NOTICE

The quality of this microfiche is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us a poor photocopy.

Previously copyrighted materials (journal articles, published tests, etc.) are not filmed.

Reproduction in full or in part of this film is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30. Please read the authorization forms which accompany this thesis.

THIS DISSERTATION
HAS BEEN MICROFILMED
EXACTLY AS RECEIVED

AVIS

La qualité de cette microfiche dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de mauvaise qualité.

Les documents qui font déjà l'objet d'un droit d'auteur (articles de revue, examens publiés, etc.) ne sont pas microfilmés.

La reproduction, même partielle, de ce microfilm est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30. Veuillez prendre connaissance des formules d'autorisation qui accompagnent cette thèse.

LA THÈSE A ÉTÉ
MICROFILMÉE TELLE QUE
NOUS L'AVONS REÇUE

SYSTOLIC TIME INTERVALS OF THE CARDIAC CYCLE AS AN INDEX OF EARLY CARDIAC INVOLVEMENT IN HYPERTENSIVE AND ISCHEMIC HEART DISEASE

by

Allan George Davison Jost

Submitted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy at Dalhousie University, Halifax, Nova Scotia, October 13, 1976.

Approved by the Members of the Official Examining Committee, appointed by the Faculty of Graduate Studies.

Dr. Gunnar Blomqvist
External Examiner

Dr. George Fodor
External Examiner

Dr. Brian Chandler

Dr. William Eifler

Dr. Robert March

Dr. Larry Weldon

Ex Officio: Dr. D.J. Ecobichon
Department of Pharmacology
Chairman of the Committee

TABLE OF CONTENTS

ABSTRACT

A computer program is developed for the automatic measurement of the principal systolic time intervals (STI) of the cardiac cycle consisting of the left ventricular ejection time (LVET), pre-ejection period (PEP), and electromechanical systole (QS_2) together with heart rate (HR) and the computed ratio PEP/LVET. Statistical distributions of these variables in a large group of normal male subjects are determined for the resting state in the supine and upright positions and immediately after submaximal exercise.

In order to assess the usefulness of these intervals as indices of early cardiac involvement in hypertensive and coronary heart disease, STI were measured in groups of subjects with hypertension, sustained hypertension, hypertensive heart disease, noticeable cardiac enlargement over a 5 year period, cardiac enlargement with hypertension and cardiac enlargement with sustained hypertension; and in groups with exercise ECG S-T depression, angina pectoris, old myocardial infarction, and acute myocardial infarction with and without heart failure. Statistically significant trends were observed in STI in these series, but with the exception of the group with acute infarction, the magnitudes of the differences in STI compared to the normal group were not large enough to permit useful discrimination of the groups from normal. Limited measurement accuracy with the current non-invasive techniques may contribute to the poor discriminatory power of the method. It is concluded that although the use of a computer measurement program makes it practical to measure STI on a large scale, the results do not indicate that STI are sufficiently sensitive indices of early cardiac involvement in either hypertensive or ischemic heart disease.

LIST OF SYMBOLS AND ABBREVIATIONS

A	- covariance matrix computed from a group of normal subjects
A	- also denotes averaged ECG signal
AMI	- denotes group of subjects with acute myocardial infarction
AP	- denotes group of subjects with angina pectoris
CAP	- carotid arterial pulse
CE	- denotes group of subjects with cardiac enlargement
D1	- first derivative of carotid arterial pulse
D2	- second derivative of carotid arterial pulse
D^2	- Mahalanobis generalized statistical distance (squared)
db	- decibel, unit of signal intensity
d.f.	- degrees of freedom
ECG	- electrocardiogram
EML	- electro-mechanical lag
F	- symbol which represents "integrated power function" computed from the phonocardiogram
F	- also denotes a statistical distribution
F	- also denotes female
FM	- frequency modulation
FSV	- filtered spatial velocity
H	- (head), an electrode location used in ECG recording
H_0, H_1, H_2	- denote statistical hypotheses
HHD	- denotes group of subjects with hypertensive heart disease
HR	- heart rate
HT	- denotes group of subjects with hypertension
i	- running index
ICT	- isovolumic contraction time

In - incisura of arterial pulse

IP1 - sample point number corresponding to upstroke in carotid arterial pulse

IP2 - sample point number corresponding to incisura in carotid arterial pulse

IS1 - sample point number corresponding to beginning of first heart sound

IS2 - sample point number corresponding to beginning of second heart sound

j - running index

k - represents number of variables used in statistical calculations

LVET - left ventricular ejection time

M - male

m - meter, unit of length

m^2 - square meter, unit of area

MI - denotes group of subjects with myocardial infarction

ml - milliliter, unit of volume

mm - millimeter, unit of length

mm Hg - millimeters of mercury, unit of pressure

msec. - millisecond, unit of time

N,n - sample size

p - probability that the null hypothesis is true

PCG - phonocardiogram

PEP - pre-ejection period

Q - onset of QRS wave of the electrocardiogram

QRS - a wave in the electrocardiogram caused by ventricular depolarization

Q-1 - interval from onset of QRS wave to onset of first Heart sound

Q-P1 - interval from onset of QRS wave to upstroke of carotid arterial pulse

Q-P2 - interval from onset of QRS wave to incisura of carotid arterial pulse

r - correlation coefficient

RHV - relative heart volume, volume of the heart divided by body surface area

RON - variable in computer program representing onset of QRS wave

RR - length of time between consecutive QRS waves in the electrocardiogram

S - represents digitized phonocardiogram

S_1,S1 - first heart sound

S_2,S2 - second heart sound

S_1S_2 - interval between first and second heart sounds

sec - seconds, unit of time

S.D. - standard deviation

SHT - denotes group of subjects with sustained hypertension

SINT - sampling interval

S-T - segment of electrocardiogram between QRS and T waves

STD. - denotes group of subjects with S-T depression

STI - systolic time intervals

t - "Student's t", a statistical distribution

T_o^2 - "Hotelling's T_o^2", a statistical distribution

THR - target heart rate

u - upstroke of the carotid arterial pulse

uVs - micro-volt seconds, unit of area in the voltage-time domain

W - within-groups covariance matrix

X - component of the vectorcardiogram

X - also represents independent variable in a regression analysis

x - also denotes multiplication

Y - component of the vectorcardiogram

Y - also represents dependent variable in a regression analysis

Z - component of the vectorcardiogram

Δ - (delta), denotes change in a variable

Σ - (sigma), denotes summation

μ_j - mean value of variable j for a population

χ^2 - (chi squared), a statistical distribution

% - percent

/ - denotes division

< - less than

° - degrees, unit of angular displacement

$^{-1}$ - (superscript), represents the inverse of a matrix

$\bar{}$ - (overscore), represents mean or average value of a variable

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENTS

I would like to express special thanks to my supervisor, Professor Pentti M. Rautaharju, who suggested the research topic, and whose constant guidance and encouragement made the completion of this thesis possible.

The Helsinki Policemen Project was conducted in collaboration with Dr. Pentti Siltanen and Dr. Kalevi Pyorala, and the East and West Finland Project in collaboration with Dr. Martti Karvonen and Dr. Sven Punsar. The author also wishes to acknowledge the collaboration of Dr. Alessandro Menotti and Dr. Flaminio Fidanza in connection with the field study in Montegiorgio, Italy.

I am indebted to Dr. John Stewart, Dr. Brian Chandler and Dr. George Wang of the Victoria General Hospital for their cooperation in the acute infarction study, and for their help in obtaining catheterization records.

Thanks are due to many members of the staff of the Biophysics Laboratory who were involved in the processing of thousands of records, and especially to Mrs. Farida Hosein, who has somehow managed to keep them all organized. Mr. Paul MacInnis and Mr. John Sherwood were invaluable in overcoming many technical problems and Mrs. Glenda Sherwood obtained all of the records from the acute infarction patients. My thanks go to Mr. Jim Warren for his assistance in developing the logic for the measurement program, and for many helpful statistical discussions.

I am grateful for the efforts of Mrs. Norma Gerogiannis, who worked many long hours typing the manuscript.

During the course of the work, I was supported by several scholarships from the Faculty of Graduate Studies of Dalhousie University. This study was supported in its various phases by research grants to Dr. Rautaharju from the Nova Scotia Heart Foundation and the Medical Research Council.

CHAPTER I

Introduction and Literature Review

A. Introduction

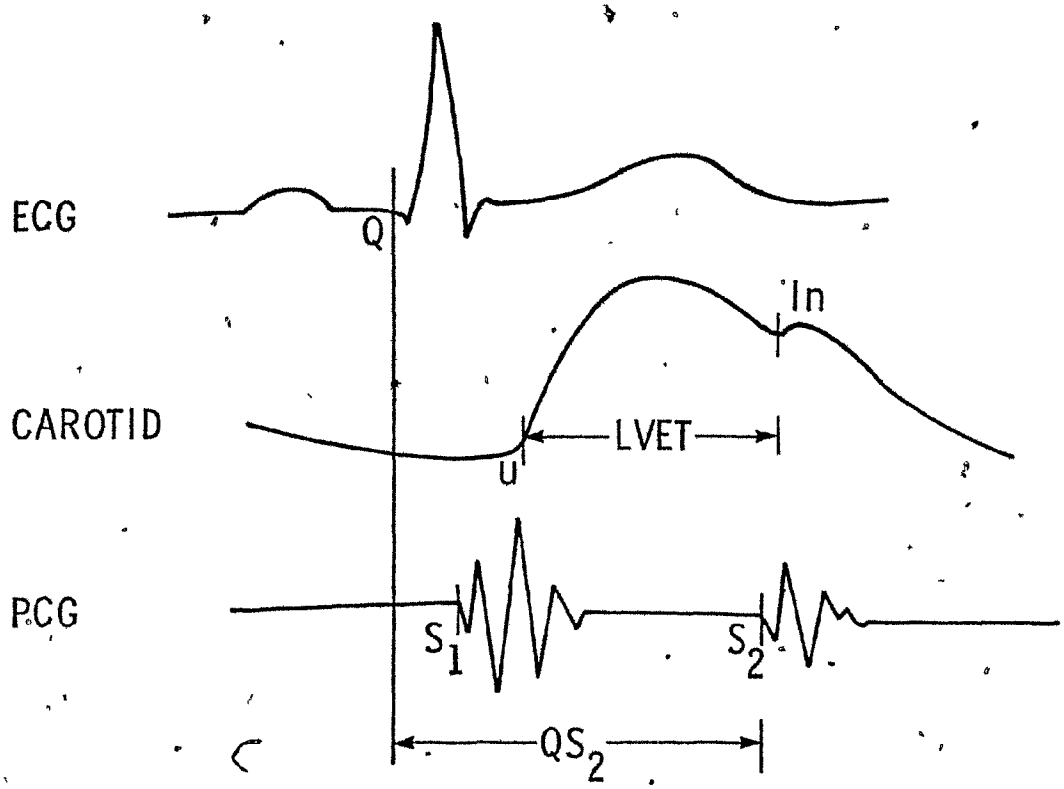
The application of non-invasive techniques to the examination and observation of the cardiovascular system is not a new phenomenon. The examination of arterial pulse waves was widely practiced already by ancient Chinese physicians who were fascinated by the phenomenon of the pulse in various parts of the body and regarded it as a link between the cosmos and man. As their medicine developed, it came to be the most important sign by which they determined "internal processes". They divided the radial pulse on each wrist into zones which gave them information about the condition of the lungs, stomach, spleen, bile, liver and the heart (54).

For over a century modern researchers have used the arterial pulse to study the timing of the mechanical events of the human heart. The inverse relationship between heart rate and the duration of left ventricular ejection was known by 1874 (16, 17). In 1904 the effect of exercise on systole was reported (8), and by the 1920's considerable work had been done (67, 22), including investigations on sex differences and the influence of posture on the ejection period (29). In recent years, the work of Weissler, Spodick and others has stimulated a great deal of clinical interest in what has become known as the Systolic Time Intervals (STI).

The intervals most frequently considered are the pre-ejection period (PEP), defined as the time from the onset of ventricular depolarization (the QRS complex in the electrocardiogram) to the beginning of left ventricular ejection, and the left ventricular ejection time (LVET), usually measured from an external recording (e.g. carotid artery) of the

central arterial pulse, as the time from the initial rapid upstroke to the dicrotic notch. These two intervals combined make up what is called total electromechanical systole, QS_2, which can be determined as the time from the onset of QRS in the electrocardiogram to the initial vibrations of the aortic component of the second heart sound in the phonocardiogram (see Figure 1.1). In practise LVET and QS_2 are measured and PEP is obtained by subtraction. It is possible to further subdivide PEP into two additional intervals known as electromechanical lag, or EML (QRS onset to initial ventricular contraction) and isovolumic contraction time, or ICT (initial contraction to aortic valve opening), but the precise definition of these intervals is difficult technically, and for that matter is in some dispute. Since the clinical interest is primarily in the mechanical aspects of contraction, it is usually assumed that EML is relatively constant and that changes in PEP, therefore, reflect changes in ICT, and so most current work centers around PEP, LVET and QS_2.

Since the pioneering clinical studies of Weissler, Spodick and others were reported in the 1960's, a large number of articles on STI have appeared. The selective literature review, following next, is limited mainly to those papers which deal with statistical analysis of the internal relationships of the STI in normal and abnormal conditions, with a particular emphasis on observations which can be considered as potentially valuable clues of the utility of STI measurements for screening of cardiovascular diseases and early detection of cardiac involvement in coronary and hypertensive heart disease.



$QS_2 = S_2 - Q$

LVET = In - u

PEP = QS_2 - LVET

RATIO = PEP/LVET

Figure 1.1 - Sketch illustrating the measurement of the principal systolic time intervals from simultaneous tracings of the electrocardiogram (ECG), carotid arterial pulse (CAP) and phonocardiogram (PCG). Total electromechanical systole (QS_2) is measured from the onset (Q) of the QRS complex in the ECG to the onset of the aortic component of the second heart sound (S_2) of the PCG. Left ventricular ejection time (LVET) is measured as the time from the rapid upstroke (U) to the incisura (In) of the CAP. Preejection period (PEP) is then computed as QS_2-LVET.

B. Review

1. Measurement Techniques

The earliest observations on the duration of "systole" were based on tracings of the apex heart beat or of an arterial pulse. At that time the relationship between the electrical and mechanical activity of the heart was not well understood and it is clear now that "systole" as defined from a pulse tracing was probably what we now refer to as left ventricular ejection time. Katz and Feil (22) introduced the contemporary practise of utilizing simultaneous tracings of the electrocardiogram, phonocardiogram and arterial pulse. This has remained the predominant technique although some authors have advocated the use of the apexcardiogram (6, 53, 24, 47) or other tracings of pre-cordial motion. The review article by Kumar and Spodick (24) contains an extensive bibliography. Pressure recordings from the brachial and radial arteries have been used by some, but external recordings from the external carotid artery has been preferred because this most closely approximates the central arterial pulse.

Most investigators still work from polygraphic tracings. There is some debate over the choice of paper speeds, with Weissler and his associates recommending at least 100 mm/second (63, 61), although a study by Spodick et al in 1969 (48) of the ejection time indicated no significant improvement in the net precision of measurement over the paper speed range of 25 to 200 mm/second. This particular study was restricted to ejection time measurement from the carotid pulse and may simply reflect the limited frequency response inherent in the pulse wave recording system. In any case, the precision of measurement is improved by averaging the measurements from several consecutive beats and most investigators recommend averaging at least 5 and up to 30 beats.

Obviously, the combination of high paper speed and the need to make measurements on several beats would make both the quantity of tracings and the effort involved overwhelming in any large scale application of the technique. The solution to this problem would seem to lie in the development of an effective computerized measurement technique. There has been some work in this direction, although up to the time of this study no large scale application of a computerized system had been reported. Kyle and Freis (14, 26) developed computer programs to analyse brachial and carotid pulse waves in 1968, but their work at that time was not oriented to the measurement of systolic time intervals. In 1971, they reported a program for the measurement of STI from a single ECG lead, the phonocardiogram and carotid pulse (25). For this purpose they digitized a 5 second segment of record at a sampling interval of 4 msec. for each signal, performed automatic measurements for as many beats as possible, discarded the two beats furthest from the median measurements and averaged the measurements from the beats which remained. Since they worked with resting subjects, their measurements were usually based on an average from two or three beats and they reported that their figures for LVET and QS_2 generally agreed with visual readings of the same records to within 4 msec.

In 1974 Zoneraich, Zoneraich and Rodenrys (72) reported a study of 100 normal individuals in which the STI measurements were performed by a computer program provided by Medical Data Systems, Inc. After correcting both manual and computer measurements for heart rate, they performed Student t tests on the mean values of the results for the two measurement methods and on this basis report that the computer results were not statistically different from the manual ones. The appropriateness of the statistical procedure used can be questioned, however, since the test performed shows only that the group means were not different and proves

nothing about the accuracy of the individual measurements. The authors also claim to be the first users of a fully automatic measurement system, being obviously unaware of the two papers by Kyle et al (25, 26) in 1968 and 1971. They give no details of the computer algorithm used, since the proprietary programs in question were developed by a commercial company.

Starmer, McHale and Greenfield (52) in 1973 described a computer program which they developed to identify the onset and end of ejection from the central aortic pressure signal obtained by catheterization in mongrel dogs. They report very close agreement between time points identified in this way and the same time points defined with another computer program using the ascending aortic blood flow obtained with an electromagnetic flow meter probe. They have apparently not attempted to use their algorithm in a non-invasive setting using the external carotid pressure signal.

It is not yet common practise to record more than one electrocardiographic lead at a time for STI measurements so as a result in STI studies the onset of electrical depolarization is usually identified from a single lead. This can lead to errors in the estimation of QS_2, and thus PEP, since the earliest deflection in the QRS complex does not come consistently in any one lead. Recognizing this, many researchers attempt to select the lead which most commonly shows the initial activity, generally lead II. No one seems to have taken the approach of recording more than one lead simultaneously, which would appear to be the most dependable way to minimize errors of this type.

2. Systolic Time Intervals In Normal Subjects

There have been numerous studies of the various systolic intervals in normal subjects. Only those which are directly relevant to the present investigation will be mentioned here. An extensive discussion and

bibliography can be found in the review articles of Kumar and Spodick (24) and Weissler and Garrard (61, 62).

In 1961 Weissler et al (65) found linear correlations between LVET and both heart rate and stroke volume. Later Jones and Foster (20) performed an experiment in 20 normal young men using a pressure catheter and obtained 207 sets of measurements including a large number of observations during supine leg exercise. They developed a single multiple regression equation indicating an inverse dependence of LVET on heart rate and diastolic pressure, and a direct relationship with stroke index. However, the examination of the scattergram presented by the authors for the LVET-heart rate relationship clearly reveals that the resting and exercise data have separate regression relationships and their combination to a single regression can be questioned.

In 1967 Willems and Kesteloot (69) reported on a study of 219 normal men and 70 normal women using the external carotid pulse to measure ejection time. Their best linear regression relating LVET with heart rate is shown in Table 1.1, along with the results of several other authors. They also studied 15 male subjects during supine leg exercise and developed both linear and non-linear regressions in an attempt to derive a single equation which could be used for both resting and exercise data.

Spodick and Kumar (47) studied the ejection time in 50 normal young men and compared results obtained from the external carotid tracing and from the apex cardiogram. For this purpose the subjects were resting in the semi-left decubitus and in expiratory apnea. The special position was required apparently to obtain good quality apex cardiograms. They found poor agreement between apex-derived and carotid-derived measurements and recommended the carotid method because of the smaller scatter observed and

TABLE 1.1

A summary of reported heart rate regressions for systolic time intervals for normal subjects at rest

All intervals are expressed in milliseconds

Interval	Sex	Regression Equation	Standard Deviation About Line	N	Correlation Coefficient	Authors
LVET	M&F	377.4 - 1.16 HR	11.3	289	-.831	Willems & Kesteloot (69)
	M	375.7 - 1.22 HR		50	-. 8	Spodick & Kumar (47)
	M	413 - 1.7 HR	10	121		Weissler et al (63)
	F	418 - 1.6 HR	10	90		Weissler et al
	M	383.6 - 1.52 HR		139	-. 69	Luomanmäki & Heikkilä (30)
	M&F	417.5 - 1.59 HR		93	-. 67	Zoneraich et al (72)
ICT	M	38 (no sig. regression)	11	121		Weissler et al
	F	39 (no sig. regression)	9	90		Weissler et al
	M	65.6 - 0.17 HR		139	-. 18	Luomanmäki & Heikkilä
	M&F	66.4 (no sig. regression)	12.6	93		Zoneraich et al
PEP	M	131 - 0.4 HR	13	121		Weissler et al
	F	133 - 0.4 HR	11	90		Weissler et al
	M&F	88.1 (no sig. regression)	12.9	93		Zoneraich et al
QS_2	M	546 - 2.1 HR	14	121		Weissler et al
	F	549 - 2.0 HR	14	90		Weissler et al
	M&F	520.4 - 1.79 HR		93	-. 68	Zoneraich et al

because of previous studies indicating close agreement between ejection time measurements obtained from signals and measurements derived from the central aortic pressure (65). Their regression equation based on the carotid measurements is similar to that of Willems and Kesteloot (see Table 1.1).

In 1968, Weissler, Harris and Schoenfeld (63) published a study involving 121 normal men, 90 normal women and a group of 27 patients with clinically conspicuous heart failure. Recordings were made in the morning in the supine position during normal respiration. Using simultaneous tracings of the electrocardiogram, phonocardiogram and external carotid pressure, they measured heart rate, QS_2, LVET, PEP, S_1S_2 (first heart sound to second heart sound), Q-1 (beginning depolarization to first sound) and isovolumic contraction time ("ICT", calculated as S_1S_2-LVET). Their normal heart rate regressions for LVET, ICT, PEP and QS_2 are in Table 1.1 and have been adopted by most current workers as a standard. In a paper published the following year (64) they introduced as a new parameter the ratio PEP/LVET which they state to be heart rate independent, with a normal value of 0.345 ± 0.036. This parameter is especially sensitive to simultaneous but opposite changes in PEP and LVET, which is the situation they found in their patients with heart failure.

Luomanmaki and Heikkilä (30) used the "kinetocardiogram" (apex cardiogram) instead of the carotid pulse in a study of 139 healthy male subjects between the ages of 45 and 64 years. Their regression equations for ICT and LVET are also given in Table 1.1. When they divided their subjects into four age classes they found no significant differences.

Zoneraich et al (72) in their computerized study derived regression equations for 93 normal subjects (of both sexes), some of which are included in Table 1.1. They obtained a normal value for PEP/LVET of

0.287 ± 0.055, which is considerably lower than that reported by Weissler. They obtained their data in the early morning with their subjects in the left lateral decubitus in expiratory apnea. Their equations for LVET and QS_2 are similar to those of Weissler, but their values for PEP (and PEP/LVET) are lower. Their estimate of ICT agrees with that of Luomanmäki et al, but is much higher than Weissler's figure. This underlines the difficulty encountered with ICT because of differences in definition and method of measurement.

