important to remember that it is the nature of the cardiac contraction to accelerate the blood very rapidly to a maximum velocity and momentum early in the cardiac ejection period. After this maximum has been reached, systolic flow continues because of the momentum already given to the blood, and not because of further cardiac contraction (Noble, 1968). Rushmer (1964) likened ventricular ejection to striking a piston with a mallet as opposed to squeezing an orange. The power to expel the blood in this way is stored up by the elastic and resistive elements of

the ventricle during the isovolumetric contraction period (Hunter, Janicki, Weber, and Noordergraaf, 1979), and the rate of pressure rise in the ventricle during this period has frequently been used as a measure of cardiac contractility (eg, Martin et al, 1971; Talley et al, 1971, McConahay et al, 1972). Because the rate of pressure rise in the ventricle during the isovolumetric contraction period has been found to be of use as a measure of cardiac contractility and because George, Taylor, and Ramsay (1967) found that the rate of pressure rise in the ascending aorta immediately after the opening of the aortic valves bore a constant and direct relationship to the rate of pressure rise in the ventricle during the immediately preceding isovolumetric contraction period, it would appear that the initial rate of pressure rise in the ascending aorta is directly related to cardiac contractility.

The relationship between the initial rate of pressure rise in the brachial artery and that in the ascending aorta is complicated by the fact that the arterial pressure wave changes in shape as it travels towards the periphery (Kroeker and Wood, 1955; McDonald, 1974, p 332). Although some change in shape is caused by nonlinear properties of the arteries, particularly the fact that peripheral arteries are less distensible than the aorta, the most important factor is the presence of reflected waves (Taylor, 1966). However, because of the time it takes reflected waves to

travel to the peripheral reflecting sites and back to the point of measurement, they do not alter the initial, linear portion of the anacrotic slope. McDonald (1968) superimposed arterial pressure pulse waves measured at various locations 5 cm apart, and found that the first 60-80% of the anacrotic slope was not changed by transmission along the arteries, although the shape of the remaining portion was noticeably altered and systolic pressure was increased. This would seem to indicate that the initial rate of pressure increase (gradient) in the brachial artery is directly related to that in the ascending aorta.

Consequently, because the initial rate of pressure rise in the ascending aorta has been found to be directly related to cardiac contractility, and because the initial rate of pressure rise in the brachial artery has been found to be directly related to that in the ascending aorta, the hypothesis "that cardiac contractility is a major factor affecting the gradient of the initial, linear portion of the anacrotic slope" would appear to be justified.

To test this hypothesis further it remains to be seen whether the factors affecting cardiac contractility (ie age, exercise, drugs, and disease) correspondingly affect the gradient of the initial, linear portion of the anacrotic slope.

i. Age

Hancock and Abelmann (1957) measured intra-arterial pressure directly in two groups each consisting of twenty subjects: they found that the gradient of the initial, linear portion of the anacrotic slope was 850±430 mmHg/sec in the group aged twenty to thirty-seven years, and 930±600 mmHg/sec in the group aged thirty-eight to eighty-four years. From these values there would appear to be no significant change in the gradient of the initial, linear portion of the anacrotic slope with age, although cardiac contractility is expected to decrease gradually with age. It is likely that the decrease in gradient expected to result from the anticipated decrease in cardiac contractility with age was confounded by the increase in gradient expected to result from the anticipated increase in pulse wave velocity with age. (O'Rourke [1976] observed that both cardiac contractility and pulse wave velocity directly affect the gradient and that therefore an increase in pulse wave velocity will increase the gradient.)

ii. Exercise

Inagaki et al (1976), using Rodbard's method, found that the gradient was 590±220 mmHg/sec in sixteen subjects aged eighteen to sixty-one years resting in the supine position, and that this increased to 1298±378

mmHg/sec after four minutes of walking on a treadmill at 4.0 km/h on a 10% grade.

This increase in gradient with exercise is what one would anticipate because of the known inotropic effects of exercise. In this experiment the relationship between gradient and cardiac contractility was not confounded by pulse wave velocity because diastolic pressure was found to have remained constant, and age was not a factor in these comparisons within the individual.

iii. Disease

Hancock and Abelmann (1957), in a study of the brachial artery pulse form in five different cardiovascular disease groups, found that the group with aortic insufficiency (and hence markedly increased cardiac contractility) had a gradient far steeper than that of the healthy age-related control group: 2350 ± 1490 mmHg/sec as compared with 930 ± 600 mmHg/sec. The gradient of the group with mitral insufficiency (and hence, again, increased cardiac contractility) was 1410 ± 1153 mmHg/sec. Hasegawa and Rodbard (1976) found that the gradient was reduced from 680 ± 490 mmHg/sec to 530 ± 220 mmHg/sec following pacemaker stimulation of the heart: here cardiac contractility is expected to be reduced because of the less efficient electrical conduction of the ectopic pacemaker stimulus. From graphs of the anacrotic slope presented by Rodbard and Kramer

(1966) it can be seen that the gradient was clearly greater in hypothyroid patients following treatment with thyroid extract, which increases cardiac contractility. Although all the above changes in gradient were not significant they nevertheless were in the direction in which cardiac contractility changed.

Hancock and Abelmann (1957) found that the gradient was reduced from the 930±600 mmHg/sec for the healthy, age related, control group to 656±293 mmHg/sec in the group having moderate aortic stenosis and to 501±170 mmHg/sec in the group having severe aortic stenosis. In aortic stenosis this reduction in the gradient does not necessarily indicate a reduction of cardiac contractility because the relationship between gradient and cardiac contractility is confounded where cardiac emptying is obstructed by aortic stenosis: even where cardiac contractility is increased to force blood past the damaged valves the gradient of the initial portion of the anacrotic slope is in the low to normal range.

To summarize: The data available in the literature would seem to support the hypothesis that cardiac contractility is a major factor affecting the gradient of the initial, linear portion of the anacrotic slope. However, the relationship between cardiac contractility and gradient can be confounded by changes in pulse wave velocity and

where cardiac emptying is unusually obstructed by aortic stenosis. The large variation found in healthy subjects, and the even larger variation found in groups having cardiovascular disease mean that the gradient of the initial, linear portion of the anacrotic slope probably lacks the sensitivity and specificity required for population screening. No prospective studies designed to investigate the relationship between the gradient of the initial, linear portion of the anacrotic slope and subsequent cardiovascular health have been reported.

b. The factors affecting the shape of the remaining, nonlinear portion of the anacrotic slope

Because mathematical equations derived by Fourier analysis have been used to describe the shape of the entire brachial pressure pulse wave in terms of its harmonic energy, it was decided to investigate the factors affecting the entire pressure pulse wave in order to determine the factors affecting the nonlinear portion of the anacrotic slope.

1. The factors affecting the shape of the entire nonlinear portion of the brachial artery pressure pulse wave

From a study by McDonald (1968) of the pressure pulse wave as it travelled along 5 cm sections of the major arteries it can be seen that the gradient of the initial, linear portion of the pressure pulse wave did not alter from

section to section although the shape of the remaining portion altered noticeably. Like Taylor (1966), McDonald attributed this change in shape primarily to waves reflected from the periphery: a reflected pressure wave combines with the incident wave to produce a higher pressure. When a reflected wave arrives close to the peak of the incident wave it increases systolic pressure; and when a reflected wave arrives after the peak of the incident wave has passed, it does not increase systolic pressure but produces a secondary peak in the diastolic portion of the arterial pressure pulse wave.

Factors affecting wave reflection and hence the entire nonlinear portion of the pressure pulse wave were investigated by among others O'Rourke (1970, 1971, 1976); O'Rourke and Taylor (1966, 1967); O'Rourke, Blazek, Morreels, and Krovetz (1968); O'Rourke and Cartmill (1971); Avolio, O'Rourke, Mang, Bason, and Gow (1976); and O'Rourke and Alvolio (1980). These factors were found to be left ventricular ejection time, pulse wave velocity, and peripheral resistance: left ventricular ejection time because the amount of wave reflection depends upon the harmonic pattern produced by the heart's contraction; pulse wave velocity because the time taken for the pressure wave to travel to and from the reflecting sites depends upon pulse wave velocity; and peripheral resistance because the

proportion of the incident wave that is reflected depends upon peripheral resistance.

The effect of i) left ventricular ejection time, ii) pulse wave velocity, and iii) peripheral resistance on wave reflection and thus the shape of the entire nonlinear portion of the brachial artery pressure pulse wave will now be studied in detail.

i. Left ventricular ejection time

O'Rourke (1970) found that in a group of thirty-two cardiovascular patients aged twenty-one to sixty-four years the amount of amplification of brachial pulse pressure due to wave reflection was not related to the age, mean blood pressure, cardiac output, stroke volume, or peripheral resistance of the subject, but was correlated with left ventricular ejection time (as measured from the beginning of the upstroke of the aortic pressure wave to the first nadir of the incisura). The correlation for the entire group was $r = -.53$ ($P<.01$), and for one of the patients (with atrial fibrillation) was $r = -.8$ ($P<.001$). He suggested that this correlation depended upon the fact that the amount of amplification of brachial pulse pressure was dependent upon the moduli of the harmonics occurring in the ascending aorta, which, in turn, were dependent upon left ventricular ejection time. He compared the harmonic moduli of the pressure waves of the ascending aorta with those of the

brachial and femoral arteries and found that the harmonics undergoing peak amplification were different in the two arteries. In the brachial artery, peak amplification occurred in the 4-5 cps harmonics while in the femoral artery peak amplification occurred in the 1.5-3.5 cps harmonics. He found that these experimental results matched the theoretical values calculated from the impedance curves of the two arteries and the difference between brachial and femoral arteries was due to the different lengths and pulse wave velocities of these two arterial pathways. With reference to the brachial artery, this means that where more of the energy of the aortic pressure wave is in the range of 4-5 cps, amplification will be greater than where less of the harmonic energy is in this range.

In support of his hypothesis that the harmonic moduli contained in the aortic pressure wave were dependent upon left ventricular ejection time he

1) reported experimental results from a BSc thesis (Morris, 1965) which showed that moduli of the harmonics of greater than 2 cps were increased when left ventricular ejection time was decreased and were decreased when left ventricular ejection time was increased;

2) presented experimental evidence which showed that the moduli of the harmonics above 2 cps and especially 3 cps were far less in the subgroup of thirteen patients with moderate to severe aortic stenosis as compared with the

remaining nineteen patients who did not have aortic stenosis. This reduction in the moduli of the harmonics above 2 cps and 3 cps resulted in less brachial pulse pressure amplification in the aortic stenosis subgroup: 10±8% as compared with 23±20% in the patients without aortic stenosis. Left ventricular ejection time was 332±40 msec in the aortic stenosis patients and 276±100 msec in the patients without aortic stenosis. (Mason, Cohen, Spann, Demaria, Joye, and Miller [1978] also found brachial pulse pressure amplification was reduced in aortic stenosis.)

3) reported an extreme case of high brachial pulse pressure amplification (150%) in a fifty-five-year-old man who was in shock. Here the high amplification was due to the short left ventricular ejection time, and the associated increase in the moduli of the 3-4 cps harmonics. (Brachial blood pressure was only 85/55 mmHg in this patient at the time.)

4) re-evaluated the results which Kroeker and Wood (1955) obtained during prolonged expiration and those that Rowell, Brengelmann, Blackmon, Bruce, and Murray (1968) obtained during exercise, and was again able to explain the increased amplification of brachial pulse pressure as being due to an increase in the higher frequency harmonic moduli of the aortic pressure waves.

Left ventricular ejection time has been found to be highly correlated with heart rate and cardiac contractility (Fabian et al, 1972; McConahay et al, 1972; Spodick and Quarry-Pigott, 1973; Spitaels et al, 1974; Van der Werf, Piessens, Kesteloot, and De Geest, 1975; Van der Hoeven et al, 1977). It can thus be assumed that because the amount of amplification of brachial pulse pressure was found to be correlated with left ventricular ejection time, this amplification is also correlated with heart rate and cardiac contractility.

ii. Pulse wave velocity

The time taken for the pressure wave to travel from the point of measurement to a peripheral reflecting site and back again depends upon the length and pulse wave velocity of the section of artery traversed. Unlike most arteries, which have one mean reflecting site, the ascending aorta has two, the cephalic and the caudal, the positions of which are calculated from the ascending aorta's impedance modulus. The distance between the ascending aorta and the mean cephalic reflecting site represents the mean distance between the ascending aorta and all the reflecting sites of the upper body, while the distance between the ascending aorta and the mean caudal reflecting site represents the mean distance between the ascending aorta and all the reflecting sites of the lower body.

Because of the heart's eccentric position, the mean cephalic and caudal reflecting sites are at different distances from the ascending aorta (O'Rourke and Taylor, 1967); for humans these distances were found to be in a ratio of 1:1.5 (O'Rourke and Alvolio, 1980). The mean cephalic reflecting site was found to be equivalent to a point either towards the distal end of the upper arm or in the angle of the jaw; and the mean caudal reflecting site was found to be equivalent to a point close to the bifurcation of the aorta (Mills et al, 1970; Alvolio et al, 1976; and O'Rourke and Alvolio, 1980). The cephalic reflected wave thus returns earlier than the caudal reflected wave to the ascending aorta.

When a reflected wave returns at a time close to the systolic peak of the incident wave, the systolic peak is increased and pulse pressure is amplified. If it returns after the systolic peak has passed and pressure is falling, the reflected wave produces a secondary peak in the diastolic portion of the pressure wave but pulse pressure is not amplified. As pulse wave velocity increases, the cephalic and the caudal reflected waves return earlier and closer together. For the brachial artery, this means that when pulse wave velocity is low (as in a young normotensive adult) the cephalic reflected wave increases the systolic peak and the caudal reflected wave produces a marked peak in the diastolic portion of the pressure wave (see figure 3,

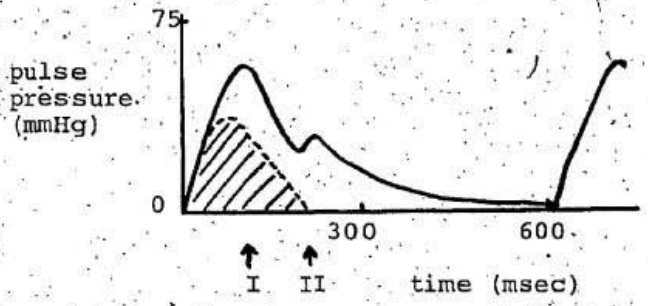
graph a). When pulse wave velocity is intermediate the cephalic reflected wave again increases the systolic peak and the caudal reflected wave produces a less marked peak earlier in the diastolic portion of the pressure wave (see figure 3, graph b). When pulse wave velocity is high (as in an elderly hypertensive adult) both the cephalic and the caudal reflected waves arrive in time to increase the systolic peak and there is no discernable peak in the diastolic portion of the pressure wave (see figure 3, graph c). The explanation in the paragraph above is based on information provided by O'Rourke (1971).

iii. Peripheral resistance

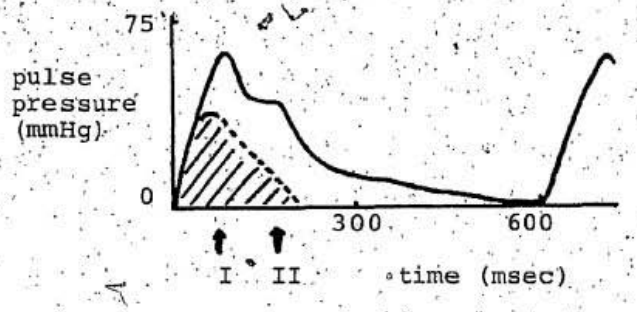
Peripheral resistance is known to affect wave reflection and hence the shape of the arterial pressure pulse wave. Peripheral resistance is in turn affected by blood viscosity, the structure of the microvasculature, and swift-acting vasoactive substances. The effect of peripheral resistance upon wave reflection has been demonstrated experimentally only where peripheral resistance has been modified by swift-acting vasoactive substances.

Using data obtained from canine femoral arteries, O'Rourke and Taylor (1966) investigated the effect of vasoactive medication upon wave reflection and calculated that under control conditions the reflection coefficient (the

a. Comparatively slow pulse wave velocity



b. Intermediate pulse wave velocity



c. Comparatively fast pulse wave velocity

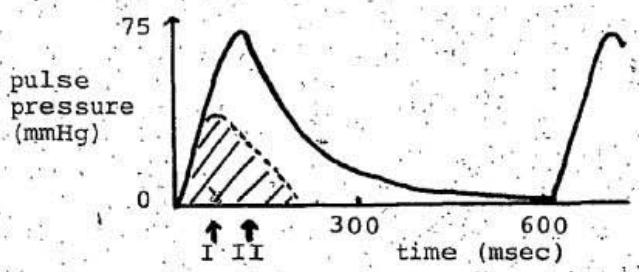


Figure 3. A diagram to illustrate the changes in the shape of the brachial artery pressure pulse wave which result from changes in pulse wave velocity. The arrows indicate the time of arrival of the cephalic (I) and the caudal (II) reflected waves. The shaded area indicates the incident pressure wave.

proportion of the incident wave reflected) was 0.8. (It is possible that their control value of 0.8 was unduly high because of the stress of anesthesia and experimental manipulation, and that under physiological conditions the reflection coefficient is less than 0.8.) The authors found that variations in vasomotor tone altered the reflection coefficient: intra-arterial injection of acetylcholine decreased the reflection coefficient towards zero, and intra-arterial injection of norepinephrine increased the reflection coefficient towards unity. Thus it can be seen that the decrease in peripheral resistance caused by the acetylcholine decreased wave reflection, while the increase in peripheral resistance caused by the norepinephrine increased wave reflection.

From the effects of changes in peripheral resistance on the shape of the femoral pressure pulse wave recorded by O'Rourke and Taylor (1966) it would appear that the secondary (or caudal) peak in the diastolic portion of the brachial pressure pulse wave increases in amplitude when peripheral resistance increases, and decreases when peripheral resistance decreases. The systolic (or cephalic) peak, on the other hand, is not influenced by peripheral resistance (O'Rourke, 1970). These observations are supported by data obtained by Freis, Heath, Lucksinger, and Snell (1966) if what they called the early systolic and late systolic peaks were, as seems most likely, the cephalic and

caudal peaks referred to in the two previous sections. By expressing the height of the late systolic (caudal) peak as a fraction of the height of the early systolic (cephalic) peak, the authors determined the effect of drug-induced changes in peripheral resistance upon the shape of the external carotid pulse volume wave. (Volume and pressure waves were said to be virtually identical by O'Rourke [1971]). In their seventeen human subjects they found that the height of the late systolic peak relative to the height of the early systolic peak increased after treatment with the vasoconstrictors methoxamine and angiotensin II (which increase peripheral resistance and hence wave reflection), and decreased after treatment with the vasodilators amyl nitrite and trimethaphan (which decrease peripheral resistance and hence wave reflection).

As has already been stated, peripheral resistance (and hence wave reflection) is also affected by the structure of the microvasculature, especially the resistance arterioles. Freis et al (1966) classified eighty human subjects into four groups according to age, and found that as age increased, the height of the late systolic peak increased relative to that of the early systolic peak until in the group aged forty to forty-nine years the two peaks were almost equal in height, and in the age group over forty-nine years the late systolic peak was higher than the early systolic peak. This is what would be expected, because it is known that although cardiac output decreases, peripheral

resistance increases with age (Amery, Wasir, Bulpitt, Conway, Fagard, Lijnen, and Reybrouck, 1978; De Leeuw, Kho, Falke, Birkenhager, and Wester, 1978; Lakatta, 1979). Why peripheral resistance increases with age is not clear, but it is probably the result of changes in the microvasculature, especially the number, internal diameter, and wall properties of the resistance arterioles. Little is known of how these factors vary with age because simple noninvasive methods are not available to measure them. Some data concerning the relationship between the structure of the microvasculature and peripheral resistance are, however, available from studies of hypertension in both human subjects and pure-bred rats.

Folkow, Hallback, and Noresson (1978) described two types of change in the microvasculature found to occur in response to a rise in arterial pressure. The first of these was a rapid but reversible hypertrophic media growth in the resistance arterioles. This was followed by a slower but irreversible build-up of intercellular connective tissue (especially collagen), which strengthened the wall. These structural changes raised peripheral resistance even at maximum vasodilation, and the authors hypothesized that these alone were responsible for increased peripheral resistance. Mulvany, Hansen, and Aalkjaer (1978) came to the same conclusion from their investigation of the mesenteric vessels of spontaneously hypertensive rats. When

resistance vessels were measured at constant pressure, those of spontaneously hypertensive rats had a 16% smaller lumen diameter and a 49% thicker media layer ($P<.01$) than those of Wistar-Kyoto normotensive rats. The spontaneously hypertensive rats had four layers of smooth muscle cells instead of three and these would have been able to contract against a 45% greater transmural pressure. The authors concluded that these results supported the hypothesis of Folkow (1956) that, in hypertension, increased peripheral resistance is associated with structural changes in the resistance vessels. A change in the structure of the microvasculature similar to that reported by the authors was found by Short (1966) in his post mortem studies of humans known to have had essential hypertension. Hartling, Svendsen, Neilson, and Trap-Jensen (1978) found reduced distensibility of the resistance vessels in the skeletal muscles of hypertensive human subjects as compared with those of normotensive subjects. Prewitt and Dowell (1978), in a comparative study of spontaneously hypertensive rats and Wistar-Kyoto normotensive rats, found that the increased arterial pressure of the former was not associated with an increased cardiac index but rather with an increased vasodilated peripheral resistance, which increased with age from four to fourteen weeks in both strains: from 0.16 to 0.36 mmHg·min·kg/ml for the Wistar-Kyoto rats, and from 0.19 to 0.47 mmHg·min·kg/ml for the spontaneously hypertensive rats.

The authors concluded that because the vessels were maximally dilated, the differences in peripheral resistance were due to differences in the structure of the microvasculature between the strains, and between different age groups within the strains.

In addition to the evidence linking changes in peripheral resistance with changes in the internal diameter and wall properties of resistance arterioles, there is some evidence to suggest that increased peripheral resistance can also be produced by a reduction in the number of the resistance arterioles. Hutchings and Darnell (1974) found that the number of small arterioles was reduced by almost 50% in the cremaster muscle of young spontaneously hypertensive rats. Henrich, Hertel, and Assmann (1978) obtained similar results from the mesenteric vessels of spontaneously hypertensive rats with established hypertension.

Peripheral resistance (and hence wave reflection) is also profoundly influenced by blood viscosity: peripheral resistance has been found to increase directly with an increase in blood viscosity when viscosity was measured at a low shear rate (Dintenfass, 1976, pp 29, 186-87). Blood viscosity at a low shear rate depends primarily upon the erythrocytes: the hematocrit, the degree of aggregation, and the properties of the erythrocyte membrane and internal contents (Dintenfass, 1976, pp 16-22). All these factors are particularly important as blood flows through the

microvasculature. In healthy individuals blood viscosity measured at a low shear rate remains constant from youth to old age, and any significant change can be taken as a sign of current or approaching disease (Dintenfass, 1976, p 4). According to Dintenfass blood viscosity measured at a low shear rate is increased by hypoxia (p 15), lowered blood temperature (p 94), the release of catecholamines (p 235-37), elevated blood cholesterol levels (p 93), the presence of infections (p 28), diabetes (p 133), a high hematocrit (p 249), smoking (p 248), and by chronic over-indulgence in alcohol (p 252). It is perhaps significant that most of these factors are also known risk factors in cardiovascular disease. The factors producing an increase in blood viscosity measured at a low shear rate may play a causative role in the development of cardiovascular disease, either by reducing tissue perfusion in the marginal areas supplied by arteries, or through the hypertensive and flow-related effects of the increased reflection coefficient expected to result from the increased peripheral resistance.

2. The factors affecting the shape and duration of the anacrotic slope: pulse wave velocity, left ventricular ejection time and peripheral resistance

Because that which affects the whole also affects the part, it can be hypothesized that pulse wave velocity,

left ventricular ejection time, and peripheral resistance also affect the shape of the nonlinear portion of the anacrotic slope through the same mechanisms by which they affect the shape of the entire nonlinear brachial artery pressure pulse wave. However, it was found that in effect this hypothesis had to be expanded to include the duration of the entire anacrotic slope, because the only measurements available in the literature which related to the shape of the nonlinear portion of the anacrotic slope were measurements of the duration of the entire anacrotic slope. The hypothesis as expanded is therefore: "Pulse wave velocity, left ventricular ejection time, and peripheral resistance affect the shape and hence the duration of the entire anacrotic slope through the same mechanisms by which they affect the shape of the nonlinear portion of the brachial artery pressure pulse wave."

Two points should be remembered with respect to this hypothesis

1) Although the hypothesis speaks of "the duration of the entire anacrotic slope", this measurement primarily relates to the shape of its nonlinear portion because the return of reflected waves, which determines the duration of the entire anacrotic slope, affects only its nonlinear portion;

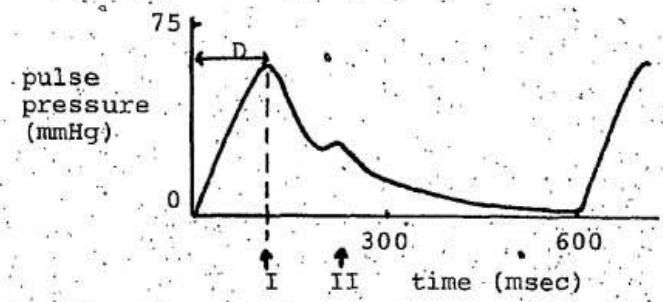
2) Rodbard's method provides a simple noninvasive determination of the duration of the anacrotic slope, and this present thesis is concerned with an evaluation of

cardiovascular data obtained by Rodbard's method with a view to determining from them the value of Rodbard's method in epidemiological research.

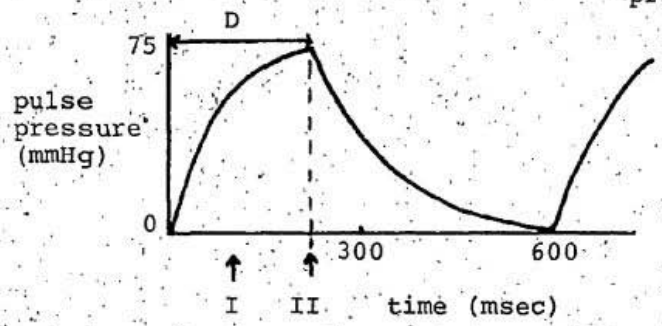
Various aspects of the hypothesis will now be examined in detail because of the complexity of the subject.

The duration of the entire anacrotic slope is the time taken for arterial pressure to rise from its lowest level (diastolic pressure) to its highest level (systolic pressure). If the above expanded hypothesis is true, this duration is determined by whether it is the cephalic reflected wave, the caudal reflected wave, or a combination of the two that produces the highest pressure. When the cephalic reflected wave produces the highest pressure, the duration of the anacrotic slope is close to the arrival time of the cephalic reflected wave (see figure 4a), which is determined by pulse wave velocity, and the distance to the cephalic reflecting site from the point of measurement. When the caudal reflected wave produces the highest pressure, the duration of the anacrotic slope will be close to the arrival time of the caudal reflected wave (see figure 4b), which is determined by pulse wave velocity, and the distance to the caudal reflecting site from the point of measurement. When the cephalic and the caudal reflected waves combine to produce the highest pressure, the duration of the anacrotic slope lies somewhere between the arrival times of the cephalic and caudal reflected waves (see figure

a. The cephalic reflected wave producing the highest pressure



b. The caudal reflected wave producing the highest pressure



c. The cephalic and caudal reflected waves combining to produce the highest pressure

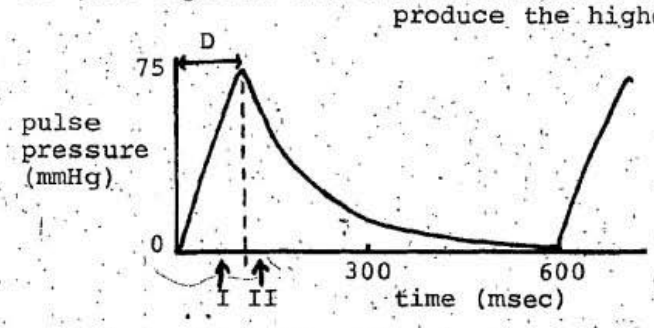


Figure 4. A diagram to illustrate how the time of arrival of the reflected waves affects the duration of the anacrotic slope (D). The arrows indicate the time of arrival of the cephalic (I) and the caudal (II) reflected waves.

4c), which are determined by pulse wave velocity and the distance to their respective reflecting sites.

Inasmuch as the cephalic reflecting site is closer to the point of measurement than is the caudal reflecting site, the duration of the anacrotic slope will always be shorter when the highest pressure is produced by the cephalic, as opposed to the caudal, reflected wave. The cephalic reflected wave returns to the point of measurement 70-110 msec after the foot of the pressure pulse wave when it has travelled at 4.7-7.5 m/sec to and from the cephalic reflecting site, whereas the caudal reflected wave returns to the point of measurement 110-200 m/sec after the foot of the pressure pulse wave when it has travelled at 4.5-8.0 m/sec to and from the caudal reflecting site (calculations based on values presented by McDonald [1974, p. 418] and Mills et al [1970]).

This means that

1) if the duration of the anacrotic slope is 70-110 msec the cephalic reflected wave is producing the highest pressure;

2) if the duration of the anacrotic slope is 110-200 msec the caudal reflected wave is producing the highest pressure; and

3) if the duration of the anacrotic slope is 90-120 msec both the cephalic and the caudal reflected waves may be combining to produce the highest presssure.

It is obvious from the overlap of values that it cannot always be determined for certain which of the reflected waves or combinations of waves is responsible for the highest pressure where only the anacrotic slope is available.

The three factors which, by affecting the reflected waves, affect the shape and duration of the anacrotic slope are pulse wave velocity, left ventricular ejection time and peripheral resistance.

1) Changes in pulse wave velocity (due to changes in the condition of the arteries and level of diastolic pressure), by changing the arrival times of the cephalic and caudal reflected waves, change the shape and hence the duration of the anacrotic slope;

2) changes in left ventricular ejection time (due to changes in heart rate and the strength of the cardiac contraction), by changing the strength of the cephalic reflected wave, change the shape and hence the duration of the anacrotic slope;

3) changes in peripheral resistance (due to changes in the microvasculature, blood viscosity, vasoactive medications), by changing the strength of the caudal reflected wave, may change the shape and hence the duration of the anacrotic slope.

It must be remembered, however, that these three factors do not affect the anacrotic slope in isolation but in concert. Thus, for example, when pulse wave velocity is

low, a moderate degree of peripheral resistance may act together with a long ventricular ejection time (and its associated weak cephalic reflected wave) to cause the caudal peak to be higher than the cephalic peak and thus lengthen the duration of the anacrotic slope. On the other hand with a short ventricular ejection time (and its associated strong cephalic wave) a much higher degree of peripheral resistance is required to cause the caudal peak to be higher than the cephalic peak and thus lengthen the duration of the anacrotic slope.

Thus far an examination has been conducted into the effect of pulse wave velocity, left ventricular ejection time, and peripheral resistance on the shape and hence the duration of the anacrotic slope. To test the hypothesis that these factors, which affect the entire brachial artery pressure pulse wave, affect also the shape and duration of the anacrotic slope and in the same way, it remains to be seen whether various changes in the duration of the anacrotic slope reported in the literature without an adequate explanation of their underlying cause can be explained in terms of the hypothesized effect of these three factors on the duration of the anacrotic slope.

i. Age

When intra-arterial pressure was measured directly the duration of the anacrotic slope was found to increase

significantly with the age of the subject: it was 94±31 msec in a group of twenty subjects aged twenty to thirty-seven years as compared with 129±40 msec for a group of twenty subjects aged thirty-eight to eighty-four years (Hancock and Abelmann, 1957); it was 91±20 msec for a group of sixteen men aged sixteen to twenty-eight years as compared with 136±24 msec for a group of ten men aged fifty to seventy-five years (Dontas and Cottas, 1962); and it was 80±31 msec for thirteen subjects up to ten years of age, 120±33 msec for thirty-nine subjects aged ten to thirty-nine years, and 160±45 msec for fifty-seven subjects aged forty to seventy-nine years (McLean et al, 1964). This increase in the duration of the anacrotic slope with age reported by the authors without an explanation of the underlying mechanism can be explained in terms of the present hypothesis as follows: Peripheral resistance increases with age (Amery et al, 1978; De Leeuw et al, 1978; Lakatta, 1979), and an increase in peripheral resistance increases the strength of the caudal reflected wave. When the caudal reflected wave becomes strong enough to produce the highest pressure, the duration of the anacrotic slope increases to 110-200 msec from 70-110 msec, which is the duration when the cephalic reflected wave produces the highest pressure (this thesis, pp 93-95). It is reasonable to assume that the duration of the anacrotic slope increases in this way only in those individuals in whom peripheral

resistance is high enough to cause the caudal reflected wave to form the highest peak, and that it is the resulting long durations of the anacrotic slope of these individuals which increase the means and standard deviations of the groups as age increases.

When arterial pressure was measured indirectly by Rodbard's method (Murata et al, 1976) the duration of the anacrotic slope was again found to increase with age of the subject (see Table 7). Using the same line of reasoning as in the previous paragraph, these increases can again be explained in terms of the hypothesis. It should be pointed out that it is likely that the presence of the inflated cuff eliminates the brachial reflected wave for that arm, with the result that the anacrotic slope provided by Rodbard's method represents only the sum of the incident wave, the cephalic wave from the head and the other arm, and the caudal reflected wave. (This absence of part of the cephalic reflected wave when arterial pressure is measured by Rodbard's method may account to some extent for the way in which this method consistently underestimates intra-arterial systolic pressure [this thesis, pp 6-8]).

ii. Heart rate

Although no significant relationship between the sex of the subjects and the mean duration of the anacrotic slope

Table 7. The duration of the anacrotic slope in males and females at rest in the supine position, classified into eight groups according to age, compiled from Murata et al (1976).

	Males		Females	
Age (years)	QKS-QKD (msec)	Number of Subjects	QKS-QKD (msec)	Number of Subjects
6 - 9	97±24	5	100±12	5
10 - 19	84±17	19	93±20	13
20 - 29	98±14	48	104±17	23
30 - 39	107±17	19	110±14	13
40 - 49	104±17	11	119±28	11
50 - 59	127±32	10	135±25	10
60 - 69	123±36	7	154±28	6
70 - 79	152±32	13	161±35	11

Using the duration of the anacrotic slope of the groups aged twenty to twenty-nine years as their basis of comparison, Murata et al (1976) found that the duration was significantly longer ($P<.01$) in both males and females over fifty years of age. The difference in duration between males and females was not significant.

has been found (McLean et al, 1964; Da Costa et al, 1973; Murata et al, 1976). Da Costa et al (1973), using Rodbard's method, did find a significant correlation ($r = -.45$, $P<.005$) between the duration of the anacrotic slope and heart rate in their group of forty men but not in their group of forty women. Because of the shortness of the durations involved (99 ± 25 msec) it does not seem likely that this correlation can be explained in terms of the hypothesis. The most probable explanation is that adrenergic stimulation of the heart in a proportion of the male subjects was high enough to cause both a faster heart rate and a faster rise (and hence an earlier peak) in the pressure pulse wave. The possibility remains, however, that this significant correlation found by Da Costa et al (1973) was adventitious. Murata et al (1976), also using Rodbard's method, found no significant relationship between the duration of the anacrotic slope and heart rate in their group of seventy-eight men ($r = .003$) or in their group of forty-seven women ($r = .2$).

iii. Disease

McLean et al (1964), using brachial intra-arterial pressure tracings, found that the duration of the anacrotic slope did not vary significantly between groups of patients classified into nine cardiovascular disease categories and normal age-related subjects. Similarly,

Freis et al (1966), using a carotid volume recorder, found that the duration of the anacrotic slope was essentially the same in patients with atherosclerotic complications as it was in normal subjects of the same age. However, one of the findings reported by McLean et al (1964) calls for comment. The authors subdivided the patients with mitral stenosis and aortic stenosis into those without, and those with, a shoulder in the anacrotic slope. (A shoulder is a pronounced bend in the anacrotic slope.) The mean duration of the anacrotic slope increased from 110 msec (mitral stenosis) and 130 msec (aortic stenosis) for patients without a shoulder in the anacrotic slope to 190 msec (both conditions) for patients with a shoulder in the anacrotic slope. This increase in the duration of the anacrotic slope, reported by the authors without an explanation of the underlying mechanism, can be explained in terms of the hypothesis if the patients with a shoulder in the anacrotic slope also had their peripheral resistance so high that the caudal reflected wave produced the highest pressure, and if they also had a pulse wave velocity so low that this caudal reflected wave returned 190 msec after the foot of the pressure wave. It is significant, therefore, that abnormally high peripheral resistance and abnormally low diastolic pressure (with which is associated low pulse wave velocity) are both characteristic of advanced mitral and aortic stenosis.