Aronow (5) studied LVET and ICT (calculated using the same method as Weissler) in the supine position in 60 normal men before and after exercise. He performed no rate correction, and reported a decrease in mean ICT from 41 to 24 msec. after exercise, recovering in three minutes to 36 msec. He does not quote values for LVET, but reports that the ratio LVET/ICT increased from 7.4 to 11.0 in exercise recovering to 8.2 in three minutes post-exercise. These results are difficult to compare with other studies, but would have to be interpreted as a decrease in both PEP and PEP/LVET.

Hardarson et al (18) did a study of 9 sedentary middle-aged men during graded bicycle ergometer exercise. They reported a progressive shortening of LVET, QS_2 and PEP at increased work rates. They then applied Weissler's heart rate corrections to their data and reported significant lengthening of the QS_2 and LVET indices and a shortening of the PEP index. The small sample size prevents generalization of the results and their application of heart rate correction using resting regression coefficients can be questioned since it has not been shown that the resting rate relationships hold in either the upright position or in the exercise state.

Xenakis, Quarry and Spodick (71) have recently reported the results of

beat-to-beat observations of HR, PEP, LVET (rate corrected) and PEP/LVET in 5 normal young men at three separate work loads. The noted responses immediately at the onset of exercise followed by a gradual levelling off to values which were related to the work load. In all cases, PEP decreased by about 25 msec., PEP/LVET decreased from control values of about 0.49 (resting upright) to about 0.36 and LVET index increased by 40 to 50 msec. Again, the rate correction is probably questionable and the sample size is inadequate.

Maher et al (32) conducted a study of 10 physically active normal young men during submaximal and maximal supine exercise and used repeated observations from their 10 subjects to derive regression equations for LVET, PEP and QS_2 for the two exercise states in a range of heart rates from 120 to 170 beats per minute. For the submaximal state they obtained regression slopes nearly identical to the resting values of Weissler and his colleagues. The intercepts for LVET and QS_2 were higher than the resting ones by 38 and 25 msec. respectively, while that for PEP was reduced slightly. At maximal exercise the slopes for LVET and QS_2 decreased to -1.4 msec./beat and the slope for PEP was not significantly different from zero. The decrease in the slope for LVET was not statistically significant (again the sample size is small) but the slope decrease for QS_2 was significant ($p < 0.001$).

3. Systolic Time Intervals In Heart Disease

The review articles of Weissler & Garrard (61, 62) contain a good overview of the variations in STI seen in a range of heart diseases. The article of Lewis et al (28) reviews some more recent work on STI and coronary artery disease.

Weissler et al (63), in the same article in which they set out their

normal regressions, studied 27 patients at rest with clinically conspicuous heart failure due to arteriosclerotic heart disease, hypertensive heart disease or primary myocardial disease. They observed a significantly prolonged PEP, accompanied by a shortened LVET with normal values for QS_2. This confirmed the earlier finds of Blumberger (7) and others. The changes in LVET and especially PEP were highly correlated with both the cardiac index and stroke index in these patients. Garrard et al (15) studied 68 patients with an assortment of heart diseases and found that PEP/LVET correlated highly ($r = -.90$) with ejection fraction but poorly with stroke volume. In a sub-series of 15 patients with ischemic heart disease and no valvular regurgitation, PEP/LVET also correlated highly ($r = -0.77$) with stroke index.

In 1969 Spodick et al (46) used the left ventricular ejection time in a study on 97 patients with a variety of heart diseases including ischemic, hypertensive and valvular heart disease and cardiomyopathy. Seventy-seven (79%) of them fell more than 1 standard deviation below the regression line

$$LVET = 376 - 1.2\ HR \pm 12$$

which they had previously reported for normal subjects (47). They also studied a group of 103 "hospital normals" (hospital patients without heart disease) and derived a new regression equation

$$LVET = 409 - 1.6\ HR \pm 29$$

for this special population. It is interesting that this regression is very close to Weissler's normal equation, while the regression coefficient for the normal group reported earlier by these authors is substantially different, with a smaller slope of the regression line. In 1970 Weissler and Schoenfeld (66) showed that digitalis administration decreased corrected PEP and LVET by about 15 msec. and QS_2 by about 30 msec., in 10 normal subjects and 13 patients with heart failure. Nandi et al (38)

studied the effect of respiration on STI in 24 hospital patients (with and without heart disease). They found that inspiration increased PEP and PEP/LVET by 2.7 msec. and 0.019 respectively, relative to expiration, and reduced LVET an average of 6.3 msec. Stafford et al (51) have reported an increase in PEP accompanied by a similar decrease in LVET in 15 normal subjects after passive head-up tilt. Three subjects with congestive heart failure failed to exhibit this postural response. Shah and Slodki (45) measured QS_2 in 112 healthy men and 15 cases of severe systemic hypertension. All of the cases were ambulatory and showed no exertional intolerance, and none were taking digitalis or anti-hypertensive preparations. From the normals they calculated the regression relationship

$$QS_2 = 61.6 + 10.24\sqrt{RR} \pm 17.5$$

where RR is the R-R interval, and found that the regression line for the hypertensive patients was parallel to this but elevated by 33.4 msec.

In 1972 Ahmed et al (2) studied 14 normal subjects and 56 patients with various forms of heart disease during catheterization. In addition to measuring STI, they computed the "Frank-Levinson index of contractility" and found a high degree of correlation ($r = -.86$) with PEP/LVET in 28 subjects without valve disease, shunts or pulmonary heart disease but a much poorer correlation ($r = -.51$) in the whole series. In the same 28 subjects PEP/LVET correlated well with ejection fraction ($r = -.73$) and to a lesser extent with cardiac index ($r = -0.53$). They conclude that PEP/LVET is a good indicator of contractility.

A recent study by McDonald and Hobson (36) considered 25 patients with primary myocardial disease, divided into two groups: 8 without dyspnea (functional Class I, New York Heart Association) and 17 with dyspnea (Class II or III). Most of the patients were on digitalis and diuretics.

The ratio PEP/LVET was measured and compared with a control group of 25 healthy subjects. The mean value for the control group was 0.325, while the mean for the combined patient groups was 0.621. There was no statistically significant difference between the two functional groups.

Margolis (33), in 1964 measured LVET and "Tension Period" (PEP) in 70 normal volunteers and 41 patients with coronary artery disease consisting of 18 old infarcts, 6 recent infarcts and 17 patients with angina pectoris. None of the patients had clinical signs of heart failure or insufficiency. He computed the ratio Ejection Period/Tension Period (essentially the reciprocal of PEP/LVET) and found it reduced in the patient group to a value of 2.68 (corresponding to PEP/LVET = 0.373) compared with 2.90 (PEP/LVET = 0.345) in the normal group. The difference was significant at $P < 0.06$.

The next year Agress et al (1) used the "vibrocardiogram" to measure LVET in 19 patients with coronary insufficiency and compared them with a group of 21 sedentary normals and 20 competitive cyclists at rest and after 3 forms of exercise (bicycle, ergometer, treadmill and the double Master 2-step test). Most of the patients had previous myocardial infarction and all had recurrent angina which interfered with normal activity. They studied the relationship between LVET and heart rate and found that they could not distinguish between the three groups.

In 1971 Pouget et al (41) measured arterial pressure, QS_2, LVET and PEP in 20 patients with angina pectoris in the supine position before and after a step test and compared the responses with those of 20 age matched controls. Fifteen of the angina patients had 50% obstruction of at least one coronary artery and all had recurrent substernal chest pain. They corrected QS_2 and LVET for heart rate using the resting regression

coefficients of Weissler et al. After the exercise diastolic blood pressure increased by 13 mm Hg in the angina group and was unchanged in the controls and QS_2 decreased by only 4 msec. in the patients compared with a decrease of 24 msec. in the control group. LVET increased by 23 msec. compared with a 4 msec. decrease in the controls and PEP decreased by 35 msec., which was 9 msec. more than the decrease observed in the control group. They concluded that the prolongation in LVET after mild exercise in the angina patients reflects impaired left ventricular performance and increased afterload and should be useful in the diagnosis of ischemic heart disease.

Noting the results of Pouget et al, Lewis et al (28) decided to assess the usefulness of the LVET response after exercise as a discriminator to identify patients with coronary artery disease. They studied 75 patients with chest pain before and after multistage treadmill testing. Twenty-one of these patients had normal coronary arteries by coronary arteriography and were used as controls to derive the heart rate regressions after exercise, which was then used to correct LVET for heart rate in the other patients. Forty-six per cent of the patients with significant disease had a prolongation of LVET of more than 30 msec., which was more than that observed in any of the normals. Fifty-two percent of the same patients had positive exercise ECG tests and the combination of the LVET and ECG tests identified 74% of the patients with coronary artery disease.

The conclusions of Lewis et al contrast with the results of McConahay et al (35), who concluded in 1971 that exercise failed to improve the sensitivity of STI to detect coronary artery disease. They compared 33 normals with 32 age and sex-matched patients with documented 50% obstruction of at least one artery before and after moderate supine leg exercise. Their data was corrected for heart rate using Weissler's resting coefficients. They found that their patients had longer PEP, shorter LVET

and increased PEP/LVET relative to normal both before and after exercise, but that both groups responded to the exercise with a reduction in PEP and prolongation of LVET of about the same magnitudes.

In 1975 Meng et al (37) studied 113 patients with possible coronary artery disease at rest and divided them into 4 groups with 0, 1, 2 or 3 vessel disease on the basis of angiography. All of the patients had chest pain, many were taking digitalis and 18% of them had congestive heart failure. They found that PEP (rate corrected) and PEP/LVET increased progressively with the number of arteries involved, LVET decreased progressively and QS_2 did not change. The total shift observed in both PEP and LVET was about 17 msec. between the extreme groups.

Lewis et al (28) found that QS_2 was decreased by about 15 msec. in 93 patients with angina and significant coronary artery narrowing, compared to their control group of 60 patients with chest pain but normal arteries. This is in obvious disagreement with Meng's result and the authors felt that the reduction reflected increased adrenergic activity in their patients with coronary disease. In 1972 Lewis et al had noted a high degree of correlation between QS_2 and urinary excretion of epinephrine and norepinephrine in a group of patients with acute myocardial infraction or acute coronary insufficiency (27).

In acute myocardial infarction, several authors have noted characteristic decreases in LVET and QS_2 with a corresponding increase in PEP/LVET and varying changes in PEP (19, 42, 44) which gradually return towards normal values in the weeks following initial hospitalization. Robijns et al (42) found that the changes observed were most marked in the presence of heart failure, while Hodges et al (19) found no significant differences in PEP, LVET, QS_2 or PEP/LVET between four groups of patients classified according

to the degree of left ventricular dysfunction ranging from no dysfunction to cardiogenic shock. Naqvi et al (40) attempted unsuccessfully to use STI to discriminate between patients with acute infarction and acute coronary insufficiency. In 37 patients with 3 to 60 month old documented transmural infarctions Stack et al (50) noted progressive increases in PEP/LVET and PEP and progressive shortening of LVET with increasing severity of dyspnea and fatigability. Lewis (28) noted that PEP/LVET was much more elevated in acute infarction patients with prior infarctions or long standing hypertension than in a group of acute infarction patients with no evidence of prior left ventricular disease.

C. Purpose of This Investigation

In spite of conflicting results revealed by the literature review on the usefulness of STI measurements in clinical diagnosis of heart diseases, there is sufficient evidence to suggest that deviations from normal values of certain STI relationships are a manifestation of disordered cardiac function in advanced ischemic and hypertensive heart disease. While clinical cardiological diagnosis rarely relies solely on non-invasive methods, there is a most pressing need for improved, quantitative non-invasive methods for early detection of cardiac involvement in ischemic and hypertensive heart disease for the purposes of clinical trials and cardiovascular epidemiological studies. These large scale, very expensive studies are presently relying almost entirely on the ECG as the primary method for the detection of non-fatal trial endpoints. The reliability of both rest and exercise ECG in terms of its diagnostic accuracy leaves much to be desired and any additional diagnostic or predictive information that could be derived from other non-invasive techniques could potentially lead

to a reduction of the cost and improvement of the power of clinical trials designed to investigate the effectiveness of intervention on heart diseases.

There are two prerequisites for the efficient, meaningful use of STI analysis methods in large-scale epidemiological applications. Firstly, automation of the measurements is required in order to make mass application feasible. Secondly, the establishment of statistically stable reliable confidence limits for normal STI values and their mutual relationships at rest and following exercise can be considered a fundamental first step for attempts to verify the diagnostic or predictive power of STI measurements. The reported normal values for STI differ widely; for instance, the LVET vs heart rate regression coefficients obtained for resting supine men range from -1.2 to -1.7.

The utility of the reported normal values for STI in exercising subjects is severely limited because of very small sample sizes in all reported studies, and also the most commonly used normal standards for resting supine male subjects are based on a sample of only 121 men. There is insufficient evidence to justify the practice of applying STI normalization with respect to heart rate in exercising subjects using the regression equations derived for resting supine subjects.

The common practice of studying individual rate corrected intervals disregards the information contained in the rate itself and fails to reveal the information contained in simultaneous changes in two or more of the intervals. The commonly used ratio PEP/LVET is sensitive only to simultaneous opposing changes in PEP and LVET. It seems surprising, therefore, that no one seems to have used the technique of multivariate discriminant analysis which has been applied with considerable success in studies of the electrocardiogram (10).

While valuable information has been learned about the links between the time intervals and hemodynamic parameters, much of it has been derived from hospital patients with relatively severe heart disease and much of it is based on very small samples. There have been relatively few attempts to use systolic time intervals to discriminate normals from subjects in early stages of heart disease which have not yet resulted in hospitalization. In particular, there appears to have been little work on subject groups with varying degrees of hypertensive heart disease.

The purposes of this investigation can be summarized as follows:

1. To develop an efficient computerized system for the acquisition of data and the subsequent measurement of the principal systolic time intervals.

2. To use this program to measure systolic time intervals in a large sample of normal male subjects and establish normal limits from the statistical distributions of these intervals in the resting state in the supine and upright positions, and immediately after submaximal exercise.

3. To observe whether any systematic trends exist in relation to normal distributions in STI values of selected subsamples of male populations reflecting milder and more advanced forms of hypertension, hypertensive heart disease, primary myocardial disease and ischemic heart disease. The ultimate enquiry is to establish whether definitive or at least sufficiently suggestive evidence exists to justify the use of STI measurements for detection of early cardiac involvement in hypertension and coronary heart disease in epidemiological studies.

CHAPTER II

Methods

A. Material

Most of the material for this study was obtained from a series of field studies conducted between 1969 and 1972 by the research group of this laboratory in collaboration with other teams of investigators. Three of the studies were total population samples of male subjects between the ages of 50 and 70 from small rural villages in Italy and East and West Finland. A fourth study was conducted on the men of the Police Department of the City of Helsinki, Finland ranging in age from 35 to 68. Data for all of the subjects, including clinical information and systolic time intervals measured by the computer program described here, was incorporated into a data pool on digital magnetic tape, and subject groups were later extracted from this pool on the basis of the clinical codes, as described in Chapters III and IV. In addition to data from this pool, data from three other special groups of subjects with primary myocardial disease and with old and acute myocardial infarction was also used. A more detailed description of the subject groups is given in Chapters III and IV.

B. Recording Procedures

Recordings were made from each subject at rest in the supine position and immediately after 3 minutes of upright exercise on a bicyle ergometer at a workload of 600 kilo-pond meters. If the heart rate after this exercise period did not reach the target heart rate the workload was increased and a second exercise was performed at the target rate. In the Helsinki Policemen Study, a recording was also obtained just before the

exercise run, in the upright position on the ergometer. The target heart rate (THR) for the submaximal exercise test was determined according to the following formula:

$$THR = 0.85 \times (230 - 1.18 \times \text{age (years)})$$

The equation estimates THR as 85% of the age specific predicted maximum heart rate. It should be noted that the heart rate decreases very rapidly at the cessation of exercise during the post-exercise period when the STI records were made.

With the exception of the acute infarction study, all signals were recorded on analog magnetic tape and processed later. The recordings were made on 7 track tape, at a tape speed of 3 3/4 inches per second, in FM mode. In the acute infarction study, this step was bypassed and the signals were transmitted directly to the computer from the bedside using telephone lines and a frequency modulation transmission system.

The electrocardiograms were recorded using Beckman electrodes arranged according to the Frank lead system. This system uses 6 bipolar signal leads which are combined by a resistor network or by a computer algorithm to form the scalar X, Y, Z leads. In this study, the signals from four of the six independent Frank lead components (with electrode H as a common reference) were recorded directly after amplification using custom-built ECG pre-amplifiers. While these do not constitute a complete orthogonal lead system, all three vector directions are represented in these four signals, providing enough information to select the earliest onset of the QRS complex. In the acute infarction study, the six signals were reduced to a three-lead vector set using an electronic network prior to transmission to the computer on telephone lines.

The phonocardiogram was recorded using a Hewlett-Packard 21050B contact microphone and a Hewlett-Packard Model 1506B Heart Sounds

Amplifier. The microphone was placed in the third intercostal space at the left sternal border, or at whatever alternate location was required to produce a sufficiently clear second heart sound.

The arterial pulse was taken with a Sanborn APT-16 variable reluctance transducer hand held over the left external carotid artery.

C. Digitization and Analysis Procedure

The procedure for digitization and preliminary data handling is based on a modified version of the Dalhousie ECG program, version 3. Figure 2.1 shows the major processing steps. The program is capable of handling three signals (one ECG lead, arterial pulse and PCG) or six (three or four ECG leads, arterial pulse and PCG). All of the data reported in this thesis used the six signal version and this is the one that will be described. The major steps up to and including signal averaging follow the principal logic of the Dalhousie ECG program which is described elsewhere (70).

1. Sampling

The operator starts the procedure by setting up a subject identification code and initiating program execution. The six signals from tape (or bedside) are sampled simultaneously at a rate of 500 samples per second per lead for a period of 15.6 seconds. Prior to sampling, the signals are filtered with a low pass filter with a cutoff frequency of 125 Hz and an attentuation slope of 24 db per octave. This is done to avoid aliasing which would introduce additional noise into the system. The sampled data is stored on disk for subsequent processing which proceeds in parallel with the sampling process.

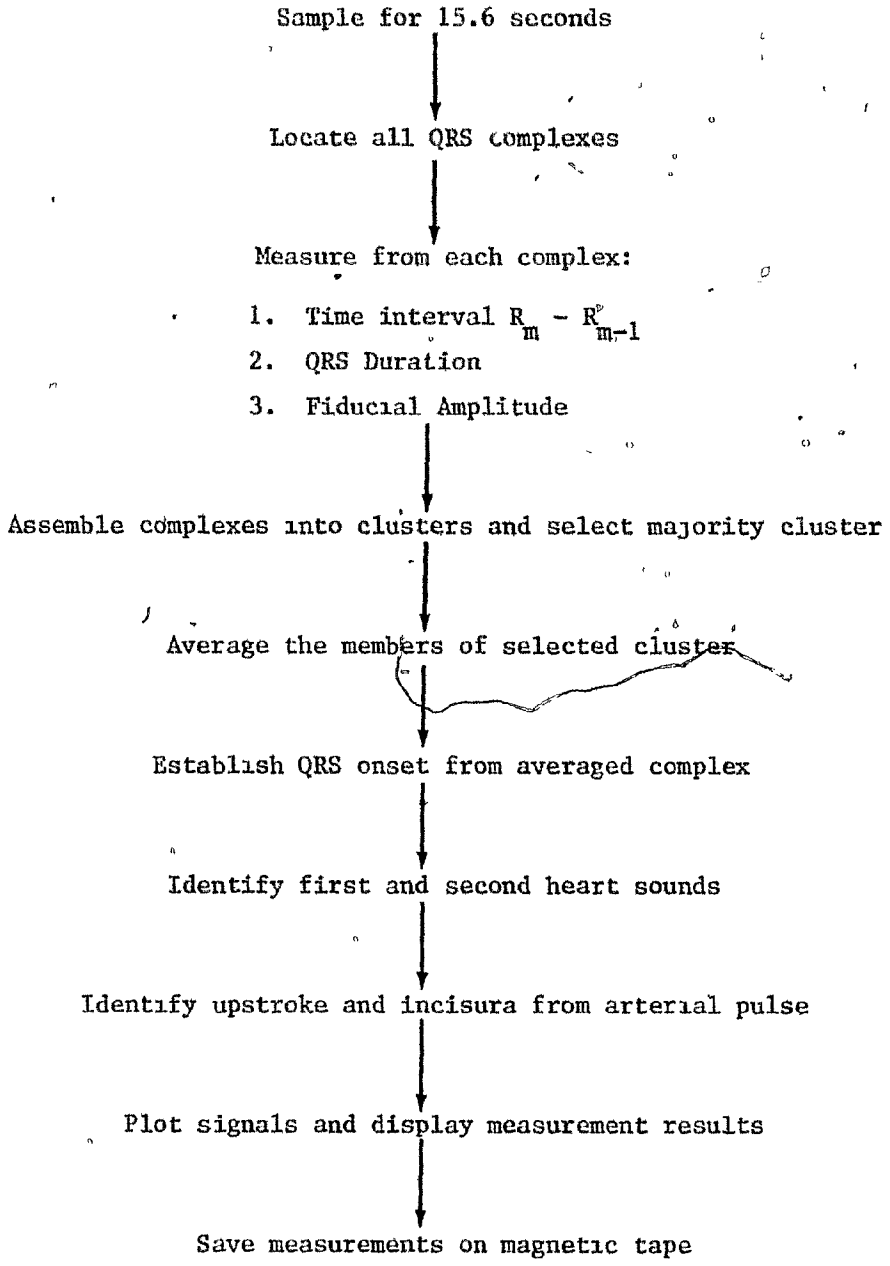


FIGURE 2.1 Processing Steps In The STI Measurement Program

2. Search For QRS Complexes

The search for QRS complexes is based on the application of a fairly simple threshold logic to the filtered spatial velocity (FSV) which is a special function derived from the three or four available ECG leads as follows. Each individual lead is pre-filtered with a digital recursive four-pole bandpass filter (58) with a center frequency of 15 Hz and a bandwidth of 20 Hz. This effectively removes the P and T waves and smooths out any high frequency noise in the signals.

Then

$$FSV_i = \sum_{j=1}^{N} (F_{i,j} - F_{i+1,j})^2$$

where N = number of ECG leads available

i = sample point number

$F_{i,j}$ = filtered sample point i for the jth lead

The details of the detection logic used on this derived function can be found in a paper by Wolf et al (70).

3. Measurement of Parameters For Clustering

For each complex found, three parameters are estimated to be used in selecting beats for averaging. These are (1) an estimate of QRS duration, (2) the preceding RR interval and (3) a fiducial amplitude called the "R tracking amplitude". This is measured from the individual lead which has the largest peak-to-peak amplitude during the QRS. The time of the minimum amplitude is determined with respect to the "onset" of QRS in the first complex detected and the amplitude is measured at this same relative time point in this lead for all other complexes.