To summarize: The factors affecting the shape of the entire brachial artery pressure pulse wave were investigated, and were determined to be pulse wave velocity, left ventricular ejection time, and peripheral resistance. It was then hypothesized that these same factors also affect the shape and duration of the anacrotic slope and in the same way. The implications of this were investigated in detail, and support for the hypothesis came from the finding that it could be used to explain the increase in the duration of the anacrotic slope with age and the presence of a shoulder in the anacrotic slope of a proportion of patients with mitral or aortic stenosis. However, since the duration of the anacrotic slope was not found to vary significantly with cardiovascular disease, it would seem that this measurement will not prove a useful tool with which to screen populations for cardiovascular disease. It may, however, provide an indication of the progress of age-related changes in the peripheral resistance and possibly the pulse wave velocity of individual subjects. No prospective studies designed to investigate the relationship between the duration of the anacrotic slope and subsequent cardiovascular health have been reported.

SECTION 4

The relationship between the anacrotic slope of the brachial artery pressure pulse wave and blood flow

Although pressure can be far more easily measured, blood flow (volume, velocity, duration, and destination) is the more important factor in cardiovascular health. Consequently, if the gradient of the initial, linear portion and/or the duration of the anacrotic slope of the brachial artery pressure pulse wave can be shown to provide information on one or more of the aspects of blood flow in addition to the factors affecting blood pressure, the value of Rodbard's method will have been enhanced. The possible relationship between the initial, linear portion and the duration of the anacrotic slope and blood flow will now be considered separately. First there will be an evaluation of the initial, linear portion of the anacrotic slope of the pressure pulse wave as an index of the power available to drive blood through the resistance arterioles. Secondly, inasmuch as both the blood velocity wave and the pressure pulse wave are strongly influenced by peripheral resistance and pulse wave velocity, an investigation will be made into the possibility of estimating the shape of the velocity flow wave from information on peripheral resistance and pulse wave velocity provided by the anacrotic slope of the brachial artery pressure pulse wave.

a. The initial, linear portion of the anacrotic slope and blood flow

Because pulsatile flow is a more efficient method of driving blood through the resistance arterioles than is nonpulsatile flow, the anacrotic slope of the pressure pulse wave, which is provided only by the pulsatile flow system with its fluctuations in pressure, may prove a useful index of the power available to drive blood through the resistance arterioles.

Both pulsatile and nonpulsatile flow systems have been extensively investigated in connection with cardiac by-pass surgery. Although some studies found no significant differences between the two systems, the overwhelming weight of evidence indicates the overall metabolic and hemodynamic superiority of pulsatile flow (Wilkens, Regelson, and Hoffmeister, 1962; Trinkle, Helton, Wood, and Bryant, 1969; Shepard and Kirklin, 1969; Jacobs, Klopp, Seamone, Topaz, and Gott, 1969; Taylor, Bain, Maxted, Hutton, McNab, and Caves, 1978; Taylor, 1979). When Sanderson, Wright, and Sims (1972) used a pump capable of giving pulse pressures of 25-90 mmHg in 80-150 msec, they did not find the collapsed capillaries which they had found after nonpulsatile perfusion, and they also noted a reduction in ischemic cell changes. The regions of the brain most affected by these ischemic cell changes were in the cerebral cortex and cerebellar Purkinje cells, especially in the boundary areas

of major cerebral arteries. It was suggested by Dunn, Kirsh, Harness, Carroll, Straker, and Sloan (1974) that pulsatile flow enhances interstitial diffusion by oscillating all fluid boundaries and by ensuring the patency of the end arterioles which tend to collapse during nonpulsatile perfusion.

Few quantitative studies of the optimum pressure pulse required for adequate tissue flow in cardiac bypass surgery have been reported, but when normal arterial pressure pulse waves and flow velocity waves are compared (McDonald, 1974, p 119) it can be seen that both rise rapidly to peak in early systole, and that maximum flow is reached at the point at which the anacrotic slope of the pressure pulse wave ceases to be linear. After this point flow declines although pressure may continue to increase. The importance for adequate tissue flow of this early sharp increase in pressure was borne out by the observation of Rainer (1966) that during cardiac by-pass surgery maintenance of a steep gradient of the pressure pulse wave resulted in normal blood pH values whereas slurring of the gradient resulted in lower pH values. Jacobs et al (1969) and Sanderson et al (1972) both emphasized that the gradient of the initial, linear portion of the anacrotic slope of the pressure pulse wave was the most important factor to be duplicated when producing pulsatile flow in cardiac by-pass surgery.

It is reasonable to assume from general principles that there is an optimum range of gradients for the initial, linear portion of the anacrotic slope of the pressure pulse that is most efficient for maintaining adequate tissue flow. It is possible that low gradients may be inadequate for tissue flow and require circulatory modifications which reduce circulatory reserve capacity, while high gradients may be too efficient and require circulatory modifications to prevent excessive tissue flow.

From these cardiac by-pass studies, it would appear possible that the gradient of the initial, linear portion of the anacrotic slope of the pressure pulse wave can be used as an index of the power available to drive blood past the resistance arterioles.

b. The shape of the anacrotic slope and blood flow

As with the pressure pulse wave, a proportion of the velocity flow wave is reflected at the resistance arterioles. However, unlike a reflected pressure wave, which is always added to the incident pressure wave, a reflected flow wave reduces the incident flow wave in the same artery while tending to increase flow in the vascular junctions (Mills et al, 1970; O'Rourke and Alvolio, 1980). This means that whereas a pressure wave reflected from the hind-limbs increases pressure in the arteries of the hind-limbs, the forelimbs, the head and the heart, a flow wave reflected

from the same location reduces flow in the arteries of the hind-limbs, but increases flow in the arteries of the forelimbs, the head and perhaps the heart (Mills et al, 1970).

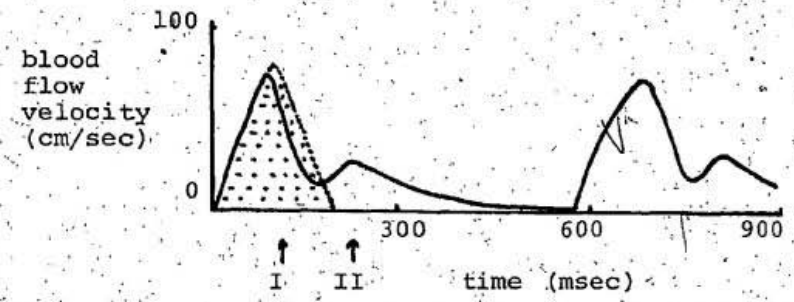
O'Rourke and Taylor (1966) demonstrated modification of the incident flow wave by reflection. When they produced temporary vasodilation and hence reduced peripheral resistance by injecting acetylcholine into the femoral artery, the mean blood pressure in this artery fell from 107 mmHg to 94 mmHg because the positive effect of the reflected pressure wave was reduced. Mean flow, however, increased from 1.08 cc/sec to 6.93 cc/sec because the negative effect of the reflected flow wave was also reduced. These findings of O'Rourke and Taylor (1966) are supported by results obtained by Lee, Castillo, and Madden (1970), Rittenhouse and Strandness (1971), and Rittenhouse, Maixner, Burr, and Barnes (1976). These authors explained their results in terms of changes in peripheral resistance but did not take the further step of associating this with wave reflection.

Because wave reflection in the femoral arteries is responsible for part of the strength of the caudal reflected pressure wave seen in the brachial artery, the effect of the caudal reflected flow wave upon the pattern of flow in the brachiocephalic artery was investigated. There was little in the literature for the brachial artery itself, and the

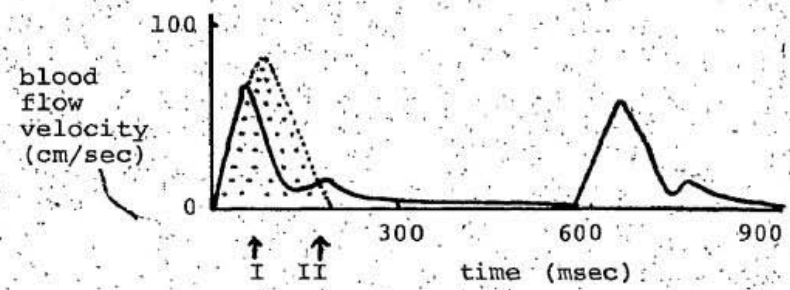
brachiocephalic artery, like the brachial artery, exhibits the flow and pressure patterns seen in the upper body.)

O'Rourke and Alyolio (1980), using their own data and those published by Mills et al (1970), described in detail the changes in the flow wave of the brachiocephalic artery which were produced by cephalic and caudal reflected flow waves: the cephalic reflected flow wave decelerated the velocity and shortened the duration of flow in early systole, whereas the caudal reflected flow wave accelerated the velocity and lengthened the duration of forward flow in late systole. As with reflected pressure waves, the time taken for these cephalic and caudal reflected flow waves to return to the point of measurement in the brachiocephalic artery and hence also the velocity and duration of flow, was affected by pulse wave velocity: when pulse wave velocity was slow both these reflected waves returned comparatively late and the maximum velocity and duration of flow were high (see figure 5a); when pulse wave velocity was intermediate both these reflected flow waves returned at an intermediate time and the maximum velocity and duration of flow were intermediate (see figure 5b); when pulse wave velocity was comparatively fast both these reflected flow waves returned comparatively early and the maximum velocity and duration of flow were low (see figure 5c); Mills et al (1970) had labelled these three types of flow waves as Types III, II,

a. Comparatively slow pulse wave velocity



b. Intermediate pulse wave velocity



c. Comparatively fast pulse wave velocity

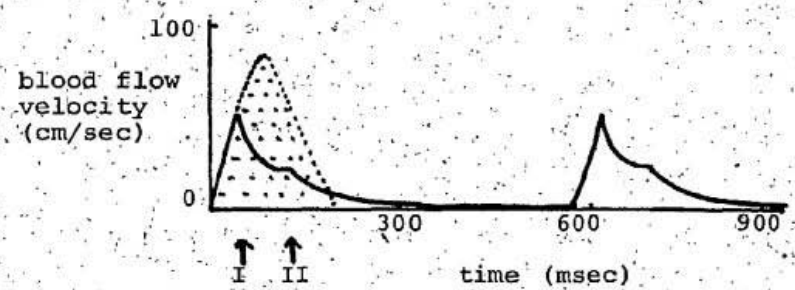


Figure 5. A diagram to illustrate the changes in the brachial artery blood velocity wave which result from changes in pulse wave velocity. The arrows indicate the time of arrival of the cephalic (I) and the caudal (II) reflected waves. The stippled area indicates the incident blood velocity wave.

and I respectively. Type III is typically found in young, normotensive adults and Type I in elderly, hypertensive adults.

From the foregoing it can be seen that the velocity flow wave is, like the pressure pulse wave, strongly influenced by wave reflection, which is in turn strongly influenced by peripheral resistance and pulse wave velocity. It is thus possible to estimate the shape of the velocity flow wave by estimating peripheral resistance and pulse wave velocity from the entire brachial artery pressure pulse wave. However, peripheral resistance and pulse wave velocity can be estimated from the anacrotic slope alone only in those subjects whose peripheral resistance has increased to the stage that it pushes the caudal reflected wave high enough to form part of the anacrotic slope. (The cephalic wave, it is to be remembered, is probably reduced by the presence of the inflated cuff - this thesis, p 99.) Thus the anacrotic slope provided by Rodbard's method is of limited usefulness in estimating the shape of the velocity flow wave.

To summarize: The possibility of using the anacrotic slope of the brachial pressure pulse wave provided by Rodbard's method as an index of one or more of the aspects of blood flow was investigated. It would appear that the gradient of the initial, linear portion of the anacrotic

slope can be used as an index of the power available to drive blood past the resistance arterioles, but that the duration of the anacrotic slope generally provides insufficient information on peripheral resistance and pulse wave velocity to make possible an estimation of the shape of the velocity flow wave.

CHAPTER II

METHODS

The aim of this thesis, as was stated in the Introduction (p 3), was to test the hypothesis that Rodbard's method is useful in cardiovascular epidemiology. The materials were records obtained in 1969-70 in Göteborg, Sweden, by Dr J G Fodor.

The selection of the subjects, the collection of the records, and the procedures used to read and analyse these records will now be described.

a. Selection of the subjects

The records for three groups of subjects were selected for the purposes of this thesis.

1. The main group

In 1969-70 as part of a fully randomized preventive study (Wilhelmsen et al, 1972) 1423 of the 1882 men selected at random from all men living in Göteborg and born 1915-16 responded to an invitation "to a screening examination at which height, weight, cholesterol, blood pressure, ECG and some interview responses (were) recorded" (Wilhelmsen, Tibblin, and Werkö, 1972). This examination was performed "after a working day between 4:30 PM and 7:00 PM" (Wilhelmsen, Berglund, and Werkö, 1973). Further

details concerning the methodology and results of this preventive study are to be found in Berglund, Wilhelmsen, and Werkö (1974); Berglund, Andersson, and Wilhelmsen (1976); Berglund, Wilhelmsen, Sannerstedt, Hansson, Andersson, Sivertsson, Wedel, and Wikstrand (1978); Berglund and Wilhelmsen (1975); Hartford, Ljungman, Andersson, Wikstrand, and Berglund (1979). Of those screened, 155 men also had their Rodbard records taken by Dr J G Fodor when time and the availability of equipment permitted. Three of these men were found to have had at least one myocardial infarction prior to study, and were thus assigned to the post-MI group (see p 115). The 152 individuals remaining (designated the main group) were subdivided

1) into two equal subgroups (random A and B) by the throwing of a die. This subdivision was made to provide replication for factor analysis;

2) into two unequal subgroups on the basis of outcome. At follow-up in 1979 the outcome of all members of the main group was ascertained. Twenty-five had either died from cardiovascular causes or had suffered at least one non-fatal myocardial infarction or stroke. The records of this group of subjects (designated the C subgroup) were compared with those of the remaining 127 members of the main group in an attempt to define components of the record which might have prognostic value. (Information as to myocardial infarctions and strokes were obtained from the City of Göteborg's

Myocardial Infarction Register and Stroke Register, for details of which see Elmfeldt, Wilhelmsen, Tibblin, Vedin, Wilhelmsson, and Bengtsson [1975] and Harmsen and Tibblin [1972], respectively.)

2. The post-myocardial infarction group

The post myocardial-infarction group consisted of

1) 16 men born 1913-18 who had had at least one documented myocardial infarction and were patients of Dr J G Fodor in Göteborg;

2) the 3 myocardial infarction subjects excluded by the present author from the main group above.

The records for this post-myocardial infarction group were selected for the following reasons:

1) It can be confidently assumed that if invasive examinations were to be carried out some differences in cardiac function would be found to exist between this group and the main group. Therefore these differences should be reflected in at least one of the seven variables unique to Rodbard's method if Rodbard's method is to be useful in cardiovascular epidemiology;

2) The records of this group also provided replication for the factor analysis and the covariance analysis to be carried out in this thesis.

3. The younger group

The younger group consisted of

1) ten subjects born 1924-55 who had no history of cardiovascular disease and from whom Dr J G Fodor took records for control purposes in Göteborg, and

2) nine subjects born 1927-69 who likewise had no history of cardiovascular disease and from whom the present author took records in 1978 in St John's.

This younger group was used to provide replication for the factor analysis and the covariance analysis to be carried out in this thesis. The St John's subgroup was added to the Göteborg subgroup to provide a number large enough to be dealt with satisfactorily by the factor and covariance analysis. The subgroups were added together only after a check had been made to verify that there were no differences in the means of the variables due to the instruments used in Göteborg and in St John's. The only significant difference ($P<.05$) was for QKD, the mean of which was 20 msec shorter in St John's. Although this difference could be due to instrumental factors, it is more likely that it was due to the larger number of subjects younger than twenty who were in the St John's subgroup (this thesis, p 60). (A table of the means and standard deviations of the variables of the Göteborg and St John's subjects is provided in Appendix A, p 259.)

Identification numbers

For the sake of confidentiality, identification numbers were assigned to each of the 190 subjects who were included in the study. The variables extracted from the records for the three groups are provided in Appendices B, C, and D, (pp 260-65).

b. Collection of the records

1. Instruments

i. In Göteborg

Dr J G Fodor used a 4-channel Mingograph (EMT 34, Elema-Schönander). Channel 1 of the machine recorded lead II of the electrocardiogram, while channels 2, 3, and 4 recorded the Korotkoff sounds after they had been picked up by a microphone (EMT 25 B) and passed through, respectively, 100 cps, 50 cps, and 25 cps filters (EMT 510 C).

ii. In St John's

A 3-channel electrocardiograph/phonocardiograph (1514C, Hewlett-Packard) was used. Channel 2 of the machine recorded lead II of the electrocardiogram, while channels 1 and 3 recorded the Korotkoff sounds after they had been picked up by a microphone (21050A) and passed through, respectively, 100 cps and 50 cps filters (1514C).

2. Procedures

In both Göteborg and St John's all the subjects rested in the supine position for at least ten minutes before the electrocardiogram, sphygmomanometer pressure, and Korotkoff sounds were recorded. During this time the standard leads of the electrocardiograph were applied in the usual way; the sphygmomanometer cuff was positioned according to the recommendations of the American Heart Association (Kirkendall, Burton, Epstein, and Freis, 1967) on either the right or left arm; and a microphone was positioned and taped lightly in place over the brachial artery immediately distal to the sphygmomanometer cuff. (Care was taken to see that the microphone did not press into the skin.)

The sphygmomanometer cuff was inflated manually to a pressure 30-40 mmHg above the anticipated level of systolic pressure, and the paper was set in motion. The sphygmomanometer cuff was then deflated, and the standardization push-button of the electrocardiograph recorder was depressed at 10 mmHg intervals, with two depressions made at the 100 mmHg level. The deflation was done manually in Göteborg, but in St John's it was regulated by a pressure release valve to give a deflation rate of 2-3 mmHg/sec. (This pressure release valve did not provide a completely linear pressure drop but it did standardize the pressure records and make them easier to read.) Each recording was stopped a few seconds after the last of the Korotkoff deflections had been

observed. One record was made for each of the Göteborg subjects, and four records were made for each of the St John's subjects.

c. Extraction of potentially useful variables from the records

Eleven variables were extracted from the records because they were judged to be important in describing the anacrotic slope (Table 8). Seven of these variables were unique to Rodbard's method, and if at least one of them was found to be useful in cardiovascular prognosis, the value of Rodbard's method as a tool in cardiovascular epidemiology would have been established. A twelfth variable, the time elapsing between the onset of the QRS complex and the onset of the T wave of the EKG (QT), was added to aid the discriminating power of factor analysis.

1. QK time intervals

The QK time interval is the time elapsing between the appearance of the Q wave of the electrocardiograph record and the beginning of the Korotkoff sound deflection on the 100 cps filter channel. The reference point used for the appearance of the Q wave was the point at which the sharp upsweep of the QRS complex began. (This point was chosen because it was the most consistent and easily seen indicator of the Q wave on all the records and thus minimized observer error.) The paper used was standard electrocardiograph

Table 8. Variables extracted from the records.

Variables not unique to Rodbard's method

SP	systolic pressure
DP	diastolic pressure
PP	pulse pressure
QT	time from onset of QRS complex until onset of T wave of electrocardiogram
RR	cardiac cycle length

Variables unique to Rodbard's method

QKD	time from onset of QRS complex of electrocardiogram until arrival of foot of pressure wave at brachial cuff
G	gradient of initial, linear portion of the anacrotic slope
LT	duration of initial, linear portion of the anacrotic slope
D	duration of anacrotic slope
NT	duration of the nonlinear portion of the anacrotic slope
NP	amount of nonlinear pressure increase
NA	area measurement related to the nonlinear portion of the anacrotic slope

paper with dark lines at centimeter intervals and lighter lines at millimeter intervals. Because paper speed was standardized at 50 mm/sec, 1 cm of paper represented 200 msec. QK time intervals were determined to the nearest 10 msec.

2. Sphygmomanometer cuff pressures

Sphygmomanometer cuff pressure was determined at the points on the record at which each of the Korotkoff sound deflections began. The start of the double calibration was used to locate the 100 mmHg cuff pressure level, and the start of the single calibrations was used to locate pressure levels above and below this level. The interval between the calibration deflections was then measured and subdivided into ten equal portions to determine to the nearest 1 mmHg the pressure in the cuff when each of the Korotkoff sound deflections began.

3. Systolic pressure and diastolic pressure

The pressures in the cuff when the first and last Korotkoff sound deflections began were systolic pressure and diastolic pressure respectively. It was rare to have a problem identifying the first Korotkoff sound deflection (and hence systolic pressure). However, although the last Korotkoff sound deflection (and hence diastolic pressure) was easily detected in most subjects, it was difficult to determine in some, particularly the youngest. In these

subjects Korotkoff sound deflections were seen to continue even when cuff pressures had fallen to unrealistically low levels, eg 20 mmHg. For these subjects diastolic pressure was judged to be the pressure in the cuff when the amplitude of the Korotkoff sound deflections diminished to a minor nudge of the pen and no further reduction in the QK time interval occurred.

4. QKS and QKD time intervals

After systolic and diastolic pressure had been determined the QK time intervals for each of these pressures were given the customary designations of QKS and QKD respectively.

5. The gradient of the initial, linear portion of the anacrotic slope

The QK time intervals and the pressure prevailing in the cuff when each of the Korotkoff sound deflections began were plotted on graph paper. The x-axis was used for the QK time intervals (scale: 1 cm/20 msec), and the y-axis was used for cuff pressures (scale: 1 cm/5 mmHg). Then the curve which was judged by eye as best fitting the nonlinear portion of the anacrotic slope was hand-drawn (figure 6). All the points between the base of this hand-drawn line and diastolic pressure (as determined p 121) were then entered into a calculator-printer combination (Texas Instruments: calculator 58, printer PG 100A) to calculate the line which

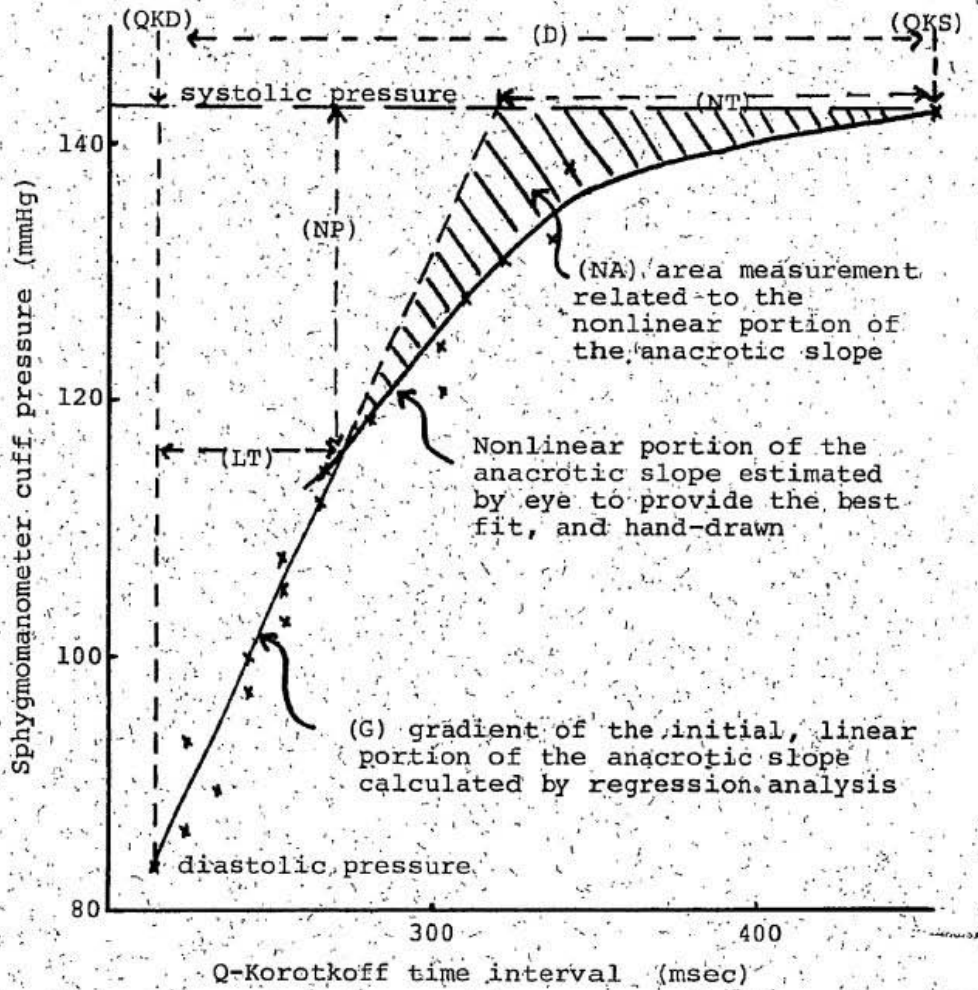


Figure 6 Graph to illustrate how the seven Rodbard variables were determined from the anacrotic slope

D: duration of the anacrotic slope
QKS, QKD: time elapsing between the Q wave of the electrocardiogram and the Korotkoff sounds signalling systolic and diastolic pressure
NT: duration of nonlinear portion
LT: duration of initial, linear portion
NP: nonlinear pressure increase

provided the best fit for the initial, linear portion of the anacrotic slope, the gradient of this line, and the correlation coefficient. Only ten percent of the lines had correlation coefficients below $r = .83$, and in the majority of these instances this was judged by the author to be due to the error that resulted from the difficulty in determining diastolic pressure where the gradient was steep. However, to reduce subjective bias, no adjustment of diastolic pressure was made and the original values were allowed to stand.

6. The duration of the initial, linear portion of the anacrotic slope

The duration of the initial, linear portion of the anacrotic slope was determined by subtracting QKD from the point at which the line calculated to provide the best fit for this portion of the anacrotic slope crossed the hand-drawn line of the nonlinear portion of the anacrotic slope (figure 6, p 123).

7. The duration of the entire anacrotic slope

The duration of the entire anacrotic slope was determined by subtracting QKD from QKS.

8. Nonlinear time, nonlinear pressure, nonlinear area

Nonlinear time was determined by subtracting from QKS the point of time at which the extension of the line

calculated for the initial, linear portion of the anacrotic slope crossed the systolic pressure level (figure 6, p 123).

Nonlinear pressure was determined by subtracting from systolic pressure the pressure at which the line calculated for the initial, linear portion of the anacrotic slope crossed the hand-drawn line of the nonlinear portion of the anacrotic slope (figure 6, p 123).

Nonlinear area was determined by measuring with a planimeter (277-132, Numonics Corp) the area bounded by the extension of the line calculated for the initial, linear portion of the anacrotic slope, the hand-drawn line of the nonlinear portion, and the line marking systolic pressure (see shaded area in figure 6, p 123). The mean of three measurements was recorded as nonlinear area.

The above three variables were measured to quantify the nonlinear portion of the anacrotic slope.

9. QT

The QT time interval was the time elapsing between the onset of the QRS complex and the beginning of the T wave of the electrocardiograph record. The mean of five measurements was recorded as QT. QT was determined to provide a "neutral" cardiovascular variable to aid the discriminating power of factor analysis.

It should be noted that QT as measured in this thesis is shorter than the standard QT measurement recommended by the Committee on Electrocardiography of the American Heart Association (Wilson, Kossman, Burch, Goldberger, Graybiel, Hecht, and Johnston, 1964) by an amount equal to ventricular repolarization time, which it does not include. It should be further noted that the QT measurement used in this thesis would appear to provide a more accurate indication of sympathetic nervous system activity than the standard QT measurement because ventricular repolarization time lengthens in response to increases in sympathetic nervous system activity at high levels (Yanowitz, 1966) whereas the standard QT measurement minus ventricular repolarization time (ie the QT measured in this thesis) shortens in response to increases in sympathetic nervous system activity at most levels (Sjostrand, 1960). In other words, the two parts of the standard QT measurement sometimes move in opposite directions with a change in the level of sympathetic nervous system activity. The unsatisfactory nature of the standard QT measurement can be seen in the conflicting results of Stern and Eisenberg (1969), Abildskov (1976), and Raine and Pickering (1977).

10. Cardiac cycle length

Cardiac cycle length was determined by dividing 20,000 msec by the number of R waves occurring during a 20 sec strip of record.

d. Statistical programs used to determine the potential usefulness of the variables extracted

All statistical analyses were carried out using programs described in The Biomedical Data Processing Manual (1979). These ready-made programs were prepared by the Health Sciences Computing Facility of the University of California (Los Angeles). The following programs were used:

BMDP4M factor analysis

BMDP6D linear correlation

BMDP1V analysis of variance and covariance

BMDP1F analysis of frequency tables

Information concerning the use of the various statistical procedures was obtained from Steel and Torrie (1960).

CHAPTER III

THE PHYSIOLOGICAL MECHANISMS AFFECTING, AND HENCE THE POTENTIAL USEFULNESS IN CARDIOVASCULAR EPIDEMIOLOGY OF, THE VARIABLES EXTRACTED FROM THE RECORDS

An investigation of the literature that was useful in establishing a theoretical understanding of the physiological mechanisms affecting the variables uniquely provided by Rodbard's method has been carried out in Chapter I. In section 1 of this chapter factor analysis will be used to determine the interrelationships between these variables in an attempt to deduce which of the physiological mechanisms actually affect them. In section 2 analysis of covariance will be used to check the groups of subjects studied for differences in the interrelationships of these Rodbard variables in an attempt to determine which of them have the potential to identify changes due to cardiovascular disease or the aging process. The purpose of this two-fold investigation is to enable attention to be focussed in Chapter IV on those Rodbard variables which exhibit potential usefulness in cardiovascular epidemiology.

SECTION 1

Factor analysis of the variables

To determine the interrelationships between the Rodbard variables extracted from the records, first the simpler varimax orthogonal factor analysis option and then the more complex quatimin oblique factor analysis option of The Biomedical Data Processing Manual (1979) were employed.

a. Varimax orthogonal factor analysis

1. Results

Varimax orthogonal factor analysis of the variables extracted from the records was carried out using the BMDP4M program for each of the six groups of subjects previously described (this thesis, pp 113-16).

The same four significant factors were extracted for each group and accounted for 67-74% of the variance. These factors were ranked by the program according to the percentage of the total variation that they explained. This ranking differed slightly in the six groups, but for ease of identification the factors have been labelled 1-4 according to their ranking in the main group. A fifth factor was identified in all groups except the random A subgroup and the post-MI group and it, too, is included in the discussion which follows. In all, these five factors accounted for 79-88% of the variance (Table 9).

Table 9. Percentage of the total variation explained by the extracted factors.

		Subgroups of the main group				
	Main group	random A	random B	C	Post-MI group	Younger group
Factor 1	24	26	22	29	20	20
Factor 2	23	24	24	24	38	26
Factor 3	13	15	15	14	16	21
Factor 4	13	14	12	15	14	
Factor 5	11		11			19
Total variance explained	84	79	84	81	88	86
Number of factors extracted	5	4	5	4	4	4

The factors were identified from the factor loading pattern produced by the program. (A factor loading pattern is provided by factor analysis, after rotation, in the form of a correlation matrix of variables and factors.) The factor loading pattern for the six groups of subjects is provided in Appendix E (pp 266-71).

Squaring the factor loading pattern provides an estimate of the percentage of variation of the variables that is explained by each of the factors. In this thesis this was done only for variables having a factor loading of .500 or more. (The figure .500 was arbitrarily chosen as the base point because it indicates that at least twenty- five percent of the variation of the variables is explained by the factor.) The percentage of variation of the variables that was explained by each of the factors is given in Appendix F (pp 272-77).

The individual factors will now be presented in detail.

i. Factor 1

The basic factor loading pattern of factor 1 (figure 7) explained a significant percentage of the variation of systolic pressure, pulse pressure, the gradient of the initial, linear portion of the anacrotic slope, and QKD. The factor loading pattern was similar in the main group and the two random subgroups. However, QKD was absent in the

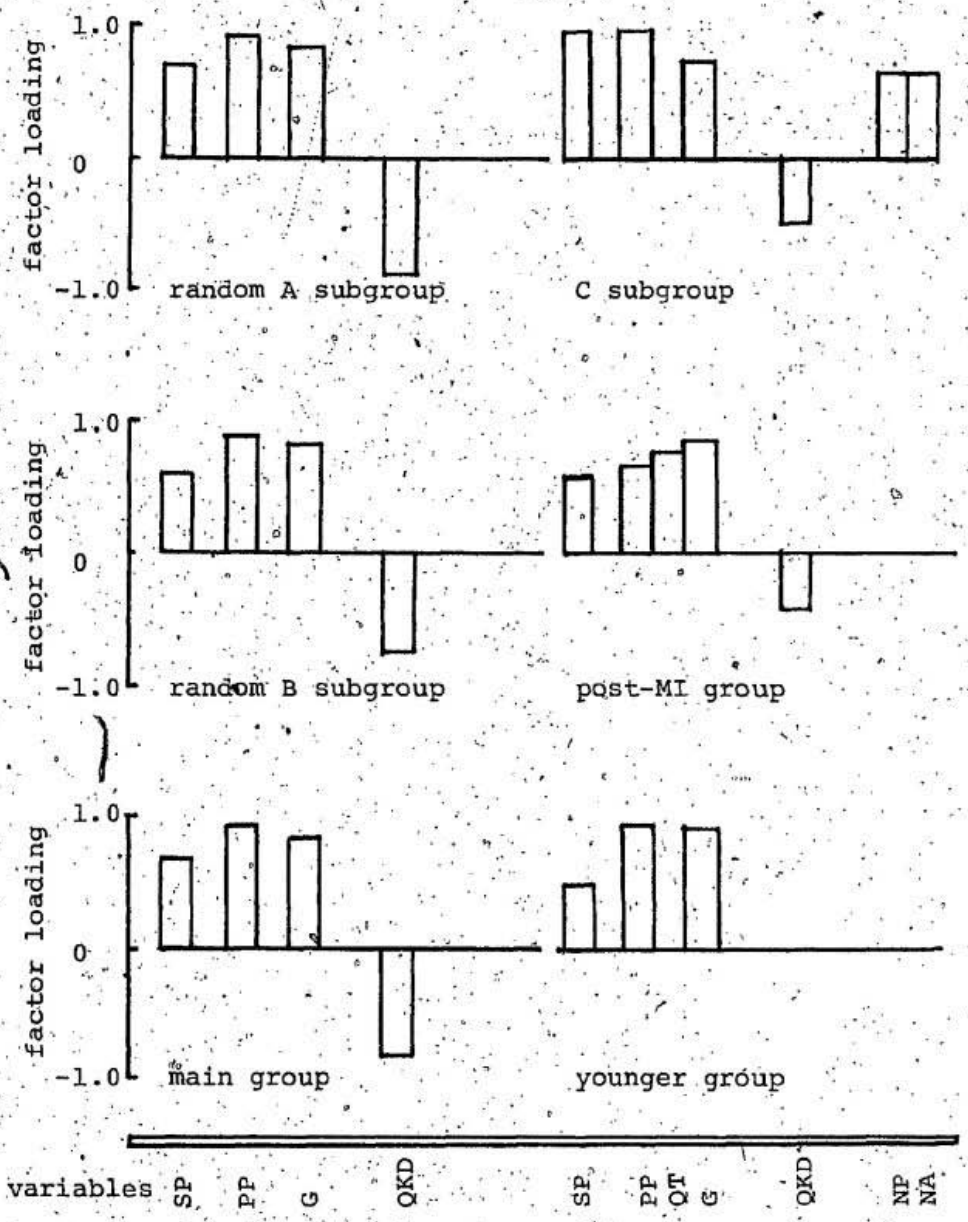


Figure 7. Histograms showing the factor loading of factor 1 for the six groups analysed. (The factor loading provides the correlation between the factors and the variables.)

younger group, and its factor loading was weak in the C subgroup (-.509) and the post-MI group (-.412). The factor loading of systolic pressure was weak in the younger group (.483) and the post-MI group (.476). Additional variables were present in factor 1 in the C subgroup (NP: .650, NA: .618) and the post-MI group (QT: .786).

ii. Factor 2

The basic factor loading pattern of factor 2 (figure 8) explained a significant percentage of the variation of the four variables chosen by the author to quantify the nonlinear portion of the anacrotic slope: the duration of the entire anacrotic slope, the duration of the nonlinear portion of the anacrotic slope, the amount of nonlinear pressure increase, and the area measurement related to the nonlinear portion of the anacrotic slope. Factor 2 was easily identified in all the groups. However, the factor loading was weak for the amount of nonlinear pressure increase in the random A subgroup (.492) and in the C subgroup (.399), and for the area measurement related to the nonlinear portion of the anacrotic slope in the C subgroup (.444). Factors 2 and 4 were not separated by the analysis in the younger group, and additional variables were present in factor 2 in the C subgroup (RR: .716, QKD: .576), and the post-MI group (SP: .586, PP: .588, QKD: -.516).

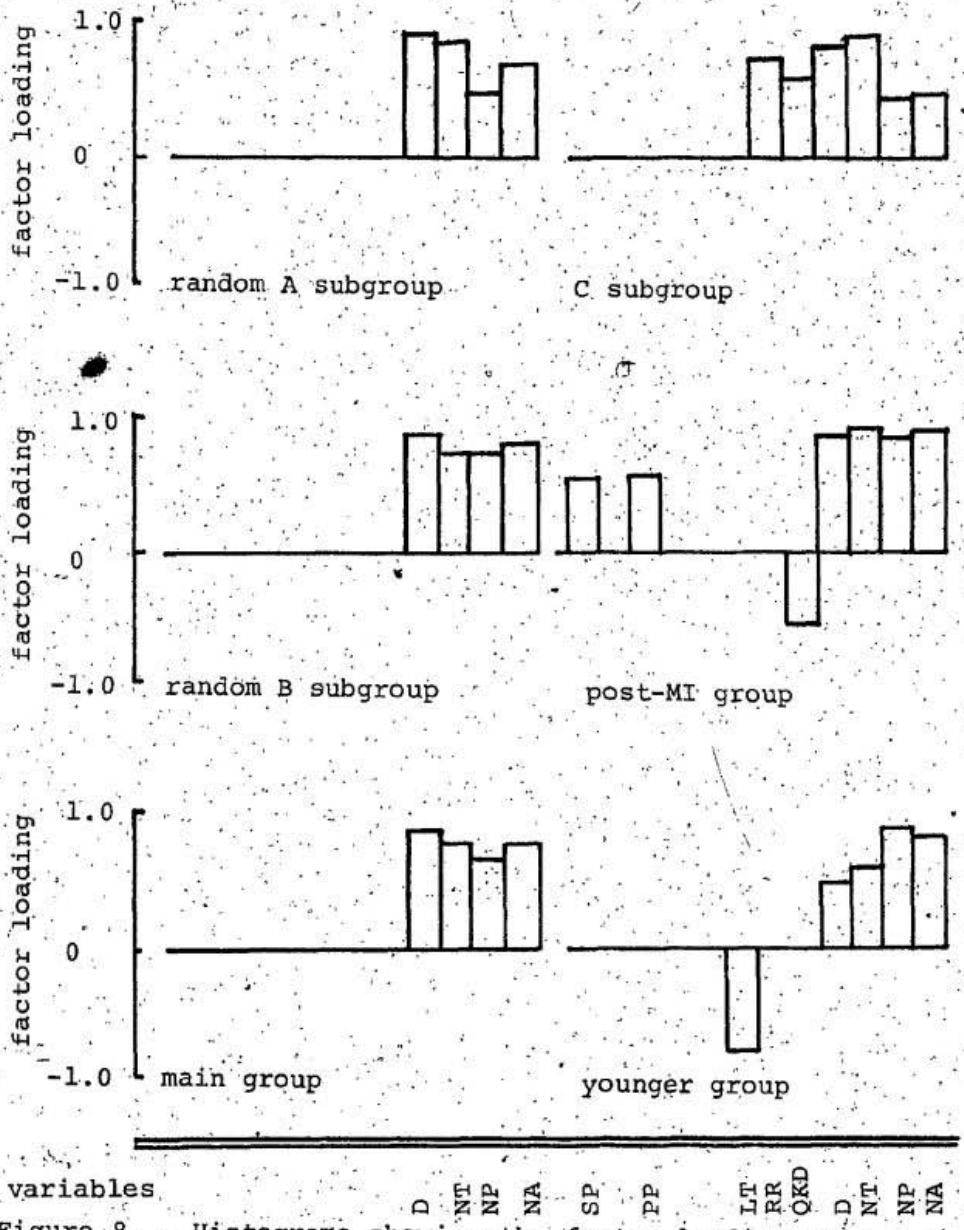


Figure 8. Histograms showing the factor loading of factor 2 for the six groups analysed. (The factor loading provides the correlation between the factors and the variables.)

iii. Factor 3

The basic factor loading pattern of factor 3 (figure 9) explained a significant percentage of the variation of diastolic pressure and a smaller but significant percentage of the variation of systolic pressure. The factor loading pattern was similar in the main group, the two random subgroups, and the post-MI group. However in the C subgroup the factor loading of systolic pressure was weak (.361), and factors 3 and 5 were not separated by the analysis. Additional variables were present in factor 3 in the younger group (D: .619, NT: .615), the post-MI group (RR: -.757) and the random A subgroup (RR: -.619).

iv. Factor 4

The basic factor loading pattern of factor 4 (figure 10, p 137) explained a significant percentage of the variation of the duration of the initial, linear portion of the anacrotic slope in all groups. However, factors 2 and 4 were not separated by the analysis in the younger group. Additional variables from factor 2 were present in factor 4 in the main group (NP: -.500), the random A subgroup (NP: -.687, NA: -.496), and the C subgroup (NP: -.539, NA: -.510). An additional factor 1 variable was present in factor 4 of the random B subgroup (G: -.501) and the C subgroup (G: -.531).

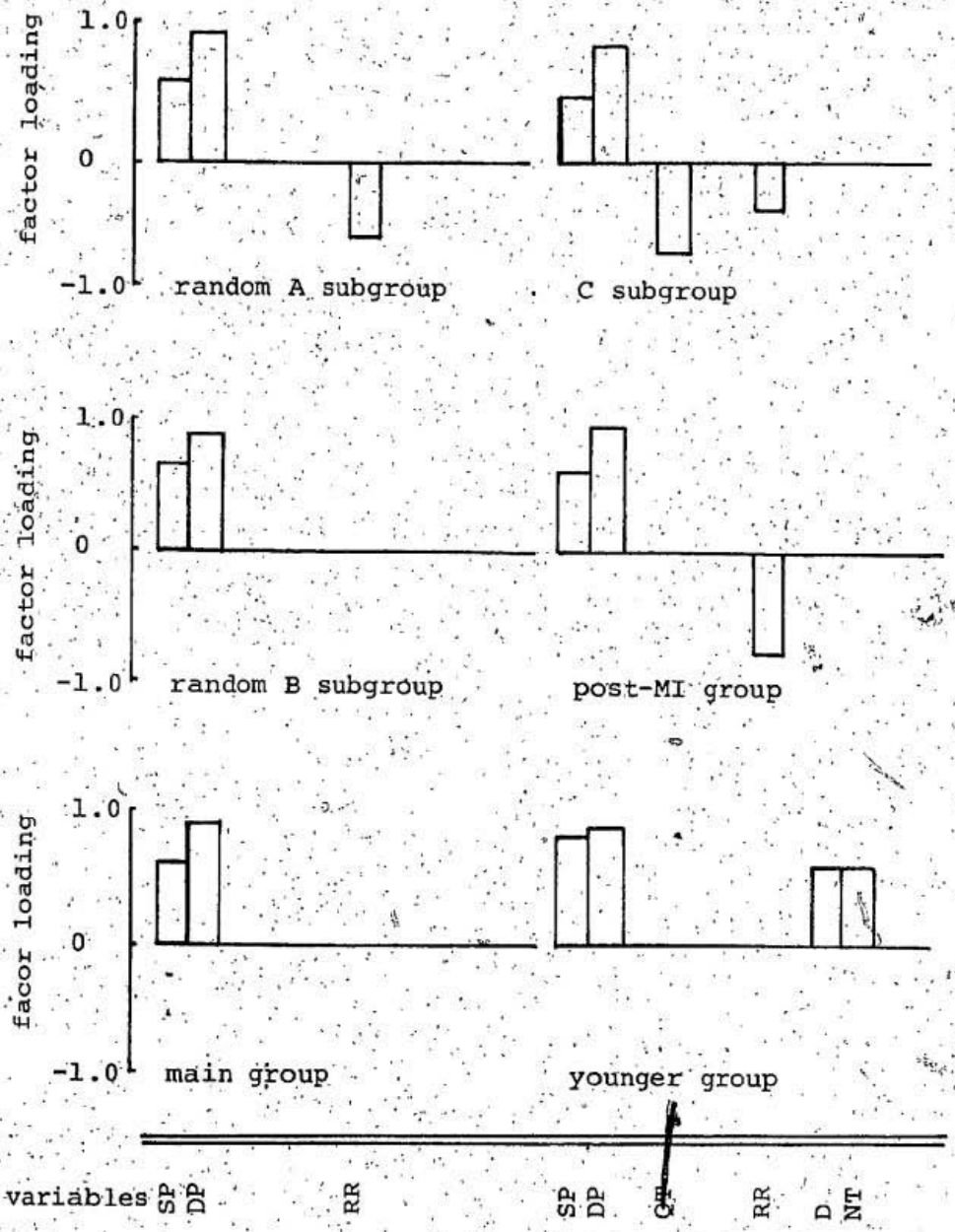


Figure 9. Histograms showing the factor loading of factor 3 for the six groups analysed. (The factor loading provides the correlation between the factors and the variables.)

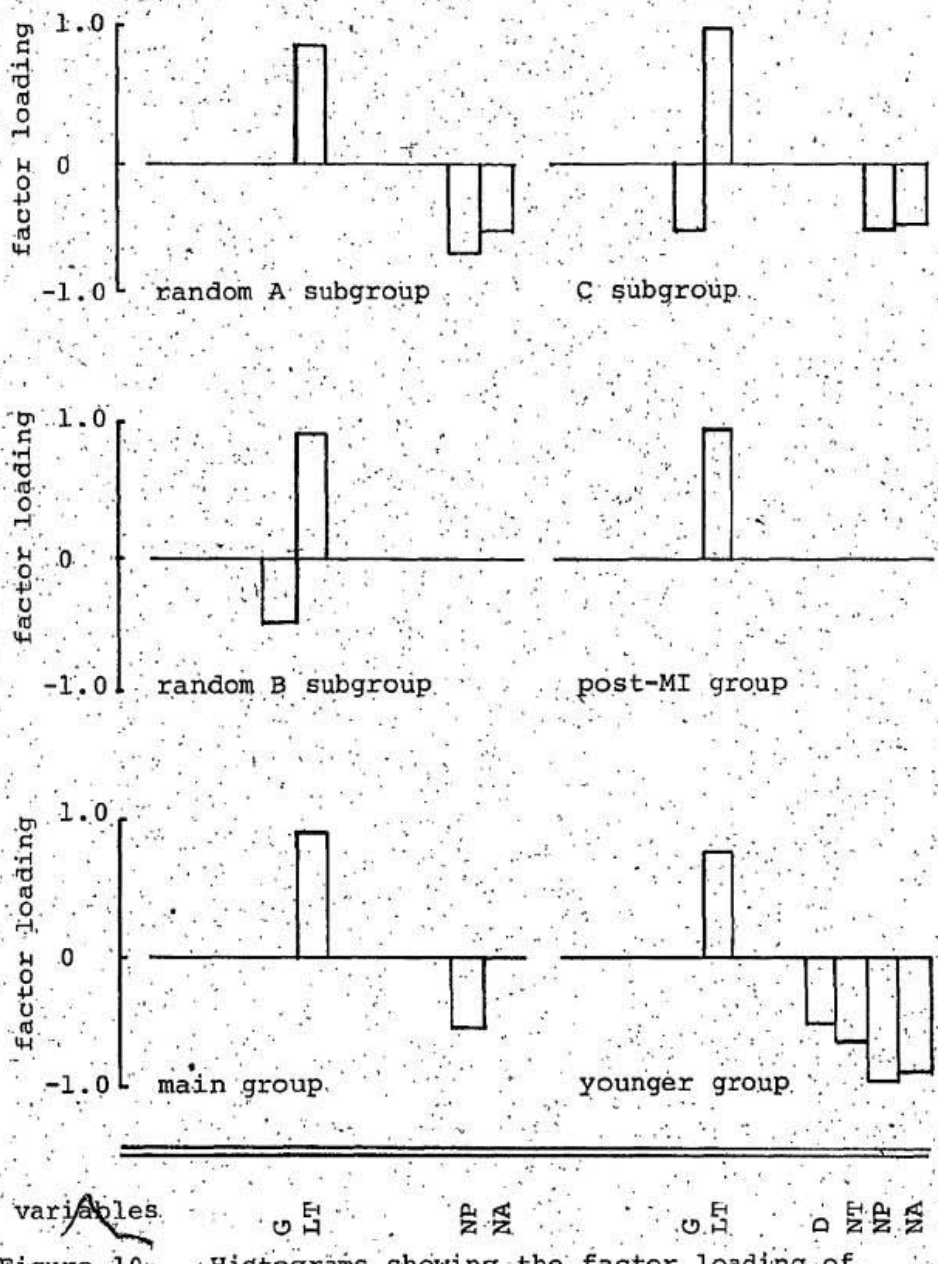


Figure 10. Histograms showing the factor loading of factor 4 for the six groups analysed. (The factor loading provides the correlation between the factors and the variables.)

v. Factor 5

The basic factor loading pattern of factor 5 (figure 11) explained a significant percentage of the variation of QT and a smaller but significant percentage of the variation of cardiac cycle length. The factor loading pattern was similar in the main group, the random B subgroup, the C subgroup, and the younger group. However, factor 5 was absent in the random A subgroup and the post-MI group, and cardiac cycle length was weak (.431) in the C subgroup. The analysis did not separate factors 3 and 5 in the C subgroup. QKD was present as an additional variable (.885) in factor 5 in the younger group.

2. Discussion

That the factors extracted by the present analysis are genuine factors and are not the result of random chance is demonstrated by the following:

1) the same four or five factors were extracted in each of the six groups of subjects;

2) the factors explained a high percentage of the total variation of the variables in all six groups: 84% in the main group, 79% in the random A subgroup, 84% in the random B subgroup, 81% in the C subgroup, 88% in the post-MI group, and 86% in the younger group.

Inasmuch as these factors are genuine factors it can be concluded that the interrelationships existing between the

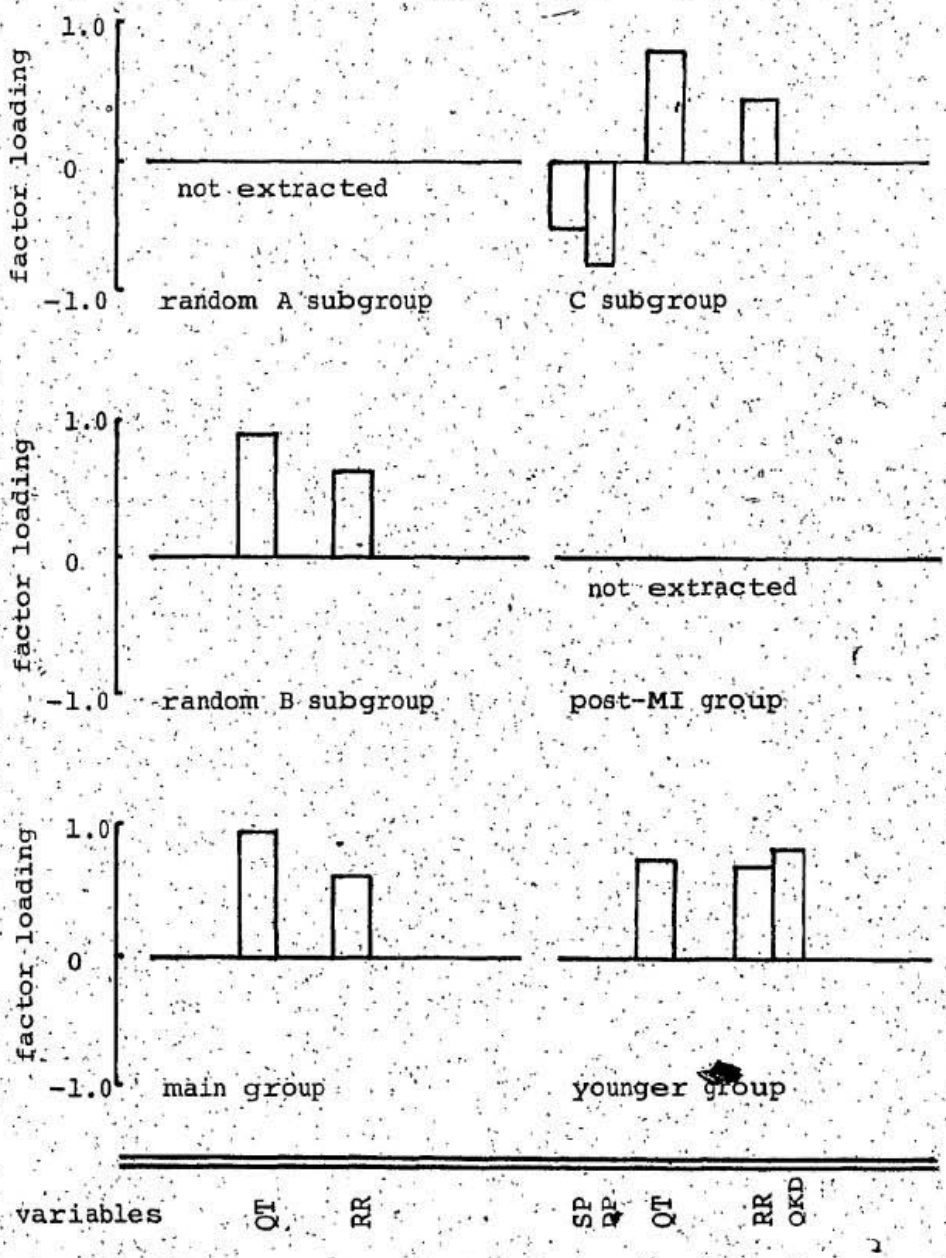


Figure 11. Histograms showing the factor loading of factor 5 for four of the six groups analysed. (The factor loading provides the correlation between the factors and the variables.)

variables linked by the factors are genuine and are caused by common physiological mechanisms. The physiological mechanisms causing the interrelationships between the variables and hence actually affecting the variables themselves can be deduced from a theoretical knowledge of the variables.

These mechanisms will now be considered factor by factor.

i. Factor 1

Inasmuch as the factor loading pattern of factor 1 (figure 7, p 132) brought together the four variables systolic pressure, pulse pressure, the gradient of the initial, linear portion of the anacrotic slope and QKD, the present author deduced that the physiological mechanisms causing this interrelationship and hence affecting the individual variables were cardiac contractility and pulse wave velocity. This deduction was made on the grounds that both mechanisms are known to affect all four variables: systolic pressure, pulse pressure (O'Rourke, 1970, 1971; McDonald, 1974, p 284), and the gradient of the initial, linear portion of the anacrotic slope (this thesis, pp 71-75) directly; and QKD (pp 53-55) inversely. The relative importance of these two physiological mechanisms on the four factor 1 variables cannot be quantified because no independent measurements of cardiac contractility or pulse

wave velocity were available for the subjects. However, the following reasoning suggested that cardiac contractility was the stronger physiological mechanism affecting the factor 1 variables:

1) Pulse wave velocity increases with age, and the younger group, which encompassed by far the widest age range (forty years), can thus be assumed to have contained the widest range of pulse wave velocity. Pulse wave velocity determines to a large extent pulse wave transmission time, which in turn accounts for approximately fifty percent of QKD (this thesis, pp 24, 59). Therefore, if pulse wave velocity were the more important underlying physiological mechanism affecting the factor 1 variables, QKD would have a high factor loading in factor 1 in the younger group. However, QKD had in fact a factor loading of only +.115 in factor 1 in this group.

2) Similarly, pulse wave velocity is reduced in the presence of advanced peripheral vascular disease while it is increased in advanced hypertension (this thesis, pp 41-42), and therefore the C subgroup and the post-MI group can thus be assumed to have contained a wider range of pulse wave velocity than the main group. Therefore, if pulse wave velocity were the more important physiological mechanism affecting factor 1, QKD would have a higher factor loading in factor 1 in these two groups than in the main group. However, QKD had in fact factor loadings of only -.509 and

-.412 respectively in factor 1 in these two groups as opposed to a factor loading of -.819 in the main group.

It is to be noted that pulse wave velocity and cardiac contractility are independent physiological mechanisms. Therefore, pulse wave velocity can act to confound the relationship between cardiac contractility and the factor 1 variables, especially QKD, a variable unique to Rodbard's method. The implications of this will be discussed later in this thesis (pp 192-93, 242).

Peripheral resistance, the physiological mechanism underlying factor 3, can be assumed to have affected systolic pressure, one of the four factor 1 variables, because systolic pressure is present in both factor 1 and factor 3. This assumption is supported by the following line of reasoning. Peripheral resistance increases with age (this thesis, p 88) and also to compensate for cardiac dysfunction. The younger group, which encompassed by far the widest age range (forty years), and the post-MI group, which encompassed a wide range of cardiac dysfunction, can thus be assumed to have contained a wider range of peripheral resistance than any of the other groups. Therefore, if peripheral resistance were an important physiological mechanism affecting systolic pressure, systolic pressure would have a low factor loading in factor 1 in the younger group and the post-MI group. This was indeed the case: the factor loading in factor 1 of systolic pressure was .483 in

the younger group and .476 in the post-MI group, whereas it was .686 in the main group and .903 in the C subgroup.

It should thus be noted that peripheral resistance can act to confound the relationship between cardiac contractility and pulse wave velocity (the physiological mechanisms affecting factor 1) and systolic pressure (one of the four factor 1 variables). The implications of this will be discussed later in this thesis (pp 190-91).

ii. **Factor 2**

The factor loading pattern of factor 2 (figure 8, p 134) brought together the four variables: the duration of the entire anacrotic slope, the duration of the nonlinear portion of the anacrotic slope, the amount of nonlinear pressure increase, and the area measurement related to the nonlinear portion of the anacrotic slope. This was only to be expected as the author had chosen these four variables to quantify the nonlinear portion of the anacrotic slope in the first place (this thesis, p 125), and thus no further understanding of the physiological mechanisms affecting the shape of the nonlinear portion of the anacrotic slope was revealed by this analysis.

iii. Factor 3

Inasmuch as the factor loading pattern of factor 3 (figure 9, p 136) brought together the two variables, systolic pressure and diastolic pressure, the present author deduced that the physiological mechanism causing this inter-relationship and hence affecting the individual variables was peripheral resistance. This deduction was made on the grounds that peripheral resistance is known to affect both variables. Indeed, where cardiac output is constant, peripheral resistance can be estimated from the weighted average of diastolic pressure plus systolic pressure (ie mean arterial pressure).

The deduction is further supported by the existence of physiologically plausible reasons for the inclusion by factor analysis of a) additional factor 2 variables in factor 3 in the younger group, and b) additional factor 5 variables in factor 3 in the post-MI group and the C subgroup.

a) The younger group: It was determined theoretically in Chapter 1 that the increase in two of the four factor 2 variables, the duration of the entire anacrotic slope and the duration of the nonlinear portion of the anacrotic slope, was affected by peripheral resistance (this thesis, pp 88-94). That these two factor 2 variables which are affected by peripheral resistance were added by factor-analysis to factor 3 in the younger group, the group assumed

to have the widest range of peripheral resistance (this thesis, p 142), lends factual support to the theory that peripheral resistance is the physiological mechanism causing the interrelationship between, and hence actually affecting, the factor 3 variables. (That the same two factor 2 variables were not added by factor analysis to factor 3 in the post-MI group, a group also assumed to have a wide range of peripheral resistance (this thesis, p 142), is perhaps to be explained by the presence in this group of the reduced cardiac output associated with severe cardiac dysfunction.)

b) The post-MI group and the C subgroup: Because of the severe cardiac dysfunction present in the post-MI group the level of sympathetic nervous system activity can be assumed to be higher in this group than in the other groups. Similarly, because of the wide range of cardiac dysfunction present in the C subgroup the level of sympathetic nervous system activity can be assumed to be higher in this group than in any of the other groups except the post-MI group. Sympathetic nervous system activity, which affects peripheral resistance, which in turn affects the factor 3 variables, systolic pressure and diastolic pressure, directly affects the factor 5 variables, cardiac cycle length and QT (this thesis, pp 147-48). Because of the comparatively high levels of sympathetic nervous system activity assumed to be present in the post-MI group and the C subgroup it is not

surprising that the one factor 5 variable, cardiac cycle length, was added by factor analysis to factor 3 in the post-MI group and the other factor 5 variable, QT, was added to factor 3 in the C subgroup. (The absence of QT in the post-MI group may perhaps be explained as having been due to the cardiac damage present in this group, and the weakness (.416) of cardiac cycle length in the C subgroup may perhaps be explained as having been due to the high levels of arterial pressure in 18 of the 25 members of this group.)

Finally, it should be noted that the presence of the factor 5 variable cardiac cycle length in factor 3 in the random A subgroup was most probably an artifact of the factor analysis. Factor 5 did not explain sufficient variation of the data to be extracted in the random A subgroup, and this left a small proportion of the variation of the factor 5 variables spread out over the remaining four factors. Apparently just enough variation of the factor 5 variable, cardiac cycle length, was added to the insignificant variation normally present in factor 3 in all groups to raise the factor loading of cardiac cycle length in the random A subgroup to .619, ie above the level required for significance (.500).

iv. Factor 4

Inasmuch as the factor loading pattern of factor 4 (figure 10, p 137) consistently contained only one

significant variable, the duration of the initial, linear portion of the anacrotic slope, the present author was unable to deduce the physiological mechanisms affecting this variable. The variable had been expected to be inversely related to the gradient of the initial, linear portion of the anacrotic slope because of the interrelationship between the corresponding cardiac variables, pre-ejection period and cardiac contractility. However, this inverse relationship reached the level required for significance only in the random B subgroup (G: -.501) and the C subgroup (G: -.531). Therefore it was concluded that other, stronger physiological mechanisms affect the factor 4 variable, the duration of the initial, linear portion of the anacrotic slope. Because of the uncertainty of the nature of the relationship between the four factor 2 variables no attempt will be made to explain the inclusion by factor analysis of factor 2 variables in factor 4 in four of the six groups.

v. Factor 5

Inasmuch as the factor loading pattern of factor 5 (figure 11, p. 139) brought together the two variables, QT and cardiac cycle length, in the main group, the random B subgroup and the younger group, the present author deduced that the physiological mechanism causing this interrelationship and hence affecting the variables was the level of

activity of the sympathetic nervous system. This deduction was made on the grounds that the level of activity of the sympathetic nervous system affects QT (Sjöstrand, 1960; Yanowitz, Preston, and Abildskov, 1966; Schwartz and Malliani, 1975) and cardiac cycle length.

Factor 5 was not extracted by the analysis in the random A subgroup probably because factor 5 did not explain a sufficiently large percentage of the total variation and not because there was no relationship between QT and cardiac cycle length. Evidence in support of the presence of such a relationship is the close similarity of the factor loading pattern in the main group and in the random B subgroup (QT: .915 and .907 respectively; RR: .586 and .601 respectively).

Factor 5 was not extracted by the analysis in the post-MI group because, most probably as a result of the severe cardiac dysfunction present in this group, there was no relationship between the two factor 5 variables, QT and cardiac cycle length. QT was in fact assigned by the analysis to factor 1 (where cardiac contractility was concluded to be the major physiological mechanism), while cardiac cycle length was in fact assigned by the analysis to factor 3 (where peripheral resistance was concluded to be the physiological mechanism).

Factors 3 and 5 were not separated by the analysis in the C subgroup, probably because of the interrelationship

between sympathetic nervous system activity and peripheral resistance, and the low factor loading of cardiac cycle length (-.431), which was most probably the result of the high levels of arterial pressure in 18 of the 25 members of this group.

The presence of QKD as an additional variable in factor 5 of the younger group may indicate that the level of sympathetic nervous system activity affected QKD more strongly in this group than in the other groups.

b. Quatimin oblique factor analysis

The quatimin oblique factor analysis option of The Biomedical Data Processing Manual (1979) was employed to determine by comparing the quatimin oblique factors with the varimax orthogonal factors whether the more complex method of rotation provided by the quatimin oblique factor analysis option was required for the adequate examination of the data. The extent of the correlation between the quatimin oblique factors was examined to see if it contributed to an understanding of the physiological mechanisms affecting the variables. Subgroups A and B (the randomly selected halves of the main group) were not used in this analysis because it was felt that the main group and the other three groups provided sufficient replication.

There were no significant differences between the factors extracted by the two methods of rotation (see

Appendix G, pp 278-81), and the levels of correlation between the quatimin oblique factors were not significant (see Appendix H, p 282). This indicated that the simpler varimax orthogonal factor analysis option was adequate to describe the interrelationships between the Rodbard variables.

SECTION 2

Analysis of covariance

In the previous section factor analysis used mathematical procedures to determine which of the variables were interrelated. These interrelationships (in the form of the factor loading patterns) were then used to deduce the nature of the underlying physiological mechanisms. In this section the variables linked by factor analysis were taken two at a time and the regression lines for the main group, the C subgroup, the post-MI group, and the younger group were plotted (using BMDP6D) and examined for significant differences (using BMDP1V). One member of each pair of variables was treated as the independent variable although both were in fact dependent upon the physiological mechanisms common to the particular factor. (This procedure was repeated for three pairs of variables which were not found to be linked by the factor analysis, but which, as was

discussed in Chapter I [pp 8, 40-42, 62-63], were regarded as being related by several authors.)

The search for differences in the regression lines of the four groups was carried out to select the variables with the potential to be useful in cardiovascular epidemiology. (See Appendix I, p 283 for the mean and standard deviations of the variables for the four groups.)

a. Results

1. Variables linked by factor analysis

i. Factor I

When pulse pressure was plotted as a function of the gradient of the initial, linear portion of the anacrotic slope no significant differences were found in either the slope or the height of the regression lines of the four groups of subjects (figure 12, p 152). The regression coefficient was significant ($b = 0.055$, $P<.0001$); and the correlation coefficients were high for all four groups: $r = .779$ for the main group, $r = .648$ for the C subgroup, $r = .759$ for the post-MI group, and $r = .842$ for the younger group (table 10, p 153).

When systolic pressure was plotted as a function of pulse pressure (figure 13, p 154) the regression line of the younger group was significantly lower than the regression lines of the other three groups ($P<.0001$). No significant differences were found in the slopes of the regression lines

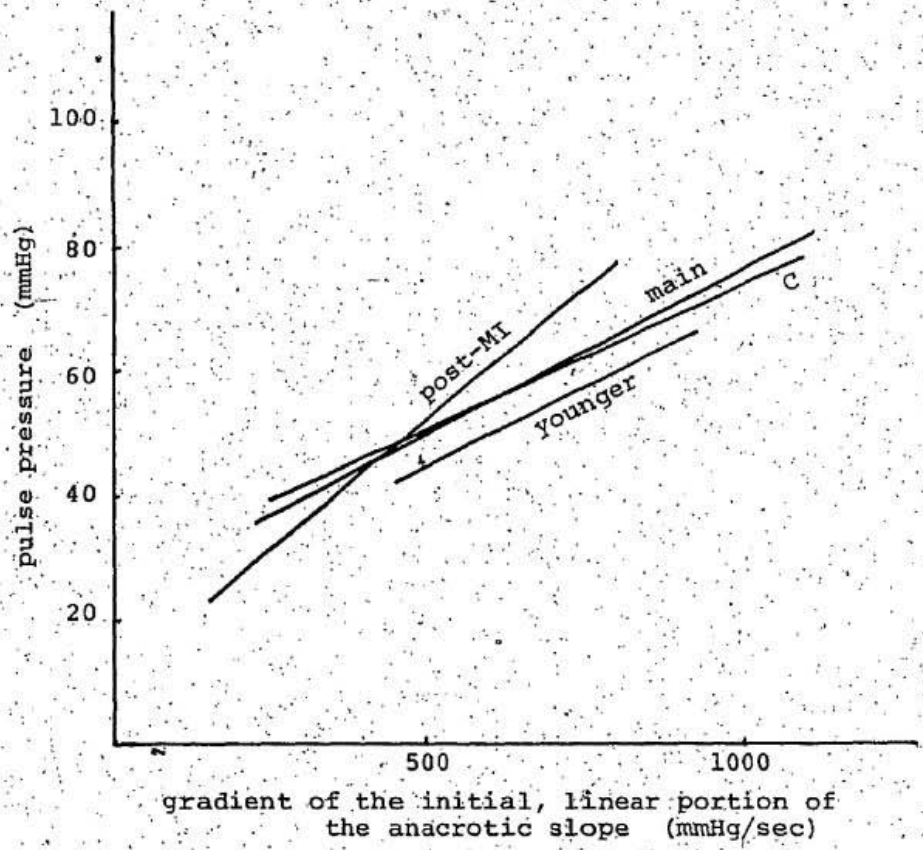


Figure 12. Graph of pulse pressure as a function of the gradient of the initial, linear portion of the anacrotic slope.

No significant differences were found between the line of the main group and the lines of the other groups. The pooled regression coefficient was significantly different from zero ($P<.0001$), $s_{y \cdot x} = 13$.

Table 10. The relationship between pulse pressure and the gradient of the initial, linear portion of the anacrotic slope for the four groups.