4. Clustering

The three sets of measurements define points in a three-dimensional space and these points are clustered using the method of MacQueen (31). The complexes corresponding to the points in the majority cluster are then selected for signal averaging.

The clustering procedure used before signal averaging has several important advantages in the subsequent processing of the signals. In the first place, it tends to select beats from the same phase of the respiratory cycle, since there is a respiratory influence both on the RR interval and on the fiducial amplitude. Since respiration may also affect the timing of the second heart sound through its effect on stroke volume (influenced both by the RR interval and filling pressures), selecting beats from the same part of the cycle minimizes the phase shift which would cause smoothing of this signal. Clustering is also a very effective way of rejecting spurious events like premature contractions and various signal artifacts.

5. Selective Averaging

An estimate is made of the random noise level in the ECG leads, and if this noise level is less than approximately 10 microvolts, averaging is not performed and the complex corresponding to the point closest to the center of the majority cluster is selected for analysis. Otherwise the signal for all of the complexes in the majority cluster are averaged using a cross-correlation on the QRS complex for alignment. At this point the signals for the PCG and carotid pulse are carried into the averaging process, although the alignment is based solely on the ECG. The result is a new set of six signals representing the "averaged complex", on which the final measurements are performed.

6. Measurement of QRS Onset From Selected or Averaged Complex

The onset of QRS (RON) is determined using a template waveform recognition technique based on that of van Bemmel et al (1973). This procedure uses a normalized spatial velocity function

$$SV_i = \sum_{j=1}^{N} |A_{i+2,j} - A_{i-2,j}|$$

where $A_{i,j}$ is the ith data point of the averaged signal for the jth lead.

A search region is established around a preliminary estimate of the onset, and the spatial velocity is cross-correlated with a six level template which was established earlier from a test library of ECG records "calibrated" to a human observer. If a sufficiently high correlation is not found in the search window, the template is elevated to a higher (amplitude) level and the procedure is repeated until an adequate correlation is achieved, or until the procedure must be abandoned. If template elevation is required, a linear correction is made to the final onset estimate to allow for the shift. This procedure has been proven to be a very effective and accurate measure of the onset of QRS both in very clean signals, and in the presence of a considerable amount of noise, such as is found in exercise recordings.

7. Timing Analysis of The Phonocardiogram

Source data for the analysis of the phonocardiogram is a set of N sampled data points S_i. N is normally 256, corresponding to 512 milliseconds of signal, beginning at RON, the estimate of QRS onset. The analysis involves the following steps:

(1) Calculate integrated power function.

$$\text{Let SBAR} = \frac{1}{N} \sum_{i=1}^{N} S_i$$

Using this as a baseline, compute the integrated power function -

$$F_i = \sum_{j=1}^{i} (S_i - SBAR)^2$$

F is a monotonic increasing function (see Figure 2.2) rising slowly during "quiet" periods between heart sounds at a rate determined by the noise level in the signal, and rising steeply during a heart sound.

(ii) Locate first heart sound.

Define k as the first point where

$$F_k > F_N \times 0.1$$

Assuming that the noise preceding the first sound accounts for less than 10% of the total energy in the signal, and that the first sound and this noise account for at least 10% of total energy, k will represent a point somewhere in the first rapidly rising segment of the function F and will lie somewhere in the first heart sound.

(iii) Estimate onset of first heart sound.

We now define a new search segment from point k-20 to point k and define I as the first point in this segment where

$$F_I > F_{k-20} + (F_k - F_{k-20}) \times 0.1$$

On the assumption that point k is somewhere within the first heart sound, and that point k-20 (40 msec. earlier) is in the noise segment preceding the sound, and again that the intensity of the sound is sufficiently greater than the noise level, point I will be in a very early phase of

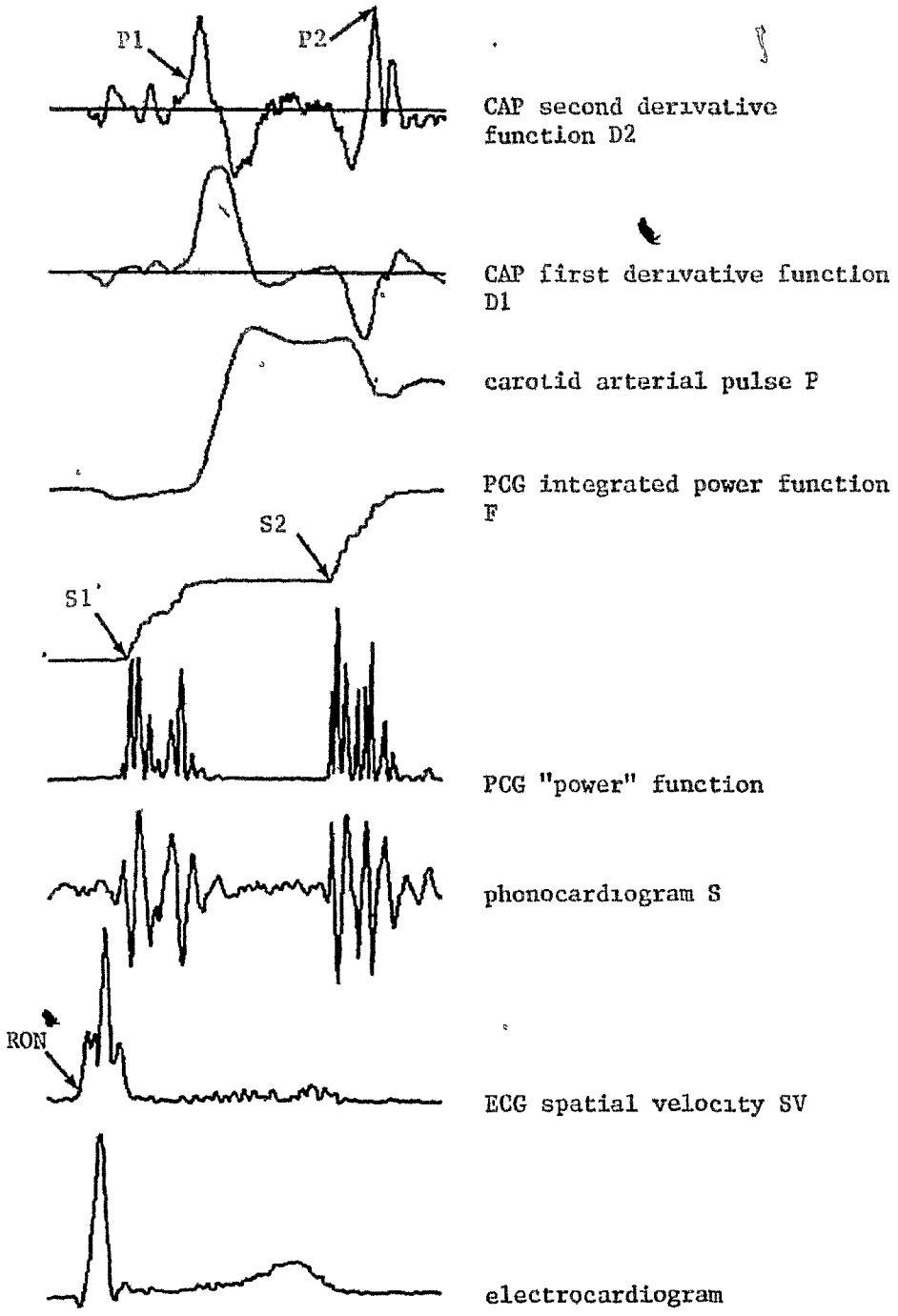


Figure 2.2 - Plot of source signals from a typical record, with derived functions used by computer program to identify the time points required to compute the systolic time intervals. The function names and symbols are as used in the text. The arrows indicate the points on the derived functions identified by the computer program.

the first heart sound. The final estimate of the onset of the first heart sound is

$$IS1 = I-5$$

(iv) Locate a "quiet" point between the first and second heart sounds. Find the point M between I+50 and N-85 where

$$F_M - F_{M-50}$$

is minimum. In the absence of a systolic murmur or other artifact and given a reasonably prominent second heart sound, M should be in the "quiet" signal segment between the first and second heart sounds.

(v) Locate second heart sound.

The procedure used for the second heart sound is similar to that used for the first sound, using point M as the origin:

Define k_2 as the first point where

$$F_{k2} > F_M + (F_N - F_M) \times 0.1$$

(vi) Estimate onset of second heart sound.

Define I2 as the first point where

$$F_{I2} > F_{k2-20} + (F_{k2} - F_{k2-20}) \times 0.1$$

The final estimate for the onset of the second heart sound is then

$$IS2 = I2 - 4$$

8. Timing Analysis of The Carotid Pulse

Source data is a set of N sampled data points P_i beginning at RON, as in the case of the phonocardiogram. The actual analysis is based on the use of two derived functions (the smoothed first and second derivatives) and the knowledge of the locations of the two heart sounds (see Figure 2.2).

(i) Calculate the first and second difference (derivative) functions.

Compute:

$$D1_i = \sum_{j=i+1}^{i+5} P_j - \sum_{j=i-5}^{i-1} P_j \qquad i = 6,N-5$$

$$D2_i = D1_{i+1} - D1_{i-1} \qquad i = 7,N-6$$

We further establish AMAX and AMIN as the maximum and minimum values of $D1_i$. These should represent the points of maximum slope (which should be somewhere on the upstroke) and minimum slope (which should be somewhere between the peak and the dicrotic notch).

(ii) Locate carotid upstroke.

Define k3 as the first point after IS1-17 for which:

$$D1_i \geq AMAX \times 0.3 \qquad i = k3,\ k3+2,\ K3+4 \ldots k3+16$$

This defines a point where the slope (first difference) of the signal goes above a threshold and remains above this threshold for 16 sample points (32 msec.). If such a point is found, it should be early in the initial upstroke of the pulse wave. If such a point is not found, a message is issued and the analysis is abandoned.

(iii) Refine estimate of carotid upstroke.

Find DMAX as the maximum value of $D2_i$ in the range from k3-3 to k3+47. Then the final upstroke estimate (IP1) is the first point before this maximum where

$$D2_{IP1} > DMAX/3$$

(iv) Locate dicrotic notch.

Find the first point after IP1 where

$$D1_i \leq 0.15 \times AMIN$$

i.e. where the slope first falls below 15% of the maximum negative slope. $D1_i$ must remain below this threshold for 9 data points (18 msec.) or point i is rejected and the search is resumed. Having found such a point i, find the point j where the slope first rises above this same threshold again. That is, find the first j after i for which:

$$D1_j > 0.15 \times AMIN$$

If this point is earlier than IS2-12 (24 msec. before the second heart sound) discard it and resume the scan looking for another section of negative slope. The final estimate of IP2 is the point of maximum second derivative in the 25 points (50 msec.) preceding point j.

9. Calculation of Systolic Time Intervals

Once the four sample points IS1, IS2, IP1 and IP2 have been established, they can be converted to milliseconds from QRS onset by simply multiplying by the sampling interval SINT (which is 2 msec.). The estimates for the

desired systolic time intervals then are:

$$QS2 = IS2 \times SINT$$

$$LVET = (IP2-IP1) \times SINT$$

$$PEP = QS2 - LVET$$

The heart rate is estimated as the reciprocal of the mean R-R interval for the beats selected by the clustering routine.

10. Display of The Analysis Results To Operator

After the analysis has been completed, the averaged signals are displayed on the screen of the computer terminal with vertical lines indicating the location of the various timing points. An example of such a display is shown in Figure 2.3. The operator then has the option of rejecting the run and retrying the analysis on a fresh signal, or accepting the analysis results, in which case the data for the averaged complex along with the measurement results is copied to digital magnetic tape for further analysis.

D. Measurement Validation

Two experiments were performed to evaluate the accuracy of STI measurements obtained with this program. The first of these sought to compare measurements of LVET from the external carotid artery pulse wave records with measurements derived from signals obtained with a fluid-filled catheter in the ascending aorta. Tape recordings were obtained from 10 patients with a variety of heomodynamic disorders during routine diagnostic catheterization at the Victoria General Hospital. The recordings were made at the end of the clinical procedures with the patient's consent and included a lead II electrocardiogram, external

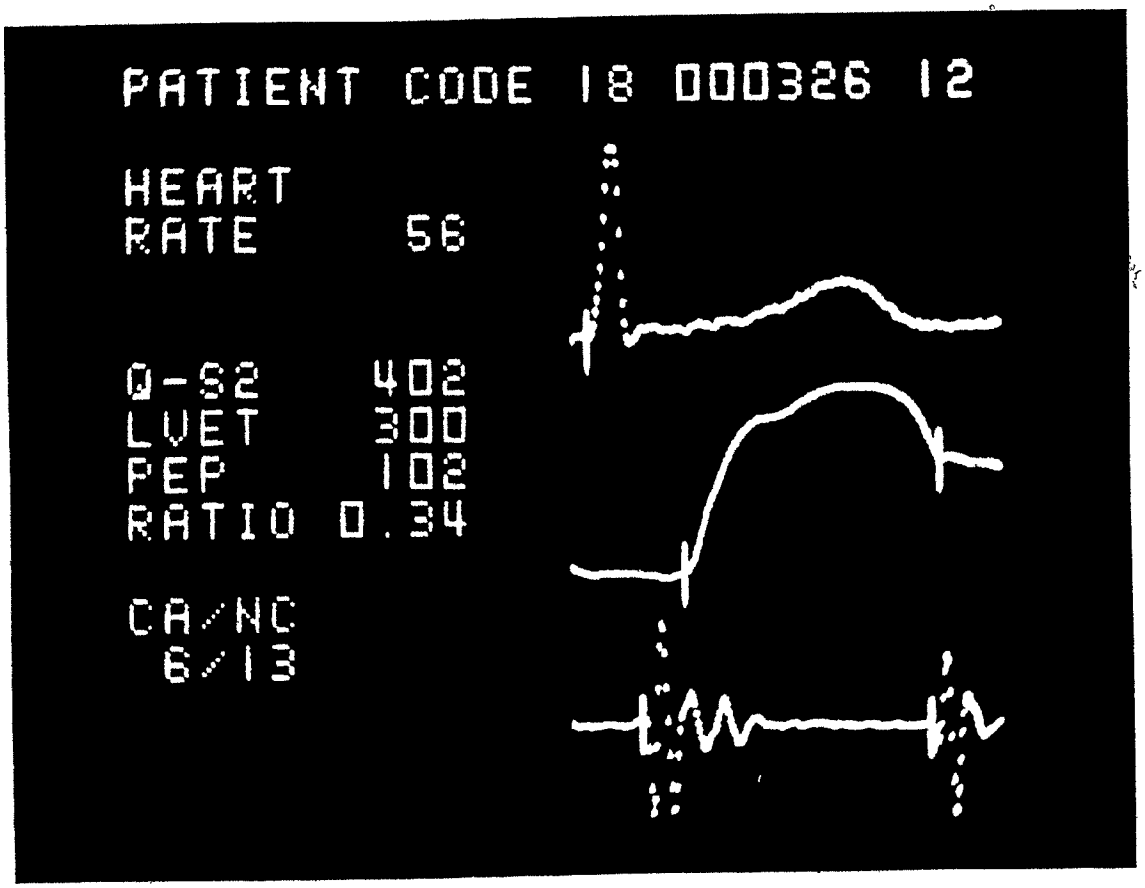


Figure 2.3 - Computer display presented to the operator by the STI measurement program. The time points identified by the program are indicated by the short vertical bars on the plotted signals. The "patient code" indicates that this record is from subject number 326 from study number 18, in state 12. The numbers under the heading "CA/NC" indicate that the plotted signals represent the results of averaging 6 of 13 beats identified in the record.

carotid pulse and the aortic pressure signal from the catheter. These signals were then processed with a version of the measurement program modified to analyse each beat, once using the carotid pulse, and a second time using the central aortic pulse. Considerable difficulty was experienced with the quality of the signals, which were obtained under less than ideal conditions. The main problems experienced were 60 Hz noise, distorted signals due to partly obstructed catheters, and occasionally a poorly defined dicrotic notch in the aortic pulse. Despite these difficulties, acceptable measurements were obtained from 155 beats from the 10 subjects, and Figure 2.4 shows a scattergram of aortic-derived LVET versus carotid-derived LVET for these beats. The regression equation for this data is:

$$\text{LVET(aortic)} = 32.2 + 0.885\ \text{LVET(carotid)}$$

with a correlation coefficient of 0.93 and a standard deviation about the line of 8.1 msec. It is interesting to compare this with the results recently reported by van de Werf et al (56) based on a group of 26 patients under what appear to be much better controlled conditions. They obtained the equation:

$$\text{LVET(aortic)} = -20.75 + 1.09\ \text{LVET(carotid)}$$

with a correlation coefficient of 0.98 using the right carotid pulse and a similar equation with a correlation coefficient of 0.99 using the left carotid. Although they do not quote standard deviations for their regressions they are clearly smaller than that obtained in the present study, judging by their correlation coefficients.

Although the slope of the regression obtained here is less than 1.0 (while it is greater than 1.0 in van de Werf's study), it should be observed that the regression line of the present study is such that it predicts equality of the aortic and carotid measurements at about 280 msec. with a difference ranging from 3.5 to -5.2 msec. over a range of ejection

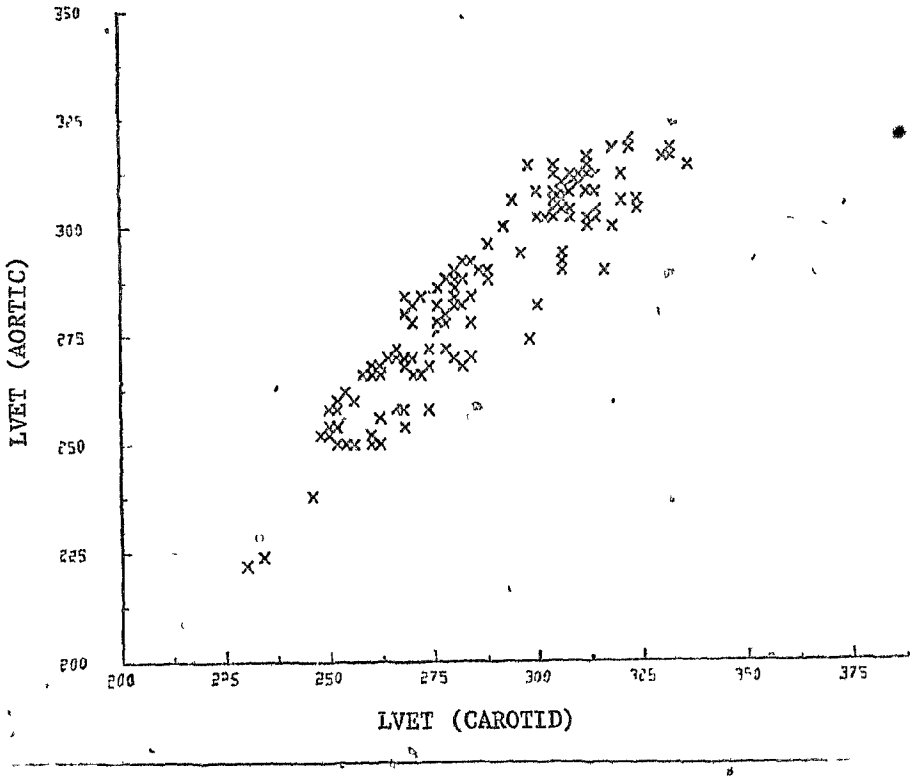


Figure 2.4 - LVET measured from the aortic pressure record versus LVET measured from the external carotid artery pulse.

times from 250 to 325 msec. In other words, the difference between internal and external measurements is not appreciably more than the 8.1 msec. scatter about the regression line. Allowing for the scatter probably introduced by the presence of 60 Hz noise noted earlier (computer logic might easily "lock in" to the 60 Hz signal), it is likely that an experiment conducted under better conditions would in fact show a much better correlation, in agreement with results already reported by others.

The second experiment conducted was designed to compare measurements obtained with the computer program with measurements obtained visually from the same records. For this purpose the averaged signals from 99 consecutive resting and exercise records which had already been measured by the analysis program were plotted using a digital incremental plotter at an effective paper speed of 4 inches per second (101.6 mm/sec) on paper with scale graduations every 0.04 inches (10 msec.). The computer indication of the onset of QRS was used as a time reference. The onsets of the first and second heart sounds (S1 and S2) and the upstroke (P1) and dicrotic notch (P2) of the pulse waves were then read visually by the author and the measurements so obtained were transcribed to punched cards for correlation with the computer measurements already available.

Figures 2.5 to 2.8 show scattergrams of the computer measurements (vertical axis) versus visual measurements (horizontal axis) for the time points S1, S2, P1 and P2 respectively, and Figures 2.9 to 2.11 show similar scattergrams of LVET, PEP and PEP/LVET computed from these time points. The regression equations corresponding to these scattergrams are summarized in Table 2.1. The agreement between computer and visual measurements of S1 is poor, but this time point is not used to compute any of the principal intervals. The agreement for the other three time points is

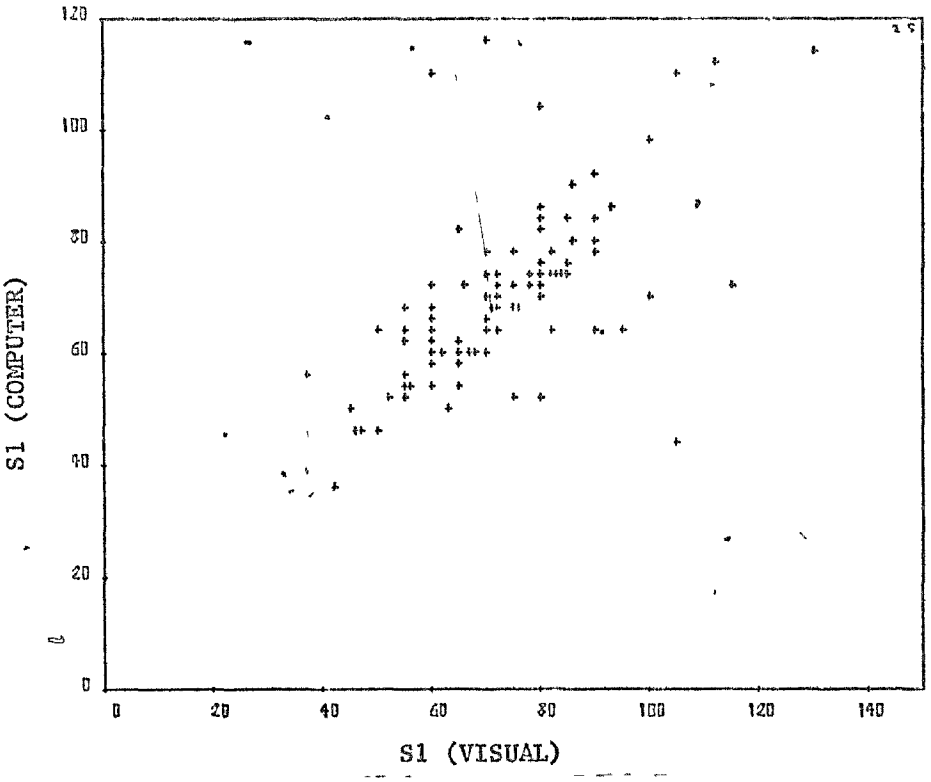


Figure 2.5 - Scattergram of computer measurements vs visual measurements of onset of first heart sound (S1) in 99 records.

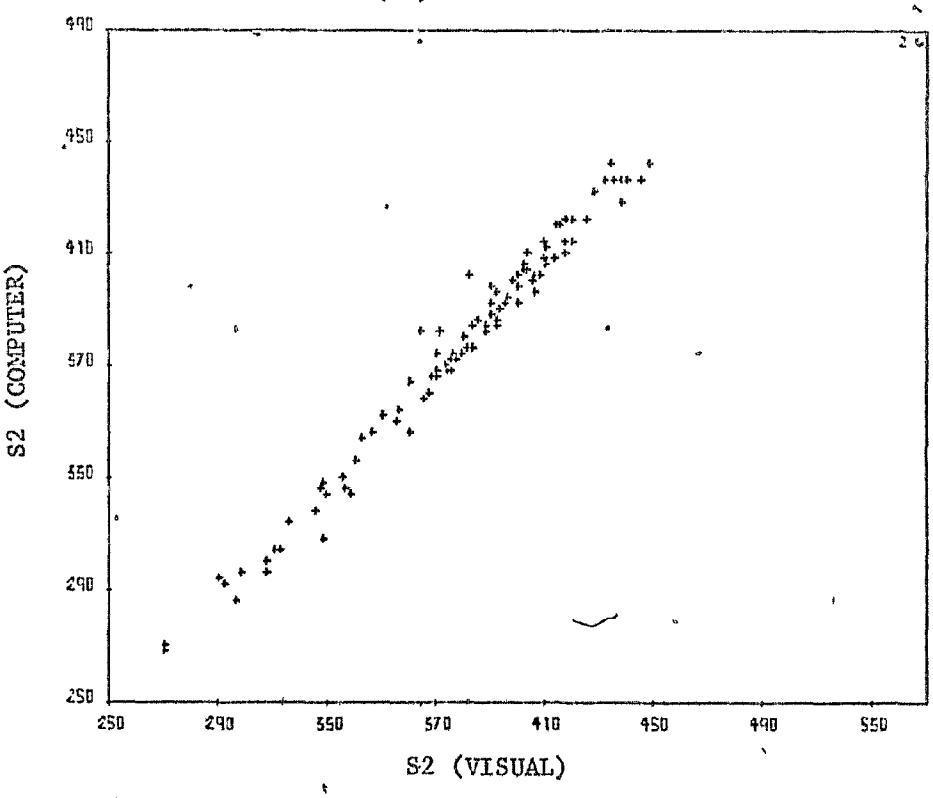


Figure 2.6 - Scattergram of computer measurements vs visual measurements of onset of second heart sound (S2) in 99 records.

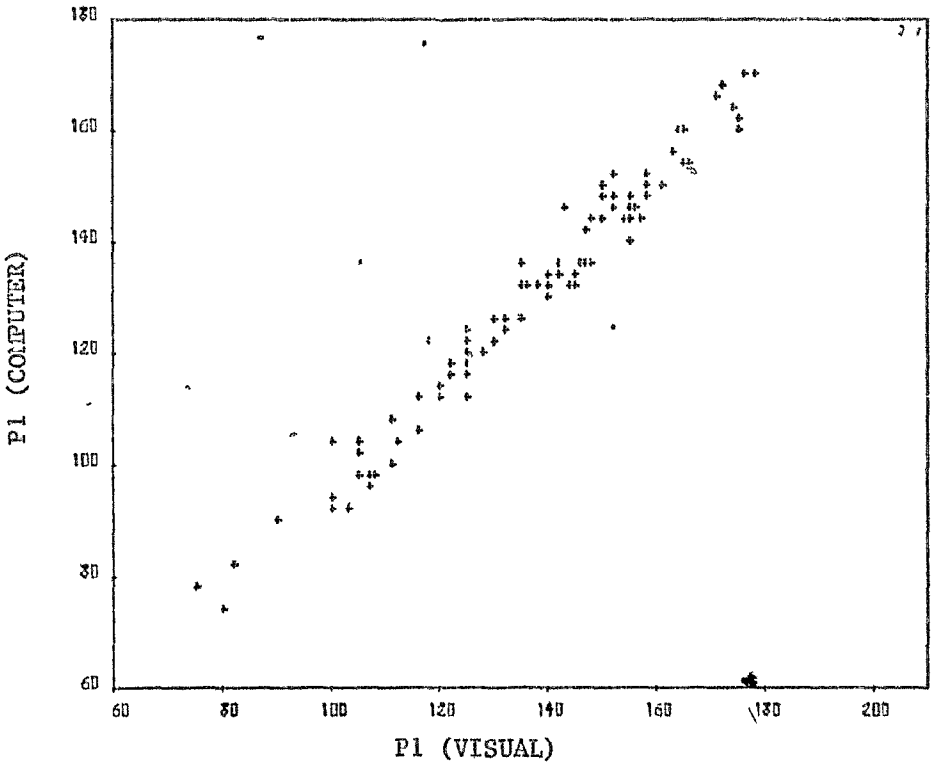


Figure 2.7 - Scattergram of computer measurements vs visual measurements of upstroke of carotid pulse (P1) in 99 records.

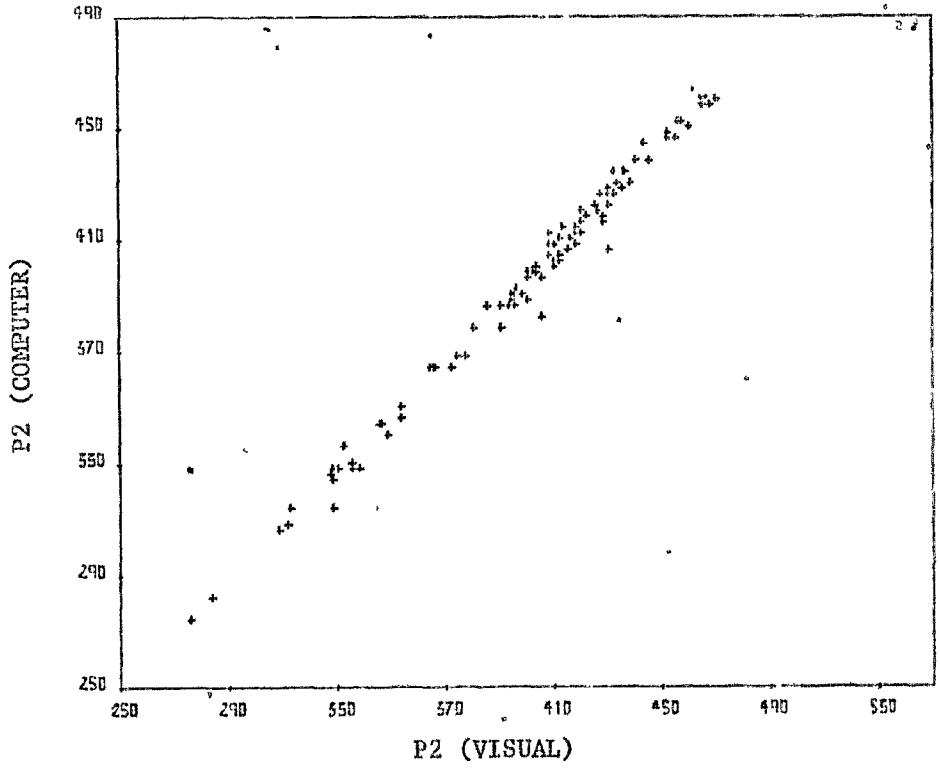


Figure 2.8 - Scattergram of computer measurements vs visual measurements of incisura of carotid pulse (P2) in 99 records.

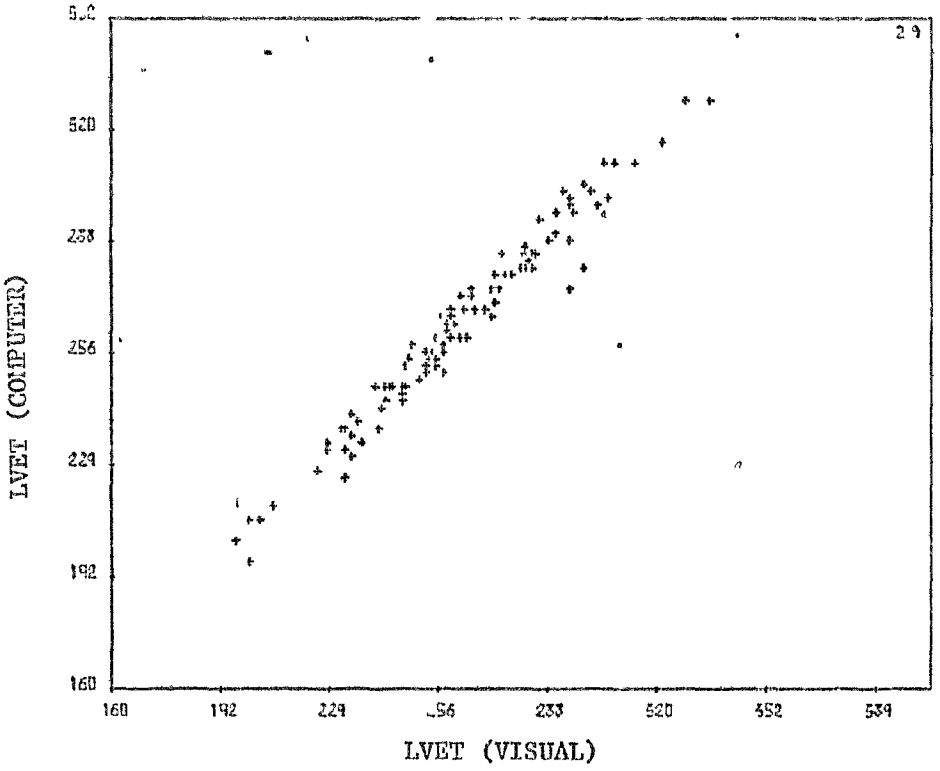


Figure 2.9 - Scattergram of computer measurements vs visual measurements of left ventricular ejection time (LVET) in 99 records.

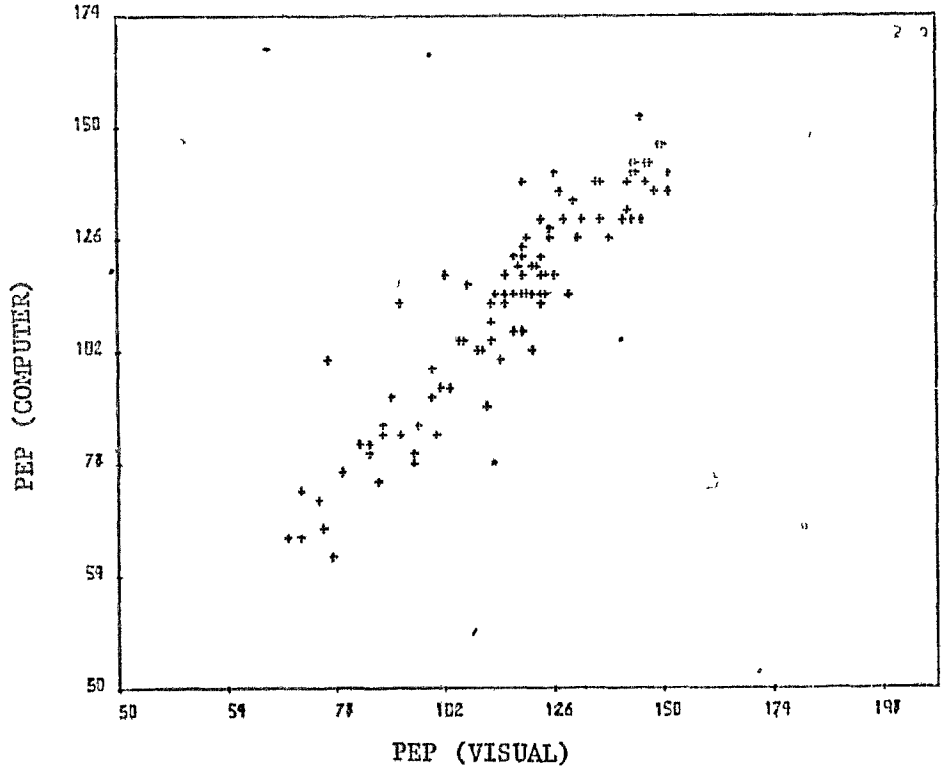


Figure 2.10 - Scattergram of computer measurements vs visual measurements of pre-ejection period (PEP) in 99 records.

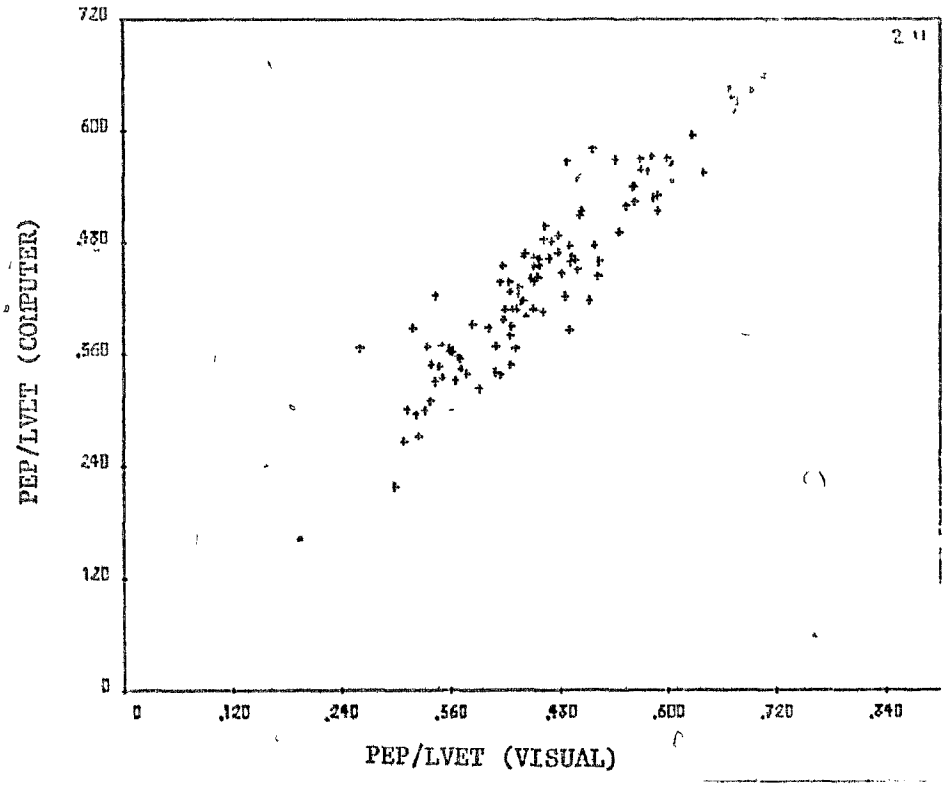


Figure 2.11 - Scattergram of computer measurements vs visual measurements of ratio PEP/LVET in 99 records.

TABLE 2.1

Regression equations relating computer (Y) to visual (X) measurements of the onsets of the first and second heart sounds (S1 and S2), the upstroke (P1) and incisura (P2) of the carotid pulse, and the STI variables LVET, PEP and PEP/LVET derived from these time points for 99 consecutive STI records. The computer measurement of the onset of QRS is used as a reference for both computer and visual measurements. The equation for QS_2 is thus identical to the equation for S2.

VARIABLE	REGRESSION EQUATION	CORRELATION COEFFICIENT	S.D. ABOUT LINE
S1	Y = 26.9 + 0.59 X	0.63	12.0
S2	Y = 11.9 + 1.03 X	0.99	5.9
P1	Y = 2.2 + 0.93 X	0.98	4.0
P2	Y = 5.2 + 0.97 X	0.99	4.5
LVET	Y = 14.2 + 0.95 X	0.98	5.1
PEP	Y = -0.6 + 0.97 X	0.93	8.3
PEP/LVET	Y = 0.039 + 0.87 X	0.89	0.037

very good, with the correlation coefficients never going below 0.98. It should be noted, however, that even with the large correlations achieved, the standard deviations about the regression lines are still at least 4 msec. This of course probably represents the measurement limit attainable from visual measurements at the effective paper speed used, and represents only 2 sample points in the digital data, sampled at 2 msec. intervals. The standard deviations in P1 and P2 are both essentially at this limit, and the standard deviation in S2 (and thus QS_2) is somewhat higher at 5.9 msec. Looking at the systolic time intervals themselves, the scatter in the time points used in their measurement is compounded, as would be expected. Although the agreement between computer and visual measurements is still very good, the correlation coefficients are lower than those computed for single time points, and the scatter is higher. The residual standard deviation for LVET (5.1 msec.) compares well with the figure of 4.8 msec. reported by Spodick et al (48) for LVET in a multiple observer study using paper tracings. The computation of PEP requires both time points involved in LVET as well as the time point S2, and the result is a higher residual standard error (8.3 msec.). This points out the advantage to be gained from the development of a methodology which eliminates the need of the phonocardiogram, as suggested recently by Spodick and Lance (49). They show that the interval Q-P1 tracks PEP closely (and that Q-P2 tracks Q-S2) and recommend taking advantage of this fact in the computation of systolic time intervals to avoid the noise problems encountered in the phonocardiogram during exercise. Although this approach is not used in the current study, it is clear from Table 2.1 that an additional advantage in measurement precision may be achievable from this technique.

The high degree of scatter seen in PEP/LVET points out the extreme sensitivity of this parameter to small errors in P1, P2 and S2 and suggests caution in trying to attach significance to small changes observed in this variable in individual subjects.

E. Statistical Procedures

The statistical tests performed on the data are all designed to test for differences between two multivariate distributions, one of which is always the appropriate sample distribution for a control group of "normal" subjects, and the other is the sample distribution for a test group which we would like to be able to separate ("discriminate") from the normal group on the basis of the variables measured. If it is assumed that the sample distributions are multivariate normal, the complete statistical description of each distribution consists of its sample size, mean vector and covariance matrix.

The computations required for multivariate statistical tests require the inverses of the covariance matrices. For this reason, the covariance matrices must be kept non-singular, which require that the measurement variables used be linearly independent. Since the interval QS_2 is a linear combination consisting of PEP and LVET, it was dropped from the computations. This implies no loss of information for the purpose of discriminant analysis. The ratio PEP/LVET, on the other hand, is a non-linear combination of PEP and LVET and does not upset the stability of the covariance matrices. The final set of variables in the measurement vector consisted of HR, LVET, PEP and PEP/LVET, giving rise to 4x4 covariance matrices. When data for two states is combined, a measurement vector of 8 variables is produced, and the covariance matrices become 8x8.

The differences between two populations can lie in differences in the means vectors, in the covariance or "dispersion" matrices, or in a combination of both. The primary statistical tests performed here are based on a set of three complementary null hypotheses:

H_0: The populations have the same means and dispersions

H_1: The populations have the same dispersions but may differ in the means

H_2: Given that the dispersions are the same, the test is that the means are the same

Each of these hypotheses can be tested using a likelihood ratio, as outlined in Chapter 42 of Kendall and Stuart (23). These likelihood ratios can be transformed (approximately) to χ^2 scores with degrees of freedom equal to the number of constraints imposed by the hypothesis being tested. In the case of 4 variables, there are 14 degrees of freedom in H_0, partitioned to 10 d.f. for H_1 (test of covariance matrices) and 4 d.f. for H_2 (test of means).

An effective linear discriminant function can only be developed when the means of two populations are separated to a sufficient degree. A good measure of this separation is the quantity D^2, the Mahalanobis (squared) generalized distance between the samples (68). This is computed for all of the subject groups considered as:

$$D^2 = \sum_{i=1}^{k} \sum_{j=1}^{k} (\bar{x}_{i1} - \bar{x}_{i2}) W'_{ij} (\bar{x}_{j1} - \bar{x}_{j2})$$

where $\bar{x}_{it}$ = mean value for variable i for group t

W'_{ij} = element ij of the inverse of the within-groups covariance matrix W

k = number of variables

For a given pair of populations, D^2 can be tested by transforming it to Hotelling's T_o^2, and thence to an F ratio as shown by Rao (41a). This test is essentially equivalent to the likelihood ratio test for H_2.

Since it was found that D^2 was frequently very small in the groups considered, but that the scatter in these groups was usually larger than the scatter in the normal population, a procedure was developed to identify sample vectors which lay beyond a 90% confidence limit from the center of the distribution for normal subjects. This was done by computing an individual D^2 for each subject, as

$$D^2 = \sum_{i=1}^{k} \sum_{j=1}^{k} (x_i - \mu_i) A'_{ij} (x_j - \mu_j)$$

where x_i = individual measurement for variable i

μ_i = mean value for variable i in normal population

A'_{ij} = element ij of the inverse of the covariance matrix A for the normal population

k = number of variables

This upper 90% limit of D^2 was established for normals, and using this limit as a threshold, the number of subjects with D^2 greater than this threshold in each abnormal group was counted and expressed as a percentage. This count is referred to as the "generalized outlier count".

CHAPTER III

Systolic Time Intervals In Normal Subjects

1. Description of Group

The normal group was extracted from a pool containing clinical data and STI measurements for the three European male population samples mentioned in the previous chapter, and for the Helsinki police department. The men in the pool cover the age range from 35 to 70 years, with most of the men under 50 coming from the police group. The original data pool contained 7380 sets of measurements from 2997 subjects. After excluding all subjects with bundle branch block or on cardioactive medications, good resting supine measurements were obtained from 2649 (88.4%) of these subjects, and post-exercise measurements from 909 (30.3%). Good resting upright measurements were obtained from 1033 (85.9%) of the 1202 policemen in the pool. 447 (10.8%) of the 4129 resting records were rejected because of measurement errors, and 2203 (67.8%) of the 3251 post-exercise records were lost for the same reason. About 50% of the 2650 measurement errors were due to a logic breakdown in the computer program caused by noisy pulse waveforms and the remainder were excluded after visual inspection of the computer plots revealed errors not detected by the program itself. In addition, a small number of records were discarded because the clinical information for some subjects was incomplete.

For each state, the normal control groups were extracted from the remaining records by excluding all subjects with any evidence of heart disease on the basis of physical examination, history or resting ECG, including all subjects with diastolic blood pressure greater than 95 mm Hg or systolic pressure greater than 160 mm Hg. The final control groups

were based on 1457 resting supine subjects, 790 resting upright subjects, and 570 subjects immediately after submaximal bicycle exercise.