Group	Mean±standard deviation	Regression equation	Standard deviation about the line	Correlation coefficient
Main group	63.5±19.7	$y = 0.054 \cdot x + 23.6$	12.4	$r = .779$
C subgroup	59.9±18.3	$y = 0.050 \cdot x + 26.7$	14.2	$r = .648$
Post-MI group	52.4±19.2	$y = 0.086 \cdot x + 9.8$	12.9	$r = .759$
Younger group	54.4± 8.8	$y = 0.055 \cdot x + 17.5$	4.9	$r = .842$

Where y is pulse pressure (mmHg)
x is the gradient of the initial, linear portion of the anacrotic slope (mmHg/sec)

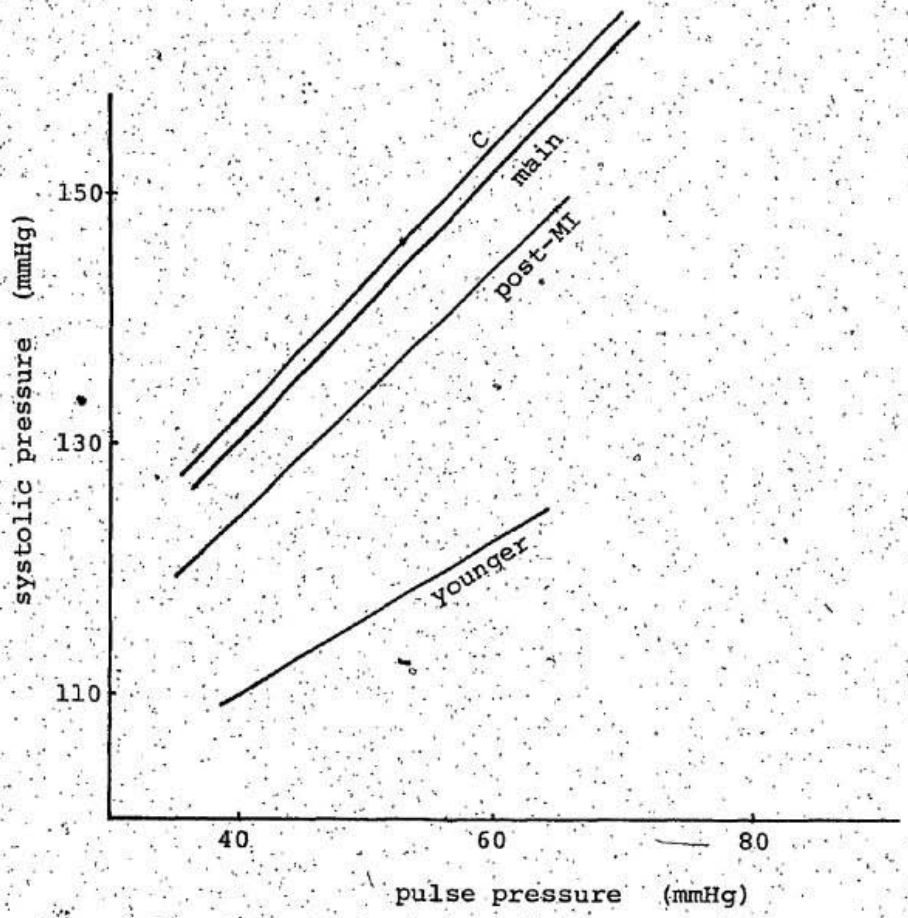


Figure 13. Graph of systolic pressure as a function of pulse pressure.

The regression line of the main group was significantly higher than the lines of the younger group ($P<.0001$) and the post-MI group ($P<.03$).
The pooled regression coefficient was significantly different from zero ($P<.0001$); $s_{y \cdot x} = 15$.

of the four groups. The regression coefficient was significant ($b = 1.044$, $P<.0001$); and the correlation coefficients were high for three of the four groups: $r = .816$ for the main group, $r = .844$ for the C subgroup, $r = .835$ for the post-MI group; and lower ($r = .538$) for the younger group (table 11, p 156).

When systolic pressure was plotted as a function of the gradient of the initial, linear portion of the anacrotic slope (figure 14, p 157) the regression line of the younger group was significantly lower than the regression lines of the other three groups ($P<.0001$). No significant differences were found in the slopes of the regression lines of the four groups. The regression coefficient was significant ($b = 0.059$, $P<.0001$). The correlation coefficients for all four groups were not as high as they were in the previous two interrelationships: $r = .657$ for the main group, $r = .667$ for the C subgroup, $r = .599$ for the post-MI group, and $r = .350$ for the younger group (table 12, p 158).

When systolic pressure was plotted as a function of QKD (figure 15, p 159) the regression line of the younger group was significantly lower than the regression lines of the main group and the C subgroup ($P<.0001$). To a lesser extent the regression line of the post-MI group was also significantly lower than the regression lines of the main group and the C subgroup ($P<.01$). No significant differences were found in the slopes of the regression lines of the four groups. The regression coefficient was significant

Table 11. The relationship between pulse pressure and systolic pressure for the four groups.

Group	Mean±standard deviation	Regression equation	Standard deviation about the line	Correlation coefficient
Main group	156±26	$y = 1.057 \cdot x + 89$	14.8	$r = .816$
C subgroup	154±23	$y = 1.052 \cdot x + 91$	12.5	$r = .844$
Post-MI group	137±23	$y = 1.009 \cdot x + 84$	13.2	$r = .835$
Younger group	120±11	$y = 0.676 \cdot x + 83$	9.6	$r = .538$
Younger group subjects aged			pooled	
21-40 yr	120± 8	$y = 0.766 \cdot x + 78$	5.8	-
9-20 yr	113±11	$y = 0.855 \cdot x + 66$	5.8	

Where y is systolic pressure (mmHg)
x is pulse pressure (mmHg)

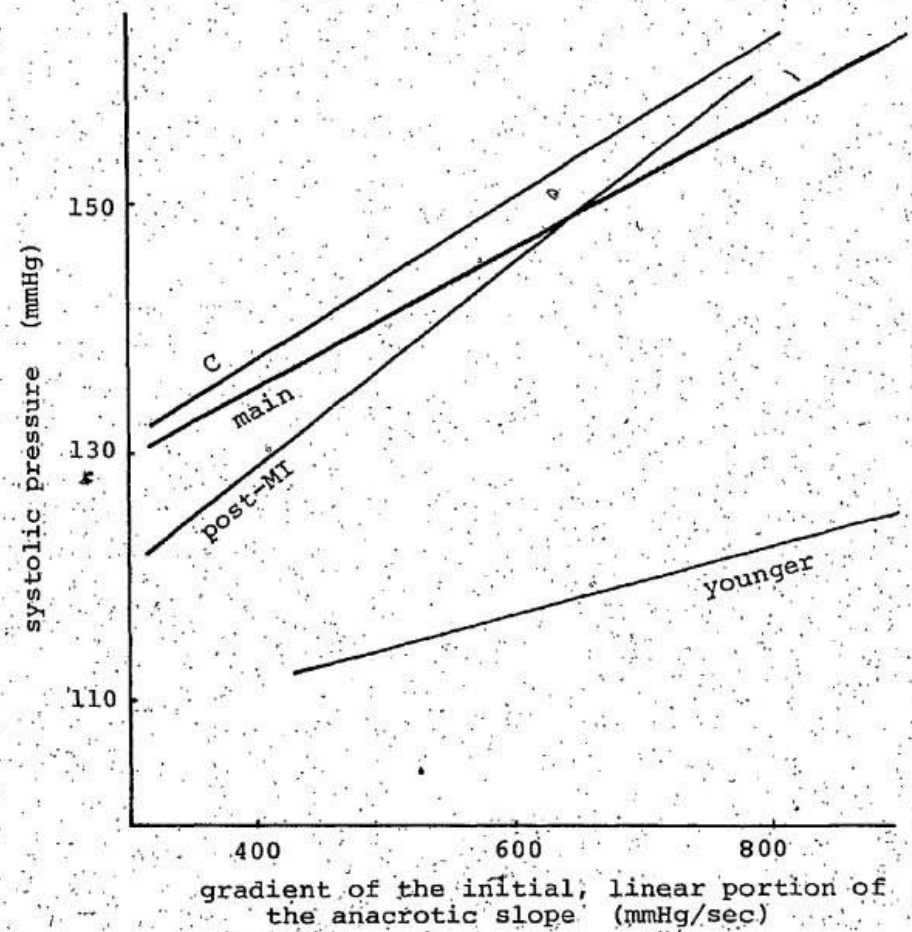


Figure 14. Graph of systolic pressure as a function of the gradient of the initial, linear portion of the anacrotic slope.

The regression line of the younger group was significantly lower than the line of the main group ($P<.0001$).
The pooled regression coefficient was significantly different from zero ($P<.0001$); $s_{y.x} = 19$.

Table 12. The relationship between the gradient of the initial, linear portion of the anacrotic slope and systolic pressure for the four groups.

Group	Mean±standard deviation	Regression equation	Standard deviation about the line	Correlation coefficient
Main group	156±26	$y = 0.059 \cdot x + 113$	19.3	$r = .657$
C subgroup	154±23	$y = 0.064 \cdot x + 112$	17.4	$r = .667$
Post-MI group	137±23	$y = 0.082 \cdot x + 97$	19.2	$r = .599$
Younger group	120±11	$y = 0.029 \cdot x + 101$	10.6	$r = .350$
Younger group subjects aged			pooled	
21-40 yr	120± 8	$y = 0.047 \cdot x + 87$	6.7	$r = .562$
9-20 yr	113±11	$y = 0.063 \cdot x + 69$	6.7	$r = .944$

Where y is systolic pressure (mmHg)
x is the gradient of the initial, linear portion of the anacrotic slope (mmHg/sec)

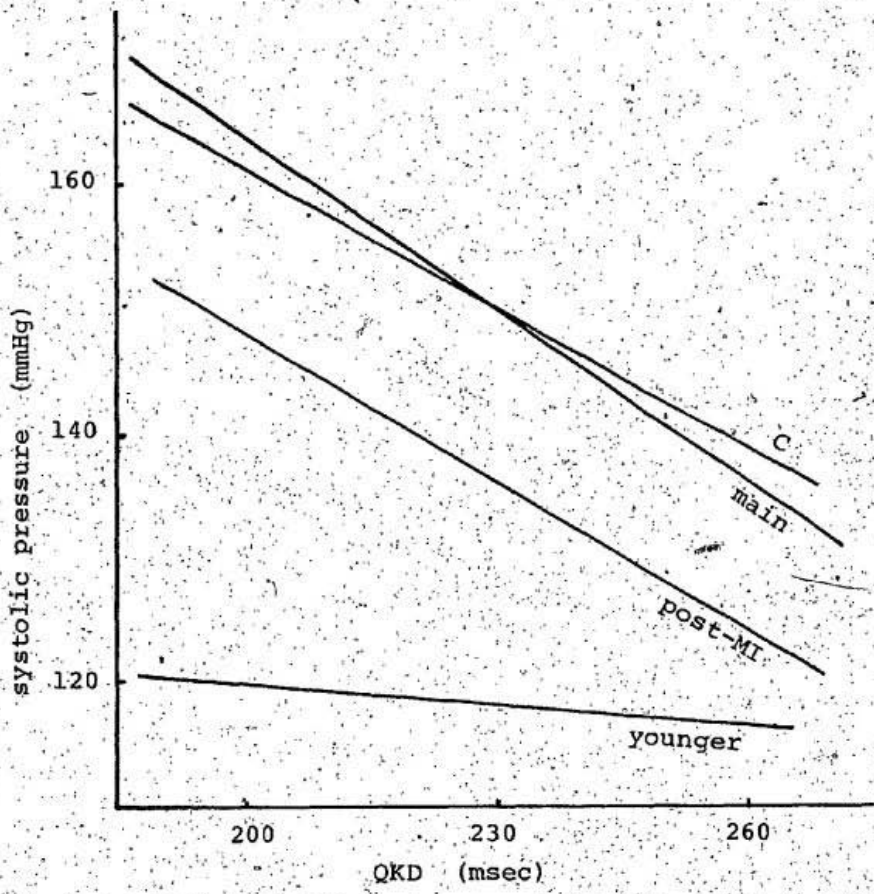


Figure 15. Graph of systolic pressure as a function of QKD.

The regression line of the main group was significantly higher than the lines of the younger group ($P < .0001$) and the post-MI group ($P < .01$).
The pooled regression coefficient was significantly different from zero ($P < .0001$); $s_{y \cdot x} = 23$.
There was no significant difference between the regression coefficients of the four groups

(b = -0.438, P<.0001). The correlation coefficients for all four groups were low: r = -.445 for the main group, r = -.338 for the C subgroup, r = -.444 for the post-MI group, and r = -.103 for the younger group (table 13, p 161).

When QKD was plotted as a function of the gradient of the initial, linear portion of the anacrotic slope no significant differences were found in either the slope or the height of the regression lines of the four groups (figure 16, p 162). The regression coefficient was significant (b = -0.047, P<.0001). The correlation coefficients were low for three of the four groups: r = -.552 for the main group, r = -.390 for the C subgroup, r = -.517 for the post-MI group, and non-existent (r = -.009) for the younger group (table 14, p 163).

It was noted that when systolic pressure was plotted as a function of pulse pressure, or the gradient of the initial, linear portion of the anacrotic slope, or QKD, the regression lines of the younger group were significantly lower than the regression lines of the other three groups. In an attempt to explain this difference, the relationship between systolic pressure and the gradient of the initial, linear portion of the anacrotic slope was chosen for further investigation. (The relationship between systolic pressure and 1) pulse pressure and 2) QKD were not chosen because in the first instance systolic pressure is one of the components used to calculate pulse pressure, and in the second

Table 13. The relationship between QKD and systolic pressure for the four groups.

Group	Mean±standard deviation	Regression equation	Standard deviation about the line	Correlation coefficient
Main group	156±26	$y = -0.470 \cdot x + 254$	23	$r = -.445$
C subgroup	154±23	$y = -0.359 \cdot x + 229$	22	$r = -.338$
Post-MI group	137±23	$y = -0.423 \cdot x + 229$	21	$r = -.444$
Younger group	120±11	$y = -0.057 \cdot x + 132$	11	$r = -.103$

Where y is systolic pressure (mmHg)
x is QKD (msec)

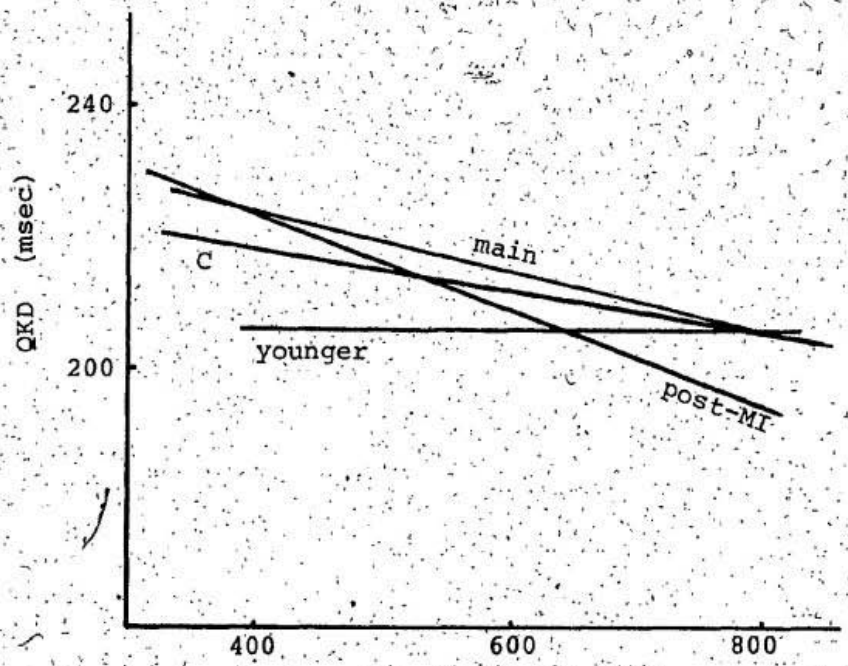


Figure 16. Graph of QKD as a function of the gradient of the initial, linear portion of the anacrotic slope.

No significant differences were found between the regression lines of the four groups
The pooled regression coefficient was significantly different from zero ($P<.0001$); $s_{y \cdot x} = .22$.

Table 14. The relationship between QKD and the gradient of the initial, linear portion of the anacrotic slope for the four groups.

Group	Mean±standard deviation	Regression equation	Standard deviation about the line	Correlation coefficient
Main group	207±24.2	$y = -0.0467 \cdot x + 241.4$	20.3	$r = -.552$
C subgroup	208±21.5	$y = -0.0352 \cdot x + 231.2$	20.2	$r = -.390$
Post-MI group	216±24.4	$y = -0.0746 \cdot x + 252.9$	21.5	$r = -.517$
Younger group	205±19.8	$y = -0.0013 \cdot x + 205.6$	20.4	$r = -.009$

Where Y is QKD (msec)
x is the initial, linear portion of the anacrotic slope (mmHg/sec)

instance the correlation coefficients were low.) The younger group was subdivided into three subgroups according to age. The regression line of systolic pressure as a function of the gradient of the initial, linear portion of the anacrotic slope of the ten subjects aged twenty-one to forty years was significantly higher ($P<.02$) than the regression line of the six subjects aged nine to twenty years, and the data points of the three subjects over forty years of age were higher than the regression line of the group aged twenty-one to forty years (figure 17, p 165).

Because it was suspected that the physiological mechanism affecting this relationship was not age itself but rather the changes in peripheral resistance which accompany the changes in age, the two variables which are affected by peripheral resistance (diastolic pressure and the duration of the entire anacrotic slope) were each superimposed on the graph of systolic pressure as a function of the gradient of the initial, linear portion of the anacrotic slope. This was done first for the entire younger group (where age varied markedly) and then for the other three groups (where age variation was minimal). Both variables affected by peripheral resistance were seen to increase with systolic pressure for constant values of the gradient of the initial, linear portion of the anacrotic slope in all four groups (figure 18a-d, and figure 19a-d, pp 166-73). This phenomenon was less marked in the C subgroup and the post-MI group.

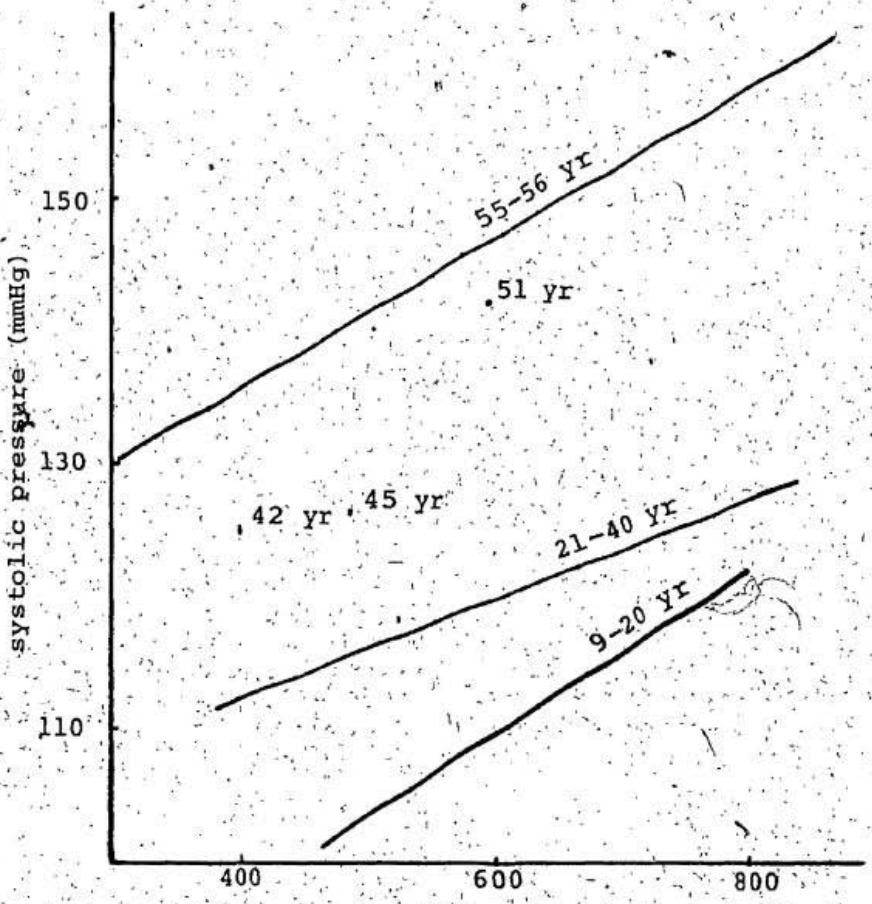


Figure 17. Graph of systolic pressure as a function of the gradient of the initial, linear portion of the anacrotic slope showing the effect of age.

The regression line of the group aged 21-40 years was significantly higher than the line of the group aged 9-20 years ($P<.02$) and significantly lower than the line of the group aged 55-56 years, i.e. the main group ($P<.0001$).
The pooled regression coefficient was significantly different from zero ($P<.0001$); $s_{y\,x} = 19$.

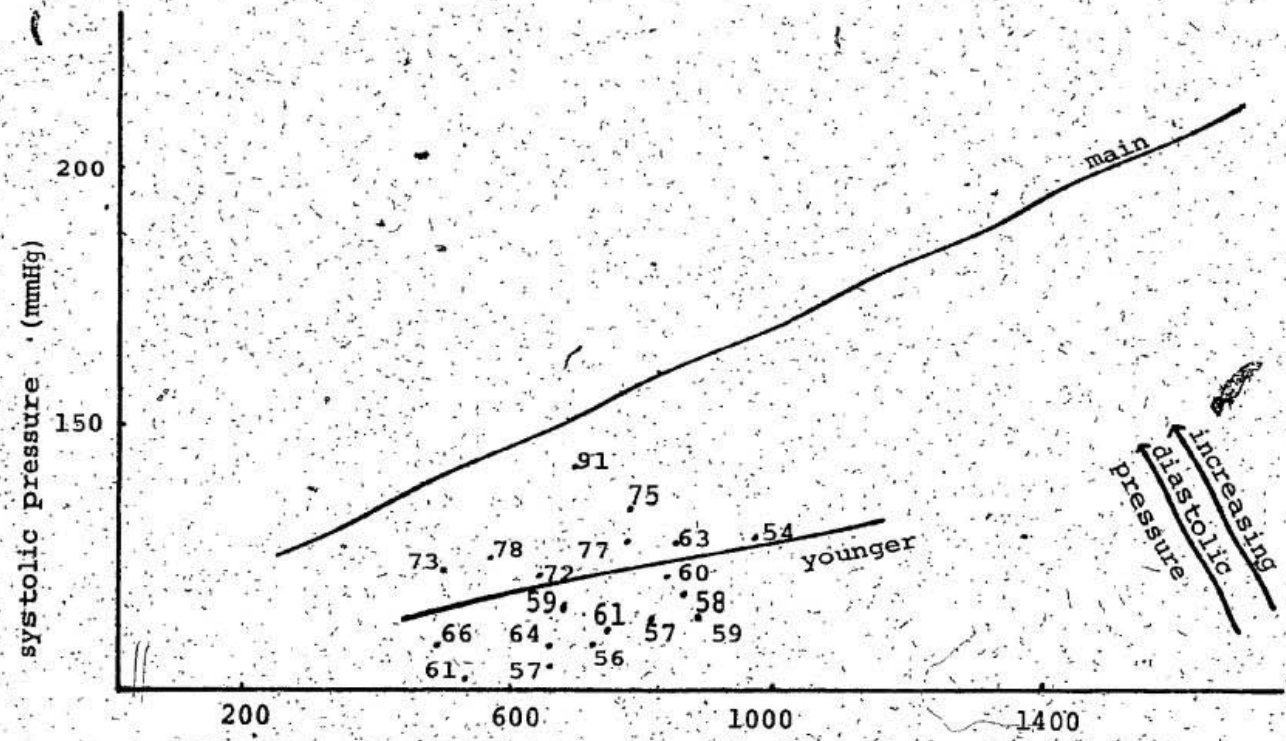


Figure 18a. Graph of systolic pressure as a function of the gradient of the initial, linear portion of the anacrotic slope giving diastolic pressure for members of the younger group. ($r = .649$ for the relationship between systolic pressure and diastolic pressure.)

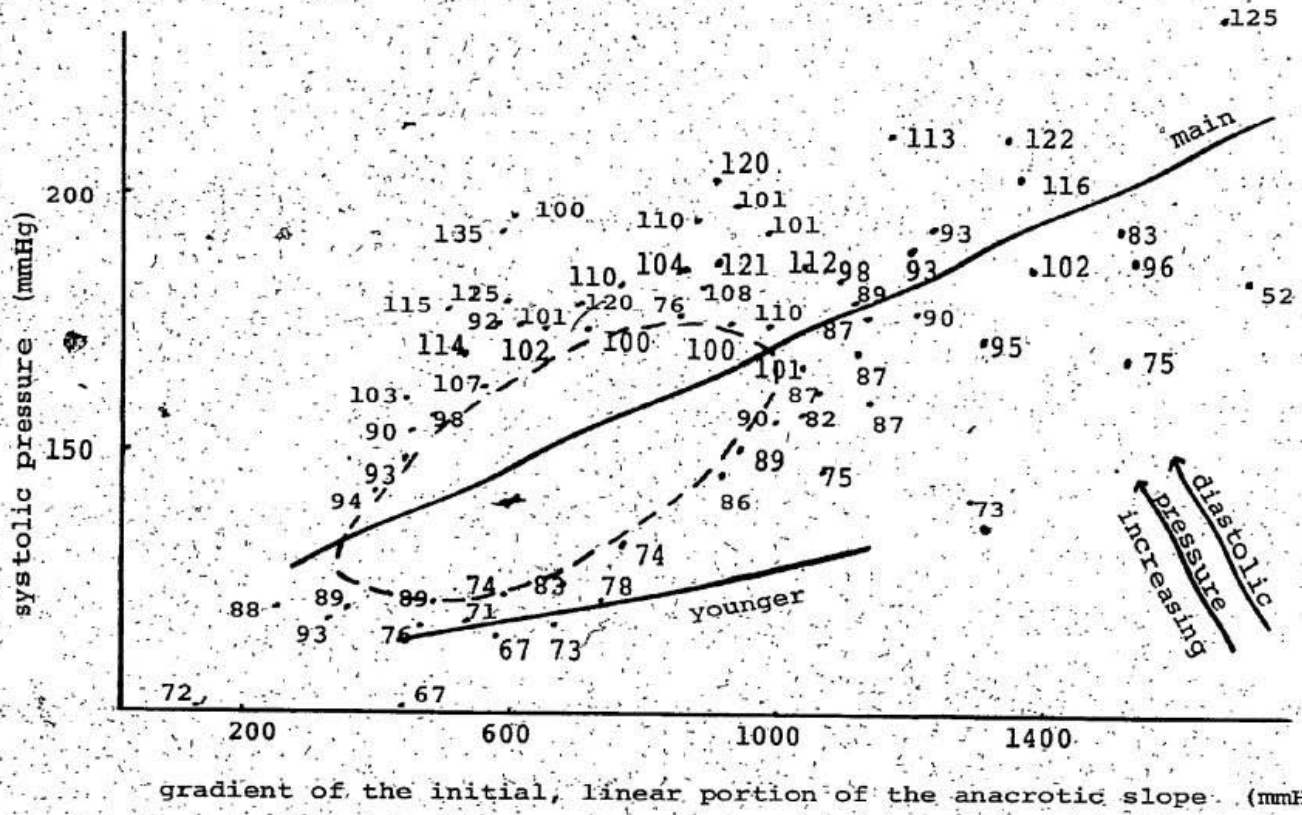


Figure 18b. Graph giving diastolic pressure for members of the main group who did not have cardiovascular disease registered in the follow-up period. The diastolic pressure is not given for members of the main group who lay within the densely packed portion of the graph indicated with the dashed line. ($r = .641$ for the relationship between systolic pressure and diastolic pressure.)

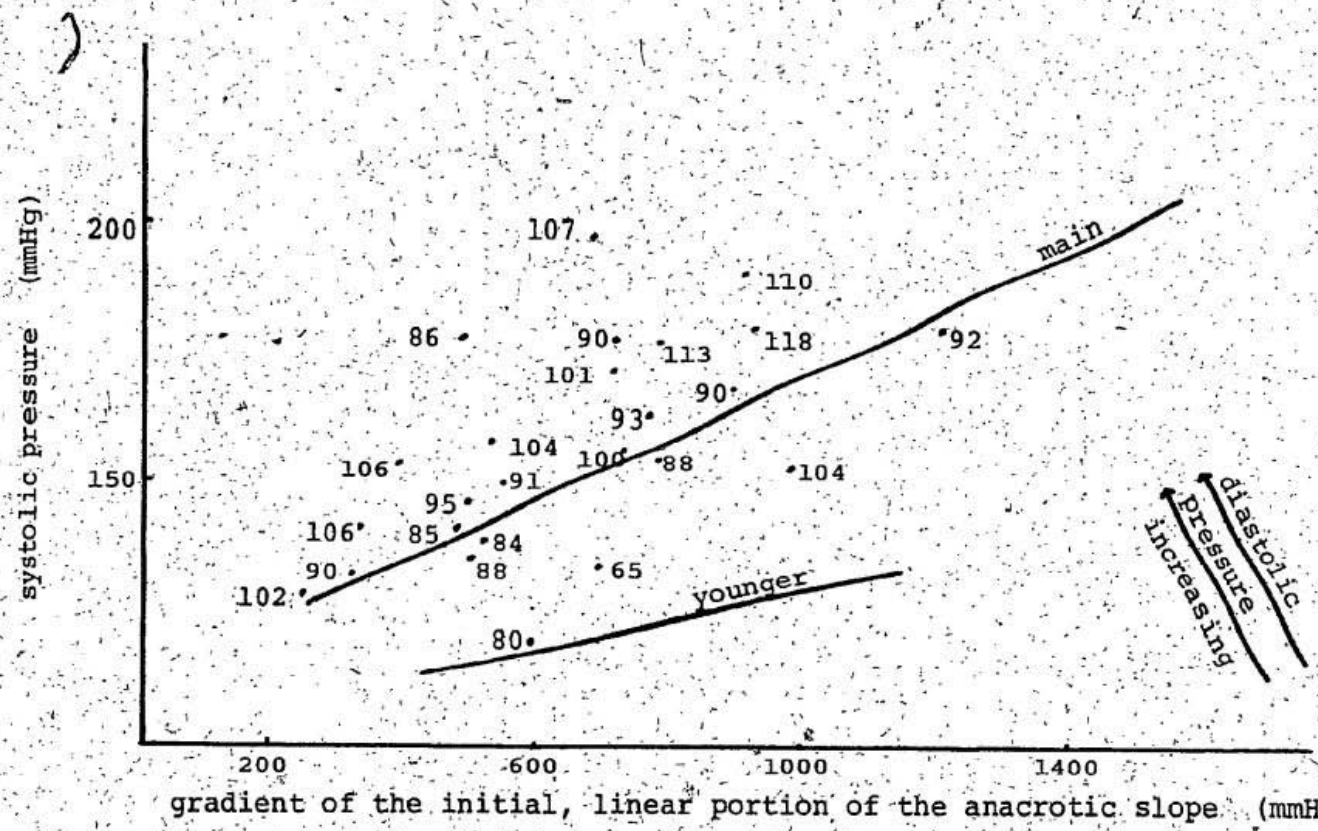


Figure 18c. Graph giving the diastolic pressure for those members of the main group who had cardiovascular disease registered in the follow-up period. ($r = .607$ for the relationship between systolic and diastolic pressure.)

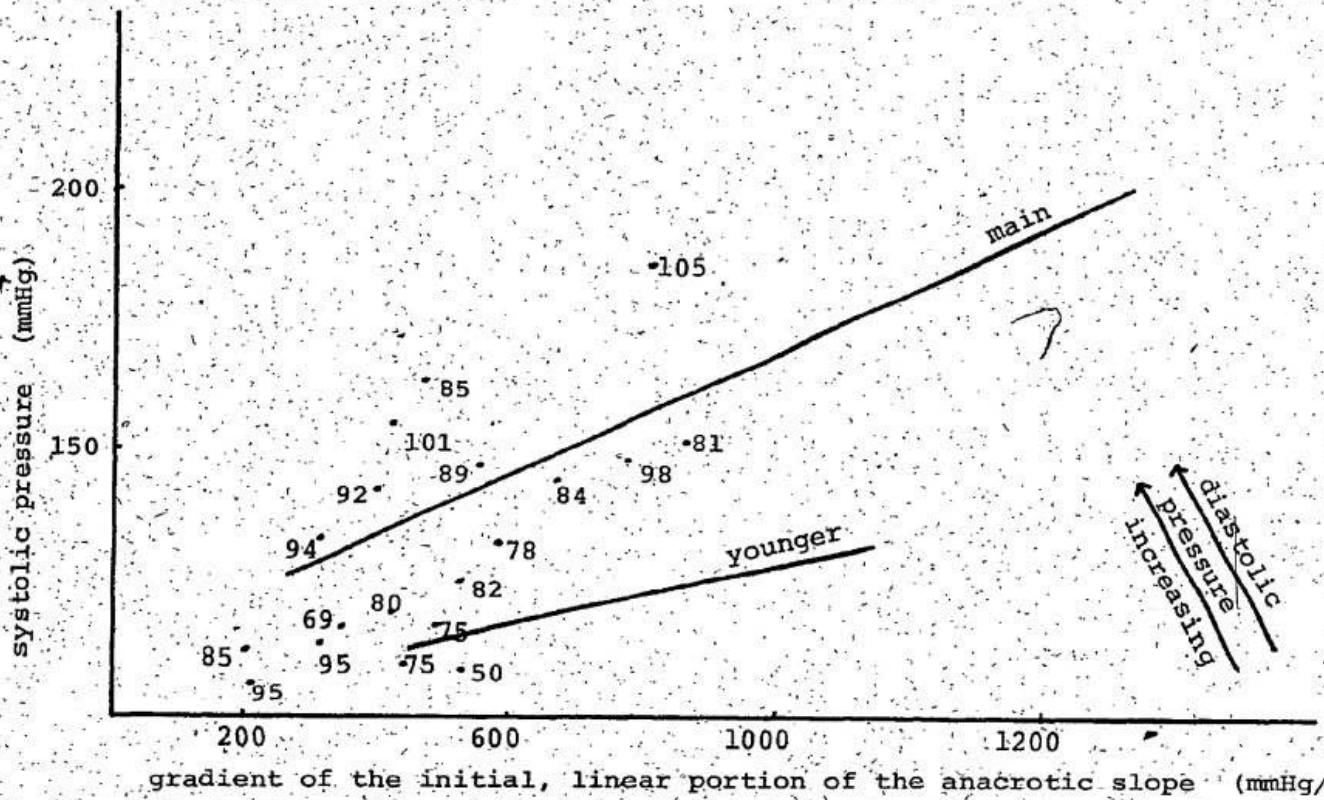


Figure 18d. Graph giving the diastolic pressure for members of the post-MI group. (r = .563 for the relationship between systolic and diastolic pressure.)

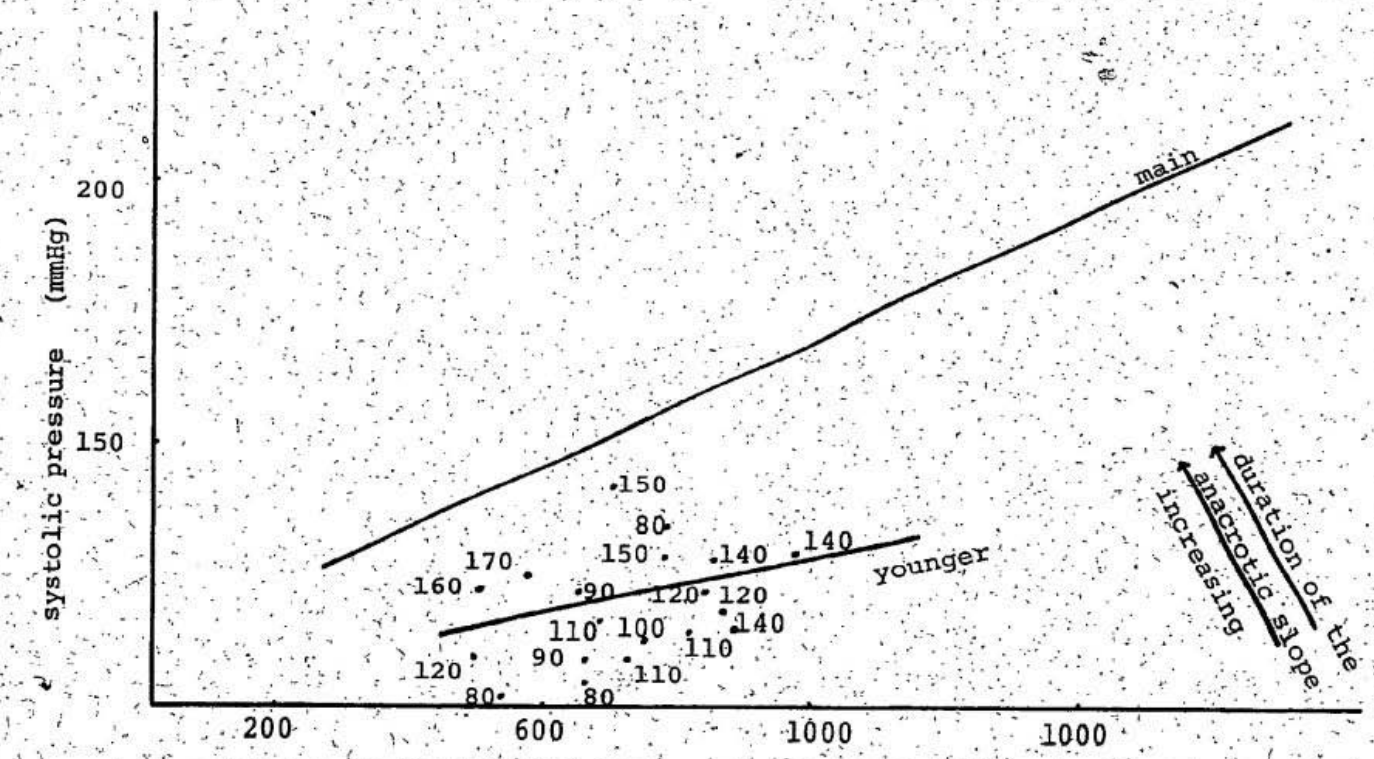


Figure 19a. Graph of systolic pressure as a function of the gradient of the initial, linear portion of the anacrotic slope giving the duration of the anacrotic slope for members of the younger group. ($r = .545$ for the relationship between systolic pressure and the duration of the anacrotic slope.)

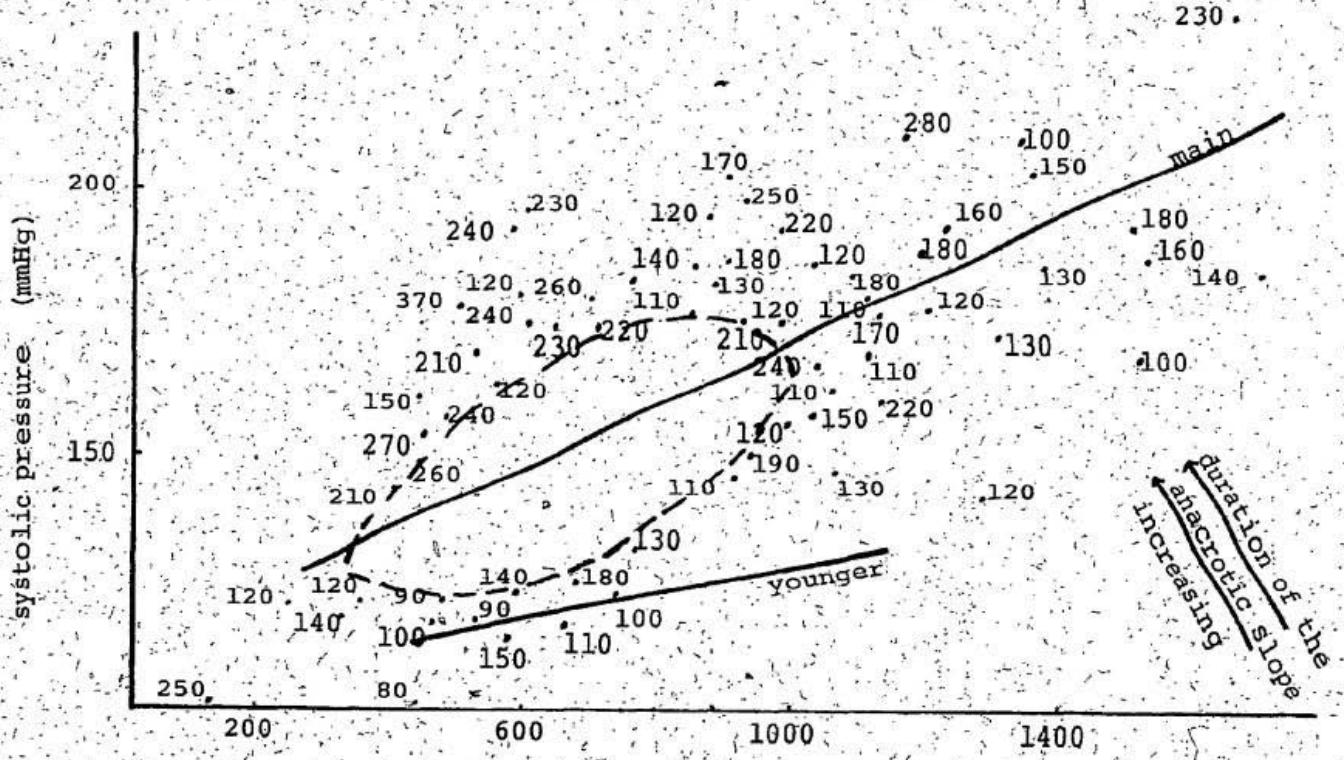


Figure 19b. Graph giving the duration of the anacrotic slope for members of the main group who did not have cardiovascular disease registered in the follow-up period. The duration of the anacrotic slope is not given for those members of the main group who lay within the densely packed portion of the graph indicated with the dashed line. ($r = .641$ for the relationship between systolic pressure and the duration of the anacrotic slope.)

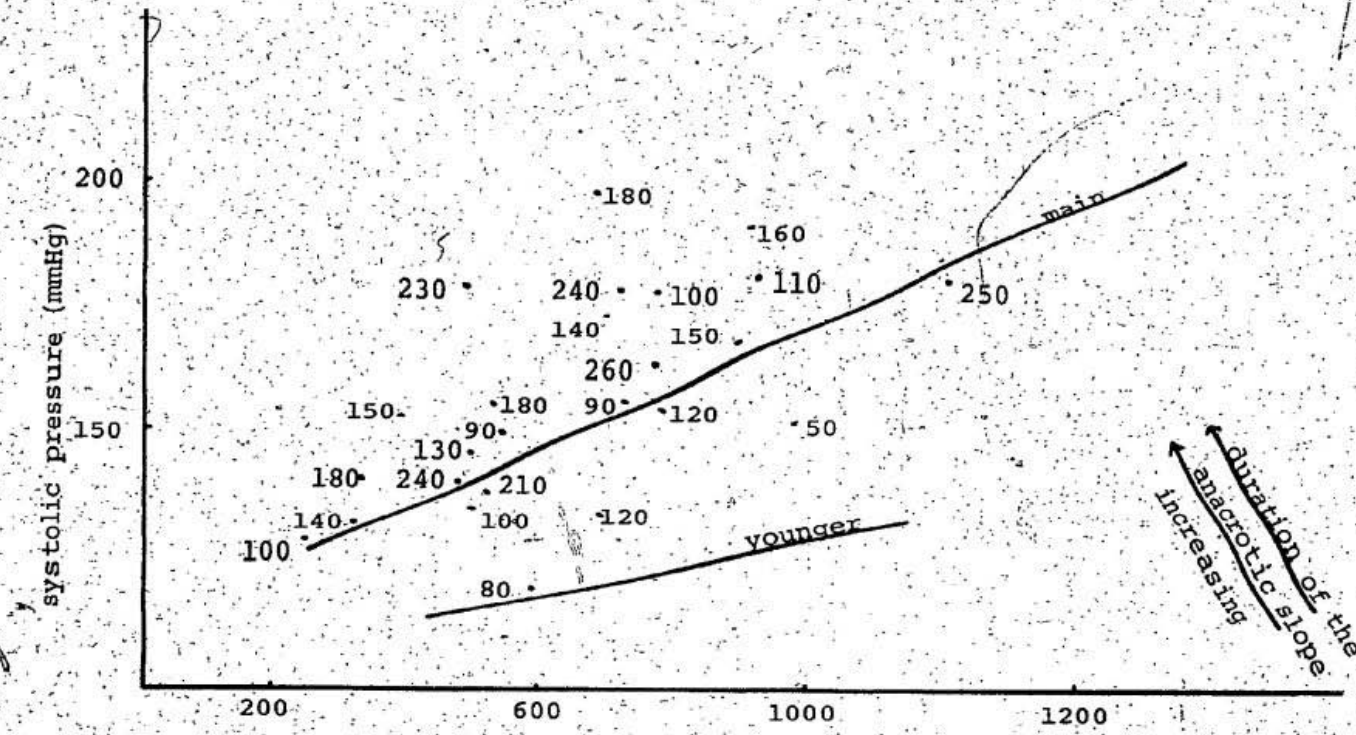


Figure 19c. Graph giving the duration of the anacrotic slope for those members of the main group who had cardiovascular disease registered in the follow-up period. ($r = .136$ for the relationship between systolic pressure and the duration of the anacrotic slope.)

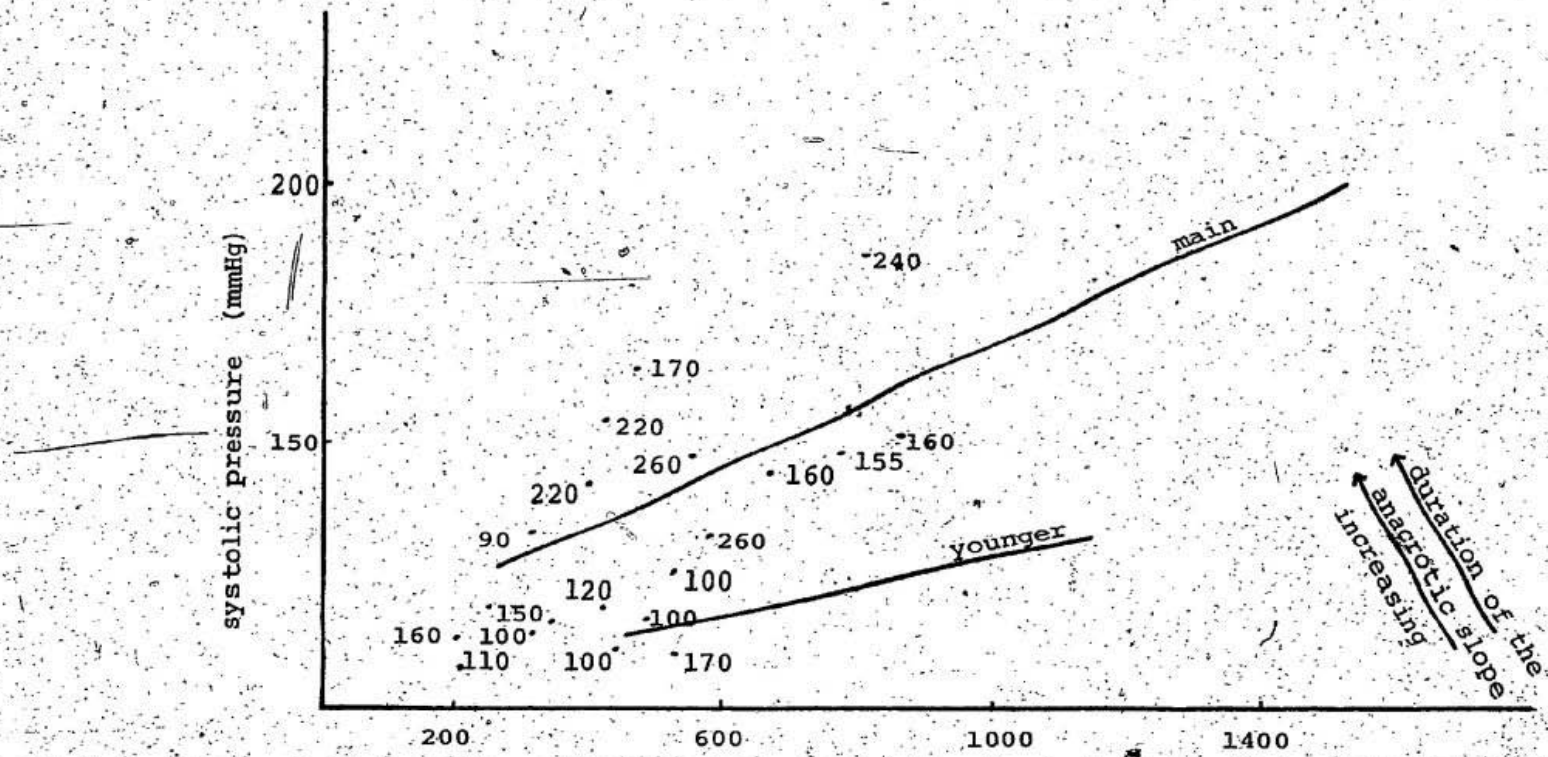


Figure 19d. Graph giving the duration of the anacrotic slope for members of the post-MI group. (r = .625 for the relationship between systolic pressure and the duration of the anacrotic slope.)

ii. Factor 2

The relative importance of the four physiological mechanisms on the four factor 2 variables was not clarified by the factor analysis and therefore the inter-relationships between the factor 2 variables was not investigated in this section.

iii. Factor 3

When systolic pressure was plotted as a function of diastolic pressure (figure 20, p 175) the regression line of the post-MI group just missed being significantly lower than the regression line of the main group ($P<.057$) but it was significantly lower ($P<.026$) when analysed with a t - test. No significant differences were found in the slopes of the regression lines of the four groups. The regression coefficient was significant ($b = 1.091$, $P<.0001$) and the correlation coefficients were $r = .641$ for the main group, $r = .607$ for the C subgroup, $r = .563$ for the post-MI group, and $r = .649$ for the younger group (table 15, p 176).

iv. Factor 4

Although factor 4 contained only one significant variable, the duration of the initial, linear portion of the anacrotic slope, it was decided to investigate the relationship between this variable and the gradient of the initial, linear portion of the anacrotic slope, a variable present in

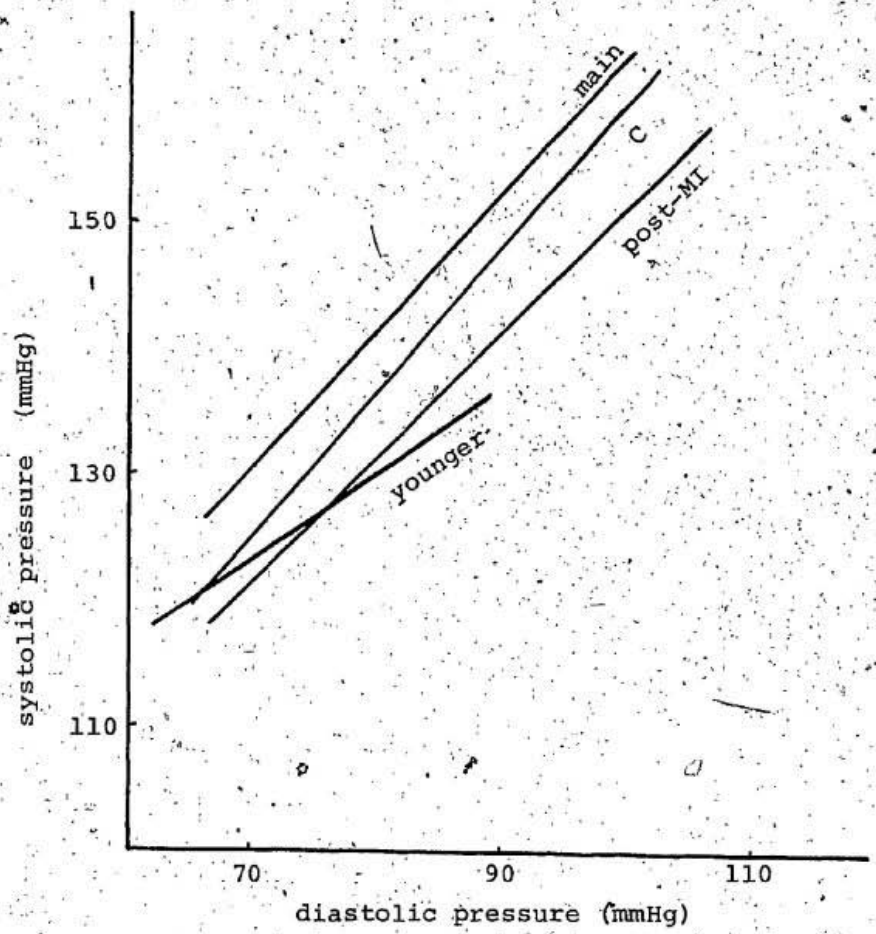


Figure 20. Graph of systolic pressure as a function of diastolic pressure.

The regression line of the post-MI group just missed being significantly lower than the main group ($P<.057$). The pooled regression coefficient was significantly different from zero ($P<.0001$); $s_{y.x} = 20$.

Table 15. The relationship between systolic pressure and diastolic pressure for the four groups.

Group	Mean±standard deviation	Regression equation	Standard deviation about the line	Correlation coefficient
Main group	156±25.6	$y = 1.116 \cdot x + 52.8$	19.7	$r = .641$
C subgroup	154±22.8	$y = 1.130 \cdot x + 47.6$	18.5	$r = .607$
Post-MI group	137±23.2	$y = 1.021 \cdot x + 50.6$	19.8	$r = .563$
Younger group	120±11.0	$y = 0.736 \cdot x + 71.6$	8.6	$r = .649$

Where y is systolic pressure (mmHg)
x is diastolic pressure (mmHg)

only two of the groups of subjects. This was because, for the reasons stated on p 147, a significant relationship had been expected to exist between these two variables. When the duration of the initial, linear portion of the anacrotic slope was plotted as a function of the gradient of the initial, linear portion of the anacrotic slope (figure 21, p 178) no significant differences were found in either the slope or the height of the regression lines of the four groups of subjects. The regression coefficient was significant ($b = -0.034$, $P<.0001$), and the correlation coefficients were $r = -.481$ for the main group, $r = -.493$ for the C subgroup, $r = -.215$ for the post-MI group, and $r = -.462$ for the younger group (table 16, p 179).

v. Factor 5

When QT was plotted as a function of cardiac cycle length (figure 22, p 180) no significant differences were found in either the slope or the height of the regression lines of the four groups. The regression coefficient was significant ($b = 0.067$, $P<.0001$), and the correlation coefficients were $r = .358$ for the main group, $r = .312$ for the C subgroup, $r = .445$ for the post-MI group, and $r = .788$ for the younger group (table 17, p 181).

2. Variables not linked by factor analysis

Although they were not linked by factor analysis, the relationship between cardiac cycle length and both QKD and

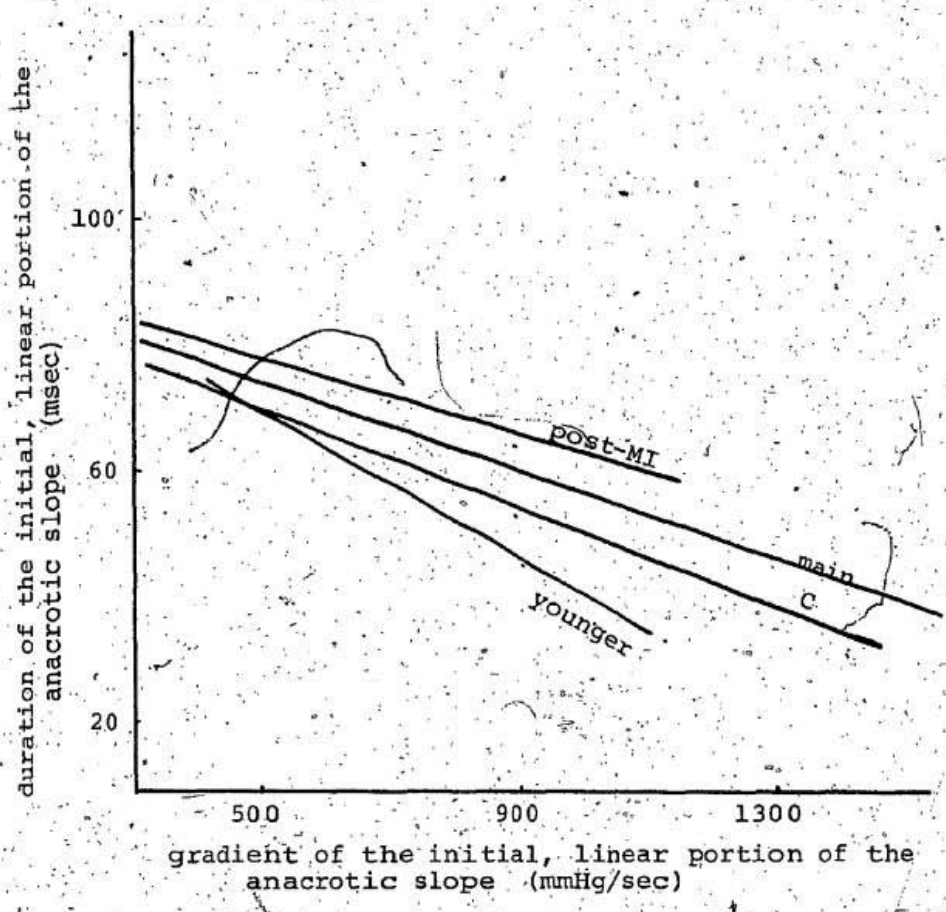


Figure 21. Graph of the duration of the initial, linear portion of the anacrotic slope as a function of the gradient of the same portion of the anacrotic slope.

There was no significant difference between the regression lines of the four groups. The pooled regression coefficient was significantly different from zero (P .0001); $s_{y\,x} = 19$.

Table 16. The relationship between the duration and gradient of the initial, linear portion of the anacrotic slope for the four groups.

Group	Mean±standard deviation	Regression equation	Standard deviation about the line	Correlation coefficient
Main group	67±19.9	$y = -0.033 \cdot x + 91.9$	17.5	$r = -.481$
C subgroup	68±21.5	$y = -0.045 \cdot x + 97.7$	19.1	$r = -.493$
Post-MI group	79±21.3	$y = -0.027 \cdot x + 92.0$	21.4	$r = -.215$
Younger group	60±16.1	$y = -0.055 \cdot x + 97.4$	14.7	$r = -.462$

Where y is the duration of the initial, linear portion of the anacrotic slope (msec)
x is the gradient of the initial, linear portion of the anacrotic slope (mmHg/sec)

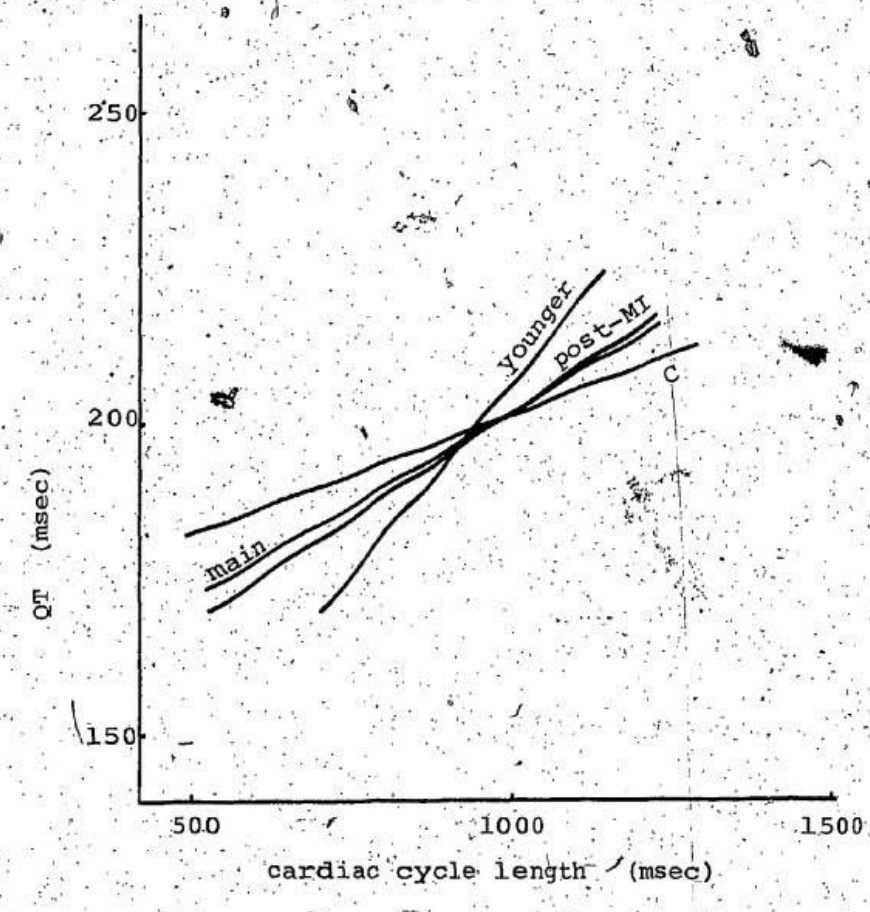


Figure 22. Graph of QT as a function of cardiac cycle length.

There was no significant difference between the lines of the four groups.
The pooled regression coefficient was significantly different from zero ($P<.0001$); $s_{y \cdot x} = 22$.

Table 17. The relationship between QT and cardiac cycle length for the four groups.

Group	Mean±standard deviation	Regression equation	Standard deviation about the line	Correlation coefficient
Main group	192±22.7	$y = 0.059 \cdot x + 143.0$	21.3	$r = .358$
C subgroup	197±20.9	$y = 0.038 \cdot x + 165.1$	20.2	$r = .312$
Post-MI group	194±28.1	$y = 0.064 \cdot x + 138.1$	25.8	$r = .445$
Younger group	197±24.4	$y = 0.124 \cdot x + 86.8$	15.5	$r = .788$

Where y is QT (msec)
x is RR (msec)

the gradient of the initial, linear portion of the anacrotic slope was examined because many authors automatically correct cardiac measurements for differences in cardiac cycle length. The relationship between QKD and diastolic pressure was examined because diastolic pressure was expected to be a factor affecting the pulse wave transmission time component of QKD.

i. QKD and cardiac cycle length

When QKD was plotted as a function of cardiac cycle length (figure 23, p 183), the regression coefficient was significant ($b = 0.035$, $P<.005$). The slope of the regression line of the post-MI group ($b = -0.038$) was significantly different ($P<.02$) from the slopes of the regression lines of the other three groups. No significant differences were found in either the slope or the height of the regression lines of the remaining three groups. The correlation coefficients were $r = .266$ for the main group, $r = -.447$ for the C subgroup, $r = -.298$ for the post-MI group, and $r = .546$ for the younger group (table 18, p 184).

ii. The gradient of the initial, linear portion of the anacrotic slope and cardiac cycle length

When the gradient of the initial, linear portion of the anacrotic slope was plotted as a function of cardiac cycle length (figure 24, p 185) the regression line of the post-MI group was significantly lower in height than the regression

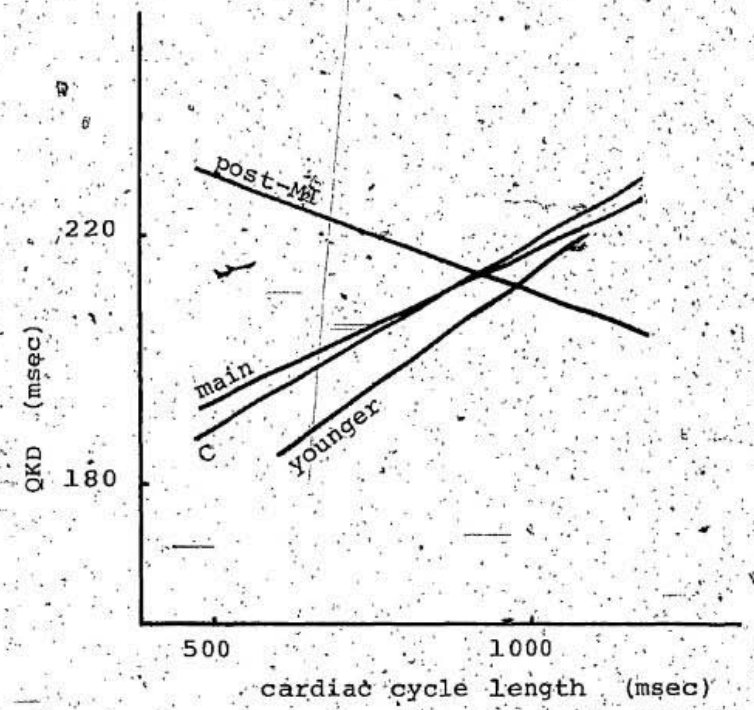


Figure 23. Graph of QKD as a function of cardiac cycle length

The slope of the regression line of the post-MI group was significantly different from the line of the main group ($P<.02$). There was no significant difference between the regression coefficients of the main group, the younger group and the C group; their pooled regression coefficient was significantly different from zero ($P<.005$); $s_{y\,x}=24$.

Table 18. The relationship between QKD and cardiac cycle length for the four groups.

Group	Mean±standard deviation	Regression equation	Standard deviation about the line	Correlation coefficient
Main group	207±24.2	$y = 0.047 \cdot x + 168.3$	23.4	$r = .266$
C subgroup	208±21.5	$y = 0.057 \cdot x + 160.5$	19.7	$r = .447$
Post-MI group	216±24.4	$y = -0.038 \cdot x + 248.7$	24.0	$r = -.298$
Younger group	205±19.8	$y = 0.070 \cdot x + 142.6$	17.1	$r = .546$

Where y is QKD (msec)
x is RR (msec)

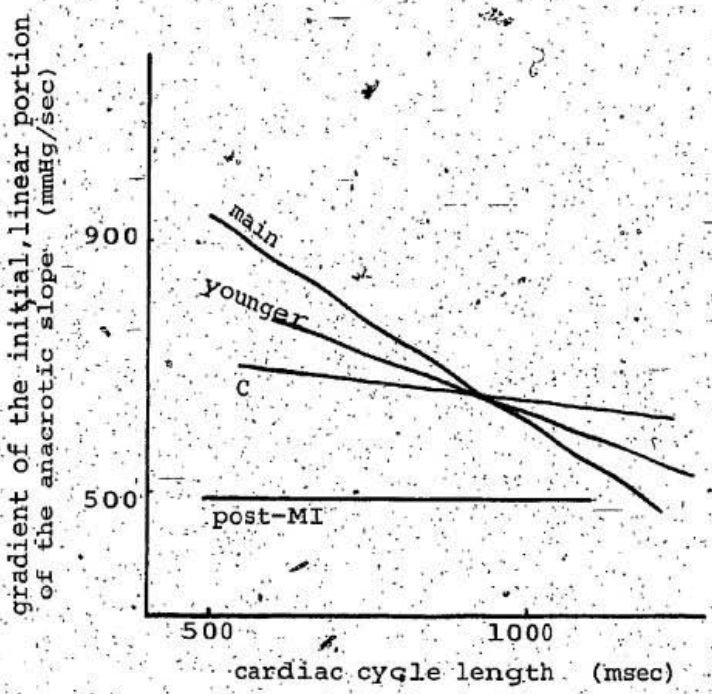


Figure 24. Graph of the gradient of the initial, linear portion of the anacrotic slope as a function of cardiac cycle length.

There was no significant difference between the regression coefficients of the main and the post-MI groups. The regression line of the post-MI group was significnatly lower than the line of the main group ($P<.001$) and the line of the younger group ($P<.03$). The pooled regression coefficient was significantly different from zero ($P<.0003$); $s_{y.x} = 272$.

lines of the main group (P<.001) and the younger group (P<.025), but was not significantly lower than the regression line of the C subgroup. No significant differences were found in the regression coefficients of the regression lines of the four groups. The pooled regression coefficient was significant (b = -0.478, P<.0003). The correlation coefficients were r = -.294 for the main group, r = -.076 for the C subgroup, r = .017 for the post-MI group, and r = -.423 for the younger group (table 19, p 187).

iii. QKD and diastolic pressure

QKD was not plotted as a function of diastolic pressure because the regression coefficient was not significant (P<.557). The correlation coefficients were r = .036 for the main group, r = -.161 for the C subgroup, r = .200 for the post-MI group and r = -.093 for the younger group.

b. Discussion

The formulae for the regression lines of the four groups were calculated and plotted, and analysis of covariance was used to check for significant differences in the height and slope of these regression lines for the following reasons:

1) Significant differences between the main group and the C subgroup and between the main group and the post-MI group could indicate which variables are potentially useful in predicting the risk of cardiovascular crises;

Table 19. The relationship between the gradient of the initial, linear portion of the anacrotic slope and cardiac cycle length for the four groups.

Group	Mean±standard deviation	Regression equation	Standard deviation about the line	Correlation coefficient
Main group	744±286	$y = -0.610 \cdot x + 1247$	274.6	$r = -.294$
C subgroup	666±238	$y = -0.107 \cdot x + 755$	242.3	$r = -.076$
Post-MI group	494±169	$y = 0.015 \cdot x + 481$	174.1	$r = .017$
Younger group	675±135	$y = -0.367 \cdot x + 1003$	126.0	$r = -.423$

Where y is the gradient of the initial, linear portion of the anacrotic slope (mmHg/sec)
x is RR (msec)

2) Significant differences between the main group and the younger group could indicate which variables are potentially useful in monitoring age-related changes in the cardiovascular system.

The levels of correlation of the regression lines for each pair of variables were examined with a view to determining from this, and from a knowledge of the physiological mechanisms involved, whether correction of one variable for differences in the other variable was necessary.

1. Variables linked by factor analysis

i. Factor 1

It was concluded that the relationship between the two variables pulse pressure and the gradient of the initial, linear portion of the anacrotic slope was not potentially useful in cardiovascular epidemiology because no significant differences were found between the regression lines of the four groups (figure 12, p 152). The two variables were highly correlated as was expected, because both are affected by the same physiological mechanisms, cardiac contractility and pulse wave velocity. Only pulse pressure is affected by the additional physiological mechanism, wave reflection. Because there were no significant differences between the regression lines it was concluded that no significant differences in wave reflection existed between the four

groups and therefore no correction of pulse pressure was necessary for this pair of variables.

Although a significant difference ($P<.0001$) was found between the height of the regression line of the younger group and the regression lines of the other three groups (figure 13, p 154) it was concluded that the relationship between the two variables systolic pressure and pulse pressure was not potentially useful in cardiovascular epidemiology because systolic pressure is one of the two components used in the calculation of pulse pressure and therefore it is not known how much of the relationship between the variables is due to the presence of the one variable in the calculation of the other. (The correlation coefficients for the main group ($r = .816$) and the younger group ($r = .538$) were similar to those obtained by Boe et al (1957) for both their two groups of men at similar ages ($r = .842$ and $r = .696$, and $r = .756$ and $r = .571$, respectively). The similarity of the correlation coefficients obtained by the present author and by Boe et al (1957) suggests that the above relationship between systolic pressure and pulse pressure can be found in populations other than that which provided the data on which this thesis is based.)

It was concluded that the relationship between the two variables systolic pressure and the gradient of the initial, linear portion of the anacrotic slope (figure 14, p 157) had

the potential to be useful in monitoring age- related changes in the cardiovascular system because the regression line of the younger group was significantly lower than the regression lines of the other three groups. The two variables were adequately correlated as was expected because both are affected by the same physiological mechanisms, cardiac contractility and pulse wave velocity. Only systolic pressure is affected by the further physiological mechanism, peripheral resistance. Because there was a significant difference in height between the regression line of the younger group and the regression lines of the three other groups it was concluded that a difference in peripheral resistance existed between the younger group and the three other groups and therefore correction of systolic pressure was appropriate to monitor age-related differences in peripheral resistance. Support for this conclusion is provided by the finding in the literature that peripheral resistance increases with age (Amery et al, 1978; De Leeuw et al, 1978; Lakatta, 1979), and the finding in this thesis that when the younger group was subdivided according to age the regression line of the subgroup aged nine to twenty years was significantly lower in height than the regression line of the subgroup aged twenty-one to forty years (figure 17, p 164).

That peripheral resistance and not some other age-related physiological mechanism was affecting systolic pressure was supported by the fact that when diastolic pressure

and the duration of the entire anacrotic slope (the two variables which are also affected by peripheral resistance) were superimposed on the graphs of systolic pressure plotted as a function of the gradient of the initial, linear portion of the anacrotic slope, both diastolic pressure and the duration of the anacrotic slope increased with systolic pressure for constant values of the gradient of the initial, linear portion of the anacrotic slope for all four groups (figures 18a-d and figures 19a-d, pp 166-73). It is to be noted that this trend occurred even in the three groups (the main group, the C subgroup, and the post-MI group) where age variation was minimal.

(In theory, the relationship between systolic pressure and peripheral resistance is confounded by changes in stroke volume because when stroke volume is low, reflected waves are weak, and hence systolic pressure amplification is low even where peripheral resistance is high; conversely when stroke volume is high, reflected waves are strong, and hence systolic pressure amplification is high even where peripheral resistance is low. This theory could not be substantiated because no measurements of stroke volume were available for the subjects in this study.)