2. Results

Regression data of systolic time intervals with the heart rate for the normal group are summarized in Table 3.1 and the corresponding scattergrams for the resting supine state are shown in Figures 3.1 to 3.4 (n=1457). The two ellipses on each plot represent the 50% and 90% limits of the assumed bivariate normal distributions corresponding to the computed regressions. The irregular elliptical curves represent the same limits for the estimated bivariate frequency distribution of the raw data. The relatively close match of these two sets of curves is an indication of the validity of the assumption of bivariate normal distribution. A slight deviation from normality is indicated by a slight skewness in the direction of higher heart rates and a slight upward deviation of the data points for LVET, PEP and QS_2 in the same region. These upward curving tails cause a slight decrease in the regression slopes computed for LVET and QS_2.

Similar data for the normal group in the resting upright state (n=790) is shown in Figures 3.5 to 3.8. The distributions display less skewness and curvature than the supine data, indicating that there is less deviation from normality in this state. The correlation coefficients are again highly significant, the "worst" being that for PEP, which is significant at a P value of 10^{-7}. The regression lines for LVET and QS_2 are a little flatter than in the supine case, and are displaced downwards in the order of 20 msec., while the behavior of PEP is largely unchanged. The ratio PEP/LVET is increased by about one standard deviation over the

TABLE 3.1

Systolic Time Intervals In Normal Subjects:
Mean Values and Heart Rate Regressions

	Mean Value		Regression With Heart Rate				
Variable	Mean	S.D.	Intercept	Slope	S.D.	Correlation	P
A - Resting Supine. N = 1457							
HR	67.0	11.3					
LVET	292.1	23.0	403.5	-1.66	13.2	-.819	<.001
PEP	112.5	14.4	132.7	- .30	14.0	-.237	<.001
QS_2	404.6	28.4	536.2	-1.96	17.7	-.781	<.001
PEP/LVET	.387	.056	.305	.00124	.054	.249	<.001
B - Resting Upright. N = 790							
HR	75.4	11.5					
LVET	260.9	22.2	376.5	-1.53	13.6	-.791	<.001
PEP	115.8	15.2	134.3	- .24	14.9	-.184	<.001
QS_2	376.7	25.7	510.7	-1.78	15.6	-.794	<.001
PEP/LVET	.448	.072	.319	.00170	.070	.270	<.001
C - Post-Exercise. N = 570							
HR	94.7	16.0					
LVET	241.0	26.5	369.0	-1.35	15.3	-.818	<.001
PEP	78.0	14.1	101.2	- .24	13.5	-.279	<.001
QS_2	319.1	31.2	480.2	-1.60	17.9	-.820	<.001
PEP/LVET	.327	.067	.242	.00090	.066	.214	<.001

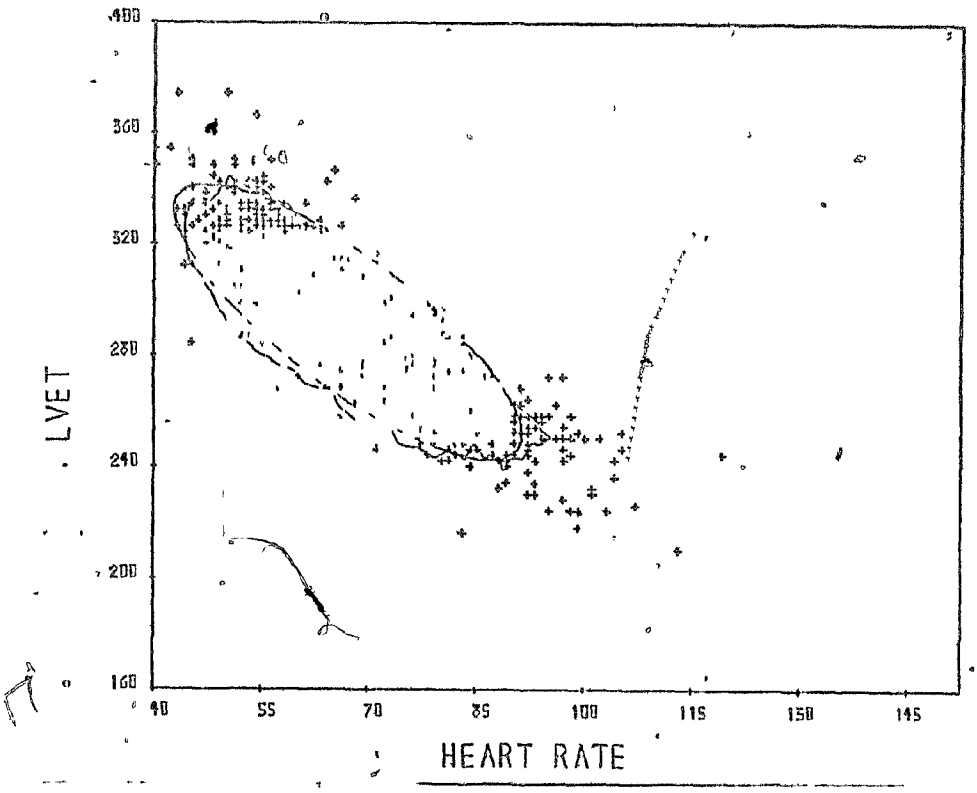


Figure 3.1 - Resting supine scattergram of LVET vs HR for 1457 normal subjects. The pair of ellipses represent the 50 and 90% confidence limits of the distribution in this plane. The irregular ellipses represent the same limits for the actual frequency distribution function computed from the raw data.

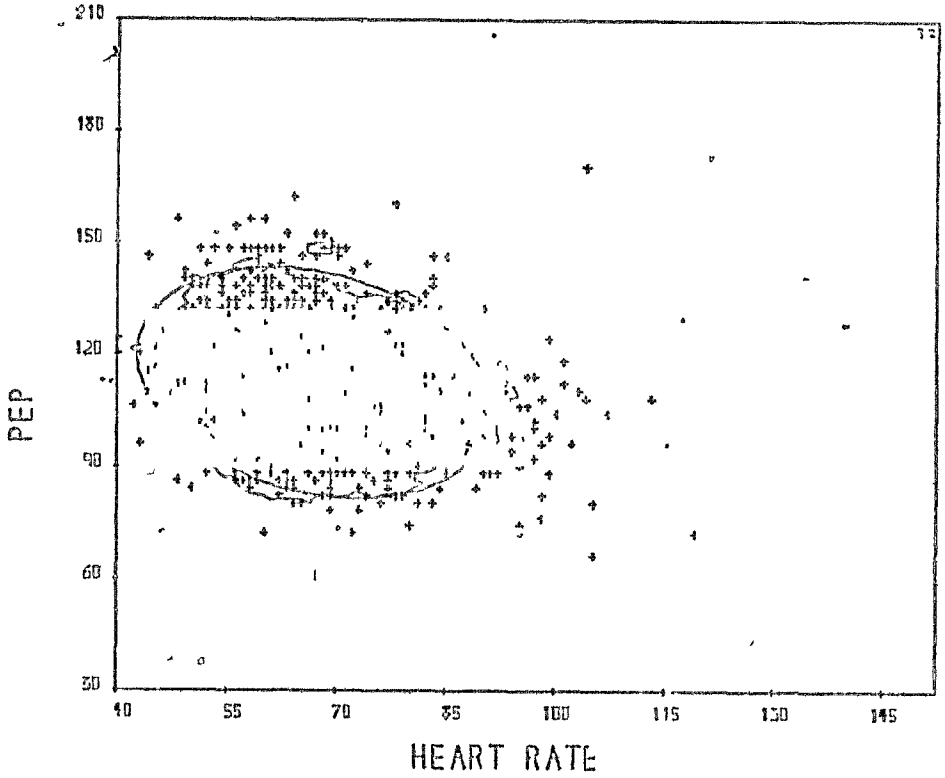


Figure 3.2 - Resting supine scattergram of PEP vs HR for 1457 normal subjects. See Figure 3.1 legend for details.

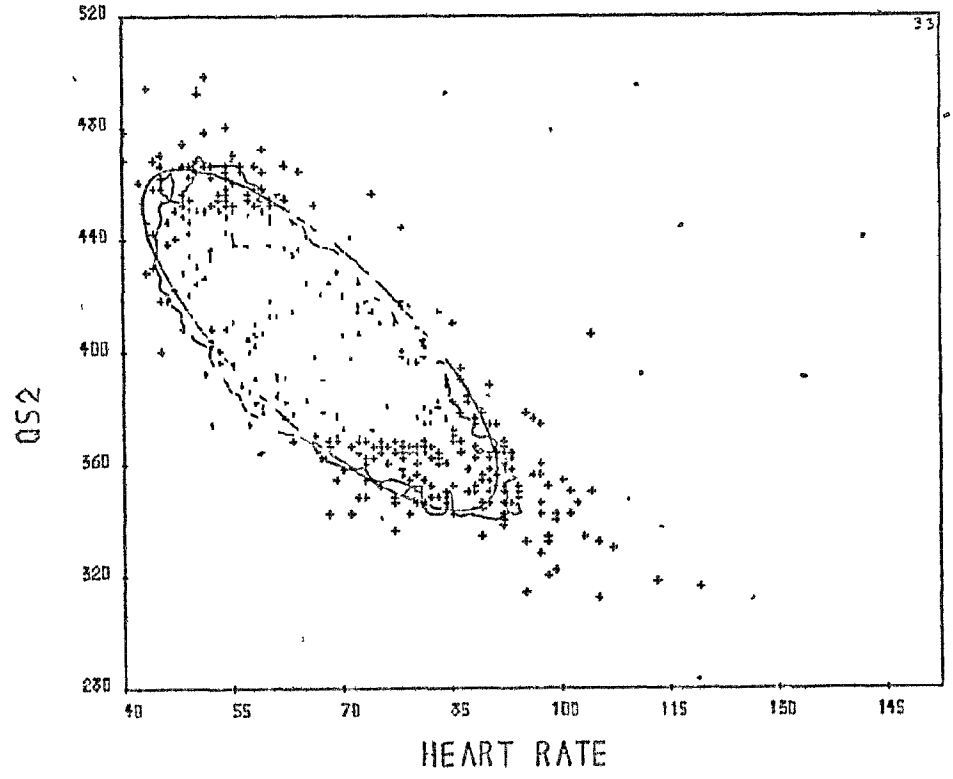


Figure 3.3 - Resting supine scattergram of QS_2 vs HR for 1457 normal subjects. See Figure 3.1 legend for details.

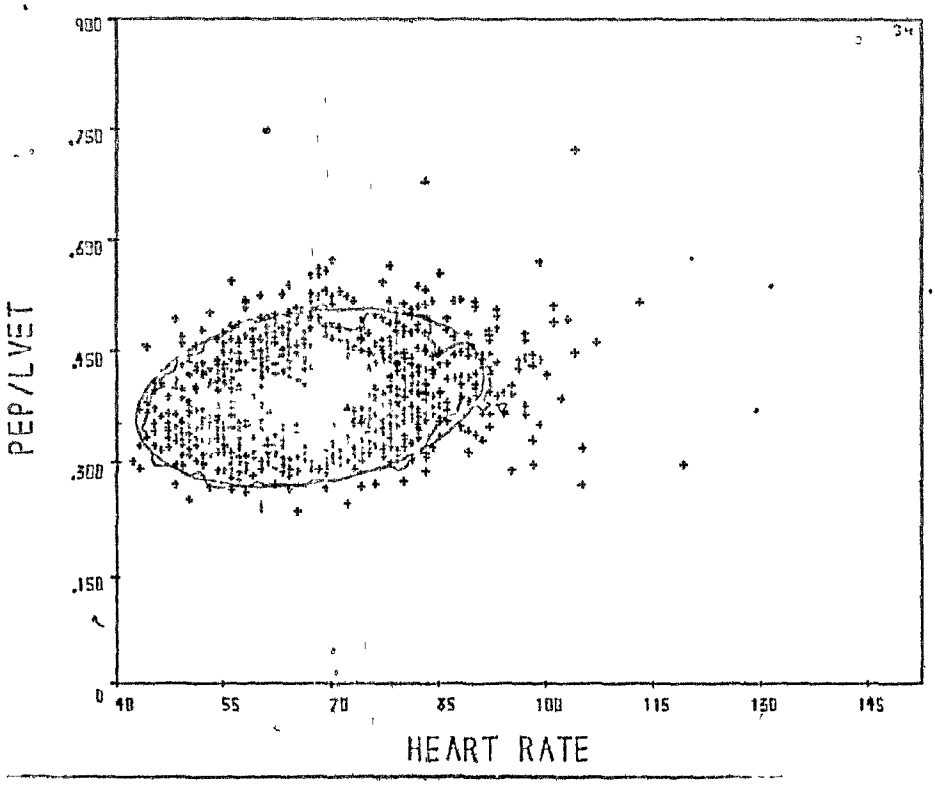


Figure 3.4 - Resting supine scattergram of PEP/LVET vs HR for 1457 normal subjects. See Figure 3.1 legend for details.

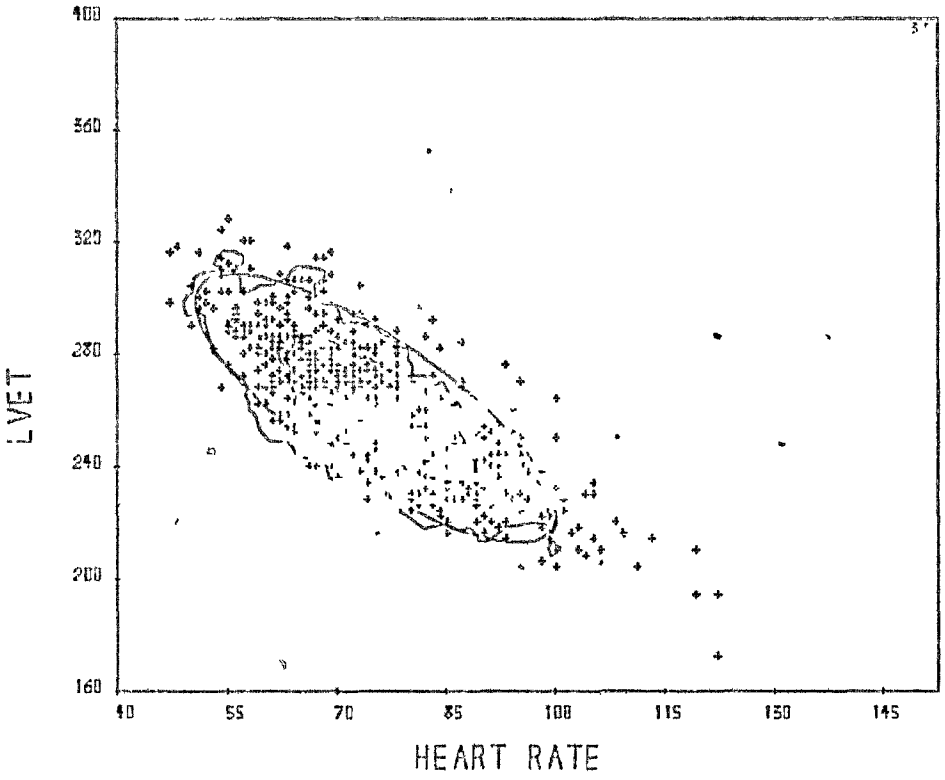


Figure 3.5 - Resting upright scattergram of LVET vs HR for 790 normal subjects. See Figure 3.1 legend for details.

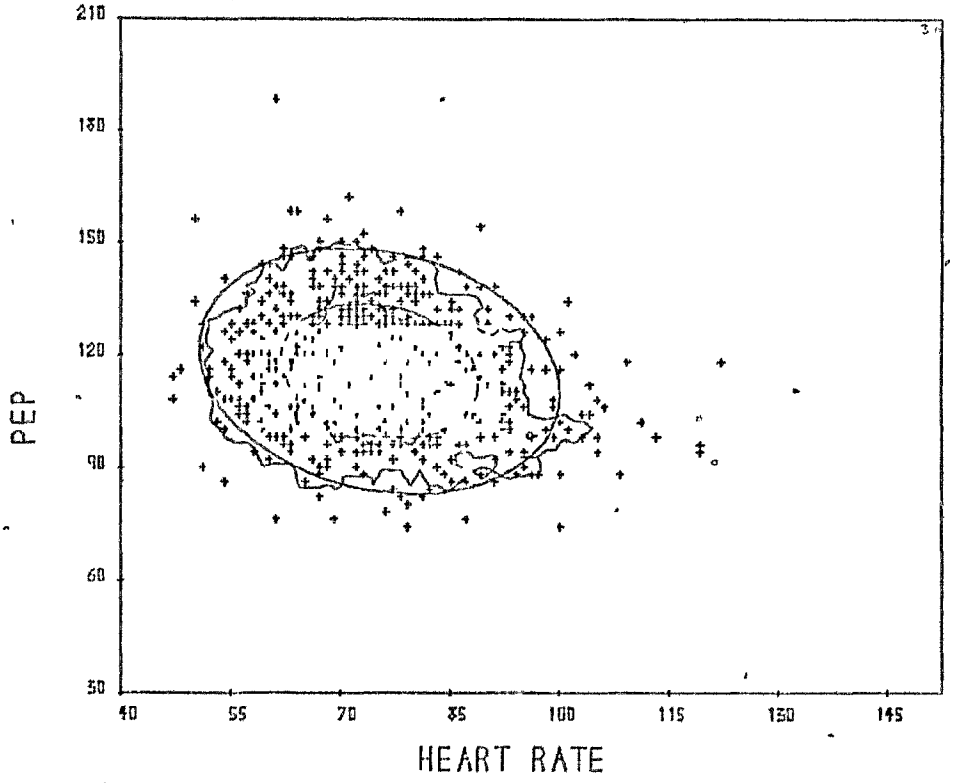


Figure 3.6 - Resting upright scattergram of PEP vs HR for 790 normal subjects. See Figure 3.1 legend for details.

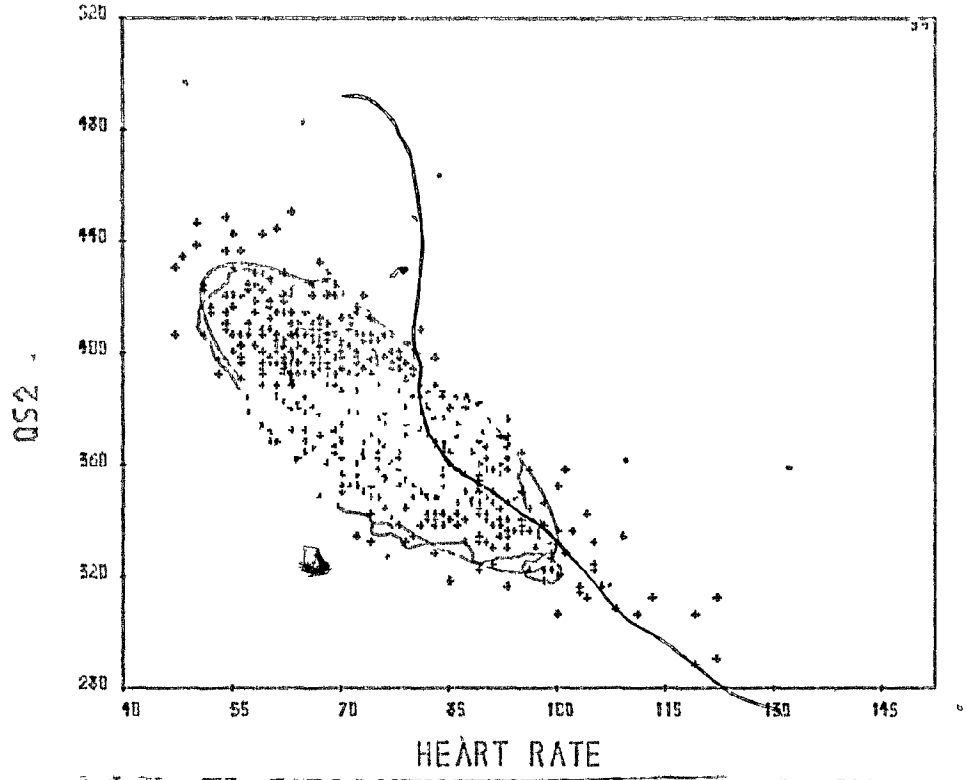


Figure 3.7 - Resting upright scattergram of QS_2 vs HR for 790 normal subjects. See Figure 3.1 legend for details.

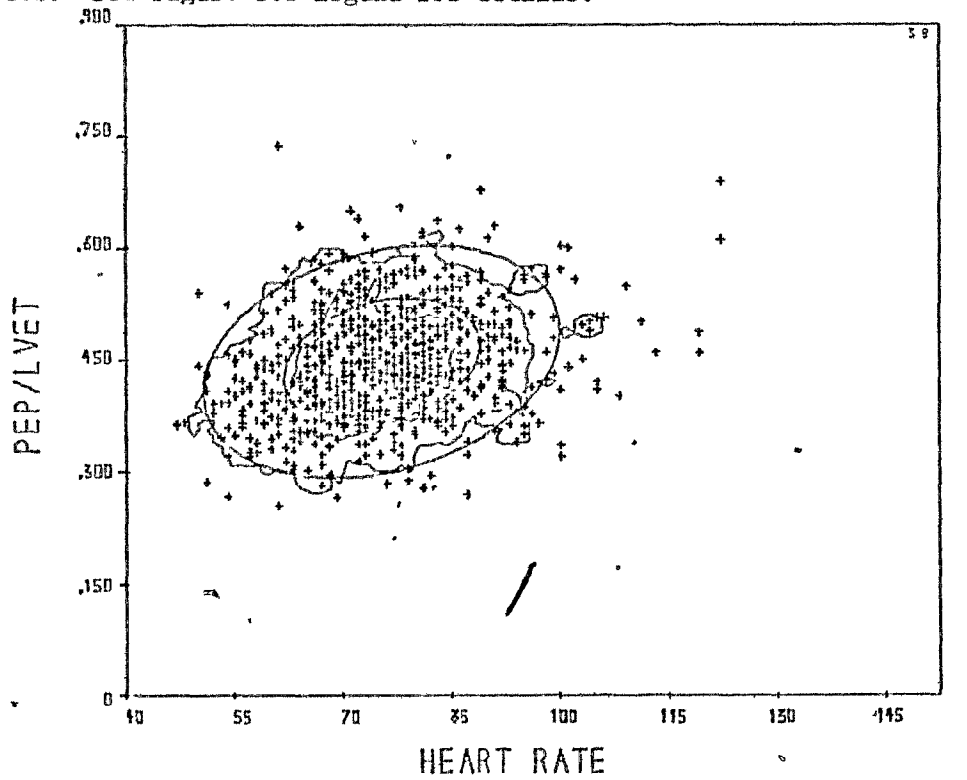


Figure 3.8 - Resting upright scattergram of PEP/LVET vs HR for 790 normal subjects. See Figure 3.1 legend for details.

mean supine value, and the mean heart rate is increased by about 8 beats per minute.

Figures 3.9 to 3.12 show the results in this group after exercise (n=570). This data is best compared with the resting upright results, since the posture was the same for both series (upright position on a bicycle ergometer). The significant increase in heart rate after exercise is accompanied by equally significant decreases in LVET, PEP, QS_2 and PEP/LVET. If the scattergrams are compared it is seen that the decrease in LVET is not very different from what you would expect to see from the increased heart rate alone, using the regression coefficient derived at rest. The decrease in PEP, however, cannot be explained on the basis of heart rate, and this applies also to QS_2, which of course contains both PEP and LVET as components. The ratio PEP/LVET decreases after exercise, from the elevated value seen in the resting upright state to a value considerably smaller than that seen in the supine position.

The multivariate statistical description of these normal groups, consisting of sample size, means vector and covariance matrix, is shown in Table 3.2. To keep the covariance matrices non-singular, the variable QS_2 has been omitted, since it is a linear combination (i.e. the sum) of LVET and PEP. Although the ratio PEP/LVET is obviously also a combination of these variables, it is a non-linear combination, and does not upset the stability of the matrices.

In 707 normal subjects a good record was obtainable for both the resting supine and resting upright states, giving rise to the 8x8 covariance matrix shown with its means vector in Table 3.3. The variables in this case consist of a set of the four STI variables for each of the two states. The corresponding correlation matrix is shown in Table 3.6.

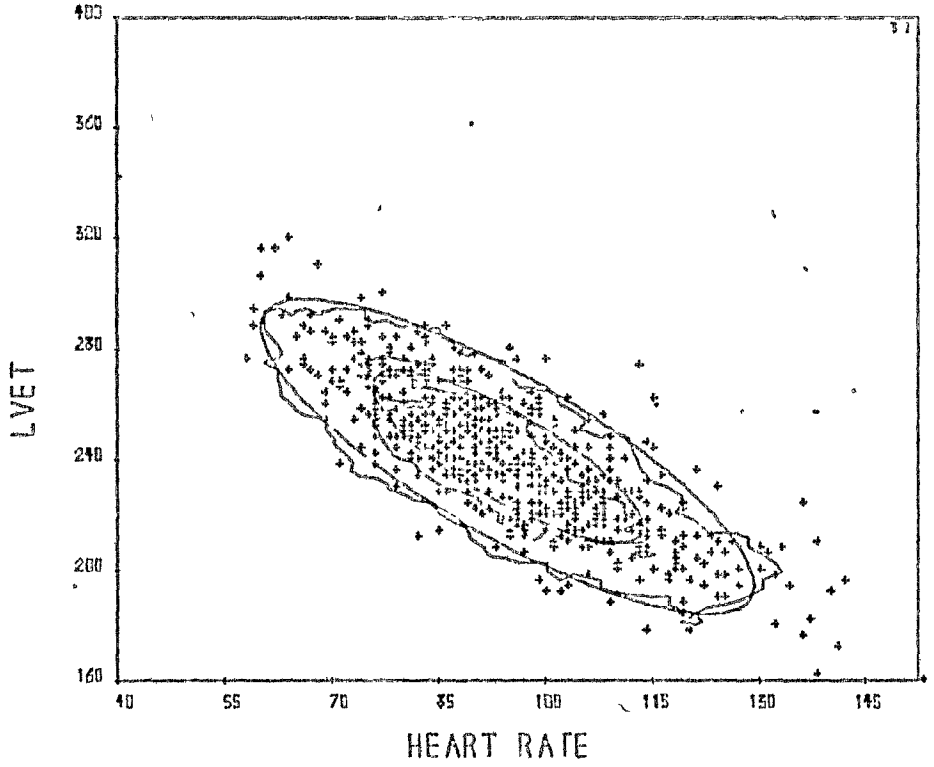


Figure 3.9 - Post-exercise scattergram of LVET vs HR for 570 normal subjects. See Figure 3.1 legend for details.

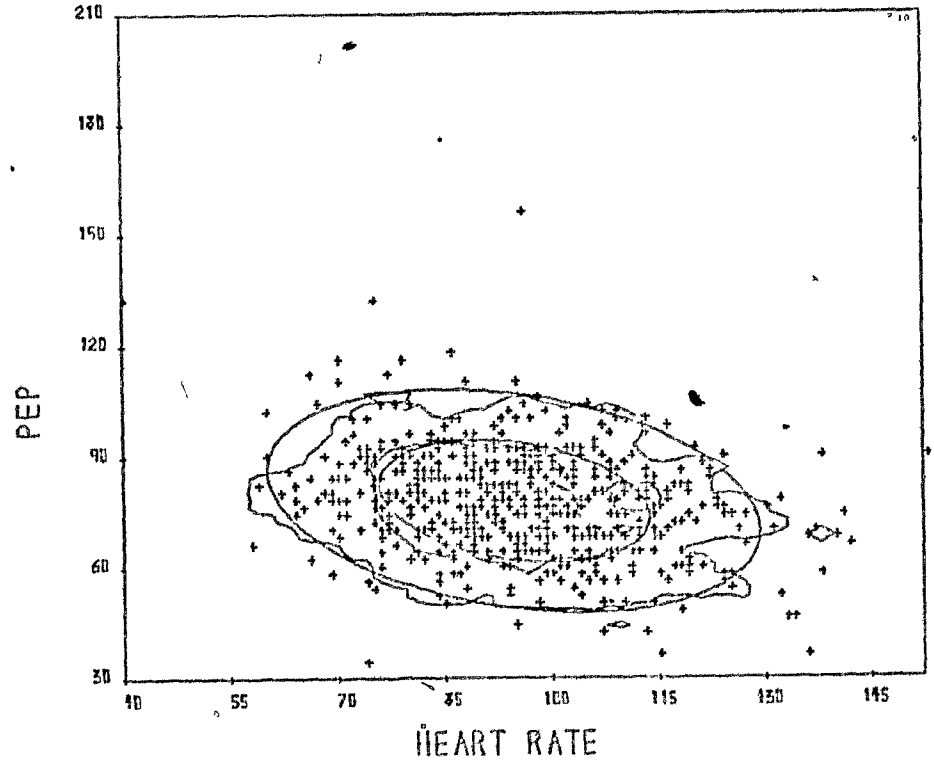


Figure 3.10 - Post-exercise scattergram of PEP vs HR for 570 normal subjects. See Figure 3.1 legend for details.

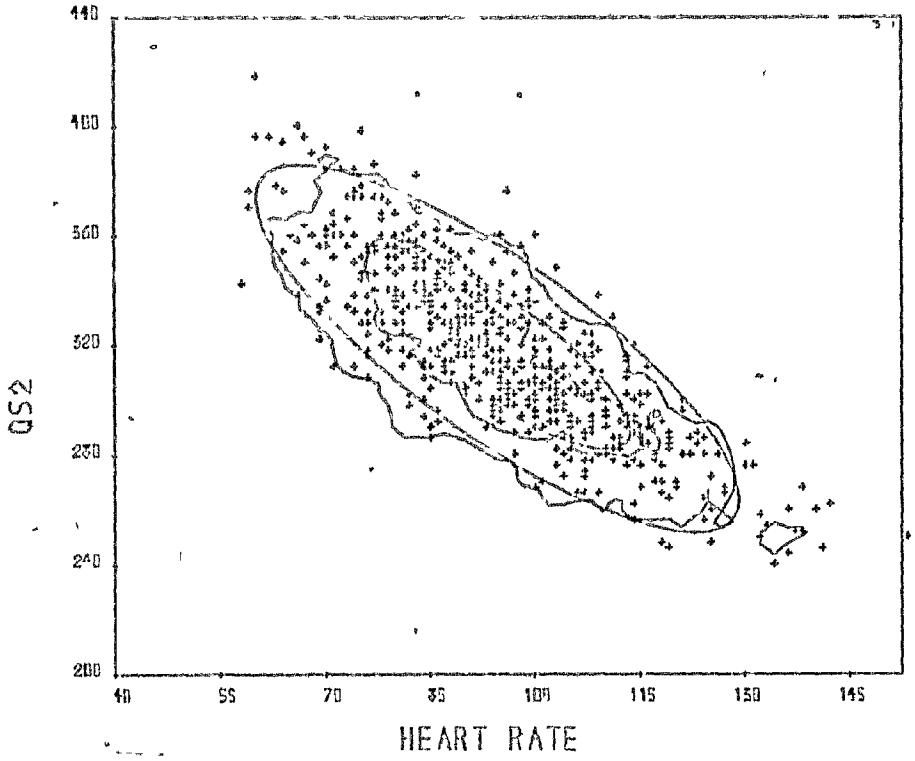


Figure 3.11 - Post-exercise scattergram of QS_2 vs HR for 570 normal subjects. See Figure 3.1 legend for details.

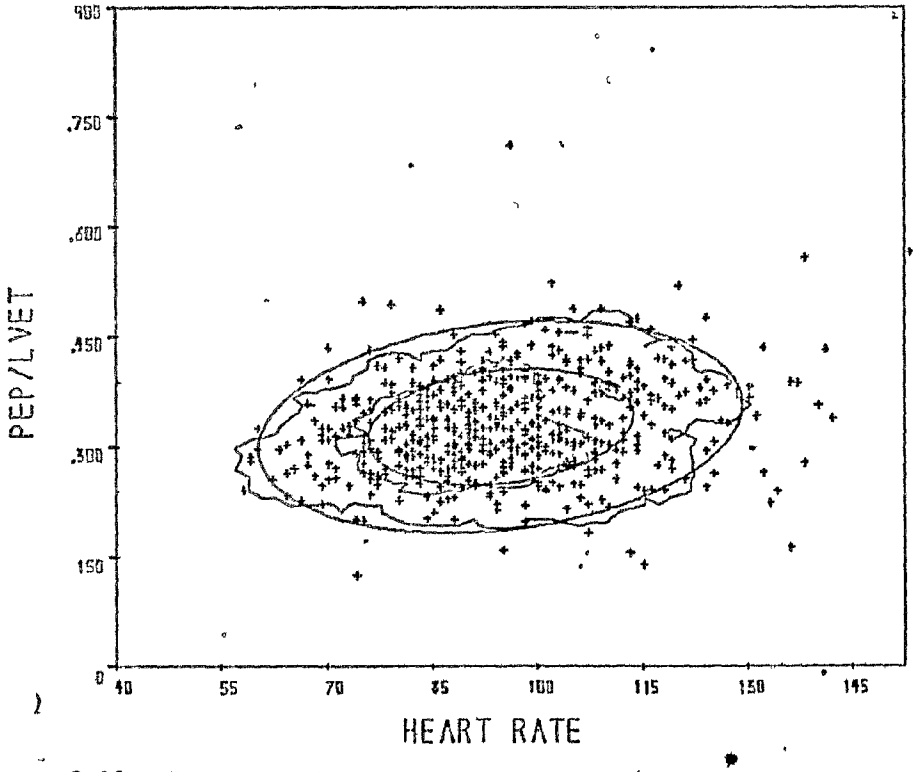


Figure 3.12 - Post-exercise scattergram of PEP/LVET vs HR for 570 normal subjects. See Figure 3.1 legend for details.

TABLE 3.2

Systolic Time Intervals In Normal Subjects:

Means Vectors and Covariance Matrices

A - Resting Supine. N = 1457

	HR	LVET	PEP	PEP/LVET
Means	67.0	292.1	112.5	.387
Covariance				
HR	127.84			
LVET	-212.55	527.46		
PEP	-38.433	36.630	206.53	
PEP/LVET	.15792	-.58926	.66595	.0031361

B - Resting Upright. N = 790

	HR	LVET	PEP	PEP/LVET
Means	75.4	260.9	115.8	.448
Covariance				
HR	131.82			
LVET	-201.99	494.26		
PEP	-32.181	-32.276	230.89	
PEP/LVET	.22429	-.96089	.93487	.0052452

C - Post-Exercise. N = 570

	HR	LVET	PEP	PEP/LVET
Means	94.7	241.0	78.0	.327
Covariance				
HR	257.57			
LVET	-347.89	702.56		
PEP	-63.032	37.096	198.68	
PEP/LVET	.23162	-.83703	.78075	.0045283

TABLE 3.3

Means Vector and Covariance Matrix:

Normal Subjects, N=707. Combined Resting Supine and Resting Upright

		Resting Supine				Resting Upright			
		HR	LVET	PEP	PEP/LVET	HR	LVET	PEP	PEP/LVET
Means		68.1	288.3	110.1	.384	75.4	260.8	116.1	.449
Covariance									
SUPINE	HR	115.27							
	LVET	-184.87	435.23						
	PEP	-22.264	5.6783	199.68					
	PEP/LVET	.17741	-.57677	.68275	.0031724				
UPRIGHT	HR	104.01	-181.30	-9.8208	.21460	123.87			
	LVET	-142.37	347.44	-13.084	-.51545	-189.51	465.98		
	PEP	-40.577	55.146	144.58	.42386	-28.527	-33.942	225.86	
	PEP/LVET	.083651	-.37666	.58046	.0025242	.21300	-.91213	.92138	.0051003

The inter-correlations, especially between the variables for the two states, are worthy of note here. It should also be remembered that this is a subgroup of normal subjects drawn only from the Helsinki Policemen Study, since resting upright records were not recorded in the other field studies.

Table 3.4 shows the same information for the 518 subjects from whom both resting supine and post-exercise records were obtained. Similarly, Table 3.5 contains the data for 264 subjects (again from the Policemen Study) for whom both resting upright and post-exercise records were available. Both correlation matrices can be seen in Table 3.6.

It is, of course, difficult to depict 8-dimensional information graphically. However, the new information obtainable from considering two states simultaneously lies in the changes in the variables from one state to the other. Figures 3.13 to 3.15, therefore, show the changes in LVET, PEP and PEP/LVET from the supine to the upright position plotted against the corresponding changes in heart rate. Similarly, the changes from the resting upright to the post-exercise state are shown in Figures 3.16 to 3.18, and the changes from the resting upright to the post-exercise state are shown in Figures 3.19 to 3.21. The mean changes and the regression relationships corresponding to these scattergrams are contained in Table 3.7.

TABLE 3.4

Means Vector and Covariance Matrix:

Normal Subjects N=518. Combined Resting Supine and Post-Exercise Upright

		Resting Supine				Post-Exercise			
		HR	LVET	PEP	PEP/LVET	HR	LVET	PEP	PEP/LVET
Means		65.6	293.8	114.3	.391	94.7	241.0	77.8	.326
Covariance									
RESTING	HR	122.47							
	LVET	-215.33	550.36						
	PEP	-37.753	47.246	184.71					
	PEP/LVET	.16776	-.58913	.57154	.0027969				
EXERCISE	HR	94.337	-152.60	-39.049	.072576	246.28			
	LVET	-121.09	275.77	63.776	-.14897	-332.46	674.13		
	PEP	2.3480	-17.419	65.497	.25018	-52.168	25.685	189.57	.0043910
	PEP/LVET	.17542	-.44503	.19045	.0012603	.24683	-.82775	.75867	

TABLE 3.5

Means Vector and Covariance Matrix:

Normal Subjects, Ages ?, Combined Resting Upright and Post-Exercise Upright

		Resting Upright				Post-Exercise Upright			
		HR	LVET	PEP	PEP/LVET	HR	LVET	PEP	PEP/LVET
Means		73.7	361.8	118.5	.456	98.2	233.1	77.6	.337
Covariance									
RESTING	HR	130.11							
	LVET	-205.02	475.22						
	PEP	-23.820	-51.150	262.04					
	PEP/LVET	.27512	-1.0212	1.0754	.0058960				
EXERCISE	HR	99.626	-123.84	-54.280	.021579	288.51			
	LVET	-142.05	265.45	44.951	-.30456	-356.04	615.08		
	PEP	23.274	-76.506	111.22	.55551	-64.047	24.390	232.01	
	PEP/LVET	.31191	-.72639	.41145	.0028750	.25343	-.81103	.96214	.0054387

TABLE 3.6

Correlation Matrices For Two-State Pairs, Normal Subjects

1. Combined resting supine and resting upright. N = 707

		Resting Supine				Resting Upright			
		HR	LVET	PEP	PEP/LVET	HR	LVET	PEP	PEP/LVET
SUPINE	HR	1.00							
	LVET	-.83	1.00						
	PEP	-.15	.02	1.00					
	PEP/LVET	.29	-.49	.86	1.00				
UPRIGHT	HR	.87	-.78	-.06	.34	1.00			
	LVET	-.61	.77	-.04	-.42	-.79	1.00		
	PEP	-.25	.18	.68	.50	-.17	-.10	1.00	
	PEP/LVET	.11	-.25	.58	.63	.27	-.59	.86	1.00

2. Combined resting supine and post-exercise upright. N = 518

		Resting Supine				Post-Exercise			
		HR	LVET	PEP	PEP/LVET	HR	LVET	PEP	PEP/LVET
RESTING	HR	1.00							
	LVET	-.83	1.00						
	PEP	-.25	.15	1.00					
	PEP/LVET	.29	-.47	.80	1.00				
EXERCISE	HR	.54	-.41	-.18	.09	1.00			
	LVET	-.42	.45	.18	-.11	-.82	1.00		
	PEP	.02	-.05	.35	.34	-.24	.07	1.00	
	PEP/LVET	.24	-.29	.21	.36	.24	-.48	.83	1.00

3. Combined resting upright and post-exercise upright. N = 264

		Resting Upright				Post-Exercise			
		HR	LVET	PEP	PEP/LVET	HR	LVET	PEP	PEP/LVET
RESTING	HR	1.00							
	LVET	-.82	1.00						
	PEP	-.13	-.14	1.00					
	PEP/LVET	.31	-.61	.87	1.00				
EXERCISE	HR	.51	-.33	-.20	.02	1.00			
	LVET	-.50	.49	.11	-.16	-.85	1.00		
	PEP	.13	-.23	.45	.47	-.25	.06	1.00	
	PEP/LVET	.37	-.45	.34	.51	.20	-.44	.86	1.00

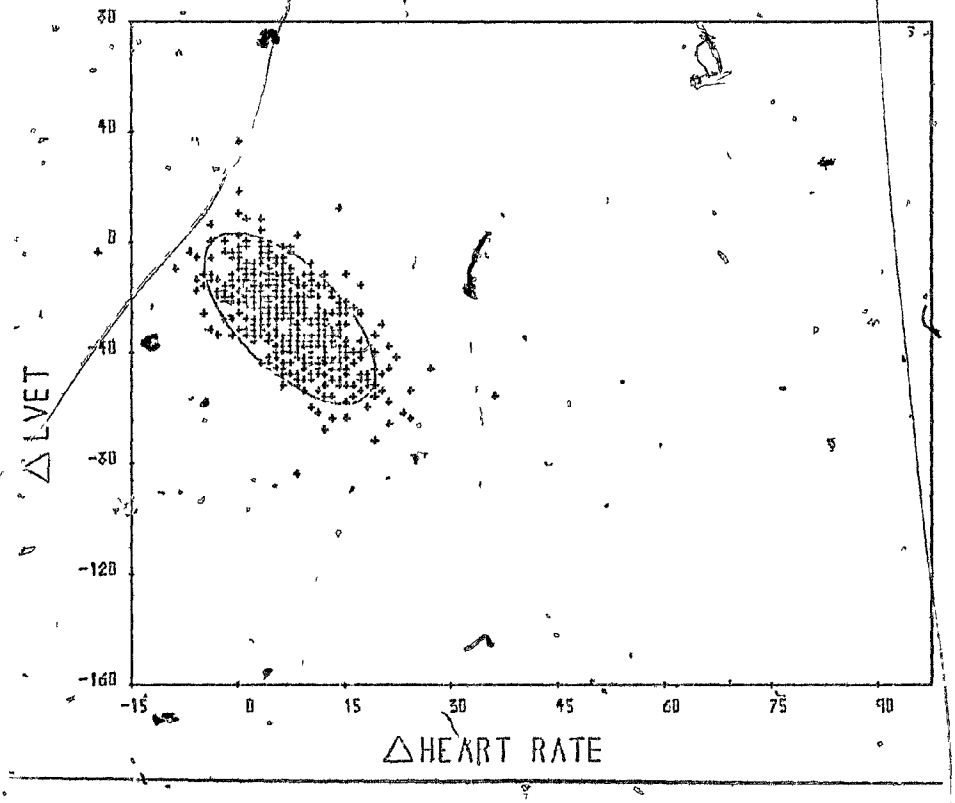


Figure 3.13 - Scattergram of change in LVET vs change in HR from resting supine to resting upright in 707 normal subjects. The pair of ellipses represent the 50% and 90% confidence limits of the distribution in this phase.

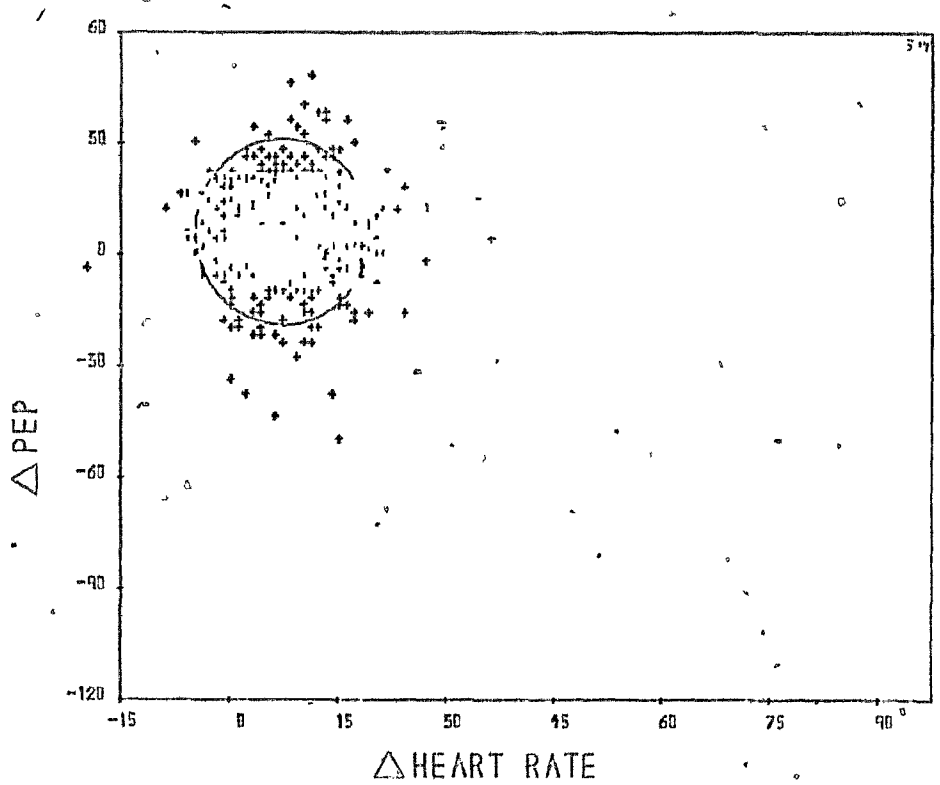


Figure 3.14 - Scattergram of change in PEP vs change in HR from resting supine to resting upright in 707 normal subjects. See Figure 3.13 legend for details.