Although a significant difference ($P<.0001$) was found between the regression line of the younger group and the regression lines of the other three groups (figure 15, p 159) it was concluded that the relationship between the

two variables, systolic pressure and QKD, was not potentially useful in cardiovascular epidemiology because the level of correlation between the two variables was low (table 13, p 161). It was also concluded that the relationship between the two variables, QKD and the gradient of the initial, linear portion of the anacrotic slope, was not potentially useful in cardiovascular epidemiology because no significant differences were found between the regression lines of the four groups (figure 16, p 162) and the level of correlation between the two variables was low (table 14, p 163).

It would thus appear from both the above relationships (systolic pressure and QKD, and QKD and the gradient of the initial, linear portion of the anacrotic slope) that QKD itself lacks the potential to be useful in cardiovascular epidemiology.

ii. Factor 2

As has already been stated, the relative importance of the four physiological mechanisms on the four factor 2 variables was not clarified by the factor analysis and therefore the interrelationships between the factor 2 variables were not investigated in this section.

iii. Factor 3

It was concluded that the relationship between the two variables, systolic pressure and diastolic pressure, was

not potentially useful in cardiovascular epidemiology because no significant differences were found between the regression lines of the four groups (figure 20, p 175). The two variables were highly correlated as was expected because both are affected by the same physiological mechanism, peripheral resistance. Only systolic pressure is affected by the additional physiological mechanisms, cardiac contractility and pulse wave velocity. Because there were no significant differences in height between the regression lines it was concluded that no significant differences in cardiac contractility and pulse wave velocity existed between the four groups for this relationship and therefore no correction of systolic pressure was necessary for this pair of variables. (It should be noted, however, that cardiac contractility was probably reduced in the post-MI group because the regression line of this group was marginally lower [$P<.057$] than the regression line of the main group. The difference was significant when a t-test was used [$P<.025$].) The correlation coefficients for the main group ($r = .641$) and the younger group ($r = .649$) were similar to those obtained by Boe, Humerfeldt, Wedervang, and Oecon (1957) for both their two groups of men at similar ages ($r = .683$ and $r = .645$, and $r' = .489$ and $r = .569$ respectively). Harlan, Osborne, and Graybiel (1962) obtained a correlation coefficient similar to that of the younger group for their group of men aged thirty-six years ($r = .640$). Again it should be noted that the similarity

of the correlation coefficients obtained by the present author, by Boe et al (1957) and by Harlan et al (1962) suggest that the above relationship between systolic pressure and diastolic pressure can be found in populations other than that which provided the data on which this thesis is based.

iv. Factor 4

It was concluded that the relationship between the two variables, the duration and the gradient of the initial, linear portion of the anacrotic slope, was not potentially useful in cardiovascular epidemiology because no significant differences were found between the regression lines of the four groups (figure 21, p 178). The two variables were correlated as was expected because both are affected by the same physiological mechanisms, cardiac contractility and pulse wave velocity. However, because the level of correlation was low it was concluded that no correction of the duration of the gradient of the initial, linear portion of the anacrotic slope was appropriate for this pair of variables.

v. Factor 5

It was concluded that the relationship between the two variables, QT and cardiac cycle length, was not potentially useful in cardiovascular epidemiology because no significant differences were found between the regression

lines of the four groups (figure 22, p 180). The two variables were correlated because both are affected by the same physiological mechanism, the level of activity of the sympathetic nervous system (this thesis, pp 147-48). The correlation coefficient for the younger group (r = .788) was similar to that obtained by Schlamowitz (1946) for his group of 495 soldiers aged eighteen to twenty-five years (r = .779). Once again it should be noted that this similarity of the correlation coefficients and the similarity in the slope of the regression lines obtained by the present author and by Bazett (1920); Adams (1936); Schlamowitz (1946); Simonson, Cady, and Woodbury (1962); and Manion, Whitsett, and Wilson (1980) (figure 25, p 196; table 20, p 197) suggest that the above relationship between QT and cardiac cycle length can be found in populations other than that which provided the data on which this thesis is based. (The difference in height between the regression lines obtained by the several authors and the regression line obtained by the present author was due to the fact that their QT measurements included ventricular repolarization time whereas this was excluded by the present author [this thesis, p 126].)

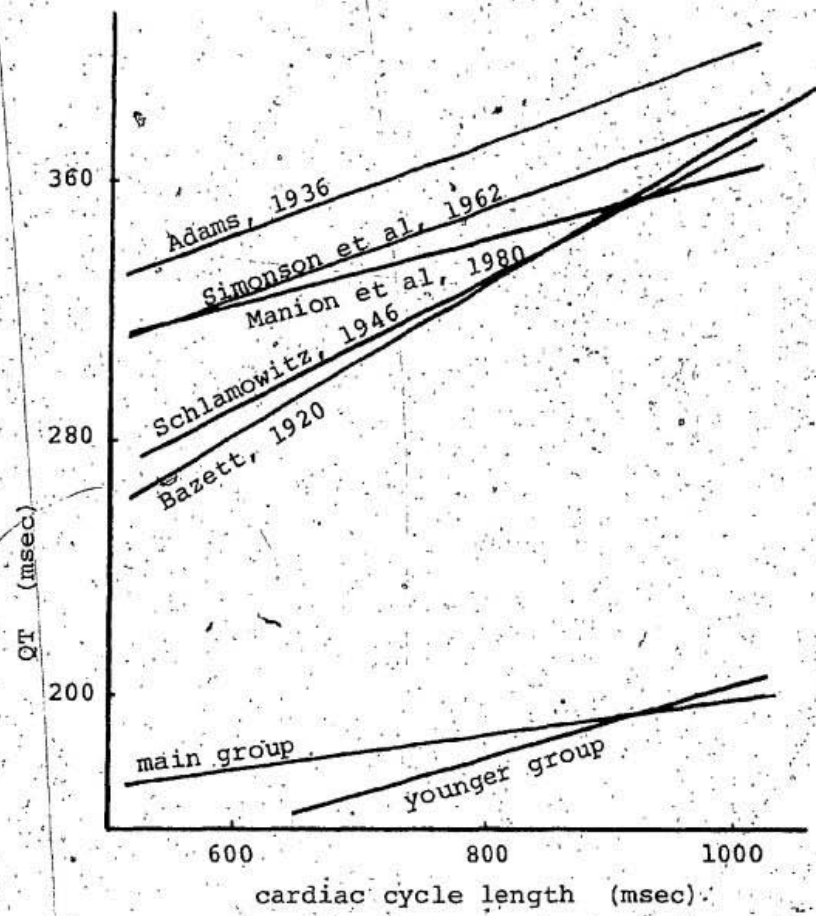


Figure 25. Graph of QT as a function of cardiac cycle length, showing the regression lines obtained by several authors for comparison with the main group and the younger group of this thesis.

The regression lines of the main and younger groups are lower because the QT measurement used in this thesis did not include ventricular repolarization time.

Table 20. The relationship between QT and cardiac cycle length as determined by different authors.

Authors	Regression equation (msec)	Age range (yr)	Number of subjects
Bazett, 1920	$y = (0.368\ x/1000)\ 1000$		
Adams, 1936	$y = 0.146 \cdot x + 257$	20-48	104
Schlamowitz, 1946	$y = 0.205 \cdot x + 167$	18-25	495
Simonson et al, 1962	$y = 0.140 \cdot x + 242$	20-59	649
Manion et al, 1980	$y = -0.913\ (60000/x) + 420$		11
(This thesis			
Younger group	$y = 0.123 \cdot x + 86$	9-51	19
Main group	$y = 0.059 \cdot x + 143$	55-56	152)

Where y is QT (msec)
x is RR (msec)

2. Variables not linked by factor analysis

i. QKD and cardiac cycle length

Although a significant difference ($P<.02$) was found between the slope of the regression line of the post-MI group and the regression lines of the other three groups (figure 23, p 183) it was concluded that the relationship between the two variables, QKD and cardiac cycle length, was not potentially useful in cardiovascular epidemiology because the level of correlation was low. The two variables were correlated because both are affected by the same physiological mechanism, the level of activity of the sympathetic nervous system. The correlation coefficient for the younger group ($r = .546$) was similar to that obtained between QKD and heart rate by Da Costa et al (1973) for females aged nineteen to forty years ($r = -.480$) (their correlation coefficient for males was not significant and therefore was not given), and to that obtained by Murata et al (1976) for males and females aged twenty to forty-nine years ($r = -.239$ and $r = -.464$ respectively). The use of heart rate instead of cardiac cycle length is responsible for the sign reversal. Again the similarity of the correlation coefficients obtained by the present author, by Da Costa et al (1973) and by Murata et al (1976) suggests that the above relationship can be found in populations other

than that which provided the data on which this thesis is based.

ii. The gradient of the initial, linear portion of the anacrotic slope and cardiac cycle length

There were no significant differences in the slope of the regression lines of the four groups ($P<.1896$) and although the regression line of the post-MI group was significantly lower in height than the regression lines of the main group ($P<.001$) and the younger group ($P<.03$) (figure 24, p 185), it was concluded that the relationship between the two variables, the gradient of the initial, linear portion of the anacrotic slope and cardiac cycle length, was not potentially useful in cardiovascular epidemiology because the level of correlation was low. The weak correlation existing between the two variables in only the two groups, the main group ($r = -.294$) and the younger group ($r = -.423$), was expected because both variables are affected by the same physiological mechanism, the level of activity of the sympathetic nervous system.

(It is to be noted that in the three relationships where cardiac cycle length was treated as the independent variable, the correlation coefficient was highest for the younger group. As this may indicate that the correlation with cardiac cycle length declines with age, it was decided to investigate these three relationships further in Chapter IV.)

iii. QKD and diastolic pressure

It was concluded that because the regression coefficient was not significant the relationship between QKD and diastolic pressure was not potentially useful in cardiovascular epidemiology.

CHAPTER IV

AN INVESTIGATION OF THE USEFULNESS OF THE VARIABLES

An attempt will be made in this chapter to determine the usefulness of Rodbard's method in cardiovascular epidemiology by determining the usefulness of the Rodbard variables in the diagnosis and/or prognosis of cardiovascular disease.

To this end there will be an examination of the relationship between the cardiovascular mortality and morbidity (nonfatal myocardial infarctions and strokes) of the main group and the post-MI group from the time the records were taken in 1969/70 until 1979.12.07 and

1) the means of the variables;
2) the variables after they had been weighted and combined to produce factor scores for each of the five factors produced by the factor analysis reported in Chapter III;
3) certain pairs of variables which were concluded in Chapter III to be potentially useful in cardiovascular epidemiology.

SECTION 1

Cardiovascular mortality and morbidity 1969/70-1979.12.07

Lists of the subjects of the main group and the post-MI group who died or who were registered as having had a non-fatal myocardial infarction or stroke in Göteborg on or before 1979.12.07, and the cause of death given on the death certificates of those who died, were provided by Dr Lars Wilhelmsen, Director of the Department of Medicine, Östra Sjukhuset, Göteborg. This information was regarded as being very reliable because over 90% of all the deaths had been subjected to post mortem examination and all clinically diagnosed cases of nonfatal myocardial infarctions and strokes (Wilhelmsen et al, 1972) had been entered in the strictly supervised Myocardial Infarction Register and Stroke Register maintained by the City of Göteborg (Elmfeldt et al, 1975, and Harmsen and Tibblin, 1972, respectively).

a. The main group

During the follow-up period, of the 152 subjects of the main group

Four died from noncardiovascular causes:

#1	amyotrophic lateral sclerosis	77.09.20
#3	cancer of the stomach	76.01.17
#113	cancer of the colon	79.05.31
#138	cancer of the colon	77.04.27

Ten died from cardiovascular causes:

#4	pulmonary embolism	71.11.27
#5	ischemic heart disease	73.10.19
#2	cardiac insufficiency	73.12.21
#9	stroke post-myocardial infarction	74.04.12
#10	myocardial infarction (21 months after stroke)	74.10.09
#7	myocardial infarction	75.10.03
#18	pulmonary embolism (32 months after stroke)	76.01.16
#103	myocardial infarction (4 days after stroke)	78.01.29
#17	cardiac insufficiency	78.05.31
#139	aortic valve failure	79.07.01

Eleven had nonfatal myocardial infarctions:

#14	71.03.25
#12	72.05.18
#11	74.06.20
#16	74.11.29, 78.08.19 and 78.09.11
#13	76.03.11
#15	76.04.19 and 77.10.02
#8	77.01.17
#6	77.05.22
#114	77.06.26
#73	77.10.31
#82	78.10.22

Four had nonfatal strokes:

#20 75.11.12

#19 76.03.20

#96 77.04.19

#81 78.11.22

b. The post-MI group

During the follow-up period, of the 19 subjects in the post-MI group

Seven died from cardiovascular causes:

#166	arteriosclerosis	71.05.14
#160	cardiac insufficiency	71.08.21
#169	myocardial infarction	75.06.07
#165	myocardial infarction	76.02.09
#163	myocardial infarction	76.10.18
#154	stroke post-myocardial infarction	77.02.14
#161	stroke post-myocardial infarction	77.08.30

Two had nonfatal myocardial infarctions:

#157 70.08.30, 73.04.06 and 74.05.29

#170 74.02.18

One had one nonfatal stroke:

#162 78.10.02

SECTION 2

The relationship between cardiovascular mortality and morbidity 1969/70 - 1979.12.07 and aspects of the variables

a. Means of the variables

1. Results

i. The main group

The means of the variables of those members of the main group who had cardiovascular disease in the follow-up period (ie the "C subgroup" of Chapters II and III) were compared with the means of the variables of those members of the main group who did not have cardiovascular disease in the follow-up period (ie the main group minus the "C subgroup"). This comparison is presented in table 21 (p 206), where it can be seen that there were no significant differences between the means of the variables (including the seven unique to Rodbard's method) of the two groups.

It is possible that the wide variety of cardiovascular diseases recorded in subgroup C could have obscured any difference between the means of the variables of the two groups. In an attempt to clarify this point, the C subgroup was classified into three divisions depending on the presence of either a fatal cardiovascular event, a nonfatal myocardial infarction, or a nonfatal stroke. (The four subjects who suffered a nonfatal myocardial infarction or stroke before succumbing to a different, fatal

Table 21. The means of the variables of those members of the main group who had cardiovascular disease recorded in the follow-up period and those who did not.

Variables	Main group Minus C subgroup	C subgroup	Fatal event	Nonfatal MI	Nonfatal stroke
SP (mmHg)	157±26	154	160	154	165
DP (mmHg)	92±15	94	97	92	100
PP (mmHg)	64±20	60	63	55	67
QT (msec)	192±23	197	199	200	192
G (mmHg/sec)	759±286	666	668	703	742
LT (msec)	67±20	68	71	65	66
RR (msec)	823±138	833	761	832	781
QKD (msec)	206±24	208	206	208	201
D (msec)	153±57	158	164	141	175
NT (msec)	76±66	63	51	54	76
NP (mmHg)	13±9	14	17	13	19
NA (mmHg·msec)	373±502	442	634	305	755
Number of subjects	127	25	10	12	7

The standard deviation given is that of the total main group. No significant differences were found.

cardiovascular event were included in both the fatal division and the appropriate nonfatal division.) The means of the variables of each of these three divisions were compared with the means of the variables of the main group minus the C subgroup. This comparison is also presented in table 21 (p 206), where it can be seen that there were no significant differences in the means of the variables of any of the three divisions of the C subgroup when compared with the mean of the main group minus the C subgroup.

Further, for each variable the relative risk of a fatal cardiovascular event, or a nonfatal myocardial infarction, or a nonfatal stroke in the follow-up period was calculated after taking the variables one by one and in each instance dividing the entire main group into 1) those subjects with values above the mean of the particular variable and 2) those subjects with values equal to or below the mean of the particular variable. (The mean value of each variable was used as the cut-off point to reduce observer bias.) The relative risks are presented in table 22 (p 208), where it can be seen that none differed significantly from unity.

ii. The post-MI group

The means of the variables of the post-MI group were compared with the means of the variables of the main group. This comparison is presented in table 23 (p 209), where it can be seen that the means of five of the variables

Table 22. The relative risk of experiencing a cardiovascular event during the follow-up period for members of the main group. The mean of each variable was used as the cut-point to divide the main group into two for each calculation.

Variable	Fatal event	Nonfatal MI	Nonfatal stroke
SP>156 (mmHg)	1.58	0.529	1.75
DP>93 (mmHg)	1.38	1.38	1.38
PP>63 (mmHg)	1.05	1.05	1.05
QT>192 (msec)	1.85	2.47	2.05
G≤743 (mmHg/sec)	1.58	1.35	0.67
LT>67 (msec)	1.50	0.71	1.67
RR≤825 (msec)	1.54	0.73	1.71
QKD≤207 (msec)	2.24	1.34	1.60
D>154 (msec)	1.49	0.746	1.49
NT>73 (msec)	0.968	0.725	1.45
NP>13 (mmHg)	1.49	0.746	1.49
NA>384 (mmHg·msec)	1.40	0.701	1.26
Number of cases	10	12	7

None of the relative risk figures differed significantly from unity.

Table 23. The means and standard deviations of the variables for the main group and the post-MI group, and for the members of the post-MI group who had and did not have cardiovascular disease recorded in the follow-up period.

Variables	Main group	Post-MI group		
			Disease	No Disease
SP (mmHg)	156±26	137±23**	143	131
DP (mmHg)	93±15	85±13*	86	84
PP (mmHg)	63±20	52±19*	57	47
QT (msec)	192±23	194±28	192	197
G (mmHg/sec)	743±286	494±169**	507	479
LT (msec)	67±20	79±21*	84	73
RR (msec)	825±138	871±194	846	900
QKD (msec)	207±24	216±24	216	216
D (msec)	154±57	160±56	174	145
NT (msec)	73±66	58±46	66	49
NP (mmHg)	13±9	13±8	14	12
NA (mmHg·msec)	384±502	352±385	392	307
Number of subjects	152	19	10	9

*Significantly different from the main group $P<.05$
**Significantly different from the main group $P<.01$

No significant differences were found between the means of the disease and no disease subdivisions of the post-MI group.

of the post-MI group were significantly different from the means of the same variables of the main group: systolic pressure ($P<.01$), diastolic pressure ($P<.05$), pulse pressure ($P<.05$), the gradient of the initial, linear portion of the anacrotic slope ($P<.01$), and the duration of the initial, linear portion of the anacrotic slope ($P<.05$). (Only the last two variables are unique to Rodbard's method.)

Next, the means of the variables of those members of the post-MI group who had a fatal cardiovascular event or a nonfatal myocardial infarction or a nonfatal stroke in the follow-up period were compared with the means of the variables of those members of the post-MI group who had no such cardiovascular crises. This comparison is presented in table 23 (p 209), where it can be seen that the means of the variables of the two divisions of the post-MI group were not significantly different.

Finally, for each variable the relative risk of a fatal cardiovascular event was calculated after taking the variables one by one and in each instance dividing the post-MI group into 1) those subjects with values above the mean of the particular variable of the main group and 2) those subjects with values equal to or below the mean of the particular variable of the main group. (The mean values of the variables of the main group were used as the cut-off points to reduce observer bias because the main group was regarded as best representing the population sample from

which the post-MI group was taken.) In two instances no relative risk could be calculated because either a numerator or a denominator was lacking. For the remainder the relative risks ranged from 0.3 - 1.3 (table 24, p 212). Because the numbers were small, no attempt was made to assess the statistical significance of these values.

2. Discussion

i. The main group

No significant differences were found between the means of the variables of those members of the main group who had, and of those members of the main group who did not have, cardiovascular disease in the follow-up period. No significant differences were found between the means of the variables of any of the three divisions of the C subgroup and of the main group minus the C subgroup. No significant difference in the relative risk of subsequent cardiovascular disease was found for any of the variables. It was therefore concluded none of the variables unique to Rodbard's method are likely to be useful in the diagnosis or prognosis of cardiovascular disease and hence in cardiovascular epidemiology. This confirms the impression obtained from the literature (see Chapter I) with respect to three of the seven Rodbard variables: QKD, p 69; the gradient of the initial, linear portion of the anacrotic slope, p 77; the duration of the entire anacrotic slope, p 103.

Table 24. The relative risk of experiencing a fatal cardiovascular event during the follow-up period for members of the post-MI group. The mean of each variable for the main group was used as the cut-point to divide the post-MI group into two for each calculation and the categories are the same as those used for the main group in table 22 to allow comparison.

Variable	Fatal event
SP>156 (mmHg)	0.88
DP>93 (mmHg)	0.86
PP>63 (mmHg)	0/46
QT>192 (msec)	0.96
G<743 (mmHg/sec)	41/0
LT>67 (msec)	0.61
RR<825 (msec)	1.28
QKD<207 (msec)	0.28
D>154 (msec)	0.96
NT>73 (msec)	1.12
NP>13 (mmHg)	0.55
NA>384 (mmHg·sec)	0.87

No significance levels were calculated because the numbers were small.

ii. The post-MI group

The means of five of the variables of the post-MI group were significantly different from the means of the same variables of the main group. The differences with respect to systolic pressure, pulse pressure, and the gradient of the initial, linear portion of the anacrotic slope can be explained as being due to the reduction in cardiac contractility in the post-MI group but no patho-physiological cause can be confidently advanced to explain the differences with respect to diastolic pressure and the duration of the initial, linear portion of the anacrotic slope. Thus while it is possible that the Rodbard variable, the gradient of the initial, linear portion of the anacrotic slope, would be useful in the diagnosis of cardiovascular disease and hence in cardiovascular epidemiology, the same cannot be said of the remaining variable unique to Rodbard's method, the duration of the initial, linear portion of the anacrotic slope.

No significant differences were found between the means of the variables of those members of the post-MI group who had, and those members of the post-MI group who did not have, cardiovascular disease in the follow-up period. Therefore, it was concluded that there was nothing to

suggest from this particular comparison that the variables unique to Rodbard's method are likely to be useful in the prognosis of cardiovascular disease and hence in cardiovascular epidemiology.

No significant difference in the relative risk of a fatal cardiovascular event in the follow-up period was found for any of the variables. This was probably because the number of the subjects involved was too small. It is possible that pulse pressure or the gradient of the initial, linear portion of the anacrotic slope (the latter being a variable unique to Rodbard's method) might be useful in predicting risk of a subsequent fatal cardiovascular event, because all six men who died had values of pulse pressure and the gradient of the initial, linear portion of the anacrotic slope less than the means of the corresponding variables of the main group. This possibility needs to be tested with far larger numbers than were available in the data obtained by Dr J G Fodor in Göteborg in 1969/70.

b. The variables weighted and combined to produce factor scores

1. Results

i. The main group.

During the factor analysis reported in Chapter III the variables were weighted and combined to produce for each subject of the main group factor scores for each of the five factors extracted. The units of the factor scores were

standardized by the factor analysis so that they were given in standard deviations about a mean of zero.

Using one factor for each axis, sets of three graphs were prepared, three being the minimum number required to ensure that all five factors were included on at least one graph of each set. The following combinations of factors were decided on for the following reasons: factors 1 and 2 because these factors explained the largest proportion of the variation (table 9, p 130); and factors 1 and 4, and factors 3 and 5 because of the possible relationship within each pair of factors (pp 147, 146, 149). First, the subjects of the main group who had a fatal cardiovascular event in the follow-up period were plotted on the first set of the three graphs and in each instance the cause of death was indicated (figure 26, pp 216-17). Secondly, the subjects of the main group who had a nonfatal myocardial infarction in the follow-up period were plotted on the second set of the three graphs (figure 27, pp 218-19). Thirdly, the subjects of the main group who had a nonfatal stroke in the follow-up period were plotted on the third set of the three graphs (figure 28, pp 220-21).

The three sets of graphs were then examined to see if the fatal cardiovascular events, the nonfatal myocardial infarctions, or the nonfatal strokes clustered in any quadrant of any of the graphs. No such clustering was found for any of the three cardiovascular crises.

Figure 26. Graphs showing the factor scores of the members of the main group who died of cardiovascular causes in the follow-up period. The origin represents the mean factor score of the main group and the factor scores are given in standard deviations.

Cause of death:

AVF	aortic valve failure
CI	cardiac insufficiency
IHD	ischemic heart disease
MI	myocardial infarction
PE	pulmonary embolism
SMI	stroke post-MI

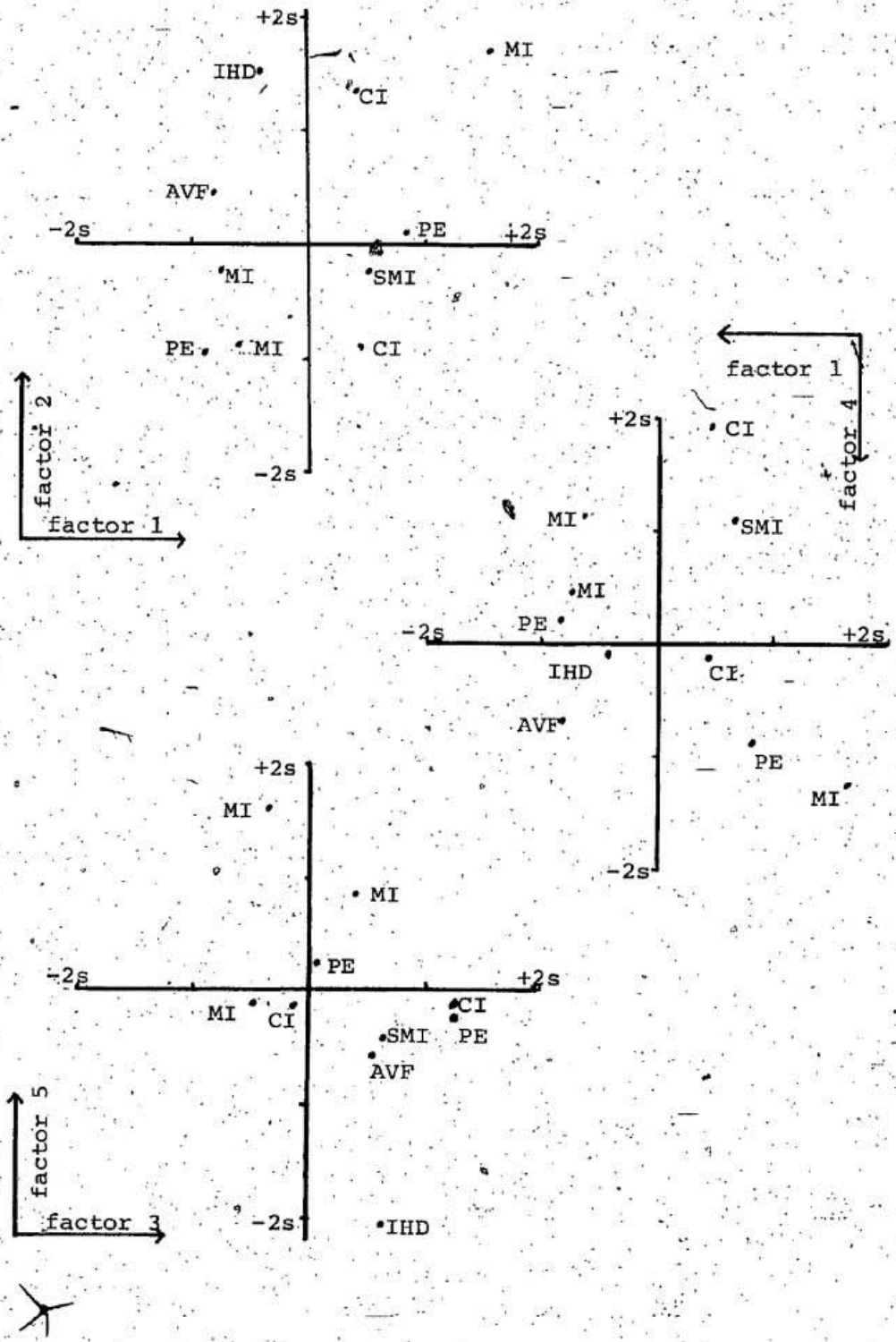

+2s
MI
IHD
CI
AVF
-2s
PE
+2s
MI
SMI
PE
MI
CI
-2s
factor 2
factor 1
factor 1
factor 4
+2s
CI
MI
SMI
MI
-2s
PE
+2s
IHD
CI
AVF
PE
MI
+2s
MI
MI
-2s
PE
+2s
MI
CI
CI
SMI
PE
AVF
factor 5
factor 3
-2s
IHD

Figure 27. Graphs showing the factor scores of members of the main group who experienced a nonfatal myocardial infarction. The origin represents the mean factor score of the main group and the factor scores are given in standard deviations.

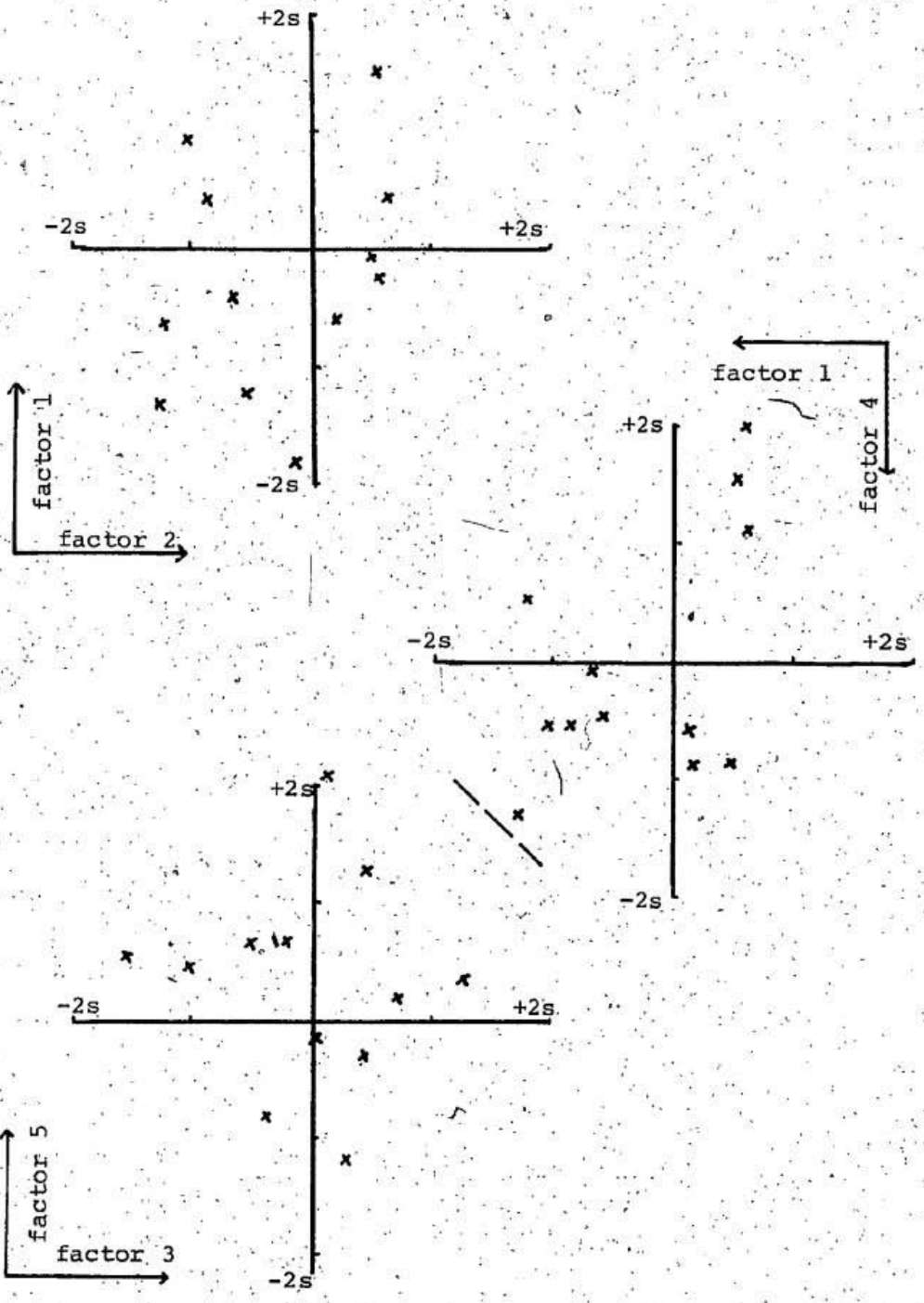
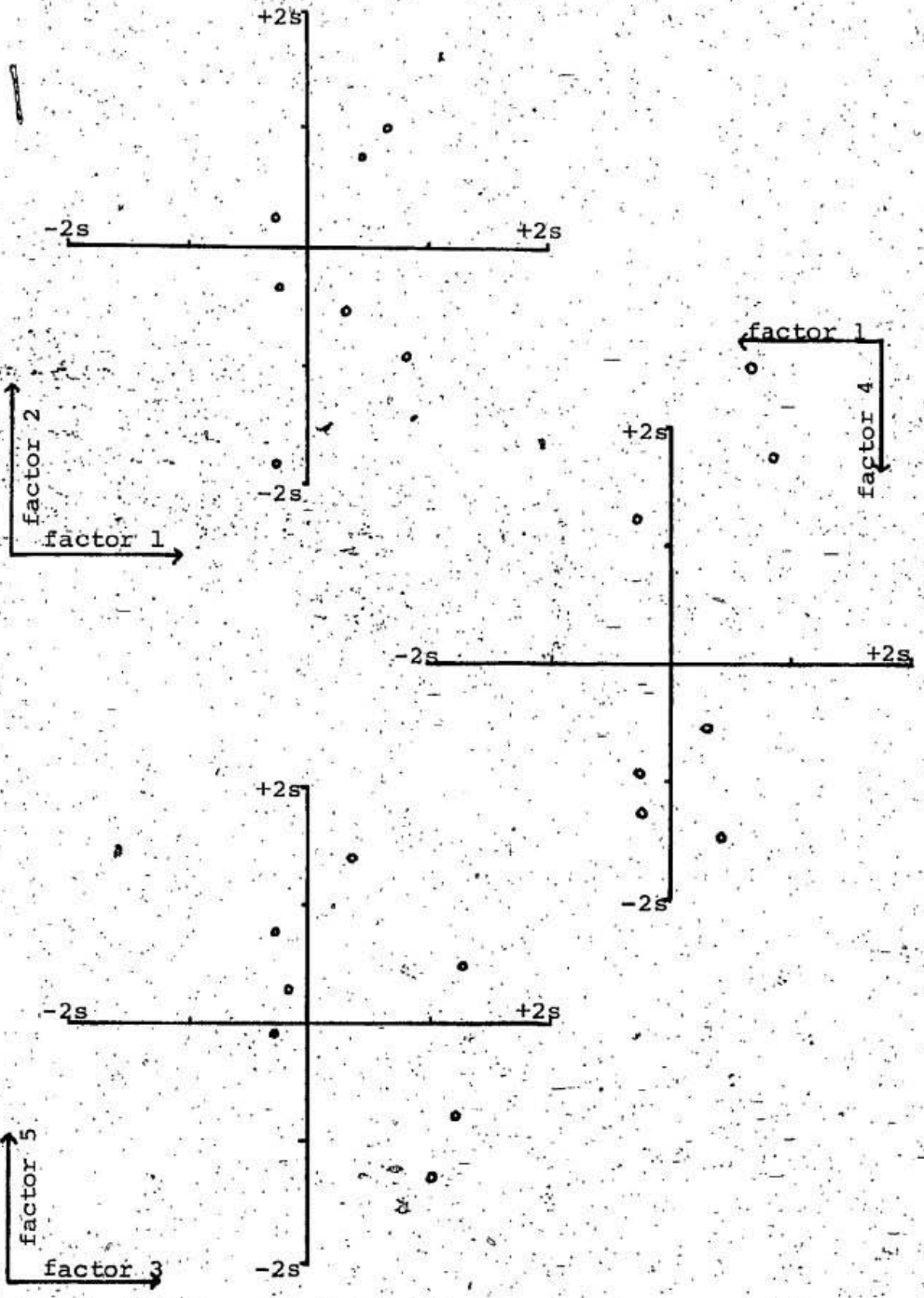

+2s
-2s
+2s
-2s
factor 1
factor 2
factor 1
factor 4
+2s
-2s
+2s
-2s
+2s
-2s
+2s
-2s
factor 5
factor 3

Figure 28. Graphs showing the factor scores of the members of the main group who experienced a nonfatal stroke. The origin represents the mean factor score of the main group and the factor scores are given in standard deviations.


+2s
-2s
+2s
-2s
factor 2
factor 1
factor 1
factor 4
+2s
-2s
+2s
-2s
+2s
-2s
+2s
-2s
factor 5
factor 3

ii. The post-MI group

Factor scores were calculated for each subject of the post-MI group by using the factor score coefficients produced by the factor analysis of the main group. These factor score coefficients (appendix J, p 284) were used: a) because the factor score coefficients of the post-MI group were judged to be unreliable as the post-MI group was small (19) and included a large proportion of subjects with serious cardiac dysfunction; b) because the main group was regarded as best representing the population sample from which the post-MI group had come; c) because using the same factor coefficients for the main group and the post-MI group would make it possible for the factor scores of the two groups to be compared.

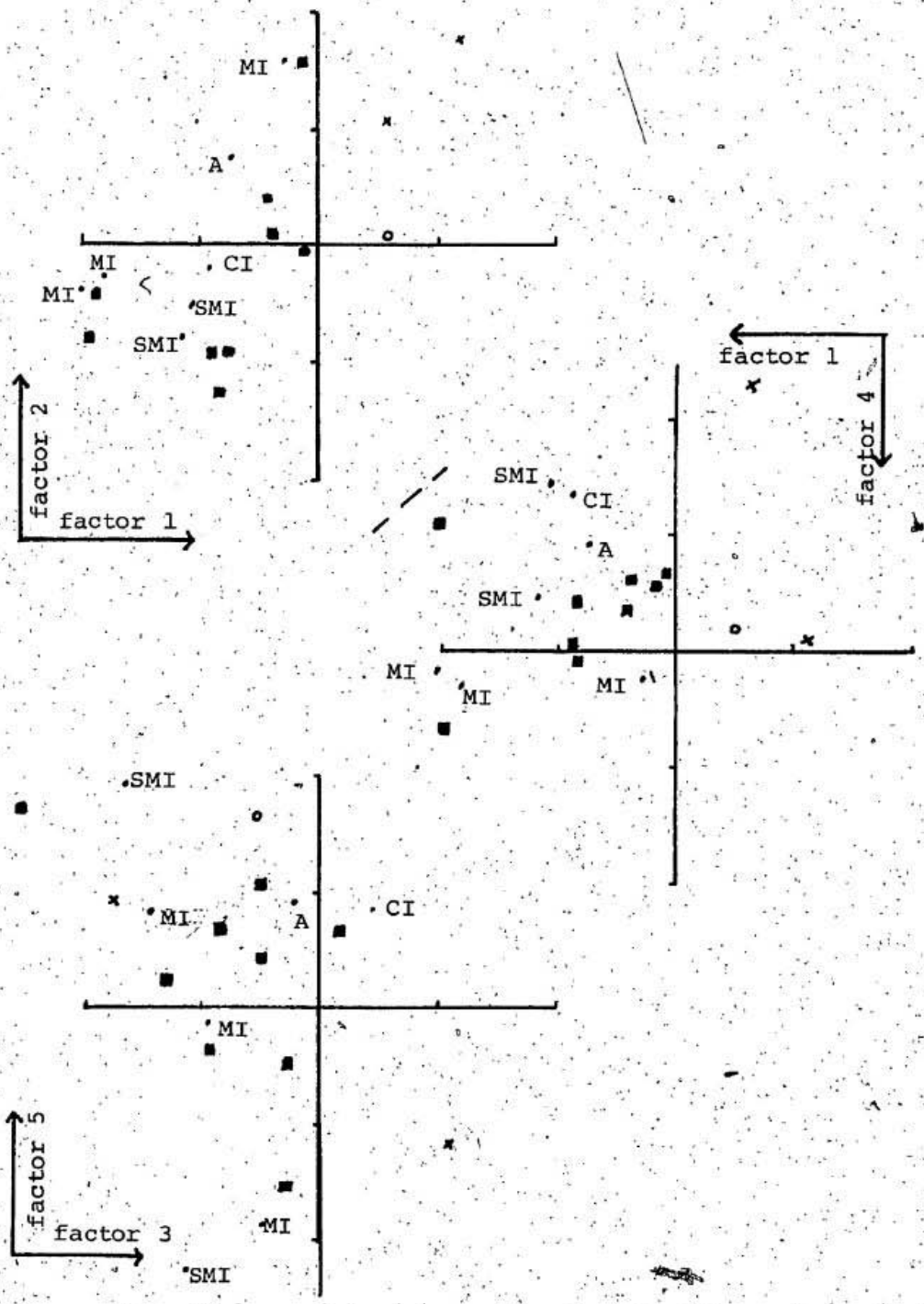
On a set of three graphs prepared in the same way as for the main group, the factor scores of all the subjects of the post-MI group were plotted (figure 29, pp 223-24). Where the subject had a cardiovascular crisis in the follow-up period, the nature of the crisis was indicated.

In the two graphs which had factor 1 as one of the factors it was seen that 16 of the 19 subjects had factor 1 scores below the mean of the main group, and that 7 of this 16 accounted for all the fatal cardiovascular events in the follow-up period. All three of the subjects with factor 1 scores above the mean of the main group had a cardiovascular crisis in the follow-up period but none of these crises

Figure 29. Graphs showing the factor scores of members of the post-MI group. The origin represents the mean factor score of the main group and the factor scores are given in standard deviations.

Cardiovascular history in the follow-up period:

A	died of arteriosclerosis
CI	died of cardiac insufficiency
MI	died of myocardial infarction
SMI	died of stroke post-MI
*	nonfatal myocardial infarction
•	nonfatal stroke
▪	no event was registered


MI
A
MI
CI
MI
SMI
SMI
factor 2
factor 1
factor 1
factor 4
SMI
CI
A
SMI
MI
MI
MI
SMI
MI
A
CI
MI
factor 5
factor 3
MI
SMI

proved fatal. No clustering was seen with regard to the remaining four factors.

2. Discussion

i. The main group

Because no clustering was seen in the graphs of the factor scores of those subjects of the main group who had cardiovascular crises in the follow-up period (figures 26-28, pp 216-21), it was concluded that weighting and combining the variables (including those unique to Rodbard's method) to produce factor scores for each of the five factors extracted by the factor analysis was not useful in the diagnosis or prognosis of cardiovascular disease and hence in cardiovascular epidemiology.

ii. The post-MI group

Sixteen of the 19 subjects of the post-MI group were seen from the graphs (figure 29, pp 223-24) to have had factor 1 scores below the mean of the main group. Because cardiac contractility is one of the two physiological mechanisms which affect all the factor 1 variables, it was concluded that a proportion of the 84% (16/19) of the post-MI subjects with factor 1 scores below the mean of the main group had reduced cardiac contractility, a phenomenon to be expected in a group (such as the post-MI group) which had known cardiac dysfunction. That factor 1 scores below the mean of the main group are indicative of reduced cardiac

contractility was supported by the fact that of the 10 members of the post-MI group who had cardiovascular events in the follow-up period, the 7 who died had factor 1 scores below the mean of the main group and the 3 who survived were the 3 of the 19 post-MI subjects who had factor 1 scores above the mean of the main group.

If this tentative conclusion that factor 1 scores below the mean of the main group are indicative of reduced cardiac contractility could be confirmed in a study of a far larger group of post-MI subjects, it could be further concluded that because two of the four variables used to calculate the factor 1 scores are unique to Rodbard's method, Rodbard's method may be useful in the diagnosis of the degree of reduced cardiac contractility after a myocardial infarction, and hence in cardiovascular epidemiology.

Because no other clustering was seen in the post-MI groups, it was concluded that weighting and combining the variables to produce factor scores for factors 2-5 was not useful in the diagnosis and/or prognosis of cardiovascular disease in post-MI subjects, and hence in cardiovascular epidemiology.

c. Certain pairs of variables potentially useful in cardiovascular epidemiology

1. Results

It was concluded in Chapter III that the relationship between four pairs of variables had the potential to be

useful in cardiovascular epidemiology. The four relationships were

1) systolic pressure as a function of the gradient of the initial, linear portion of the anacrotic slope;

2) QT as a function of cardiac cycle length;

3) QKD as a function of cardiac cycle length;

4) the gradient of the initial, linear portion of the anacrotic slope as a function of cardiac cycle length.

Sets of four graphs, one graph for each of the four relationships, were prepared. Those members of the main group who had a fatal cardiovascular event, or a nonfatal myocardial infarction, or a nonfatal stroke in the follow-up period were plotted on the first, second, and third sets of graphs respectively, and the nature of the fatal cardiovascular events was indicated (figures 30-32, pp 228-33). All the members of the post-MI group were plotted on the fourth set of graphs and the nature of all cardiovascular crises experienced in the follow-up period was indicated (figure 33, pp 234-35). The four sets of graphs were then examined to see if the fatal cardiovascular events, the nonfatal myocardial infarctions, or the nonfatal strokes clustered in any particular area of the graphs.

No such clustering was found for three of the four relationships between the variables. Two clusters were found on the graphs for the relationship between systolic

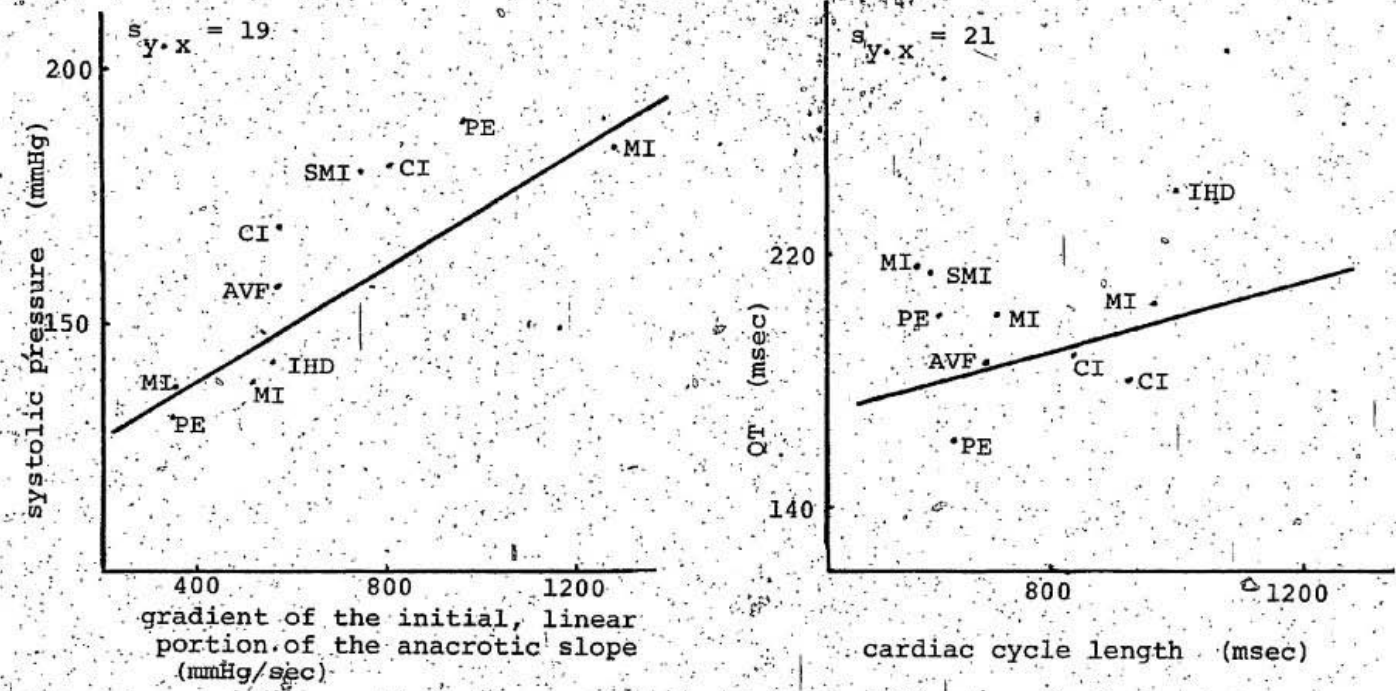


Figure 30 a. The position of members of the main group who died of cardiovascular causes in the follow-up period is given for two of the four relationships selected as having the most potential to be useful in cardiovascular epidemiology. No significant clustering was seen.

Cause of death:

AVF	aortic valve failure	MI	myocardial infarction
CI	cardiac insufficiency	PE	pulmonary embolism
IHD	ischemic heart disease	SMI	stroke post-MI

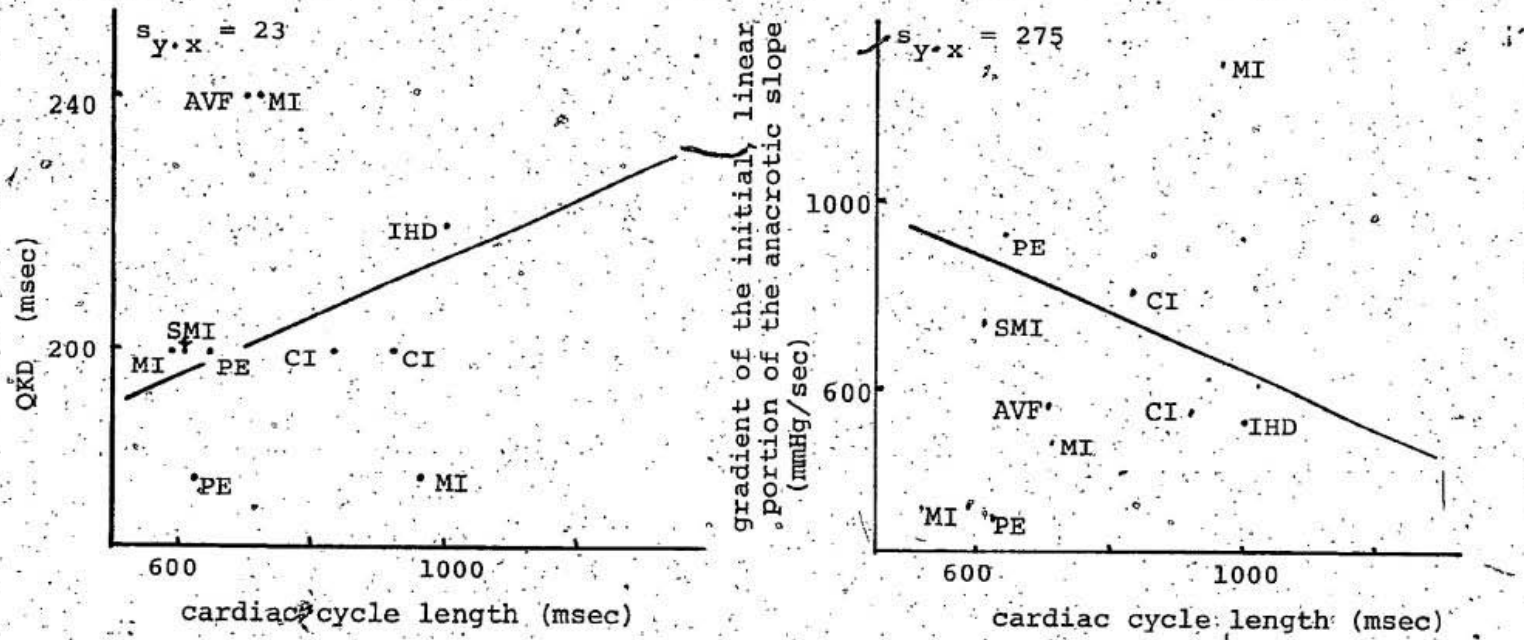


Figure 30b. Graphs showing the postion of members of the main group who died of cardiovascular causes in the follow-up period for two of the four relationships selected as having the most potential to be useful in cardiovascular epidemiology. No significant clustering was seen.

Cause of death:

AVF	aortic valve failure	MI	myocardial infarction
CI	cardiac insufficiency	PE	pulmonary embolism
IHD	ischemic heart disease	SMI	stroke post-MI

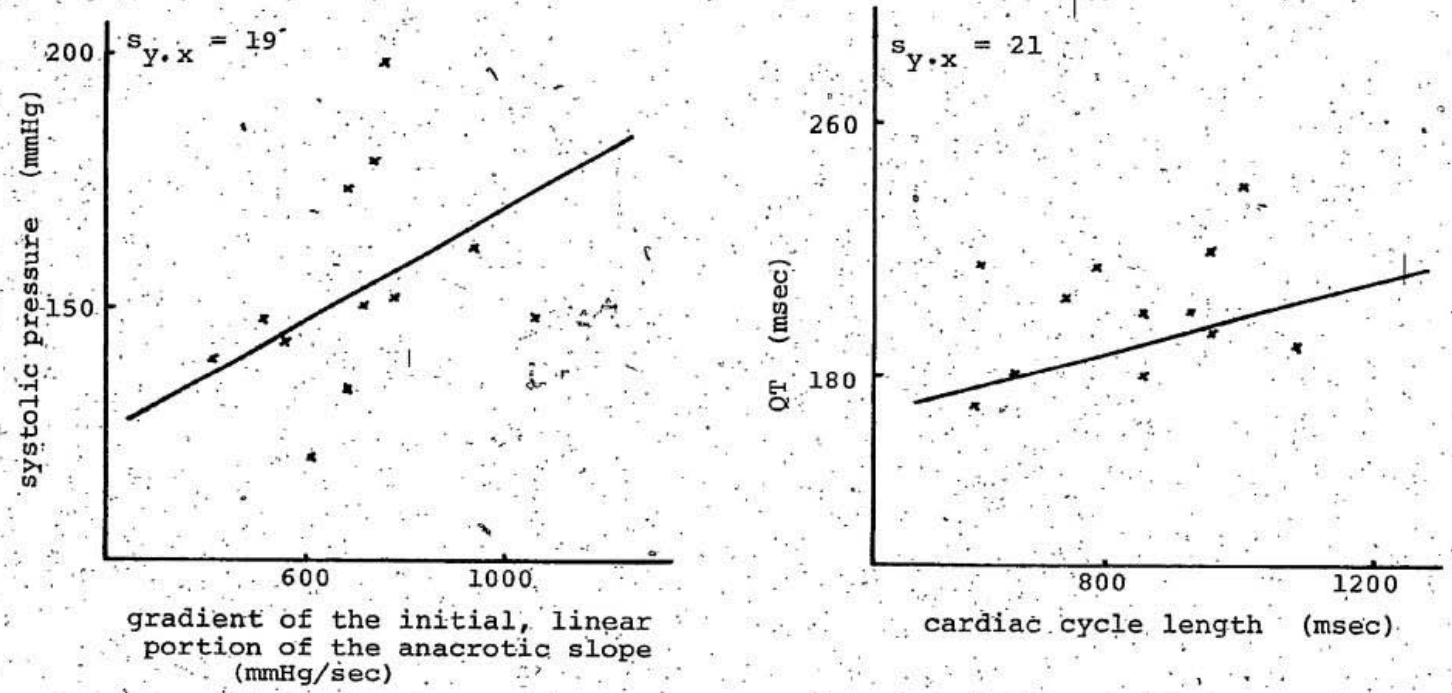


Figure 31a. Graphs showing the position of members of the main group who had a nonfatal myocardial infarction in the follow-up period for two of the four relationships selected as having the most potential to be useful in cardiovascular epidemiology. No significant clustering was seen.

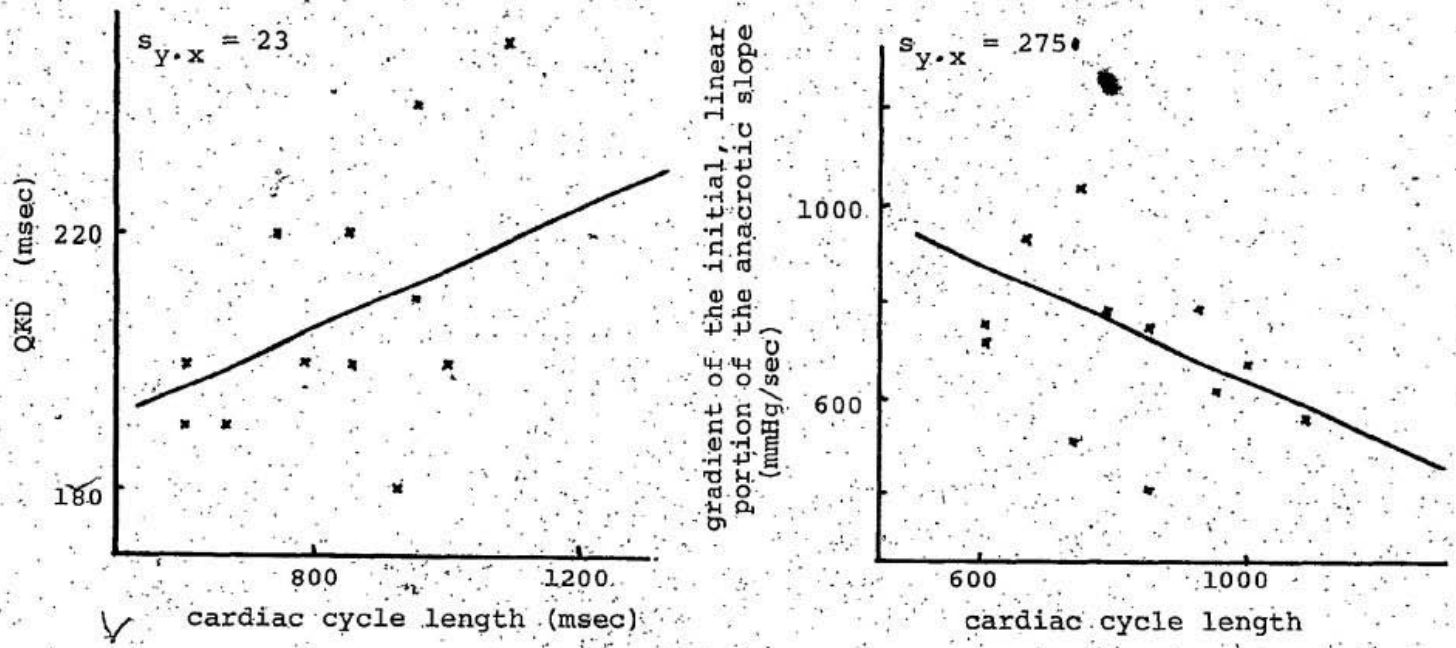


Figure 31b. Graphs showing the position of members of the main group who had a nonfatal myocardial infarction in the follow-up period for two of the four relationships selected as having the most potential to be useful in cardiovascular epidemiology. No significant clustering was seen.

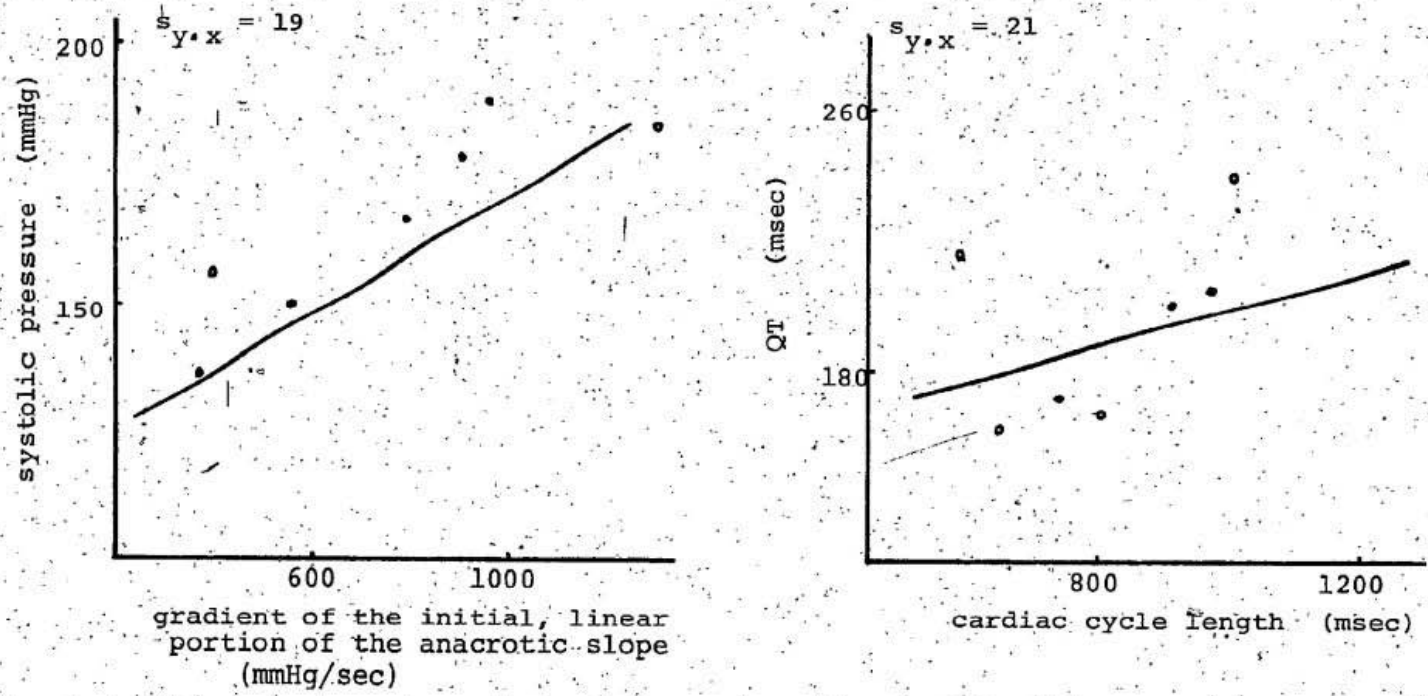


Figure 32a. Graphs showing the position of members of the main group who had a nonfatal stroke in the follow-up period for two of the four relationships selected as having the most potential to be useful in cardiovascular epidemiology. No significant clustering was seen for QT as a function of cardiac cycle length. However, the relative risk of having a stroke was significantly higher ($P<.03$) for those members of the main group who lay above the regression line of systolic pressure as a function of the gradient of the initial, linear portion of the anacrotic slope.

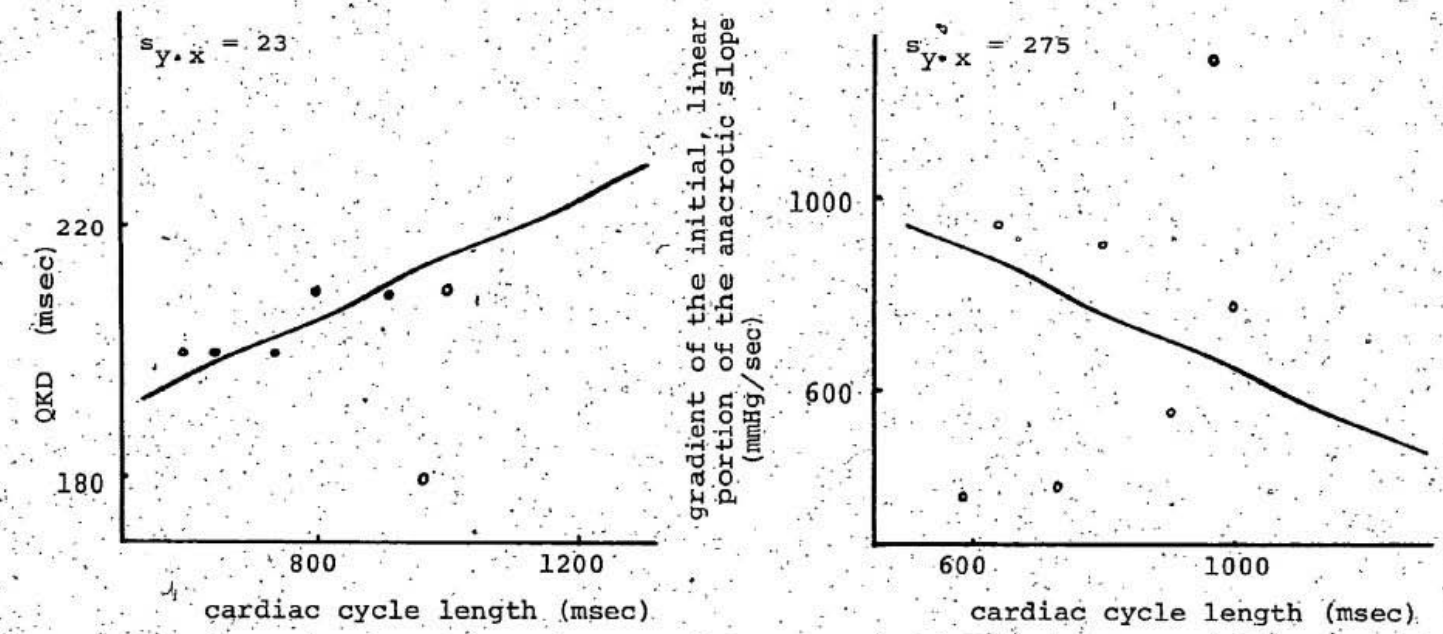


Figure 32b. Graphs showing the position of members of the main group who had a nonfatal stroke in the follow-up period for two of the four relationships selected as having the most potential to be useful in cardiovascular epidemiology. No significant clustering was seen.

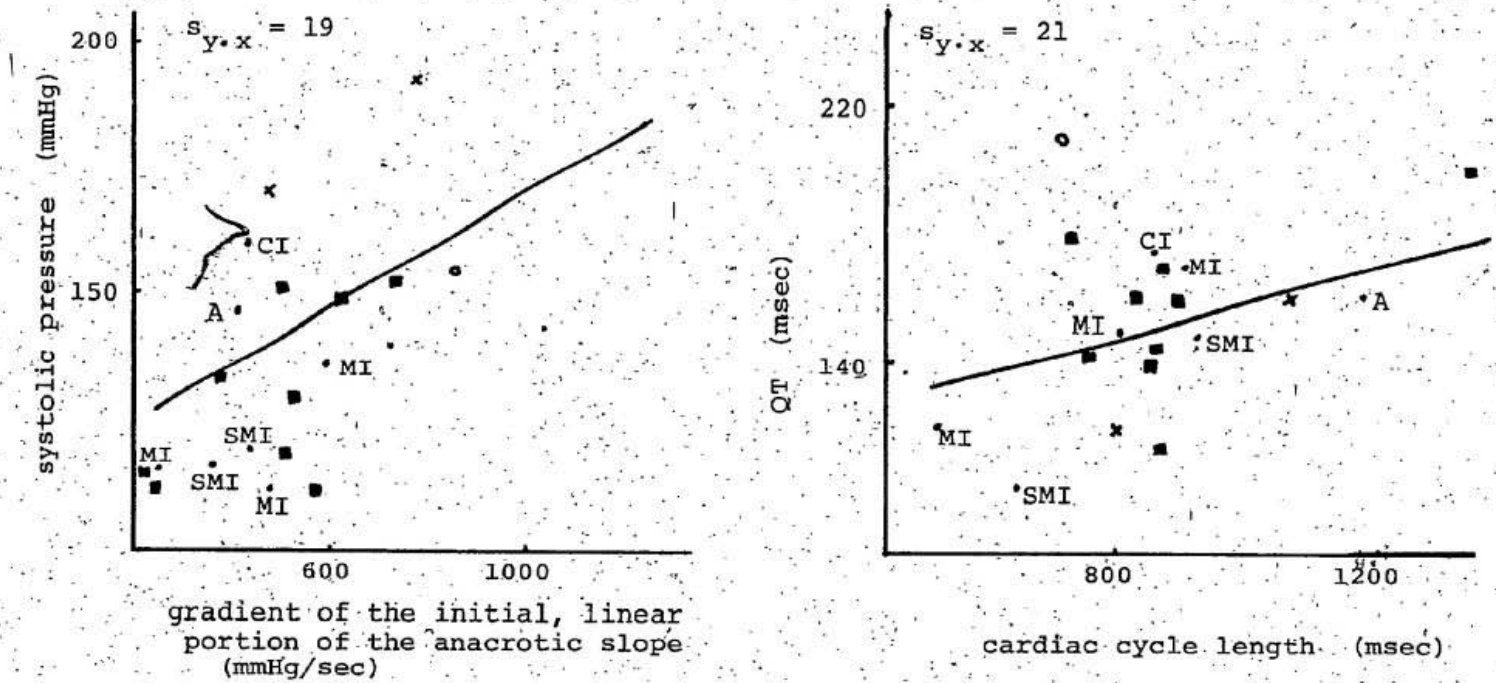


Figure 33a. The position of members of the post-MI group is given for two of the four relationships selected as having the most potential to be useful in cardiovascular epidemiology. No significant clustering was seen.

Cardiovascular history in the follow-up period:

■	no event recorded
A	died, arteriosclerosis
CI	died, cardiac insufficiency
MI	died, myocardial infarction
SMI	died, stroke post-MI
×	nonfatal myocardial infarction
o	nonfatal stroke

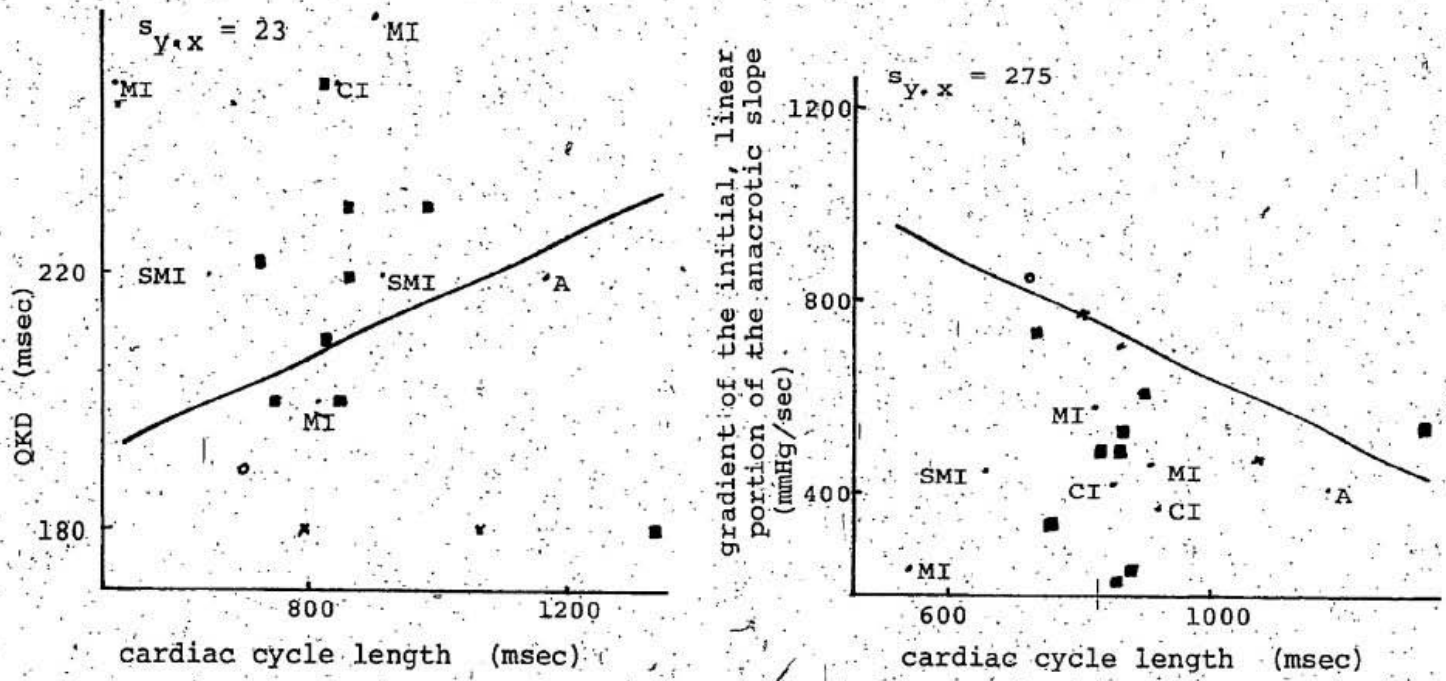


Figure 33b. The position of members of the post-MI group is given for two of the four relationships selected as having the most potential to be useful in cardiovascular epidemiology. No significant clustering was seen.