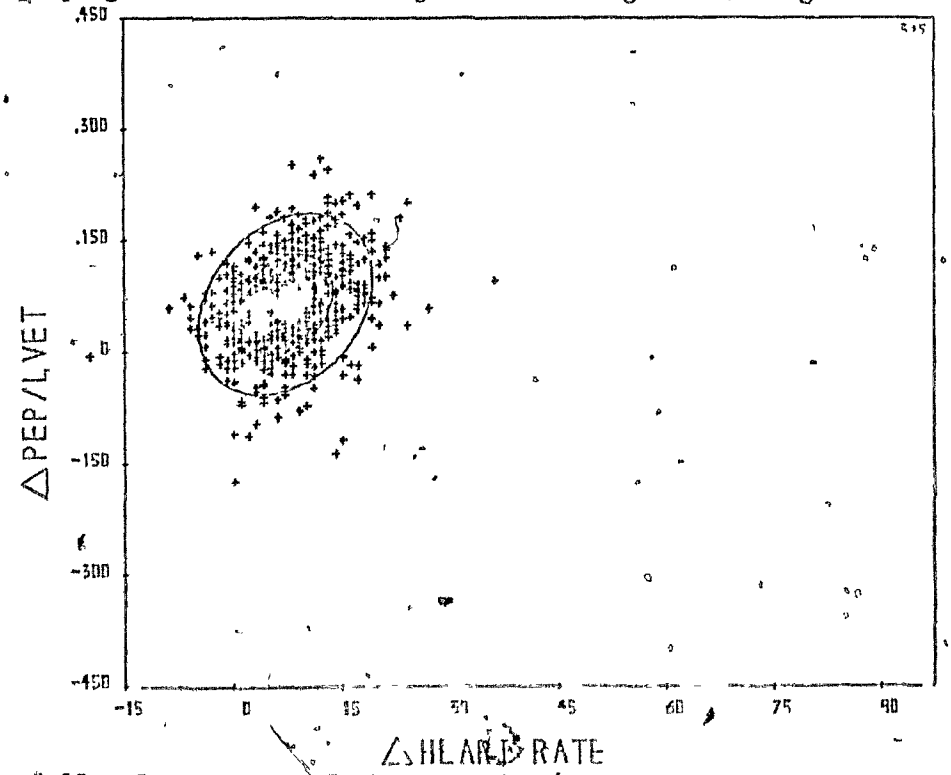


Figure 3.15 - Scattergram of change in PEP/LVET vs change in HR from resting supine to resting upright in 707 normal subjects. See Figure 3.13 legend for details.

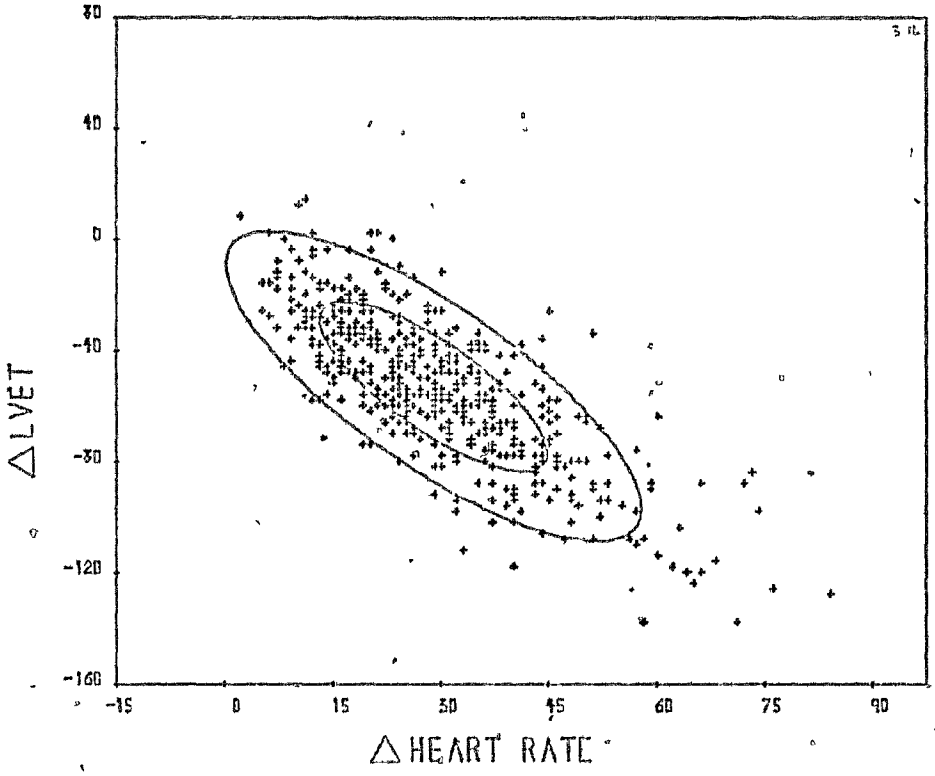


Figure 3.16 - Scattergram of change in LVET vs change in HR from resting supine to post-exercise in 518 normal subjects. See Figure 3.13 legend for details.

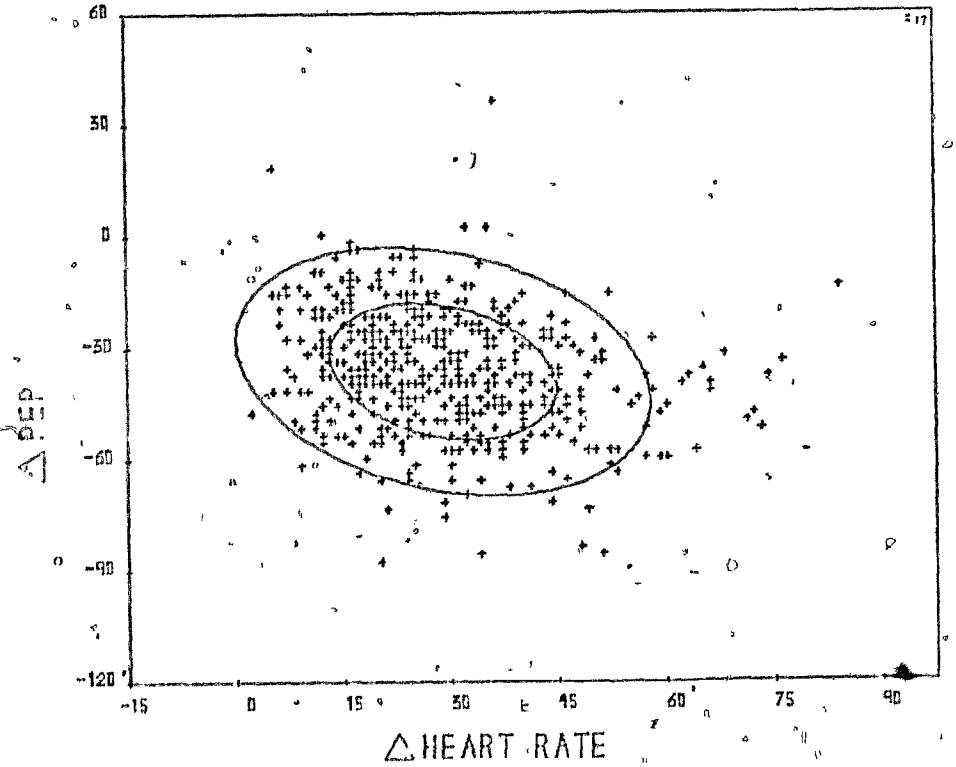


Figure 3.17 - Scattergram of change in PEP vs change in HR from resting supine to post-exercise in 518 normal subjects. See Figure 3.13 legend for details.

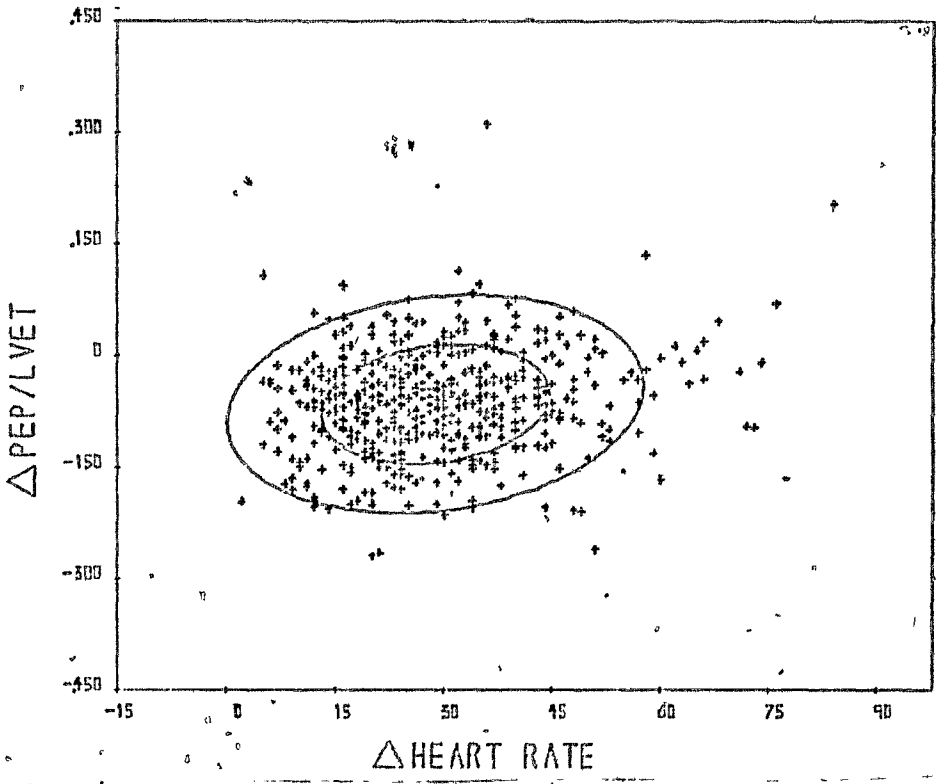


Figure 3.18 - Scattergram of change in PEP/LVET vs change in HR from resting supine to post-exercise in 518 normal subjects. See Figure 3.13 legend for details.

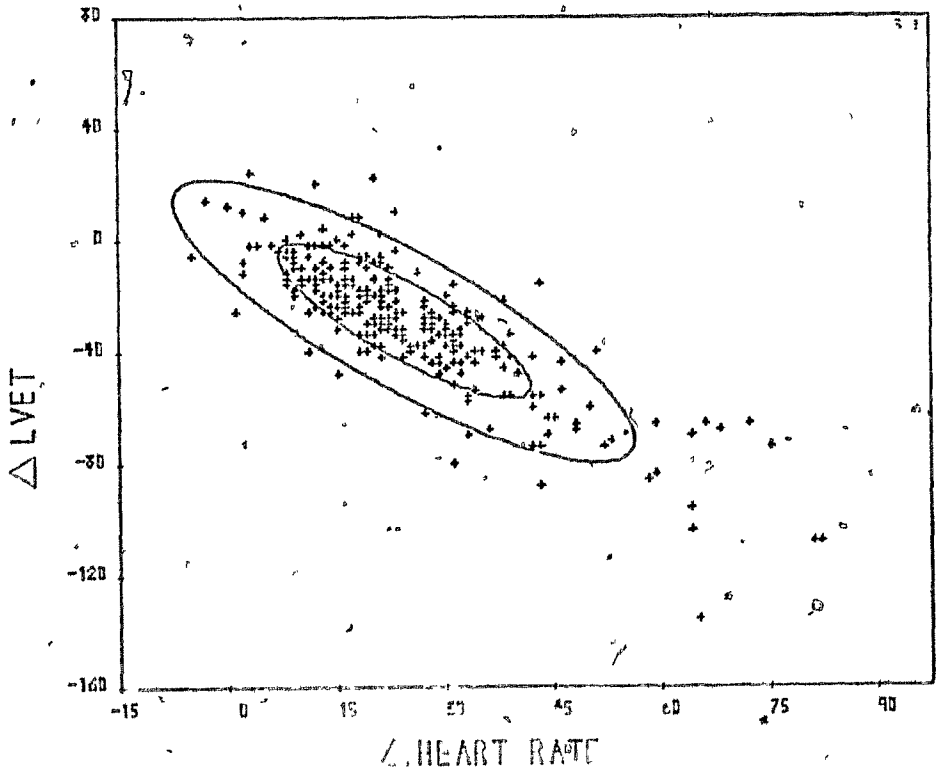


Figure 3.19 - Scattergram of change in LVET vs change in HR from resting upright to post-exercise in 264 normal subjects. See Figure 3.13 legend for details.

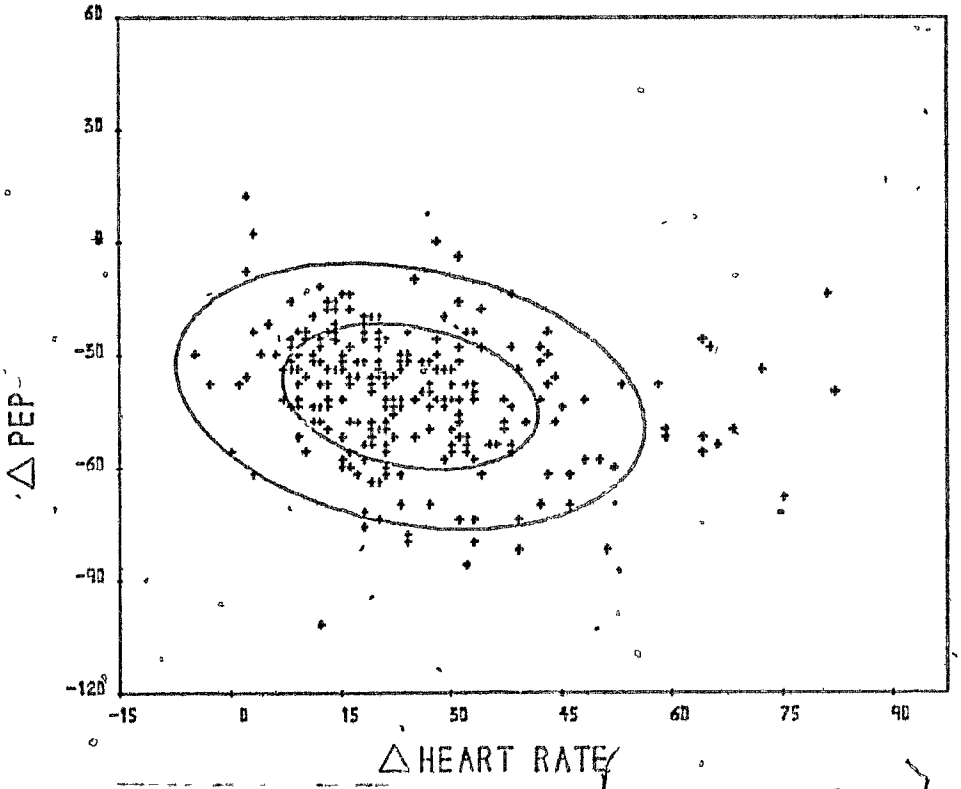


Figure 3.20 - Scattergram of change in PEP vs change in HR from resting upright to post-exercise in 264 normal subjects. See Figure 3.13 legend for details.

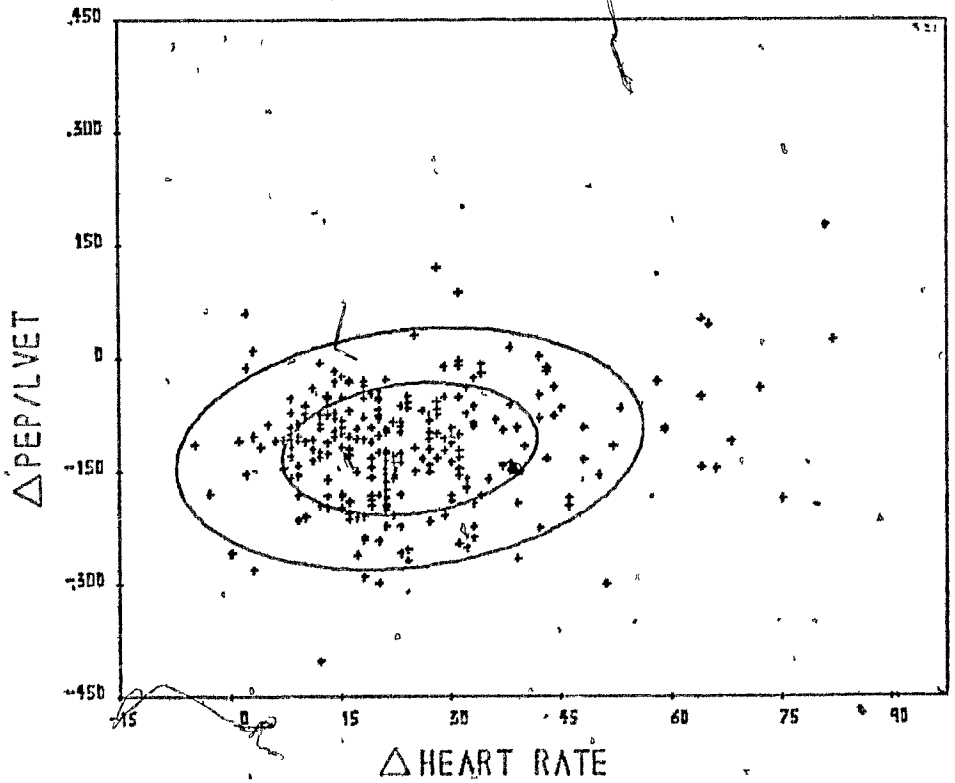


Figure 3.21 - Scattergram of change in PEP/LVET vs change in HR from resting upright to post-exercise in 264 normal subjects. See Figure 3.13 legend for details.

TABLE 3.7

Normal Subjects. Response To Posture Change and Exercise

Variable	Mean Change		Regression With ΔHR				
	Mean	S.D.	Intercept	Slope	S.D.	Correlation	P
A - Resting Upright - Resting Supine. N = 707							
ΔHR	7.3	5.6					
ΔLVET	-27.5	14.4	-15.6	-1.63	11.1	-.633	<.001
ΔPEP	6.0	11.7	6.1	-.013	11.7	-.006	n.s.
Δ(PEP/LVET)	.065	.057	.043	.00296	.054	.291	<.001
B - Post-Exercise Upright - Resting Supine. N = 518							
ΔHR	29.0	13.4					
ΔLVET	-52.8	25.9	- 8.6	-1.52	16.0	-.787	<.001
ΔPEP	-36.5	15.6	-27.9	- .30	15.1	-.254	<.001
Δ(PEP/LVET)	.065	.068	-.092	.00093	.067	.182	<.001
C - Post-Exercise Upright - Resting Upright. N = 264							
ΔHR	24.6	14.8					
ΔLVET	-28.7	23.7	4.2	-1.35	12.7	-.843	<.001
ΔPEP	-40.8	16.5	-34.5	- .26	16.0	-.233	<.001
Δ(PEP/LVET)	-.120	.075	-.142	.00089	.074	.176	<.005

CHAPTER IV

Systolic Time Intervals In Selected Heart Disease Groups

A. General Remarks

This chapter contains the results for all of the abnormal groups considered in this study. It includes a large number of two-dimensional scattergrams and a few general comments apply to them all:

Each scattergram corresponds to one of three planes in the four-dimensional observation space having the variables heart rate (HR), left ventricular ejection time (LVET), pre-ejection period (PEP), and the ratio PEP/LVET as axes. These four variables are a linearly independent set and are used as such in the multivariate computations required to perform statistical tests. The variable QS_2 is not included because it contains no additional information, it being a linear combination, i.e. the sum, of the two variables PEP and LVET. Its inclusion as an additional variable would make the covariance matrices singular, which would make the multivariate statistical computations impossible.

Each set of three scattergrams corresponds to a particular state, such as "resting upright" for a particular subject group. The scattergrams contain a number of vertical crosses or "plus signs" (+), and a pair of concentric ellipses. The plus signs represent the data points for the subject group depicted. The ellipses represent the 50 and 90% confidence limits in the corresponding plane, and for the corresponding state, for the statistical distribution describing the normal group presented in the previous chapter. The heavy arrow indicates the two-dimensional distance of the mean values of the variables in question from the corresponding mean values in the normal group. The statistical tests performed are

based on the relative distance between these means in the four-dimensional observation space. It can be seen from some of the scattergrams that the distance between the means in any given plane can be insignificant and still the group differences between the experimental groups in the four-dimensional space can be high by significant.

B. Systolic Time Intervals In Hypertensive Heart Disease

1. Description of Groups

Six groups were selected from the general data pool in an attempt to identify trends in the systolic time intervals in relation to varying degrees of expected cardiac involvement in hypertension. These groups were selected on the basis of physical examination data at the time of the STI study and examinations conducted five years previously on the same populations. The first two groups were selected on the basis of blood pressure measurement (Table 4.1). The first group consists of the subjects presenting with hypertension at the time of the STI study and normal blood pressure in the examination five years before. For this purpose hypertension is indicated if the systolic pressure is greater than 160 mm Hg or the diastolic pressure is greater than 95 mm Hg. The second, smaller group is composed of subjects who had presented with hypertension both at the time of the STI study and at the study five years earlier. The intention here was to try to distinguish between the short range effect and the cumulative effect on the myocardium of a prolonged period of sustained afterload.

The third test group consisted of those with a confirmed history of hypertensive heart disease; selection criteria included history of hyper-

TABLE 4.1

Composition of The Ten Groups of Subjects Chosen For The STI Study

Groups five and six are subgroups of group four. Cardiac enlargement, with or without evidence of hypertension, was defined as relative heart volume increase by 60 ml/m^2 in five years. The number of subjects in each group indicates only those individuals from whom good quality STI records were obtained.

GROUP	NUMBER
1. Hypertension (HT)	615
2. Sustained Hypertension (SHT)	292
3. Hypertensive Heart Disease (HHD)	99
4. Cardiac Enlargement (CE)	152
5. Cardiac Enlargement and Hypertension (CE&HT)	22
6. Cardiac Enlargement and Sustained Hypertension (CE&SHT)	9
7. S-T Depression (STD)	70
8. Angina Pectoris (AP)	245
9. Myocardial Infarction (MI)	79
10. Acute Myocardial Infarction (AMI)	16

tension and one or more episodes of cardiac failure.

The fourth test group was selected on the basis of the "relative heart volume" (R.H.V.) defined as roentgenologically measured cardiac volume per square meter of body surface area. This parameter, only available for the Helsinki Policemen Study, was determined at the time of the STI study and at the study five years previously. A subject was included in this group if his relative heart volume had increased by 60 ml/m^2 over the five-year period. The selection on this basis represents an attempt to stratify the study population using criteria which are independent from the blood pressure data obtained in a single casual act of measurement with its inherent limitations regarding the long term hemodynamic consequences. It is recognized that the population selected on this basis will contain individuals who demonstrate cardiac enlargement due to causes other than hypertension; for instance, primary myocardial disease or physiological hypertrophy in subjects engaged in vigorous physical fitness programs.

The fifth group was a subset of group four, containing only those subjects who in addition to cardiac enlargement presented with hypertension at the time of the first study. This group of 22 subjects was considered to manifest possible effects on STI of cardiac enlargement causally related to increased afterload due to hypertension.

The sixth and final group of this series was a subgroup of the fourth who presented with hypertension at the time of both examinations five years apart. This group includes only nine subjects and contains those subjects in whom possible hypertension intervention was inadequate.