Cardiovascular history in the follow-up period:

■	no event recorded
A	died, arteriosclerosis
CI	died, cardiac insufficiency
MI	died, myocardial infarction
SMI	died, stroke post-MI
x	nonfatal myocardial infarction
•	nonfatal stroke

pressure and the gradient of the initial, linear portion of the anacrotic slope

1) Six of the 7 members of the main group who had nonfatal strokes in the follow-up period lay above the regression line (ie the line that best fitted the data points for the main group as a whole), and the seventh member lay almost on, but just below, the line (figure 32a, p 232). This clustering was examined for statistical significance by calculating the incidence of nonfatal strokes in the follow-up period for the 67 members of the main group who lay above the regression line and for the 85 members who lay below it. It was found that the relative risk of a nonfatal stroke was 7.5 times greater for those members of the main group who lay above the regression line (Pearson chi-square, $P<.03$). The same relationship could not be examined in the post-MI group because only one member of this group suffered a nonfatal stroke in the follow-up period (figure 33a, p 234).

2) Of the 7 members of the post-MI group who had a subsequent myocardial infarction in the follow-up period, the 5 who died lay in the area where systolic pressure was below 140 mmHg and the gradient of the initial, linear portion of the anacrotic slope was below 600 mmHg/sec, and the 2 who survived lay outside this area (figure 33a, p 234).

2. Discussion

As can be seen from the clustering on the graphs only one of the four pairs of variables concluded in Chapter III to be potentially useful in cardiovascular epidemiology was in fact useful: systolic pressure and the gradient of the initial, linear portion of the anacrotic slope.

The finding that the relative risk of a nonfatal stroke in the follow-up period was 7.5 times greater for those members of the main group who lay above the regression line than for those who lay below it can be explained in terms of the increased peripheral resistance deduced in Chapter III to be present in the members of the main group above the regression line (pp 189-91). The increased peripheral resistance causes stronger blood flow to be required for adequate tissue perfusion, and this makes the members above the line more susceptible to inadequate tissue perfusion when cardiac contractility declines. In addition, the increased peripheral resistance generates higher blood pressure in the arteries, and that makes the subjects above the line more susceptible to blood vessel rupture. Both inadequate tissue perfusion and vessel rupture cause strokes when they occur in the brain.

Because of the finding from the graph that of the 7 members of the post-MI group who had myocardial infarctions in the follow-up period, all 5 who died lay within the area

where systolic pressure was below 140 mmHg and the gradient of the initial, linear portion of the anacrotic slope was below 600 mmHg/sec, it was concluded (tentatively, because the numbers were small) that the members of the post-MI group lying within this area were more susceptible to a fatal outcome of a subsequent myocardial infarction than were the members of the group outside this area. This tentative conclusion was supported by the fact that two of the four members of the main group who had fatal myocardial infarctions in the follow-up period lay within this area, whereas all of the eleven who had nonfatal myocardial infarctions lay outside this area. If this finding could be confirmed in a study involving a far greater number of subjects in both the main and the post-MI groups, it could be explained in terms of the reduced cardiac contractility deduced in Chapter III to be associated with below average gradients of the initial, linear portion of the anacrotic slope (and perhaps with the reduced stroke volumes combined with increased peripheral resistance which could be associated with some of the individuals located in this area of the graph [this thesis, p 191]). This reduced cardiac contractility would be reduced even further by a myocardial infarction, and would perhaps reach a point that is not compatible with the sustaining of human life.

Finally, it should be noted that of the pair of variables concluded to be useful in cardiovascular epidemiology,

one (the gradient of the initial, linear portion of the anacrotic slope) is unique to Rodbard's method.

CHAPTER V

CONCLUSIONS

Although it would appear from the literature review that the anacrotic slope of the brachial artery pressure pulse wave when measured by Rodbard's simple noninvasive method is not identical to this slope when measured intra-arterially, it was concluded that the former was a sufficiently close approximation to the latter for the purposes of cardiovascular epidemiology because there was a high level of correlation between the two slopes. (This high level of correlation is most probably due to the fact that the diameter pulse wave responsible for the Korotkoff sounds is closely related to the intra-arterial pressure pulse wave.)

Factor analysis of the 12 variables used in this thesis to describe the anacrotic slope supported:

1) the conclusions drawn from the examination of the literature that cardiac contractility affects QKD and the gradient of the initial, linear portion of the anacrotic slope, and that pulse wave velocity acts to confound this relationship, particularly with respect to QKD;

2) but to a far lesser extent, the conclusion drawn from the examination of the literature that peripheral resistance affects the duration of the anacrotic slope.

(QKD, the gradient of the initial, linear portion of the anacrotic slope, and the duration of the anacrotic slope are Rodbard variables. Factor analysis did not elucidate which physiological mechanisms affect the other four Rodbard variables.)

Covariance analysis in combination with factor analysis of the twelve variables

1) supported the conclusion drawn from the examination of the literature that it was not necessary to correct QKD for differences in cardiac cycle length. (In fact it was found that it was not necessary to correct any of the Rodbard variables for differences in cardiac cycle length.)

2) allowed the conclusion to be made that the relationship between systolic pressure and the gradient of the initial, linear portion of the anacrotic slope had the potential to be useful in cardiovascular epidemiology because correcting the former variable for its relationship with the latter provided a simple noninvasive estimate of peripheral resistance.

The analysis of the relationship between cardiovascular mortality and morbidity in the follow-up period and the 12 variables used in this thesis to describe the anacrotic slope supported the conclusions drawn from the examination of the literature that QKD, the gradient of the initial, linear portion of the anacrotic slope, and the duration of the anacrotic slope are not by themselves useful in

screening populations for cardiovascular disease. Similarly it was concluded that none of the remaining nine variables taken individually, nor the factor scores generated during factor analysis, was useful in screening populations for cardiovascular disease. However, the analysis of the relationship between cardiovascular mortality and morbidity in the follow-up period and the four pairs of variables which covariance analysis revealed as having the potential to be useful in cardiovascular epidemiology led to the conclusion that one of these pairs did in fact have this usefulness. Estimating peripheral resistance by correcting systolic pressure for differences in the gradient of the initial, linear portion of the anacrotic slope (a Rodbard variable) was found to be useful in detecting individuals at risk of having a stroke. The relative risk of a stroke was 7.5 times greater ($P \leq .03$) in those individuals whose peripheral resistance estimated in this way was greater than the mean of the main group. This compared with relative risks of 1.75, 1.38, and 1.05 where the systolic pressure, the diastolic pressure, and the pulse pressure, respectively, were greater than the mean of the main group. Therefore it would appear that the estimate of peripheral resistance obtained by correcting systolic pressure for differences in the Rodbard variable, the gradient of the initial, linear portion of the anacrotic slope, is more useful than blood pressure alone in detecting individuals at

risk of having a stroke. However, this finding needs to be repeated.

Because Rodbard's method produces only the anacrotic slope of the brachial artery pressure pulse wave, serious consideration should be given to the development of simple, foolproof, noninvasive techniques for monitoring the entire brachial artery pressure and flow waves. The examination of the literature led to the conclusion that visualising the entire waves would provide valuable additional information. Most importantly, it would allow the following:

1) a study of the time of arrival at the heart of cephalic and caudal reflected waves. Because of the eccentric position of the heart and because of the arch-like shape of the aorta, both these waves can be expected to have important positive effects on blood flow to the heart in late systole and diastole if pulse wave velocity is normal;

2) classification of pressure and flow wave types so that they could be studied in an attempt to identify individuals at risk of cardiovascular disease;

3) a study of the relationship between the cephalic and caudal reflected waves and the genesis of the Korotkoff sounds. Such a study would almost certainly lead to a deeper understanding of the nature of Korotkoff sounds, the observation of which forms the basis of what is now the most widely used method of determining blood pressure.

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APPENDICES

Appendix A. Means and standard deviations of the variables of the St John's and Göteborg subjects in the younger group.

Variable	St John's	Göteborg	Pooled standard deviation
SP (mmHg)	117	122	11
DP (mmHg)	66	65	10
PP (mmHg)	52	57	9
QT (msec)	201	194	25
G (mmHg/sec)	664	684	138
ET (msec)	57	63	16
RR (msec)	894	892	160
QKD (msec)	194	214	18
D (msec)	121	117	29
NT (msec)	46	37	28
NP (mmHg)	13	13	7
NA (mmHg·msec)	229	192	175
Subjects	9	10	

QKD is significantly longer in the Göteborg subjects ($P<.05$)

Appendix B. Data extracted from the records of the main group.

ID	SP	DP	PP	QT	G	LT	RR	QKD	D	NT	NP	NA	
1	97	72	25	190	172	94	1277	250	250	232	5	234	A
2	180	113	67	190	813	66	833	200	100	50	13	260	BC
3	148	90	58	185	790	72	714	170	90	34	5	55	B
4	130	102	26	200	346	60	625	180	100	26	6	54	AC
5	140	84	56	240	552	65	1000	220	240	138	23	658	AC
6	120	80	40	195	618	40	952	240	80	25	11	66	BC
7	137	88	49	200	518	100	714	240	100	4	1	8	BC
8	147	95	53	195	510	66	741	220	130	31	18	176	AC
9	179	101	78	215	733	100	606	200	140	35	6	76	BC
10	136	90	46	215	367	80	594	200	140	41	10	138	AC
11	142	85	57	190	563	56	1090	250	210	122	19	668	AC
12	198	107	91	200	757	82	857	220	180	85	13	380	BC
13	134	65	69	200	685	78	923	180	120	29	10	113	BC
14	150	100	50	175	715	58	606	190	90	23	8	53	AC
15	140	106	34	180	411	57	857	200	180	103	9	264	AC
16	176	90	86	240	690	90	1000	200	240	109	30	1300	BC
17	170	86	84	180	565	120	923	200	230	87	15	368	BC
18	189	110	79	160	930	42	645	200	160	85	32	1025	AC
19	178	118	60	165	900	40	800	210	110	51	19	288	AC
20	150	91	59	200	554	88	909	210	190	94	6	155	BC
21	130	77	53	180	517	50	698	220	190	118	12	280	A
22	150	90	60	165	818	50	698	180	100	29	21	256	B
23	141	95	46	190	689	30	645	200	120	65	19	432	A
24	150	85	65	185	714	58	822	200	120	36	20	334	B
25	142	94	48	185	630	66	870	210	110	37	6	41	A
26	135	74	61	195	723	68	870	200	130	583	8	108	B
27	128	89	39	170	470	70	822	210	90	12	5	15	A
28	118	73	45	185	628	54	845	240	110	49	6	102	B
29	134	77	57	195	620	97	810	240	100	1	1	1	A
30	140	82	58	200	639	74	759	190	90	12	4	8	B
31	142	85	57	175	589	78	769	190	150	62	7	10	A
32	141	93	48	170	668	58	800	220	100	35	6	54	B
33	146	90	56	190	781	64	769	240	110	37	9	119	A
34	149	84	65	160	800	60	800	180	190	115	15	490	B
35	146	108	38	170	615	54	759	240	210	150	5	142	A
36	126	85	41	215	418	80	800	260	130	39	6	53	B
37	120	89	31	150	393	68	741	240	100	22	5	29	A
38	138	73	65	160	731	76	706	190	160	78	6	150	B

Membership in the random A, random B and C subgroups is indicated by A, B, and C respectively.

Appendix B (continued). Data extracted from the records of the main group.

ID	SP	DP	PP	QT	G	LT	RR	QKD	D	NT	NP	NA	
39	146	94	52	175	389	100	741	200	210	75	13	380	A
40	125	86	39	190	471	70	741	240	70	1	1	1	B
41	135	83	52	170	598	110	882	180	120	16	1	10	A
42	143	82	61	190	521	100	1154	200	130	18	8	64	B
43	120	74	46	240	538	55	1034	230	140	59	15	235	A
44	118	71	47	200	564	90	1000	210	90	5	1	1	B
45	123	78	45	200	494	60	1000	220	90	11	11	59	A
46	100	67	33	230	433	80	870	220	80	2	1	1	B
47	124	73	51	195	761	48	1000	220	100	37	13	213	A
48	125	81	44	170	372	100	852	220	120	9	5	22	B
49	125	83	42	190	447	120	1000	260	140	52	5	80	A
50	138	85	53	160	604	52	857	220	170	101	24	702	B
51	130	74	66	195	694	64	882	220	130	52	11	160	B
52	115	67	48	190	534	64	882	240	150	66	12	153	A
53	130	83	47	180	541	64	1000	240	130	52	9	169	B
54	128	81	47	195	570	70	870	220	90	12	5	184	A
55	120	76	44	190	447	94	968	220	100	7	1	31	B
56	126	85	41	170	451	80	882	240	80	1	1	1	A
57	150	90	60	200	664	73	952	220	130	36	16	221	B
58	142	73	69	265	1250	30	952	190	120	70	28	476	A
59	140	75	65	190	545	102	870	200	160	48	7	97	A
60	127	72	55	215	636	62	967	220	180	99	13	418	B
61	130	74	56	180	525	90	967	210	150	52	6	138	A
62	144	90	54	190	451	84	870	220	180	69	14	394	B
63	150	93	47	230	431	83	1000	220	260	168	4	493	A
64	146	75	71	220	1023	51	1090	220	130	66	15	265	B
65	125	81	44	180	526	56	870	220	180	98	15	362	A
66	120	88	32	195	237	100	833	240	120	22	7	179	B
67	120	93	27	200	289	70	967	260	140	48	8	124	A
68	152	83	69	150	924	62	714	210	190	112	16	651	B
69	139	114	25	205	524	40	857	220	80	35	5	49	B
70	140	64	76	200	680	74	823	190	210	106	23	531	A
71	125	78	47	195	736	61	706	210	90	26	4	30	B
72	160	76	84	190	997	56	800	180	150	77	19	412	A
73	154	88	66	215	781	56	789	200	120	45	17	224	AC
74	151	90	61	190	435	110	939	210	270	141	10	258	B
75	157	90	67	180	1000	66	870	190	90	23	3	22	A
76	124	71	53	195	602	80	1090	200	110	24	5	37	B

Membership in the random A, random B and C subgroups is indicated by A, B, and C respectively.

Appendix B (continued). Data extracted from the records of the main group.

ID	SP	DP	PP	QT	G	LT	RR	QKD	D	NT	NP	NA	
77	130	80	50	185	527	90	870	210	90	4	7	1	B
78	157	74	83	170	918	70	723	180	120	45	8	78	A
79	163	82	81	180	1024	66	759	180	220	143	14	454	A
80	165	87	78	165	1111	54	612	170	110	41	19	357	B
81	165	93	72	230	776	68	1000	210	160	171	18	1055	BC
82	163	90	73	180	936	50	666	190	150	81	21	402	AC
83	165	86	79	195	941	72	870	180	120	41	9	137	A
84	136	90	46	160	573	70	690	170	130	49	8	139	B
85	157	89	68	180	993	52	800	190	200	131	20	1018	A
86	150	83	67	180	749	63	732	200	120	51	6	63	B
87	149	96	45	180	877	50	882	220	200	141	10	471	A
88	157	98	59	190	477	72	800	210	370	255	22	1045	B
89	188	121	67	190	875	56	723	200	180	117	9	254	A
90	191	93	98	180	1202	62	909	180	180	109	12	529	B
91	168	95	72	195	820	76	984	170	160	51	12	231	A
92	180	102	78	160	1086	68	706	210	100	31	4	33	B
93	175	102	73	190	833	72	645	210	110	29	10	121	A
94	161	103	58	190	419	125	612	220	150	22	3	12	B
95	159	96	63	175	758	70	750	180	130	51	8	143	A
96	156	106	51	170	394	80	732	200	150	44	12	221	BC
97	200	105	95	200	1061	46	882	190	250	172	36	1671	B
98	183	110	73	170	723	66	822	190	150	56	22	401	A
99	186	112	74	175	1012	53	632	200	120	59	10	119	B
100	212	113	99	225	1136	46	882	200	280	206	34	2943	A
101	170	87	83	160	1085	70	750	170	170	97	8	113	A
102	177	76	101	200	822	110	631	180	110	1	1	1	B
103	184	92	92	205	1284	33	967	180	250	84	45	3087	AC
104	178	92	86	215	560	113	1200	180	240	72	33	908	B
105	190	93	97	160	1164	56	550	180	160	93	14	310	A
106	182	52	130	210	1700	64	800	200	140	71	11	296	B
107	210	122	88	200	1290	56	714	180	100	40	6	70	A
108	204	120	84	190	856	58	789	200	170	88	23	784	B
109	174	102	72	195	670	98	779	180	130	30	2	10	A
110	170	100	70	210	666	52	1053	220	220	104	31	1792	B
111	175	110	65	180	941	50	937	210	120	60	20	496	B
112	175	100	75	200	880	60	923	190	210	131	18	981	A
113	187	96	91	210	1525	56	983	180	160	92	20	542	A
114	148	104	44	220	1042	50	952	210	50	9	1	33	BC

Membership in the random A, random B and C subgroups is indicated by A, B, and C respectively.

Appendix B (continued). Data extracted from the records of the main group.

ID	SP	DP	PP	QT	G	LT	RR	QKD	D	NT	NP	NA	
115	173	100	73	190	673	94	811	200	230	123	10	277	A
116	168	100	68	185	618	78	858	200	180	82	14	313	B
117	228	120	108	165	1068	80	588	170	170	75	17	444	A
118	178	115	63	220	462	90	938	210	370	243	18	1211	A
119	167	101	66	190	1064	44	666	210	110	58	12	152	B
120	186	98	88	180	1096	53	659	180	180	114	16	368	B
121	184	102	82	150	1344	34	645	190	130	79	24	555	A
122	173	101	72	160	674	67	682	200	200	98	26	713	B
123	168	87	81	170	1010	64	741	160	240	165	13	220	A
124	190	83	107	180	1475	47	800	170	180	117	26	493	A
125	192	101	91	180	943	50	857	200	220	136	34	1501	B
126	160	102	58	185	643	50	810	200	160	84	18	414	B
127	197	100	97	195	575	66	1132	190	230	115	39	2274	A
128	168	75	93	165	1466	54	714	170	100	39	11	154	A
129	184	108	76	260	854	76	984	170	130	45	9	128	B
130	177	90	87	195	1160	48	759	210	120	51	26	464	B
131	186	104	82	215	834	82	810	200	140	59	1	39	A
132	167	104	63	210	670	60	789	210	210	124	18	680	A
133	170	95	75	195	1267	44	652	170	130	78	13	221	B
134	180	89	91	210	1156	56	566	170	110	41	15	193	B
135	196	110	86	260	840	60	698	180	120	54	10	165	A
136	235	125	110	235	1613	30	659	170	230	163	30	1713	B
137	159	102	57	220	636	48	983	210	190	109	22	1087	A
138	165	107	58	220	489	50	770	240	120	31	7	159	A
139	157	104	53	185	576	48	706	240	180	99	21	671	BC
140	150	105	45	150	616	72	619	220	110	31	7	91	B
141	194	116	78	170	1374	35	652	210	150	101	21	644	A
142	178	120	58	220	665	58	833	240	260	187	11	729	B
143	125	111	17	200	508	18	800	260	90	36	10	119	A
144	158	104	54	230	488	68	923	220	240	136	20	907	B
145	135	106	29	180	554	30	833	220	80	32	11	157	A
146	170	80	90	235	935	78	583	240	130	47	16	235	B
147	161	116	45	165	659	58	723	250	110	39	9	117	A
148	175	125	50	205	587	83	674	240	120	37	2	20	A
149	170	114	56	250	517	72	938	230	210	108	17	336	B
150	193	135	58	205	535	58	968	300	240	140	23	1281	B
151	155	100	55	190	695	60	833	190	210	129	16	715	A
152	156	90	66	185	678	68	833	200	180	103	15	434	B

Membership in the random A, random B and C subgroups is indicated by A, B, and C respectively.

Appendix C. Data extracted from the records of the post-MI group.

ID	SP	DP	PP	QT	G	LT	RR	QKD	D	NT	NP	NA
153	154	98	56	220	735	50	732	225	155	81	23	693
154	120	80	40	140	451	80	652	220	120	28	6	52
155	116	85	31	180	237	98	857	250	160	30	9	77
156	112	95	17	155	250	48	870	230	110	43	6	75
157	194	105	89	160	760	70	800	180	240	135	29	1330
158	112	50	62	240	569	86	1429	180	170	53	15	265
159	120	75	45	200	504	68	833	210	100	14	10	57
160	161	101	60	215	427	105	857	250	170	42	11	169
161	118	69	49	190	378	107	923	220	150	28	7	78
162	155	81	74	250	845	72	714	190	160	73	15	262
163	116	95	21	160	250	62	531	240	100	27	4	268
164	135	94	41	185	357	80	759	200	90	1	1	1
165	136	78	58	190	592	60	822	200	260	165	21	700
166	146	92	54	200	414	92	1176	220	220	91	17	540
167	150	84	66	200	619	76	896	230	160	73	13	337
168	151	89	62	185	506	84	857	200	260	135	21	1200
169	112	75	37	210	474	58	909	260	100	25	9	122
170	170	85	85	200	477	132	1071	180	220	41	23	400
171	130	82	48	210	535	66	870	220	100	18	10	65

Appendix D. Data extracted from the records of the younger group.

ID	SP	DP	PP	QT	G	LT	RR	QKD	D	NT	NP	NA	AGE
172	125	78	47	175	521	58	769	200	170	85	17	360	45
173	131	54	77	200	946	52	732	180	140	63	26	666	20
174	108	66	42	235	446	58	1132	200	120	32	15	164	29
175	144	91	53	190	667	56	769	190	150	81	12	246	51
176	105	57	48	175	618	78	833	170	80	3	2	1	9
177	101	61	40	210	502	64	1176	220	80	6	7	22	14
178	114	59	55	180	838	46	750	190	140	78	15	204	13
179	120	60	60	170	806	58	732	180	110	41	13	234	11
180	109	64	45	270	635	44	1154	220	90	27	15	168	36
181	110	56	54	210	657	78	1053	240	110	22	9	52	14
182	117	59	58	200	630	78	896	210	110	21	9	49	28
183	122	59	63	215	781	40	1034	240	120	49	25	416	32
184	113	61	52	195	708	43	1034	200	100	28	22	296	34
185	129	63	66	200	796	60	909	220	140	69	10	225	24
186	123	72	51	195	595	55	750	210	90	19	11	90	27
187	116	57	59	185	778	52	769	210	110	22	15	247	33
188	134	75	59	190	732	79	870	220	80	2	2	1	38
189	130	77	53	170	712	45	750	210	150	79	21	422	34
190	124	73	51	180	452	102	857	180	160	59	10	128	42

The records of subjects ID #172-180 were obtained in St John's, those of subjects ID #181-190 were obtained in Göteborg.

Appendix E. a) The factor loading pattern of the main group.

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
SP	.686	.287	.636	-.082	.072
DP	-.034	.154	.946	-.130	-.003
PP	.916	.250	.117	-.016	.093
QT	.009	.024	.081	.024	.915
G	.825	-.011	.078	-.429	-.037
LT	-.066	-.030	-.125	.950	.080
RR	-.299	.339	-.433	.060	.586
QKD	-.819	-.023	.094	.054	.182
D	.051	.914	.124	.163	.113
NT	.040	.801	.012	-.005	-.091
NP	.311	.659	.086	-.500	.176
NA	.196	.761	.156	-.350	.258
Rank	1	2	3	4	5

Appendix E. b) The factor loading pattern of the random A subgroup.

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
SP	.705	.246	.583	-.133	
DP	-.020	.116	.933	-.138	
PP	.925	.217	.086	-.083	
QT	-.161	.317	-.232	-.241	
G	.831	-.048	.128	-.357	
LT	-.076	.122	-.187	.901	
RR	-.333	.471	-.619	-.053	
QKD	-.871	-.001	-.002	-.053	
D	.084	.949	.000	.082	
NT	.106	.860	.080	.014	
NP	.389	.492	-.087	-.687	
NA	.248	.711	.001	-.496	
Rank	1	2	4	3	

Appendix E. c) The factor loading pattern of the random B subgroup.

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
SP	.635	.352	.654	-.052	.089
DP	-.086	.245	.895	-.117	-.012
PP	.900	.271	.153	.021	.127
QT	.060	.007	.115	.020	.907
G	.824	-.013	.077	-.501	.051
LT	-.072	-.140	-.121	.963	.069
RR	-.302	.353	-.358	.102	.601
QKD	-.760	-.031	.189	-.063	.282
D	.061	.861	.251	.252	.096
NT	.047	.748	-.104	-.114	-.064
NP	.239	.752	.306	-.236	.104
NA	.141	.801	.356	-.185	.216
Rank	2	1	3	4	5

Appendix E. d) The factor loading pattern of the C subgroup.

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
SP	.903	-.043	.361	-.011	
DP	.288	-.254	.766	-.115	
PP	.936	.120	-.060	.066	
QT	.144	.037	-.798	.076	
G	.684	-.213	-.005	-.531	
LT	.028	.135	-.217	.944	
RR	-.160	.716	-.431	-.120	
QKD	-.509	.576	.116	.027	
D	.325	.837	-.230	.092	
NT	.073	.890	-.025	.080	
NP	.650	.399	-.020	-.539	
NA	.618	.444	-.181	-.510	
Rank	1	2	4	3	

Appendix E. e) The factor loading pattern of the post-MI group.

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
SP	.476	.586	.541	.350	
DP	-.149	.181	.912	.030	
PP	.675	.588	.046	.403	
QT	.786	-.101	-.388	.061	
G	.844	.434	.054	-.235	
LT	-.004	.007	-.127	.967	
RR	.121	.191	-.757	.416	
QKD	-.412	-.516	.212	-.199	
D	.052	.919	-.057	.297	
NT	.080	.943	.036	-.191	
NP	.395	.859	.053	.101	
NA	.095	.931	.224	-.064	
Rank	2	1	3	4	

Appendix E. f) The factor loading pattern of the younger group.

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
SP	.483	.081	.835		-.125
DF	-.284	-.097	.896		-.035
PP	.921	.209	.057		-.118
QT	-.262	.167	-.249		.778
G	.890	.327	-.127		-.068
LT	-.156	-.762	.088	with factor 2	-.269
RR	-.462	-.018	-.364		.724
QKD	.115	-.047	.051		.885
D	-.027	.513	.619		-.420
NT	.045	.629	.615		-.324
NP	.165	.943	.021		.049
NA	.351	.863	.178		-.149
Rank	3	1	2		4

Appendix F. a) The percentage of the variation of each variable that was explained by the extracted factors of the main group.

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
SP	47		40		
DP			89		
PP	84				
QT					84
G	68				
LT				90	
RR					34
QKD	67				
D		83			
NT		64			
NP		43		25	
NA		58			

Appendix F. b) The percentage of the variation of each variable that was explained by the extracted factors of the random A subgroup.

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
SP	50		34		
DP			87		
PP	85				
QT					
G	69				
LT				81	
RR			38		
QKD	76				
D		90			
NT		74			
NP		25		47	
NA		50		30	

Appendix F. c) The percentage of the variation of each variable that was explained by the extracted factors of the random B subgroup.

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
SP	40		43		
DP			80		
PP	81				
QT					82
G	68			25	
LT				93	
RR					36
QKD	58				
D		74			
NT		56			
NP		56			
NA		64			

Appendix F. d) The percentage of the variation of each variable that was explained by the extracted factors of the C subgroup.

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
SP	81		13		
DP			59		
PP	88				
QT			64		
G	47			28	
LT				89	
RR		51			
QKD	26	33			
D		70			
NT		79			
NP	42	16		29	
NA	38	21		26	

Appendix F. e) The percentage of the variation of each variable that was explained by the extracted factors of the post-MI group.

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
SP	23	34	29		
DP			83		
PP	46	35			
QT	62				
G	71				
LT				93	
RR			57		
QKD	17	26			
D		84			
NT		89			
NP		74			
NA		87			

Appendix F. f) The percentage of the variation of each variable that was explained by the extracted factors of the younger group.

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
SP	23		70		
DP			80		
PP	85				
QT					60
G	79				
LT		58			
RR					52
QKD					78
D		26	38		
NT		40	38		
NP		89			
NA		74			

Appendix G. a) Gives the factor loading pattern for both varimax orthogonal and quatimin oblique rotation to allow comparison of the factors provided by the two methods of rotation for the main group.

Variable	Factor 1		Factor 2		Factor 3		Factor 4		Factor 5	
	V	Q	V	Q	V	Q	V	Q	V	Q
SP	.686	.608	.287	.172	.636	.598	-.082	.022	.072	.117
DP	-.034	-.175	.154	.088	.946	.964	-.130	-.059	-.003	.025
PP	.916	.920	.250	.149	.117	.054	-.016	.067	.093	.132
QT	.009	.035	.024	-.139	.081	.075	.024	.052	.915	.947
G	.825	.794	-.011	-.121	.078	-.001	-.429	-.377	-.037	.010
LT	-.066	.061	-.030	.048	-.125	-.052	.950	.969	.080	.089
RR	-.299	-.249	.339	.310	-.433	-.443	.060	.023	.586	.534
QKD	-.819	-.858	-.023	.009	.094	.142	.054	-.106	.182	.145
D	.051	.003	.914	.926	.124	.101	.163	.197	.113	.038
NT	.040	-.015	.801	.839	.012	-.020	-.005	.008	-.091	-.169
NP	.311	.219	.659	.575	.086	.005	-.500	-.474	.176	.133
NA	.196	.106	.761	.684	.156	.091	-.350	-.319	.258	.206

V = Varimax; Q = Quatimin

Appendix G. b) Gives the factor loading pattern for both varimax orthogonal and quatimin oblique rotation to allow comparison of the factors provided by the two methods for the C subgroup.

Variable	Factor 1		Factor 2		Factor 3		Factor 4		Factor 5	
	V	Q	V	Q	V	Q	V	Q	V	Q
SP	.903	.928	-.043	-.000	.361	.331	-.041	-.008		
DP	.288	.321	-.254	-.146	.766	.750	-.115	-.090		
PP	.936	.945	.120	.102	-.060	-.085	.066	.053	with	with
QT	.144	.092	.037	-.087	-.798	-.821	.076	.045	factor	factor
G	.684	.524	-.213	-.248	-.005	-.068	-.531	-.560	3	3
LT	.028	.282	.135	.140	-.217	-.183	.944	.971		
RR	-.160	-.227	.716	.659	-.431	-.374	-.120	-.144		
QKD	-.509	-.483	.576	.613	.116	.193	.027	.036		
D	.325	.335	.837	.815	-.230	-.169	.092	.077		
NT	.073	.101	.890	.904	-.025	.056	.080	.077		
NP	.650	.491	.399	.373	-.020	-.026	-.539	-.572		
NA	.618	.454	.444	.395	-.181	-.185	-.510	-.548		

V = Varimax; Q = Quatimin

Appendix G. c) Gives the factor loading pattern for both varimax orthogonal and quatimin oblique rotation to allow comparison of the factors provided by the two methods of rotation for the post-MI group.

Variable	Factor 1		Factor 2		Factor 3		Factor 4		Factor 5	
	V	Q	V	Q	V	Q	V	Q	V	Q
SP	.476	.414	.586	.340	.541	.625	.350	.366		
DP	-.149	-.161	.181	.056	.912	.912	.030	.090		
PP	.675	.607	.588	.373	.046	.148	.403	.382		
QT	.786	.848	-.101	-.258	-.388	-.268	.061	.031	with factor 1	with factor 1
G	.844	.864	.434	.260	.054	.127	-.235	-.273		
LT	-.004	-.085	.007	-.118	-.127	-.031	.967	.995		
RR	.121	.043	.191	.250	-.757	-.737	.416	.365		
QKD	-.412	-.342	-.516	-.449	.212	.175	-.199	-.158		
D	.052	-.113	.919	.934	-.057	-.090	.297	.255		
NT	.080	-.045	.943	1.000	.036	-.043	-.191	-.247		
NP	.395	.286	.859	.785	.053	.060	.101	.058		
NA	.095	-.030	.931	.937	.224	.168	-.064	-.101		

V = Varimax; Q = Quatimin

Appendix G. d) Gives the factor loading pattern for both varimax orthogonal and quatimin oblique rotation to allow comparison of the factors provided by the two methods for the younger group.

Variable	Factor 1		Factor 2		Factor 3		Factor 4		Factor 5	
	V	Q	V	Q	V	Q	V	Q	V	Q
SP	.483	.478	.081	.002	.835	.834			-.125	.048
DP	-.284	-.290	-.097	-.077	.896	.937			-.035	.075
PP	.921	.922	.209	.088	.057	.010			-.118	-.023
QT	-.262	-.256	.167	.220	-.249	-.142	with factor 2	with factor 2	.778	.743
G	.890	.879	.327	.218	-.127	-.184			-.068	-.005
LT	-.156	.075	-.762	-.770	.088	.129			-.269	-.263
RR	-.462	-.441	-.018	.058	-.364	-.250			.724	.652
QKD	.115	.166	-.047	-.056	.051	.208			.885	.946
D	-.027	-.120	.513	.519	.619	.516			-.420	-.359
NT	.045	-.056	.629	.630	.615	.516			-.324	-.255
NP	.165	.049	.943	.951	.021	-.073			.049	.046
NA	.351	.242	.863	.839	.178	.064			-.149	-.114

V = Varimax; Q = Quatimin

Appendix H. Correlation between the quatimin oblique factors for the main group, the C subgroup, the post-MI group, and the younger group.

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Main group					
Factor 1	1.000				
2	.153	1.000			
3	.212	-.123	1.000		
4	-.212	-.132	-.189	1.000	
5	-.054	.254	-.018	-.048	1.000
C subgroup			(3+-5)		
Factor 1	1.000				
2	.003	1.000			
3+-5	.042	.240	1.000		
4	-.267	-.023	.048	1.000	
Post-MI group					
Factor 1	1.000				
2	.361	1.000			
3	-.102	.202	1.000		
4	.171	.204	-.137	1.000	
Younger group					
Factor 1	1.000				
2+-4	.258	1.000			
3	.070	.124	1.000		
5	.156	-.044	-.309		1.000

Appendix I. Means and standard deviations of the variables for the four groups.

	Main group	C subgroup	Post-MI group	Younger group
SP (mmHg)	156± 25.6	154± 22.8	137± 23.2	120± 11.0
DP (mmHg)	93± 14.7	94± 12.2	85± 12.8	65± 9.7
PP (mmHg)	63± 19.7	60± 18.3	52± 19.2	54± 8.8
QT (msec)	192± 22.7	197± 20.9	194± 28.0	197± 24.4
G (mmHg/sec)	743±286.4	666±238.3	494±169	675±135.2
LT (msec)	67± 19.9	68± 21.5	79± 21.3	60± 16.1
RR (msec)	825±138.2	833±169.7	871±194	893±155.6
QKD (msec)	207± 24.2	208± 21.5	216± 24.4	205± 19.8
D (msec)	154± 56.9	158± 59.7	160± 56.4	119± 28.3
NT (msec)	73± 66.1	63± 53.1	58± 45.7	41± 28
NP (mmHg)	13± 8.7	14± 10.1	13± 7.5	13± 6.7
NA (mmHg·msec)	384±501.8	442±630.5	352±385.1	210±171.2

For the three most important Rodbard variables the standard deviations for comparisons within four repeated measurements taken from ten subjects were found to be: G 66 msec, QKD 6 msec and D 38 msec.

Appendix J. The factor score coefficients calculated for the main group and used to calculate the factor scores of the main group and the post-MI group.

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
SP	.18571	-.01019	.36131	.12998	.08906
DP	-.16309	-.02608	.68694	.03114	.02376
PP	.36309	.00265	-.04601	.13970	.09819
QT	.06027	-.19195	.11991	.02738	.77085
G	.28941	-.11277	-.10152	-.22025	.03779
LT	.11675	.06475	.04687	.71369	.05596
RR	-.05508	.10369	-.27636	-.02345	.37143
QKD	-.35695	.00912	.18015	-.13753	.10560
D	-.04538	.39638	.02915	.22471	-.09059
NT	-.06210	.38564	-.07832	.06971	-.24453
NP	.01407	.19080	-.09104	-.28574	.03731
NA	-.02827	.23627	-.00828	-.16615	.07954