Subjects known to be using digitalis at the time of the STI study or other cardioactive drugs known to influence the ECG were excluded from all six groups.

2. Results

2.1 Hypertension

Good resting records were obtained for 615 subjects who appeared with hypertension at the time of the STI study. Mean diastolic pressure for this group was 100.9 (S.D. 10.7) mm Hg and systolic pressure averaged 170.7 (S.D. 18.0) mm Hg. The regression data for this group is in Table 4.2 and the corresponding scattergrams are Figures 4.1 through 4.3. The regression equations are seen to be very similar to those obtained from normal subjects. The mean heart rate is increased by several beats per minute, with a corresponding change in LVET and PEP/LVET, in both cases largely along the regression lines. In addition, there is a significant increase in PEP above that expected from the normal regression effect. The multivariate analysis of variance (Wilks Lambda for 4 variables) yielded a χ^2 of 439.1 on 14 degrees of freedom for a simultaneous test of the equality of both the means vectors and covariance matrices (using the normals in the previous chapter), which is significant at the .001 level. A similar test for equality of the covariance matrices alone gave a χ^2 of 309.3 on 10 degrees of freedom ($p < .001$). Using the pooled covariance, the estimate of Mahalanobis D^2 for the separation of the means is 0.310. This can be converted to Hotelling's T_o^2, and thence to an F ratio, yielding an F of 33.5 on 4 and 2067 degrees of freedom ($p < .001$). In the LVET-HR plane, 125 of the 615 data points (20.3%) fall outside of the 90% normal ellipse. On the PEP scattergram, 98 (15.9%) fall outside the normal limit, and on the PEP/LVET graph, 110 (17.9%) are outside. It should be noted that a considerable number of these fall outside in the direction of higher heart rate, although they would fall close to a normal regression line. The "generalized outlier count", based on the 4-dimensional

generalized statistical distance to the center of the normal population (see Chapter II), is 119 (19.3%).

Similar data for 110 of these subjects in the upright state can be seen also in Table 4.2 and in Figures 4.4 to 4.6. Again, the regression equations are similar to the corresponding normal ones. The relative shift in the means is similar to that seen in the resting state. The combined test for equality of means and covariance matrices yielded a χ^2 of 120.6 on 14 d.f. ($p < .001$). The F test for equality of means gave a value of 13.2 on 4 and 895 d.f. ($p < .001$) for a corresponding D^2 of 0.547. In the LVET-HR plane, 20 (18.2%) of the data points fall outside the 90% ellipse. In the PEP-HR and PEP/LVET-HR planes, the corresponding numbers are 19 (17.3%) and 20 (18.2%). Again, a fair number of these points lie near the regression lines, but are outside the ellipses because of high heart rates. The generalized outlier count is 23 (20.9%).

The scattergrams for 178 subjects after exercise can be seen in Figures 4.7 to 4.9 and the regression data can also be found in Table 4.2. Although the regression equations are again similar to those for the corresponding normals, there is this time an increase in LVET, PEP and PEP/LVET which is largely independent of the slight increase in HR. The multivariate tests yielded a χ^2 of 67.0 on 14 d.f. ($p < .001$) for the combined test of means and covariance matrices, but produced a χ^2 of only 10.5 on 10 d.f. (not significant) for the test of the equality of the covariance matrices alone. This, of course, makes the F-test of Mahalanobis D^2 more valid. In this case D^2 is 0.433 and the F-value is 14.6 on 4 and 743 d.f. ($p < .001$). The "outlier counts" (number of points outside the 90% ellipse) on the LVET, PEP and PEP/LVET graphs were respectively 26 (14.6%), 24 (13.5%) and 16 (9.0%). Since both PEP and LVET are both shifted in the same direction,

the ratio PEP/LVET, as might be expected, is not as useful as discriminator as either of the constituent variables alone. It can also be seen that HR is not a useful discriminator, in contrast to what was seen in the two resting states. The generalized outlier count is 29 (16.3%).

Because of the large size of this particular group, it was possible to obtain a reasonable sample for the three possible pairs of combined states. This results in an observation vector of 8 variables, 4 for each of the two states included. The multivariate test results quoted for these are based on an 8 variable means vector and an 8x8 covariance matrix, and are compared with similar matrices for normal subjects, as derived in the previous chapter. Since the scattergrams for each of the constituent states would be virtually identical to the ones just seen, the figures shown for these groups are based on the relative change in each variable from one state to the other. For the combined resting supine - resting upright states, for instance,

$$\Delta LVET = LVET\ (upright) - LVET\ (supine)$$

and so forth for the other variables. In other words, the axes represent the change in a variable for the second state relative to the first.

There were 100 subjects in this group for which resting supine and resting upright data was simultaneously available, and the scattergrams showing the relative change in the variables are shown in Figures 4.10 to 4.12. The mean response to this state change is seen to differ little from the normal control group. The multivariate test based on all 8 variables yielded a χ^2 of 283.8 on 44 d.f. ($p < .001$) for a combined test of means and covariances and 228.0 on 36 d.f. ($p < .001$) for a test of the for a test of the covariances alone. The Mahalanobis D^2 based on a pooled covariance (but essentially the "normal" covariance because of the

relative group sizes) is 0.658, and the corresponding F ratio is 7.15 on 8 and 798 d.f. ($p < .01$). The "outlier counts" in the three 2-dimensional planes are 12 (12%), 10 (10%) and 13 (13%) for ΔLVET, ΔPEP and Δ(PEP/LVET) respectively. The generalized outlier count based on the 8 original variables is 21 (21%). What all these results would seem to indicate is that there is little additional information to be gained from a simultaneous consideration of resting supine and upright data, above what can be extracted from the two states considered separately.

A potentially more useful pairing is the combined use of resting supine and post-exercise data. This combination of data was available for 163 of the hypertensive group. The scattergrams (of the exercise response) are seen in Figures 4.13 to 4.15. The most interesting feature of these graphs is that the average response of the hypertensive group to exercise (especially the response of LVET and HR) is somewhat less than that of the normal group. This reflects the fact that the heart rate was elevated somewhat in the hypertensive at rest, but was closer to the normal value after exercise. The test for equality of both means and covariance gave a χ^2 of 243.6 on 44 d.f. ($p < .001$) and the test of covariance matrices alone gave a χ^2 of 67.3 on 8 d.f. ($p < .001$). D^2 was 0.570 with an F of 8.74 on 8 and 672 d.f. ($p < .01$). Outlier counts were 27 (16.6%), 15 (9.2%) and 15 (9.2%). The best of these, 16.6% on the LVET-HR plane, is not as good as obtained for resting records alone (20.3%). The generalized count in 8 dimensions is also 27 (16.6%).

The third pair of states considered was resting upright and post-exercise. This would appear to be the "purest" exercise test, since both observations in this pair are taken in the same posture, eliminating the orthostatic component involved when the "reference" reading is taken supine.

TABLE 4.2

Systolic Time Intervals In Hypertension:
Mean Values and Heart Rate Regressions

	Mean Value		Regression With Heart Rate				
Variable	Mean	S.D.	Intercept	Slope	S.D.	Correlation	P
A - Resting Supine. N = 615							
HR	70.1	12.9					
LVET	288.9	28.3	409.5	-1.72	17.6	-.783	<.001
PEP	117.0	15.8	142.6	- .36	15.1	-.298	<.001
PEP/LVET	.409	.068	.322	.00124	.066	.235	<.001
B - Resting Upright. N = 110							
HR	81.2	13.3					
LVET	255.8	24.2	368.6	-1.39	15.6	-.764	<.001
PEP	119.1	14.6	140.1	- .26	14.2	-.235	<. 05
PEP/LVET	.470	.078	.347	.00152	.075	.259	<. 01
C - Post-Exercise. N = 178							
HR	96.1	15.9					
LVET	246.0	26.2	367.3	-1.26	16.8	-.767	<.001
PEP	82.7	13.6	109.2	- .27	12.9	-.322	<.001
PEP/LVET	.340	.064	.273	.00069	.063	.172	<. 05

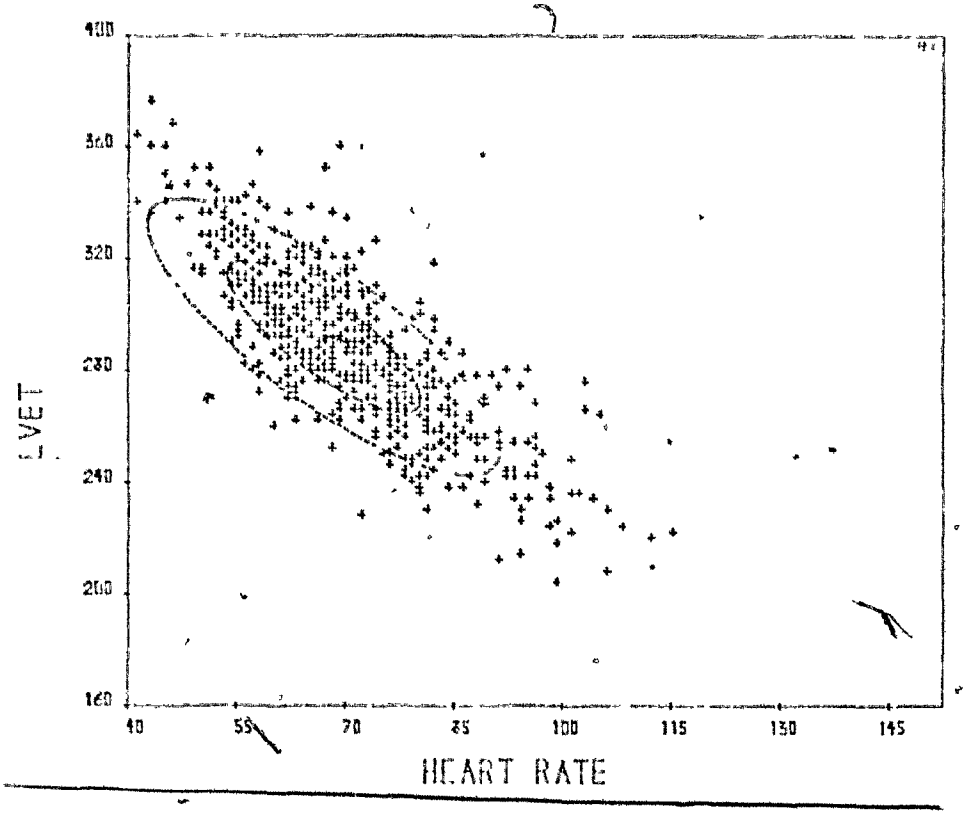


Figure 4.1 - Resting supine scattergram of LVET vs HR for 615 subjects with hypertension. The pair of ellipses represent the 50 and 90% confidence limits in the plane, for the same state, for the statistical distribution describing the normal group in Chapter III. The arrow indicates the two-dimensional distance of the mean values from the corresponding mean values for the normal group.

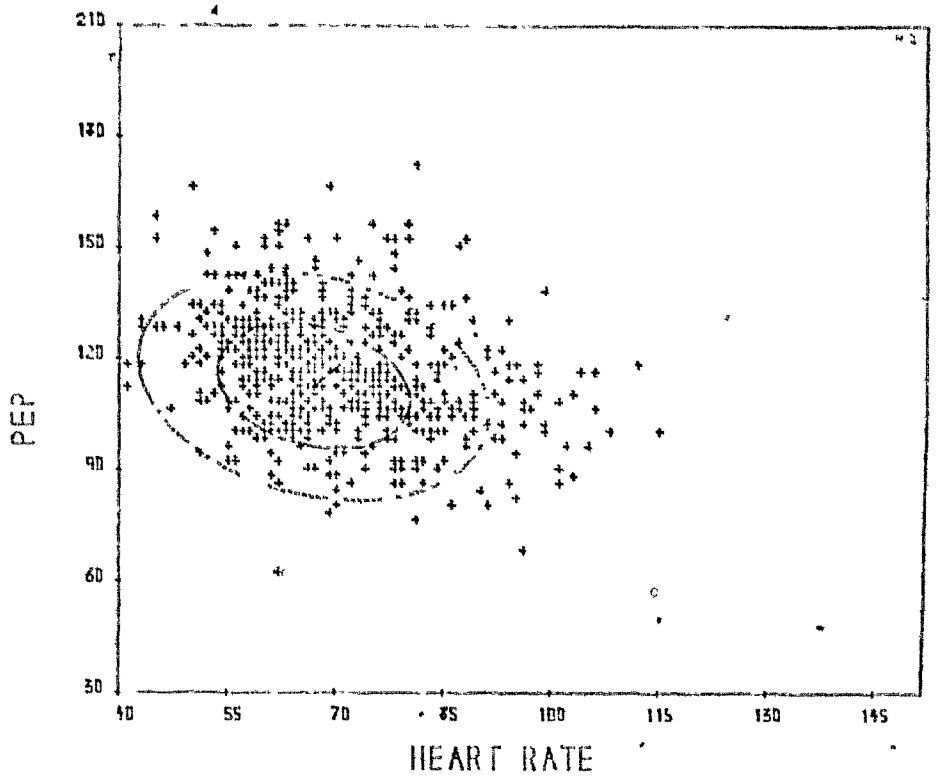


Figure 4.2 - Resting supine scattergram of PEP vs HR for 615 subjects with hypertension. See Figure 4.1 legend for details.

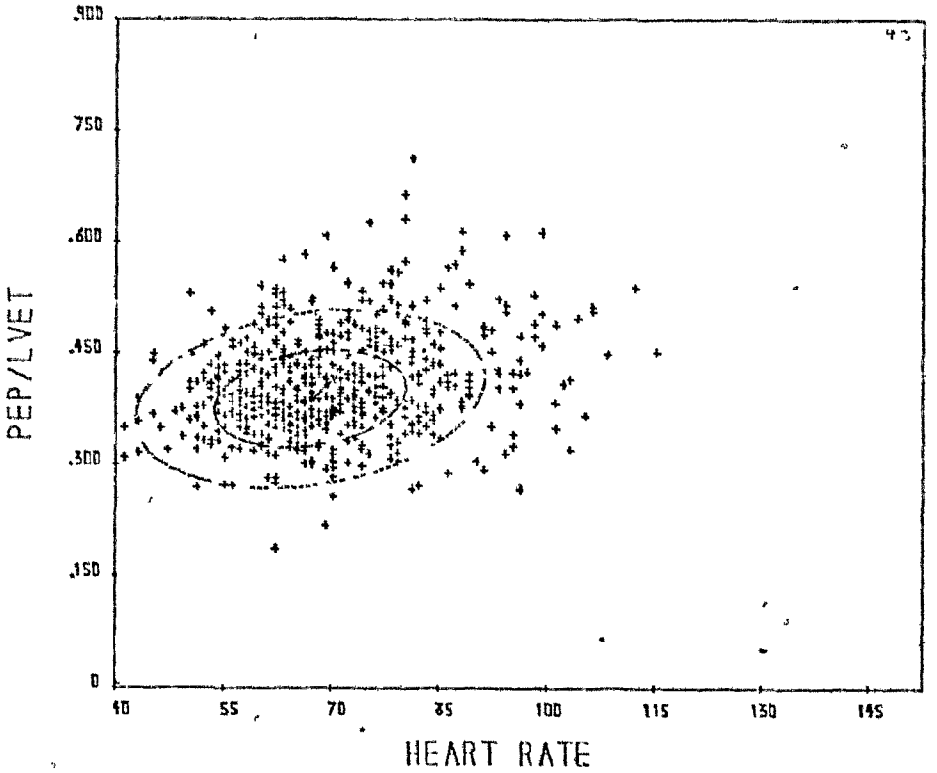


Figure 4.3 - Resting supine scattergram of PEP/LVET vs HR for 615 subjects with hypertension. See Figure 4.1 legend for details.

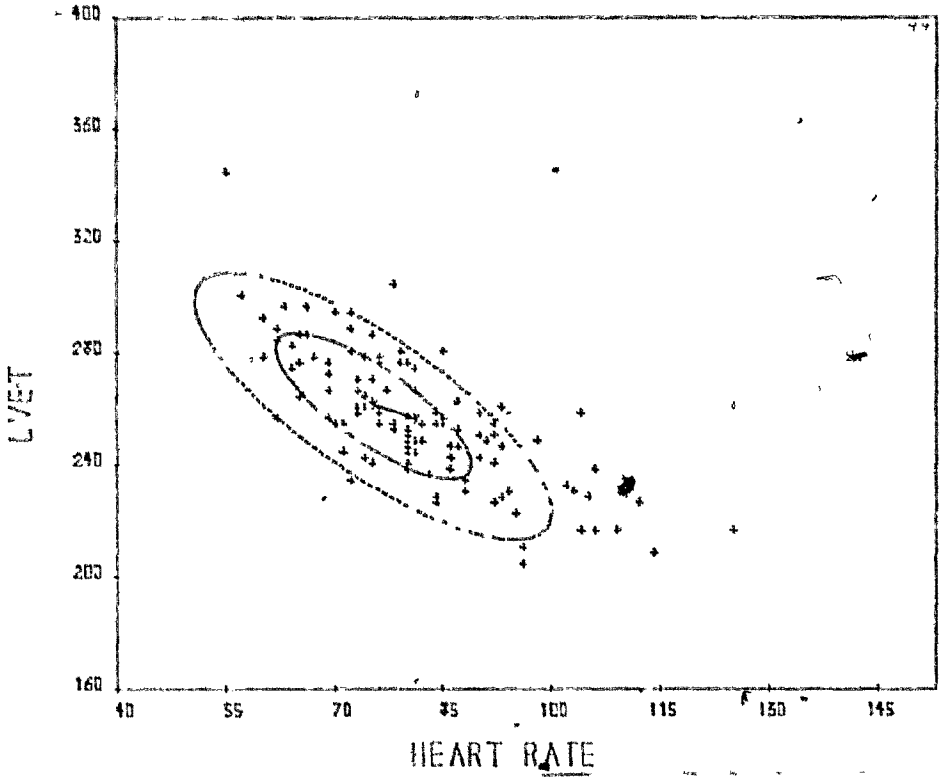


Figure 4.4 - Resting upright scattergram of LVET vs HR for 110 subjects with hypertension. See Figure 4.1 legend for details.

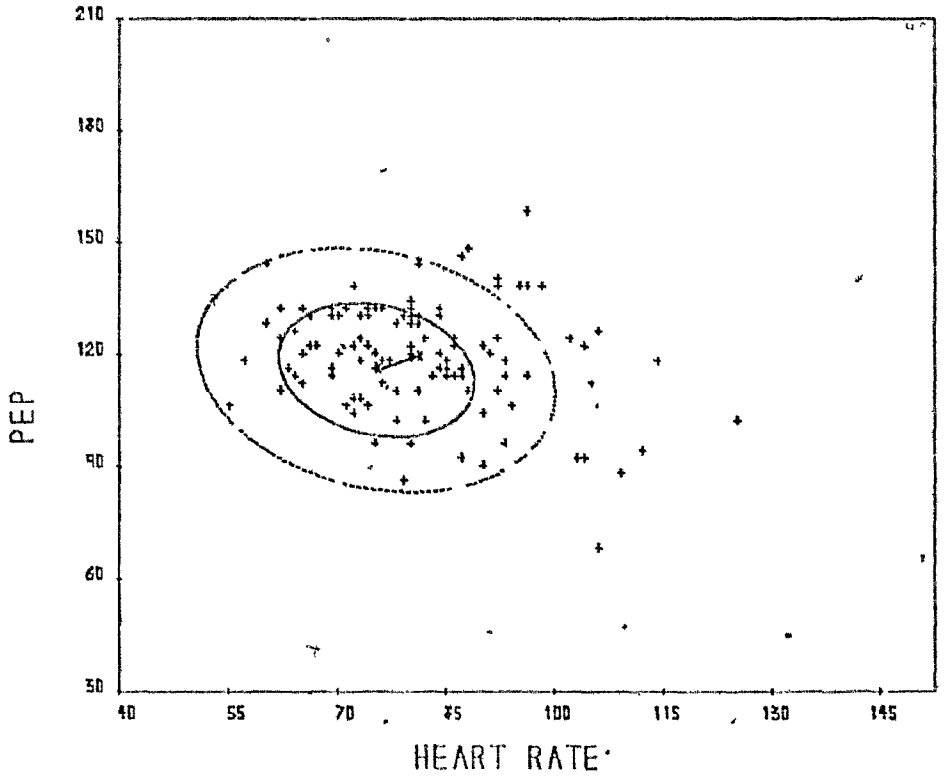


Figure 4.5 - Resting upright scattergram of PEP vs HR for 110 subjects with hypertension. See Figure 4.1 legend for details.

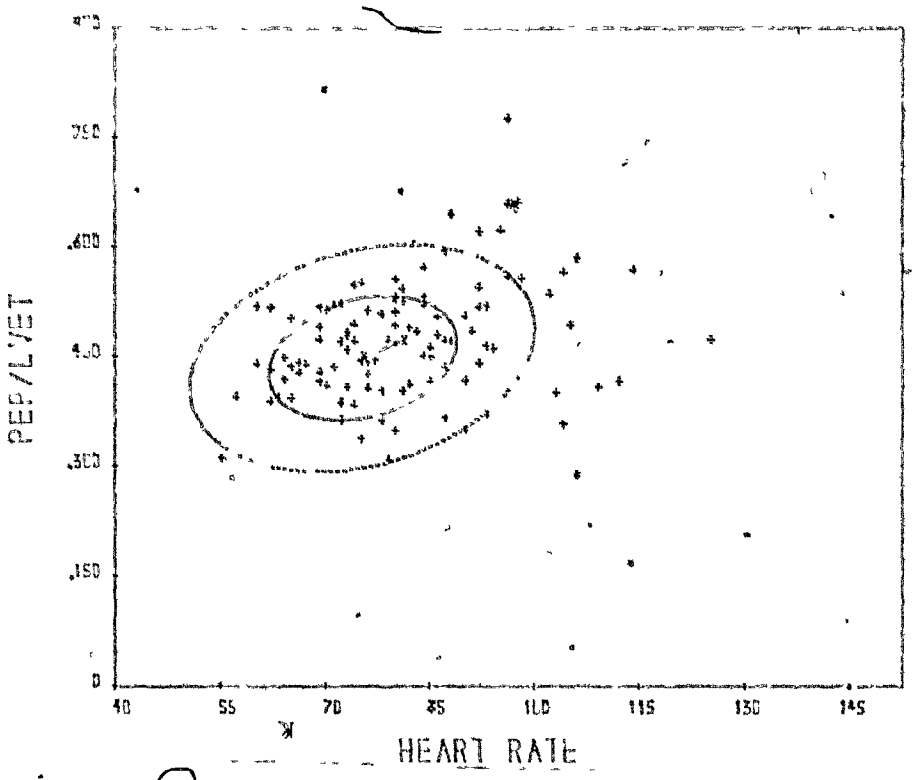


Figure 4.6 - Resting upright scattergram of PEP/LVET vs HR for 110 subjects with hypertension. See Figure 4.1 legend for details.

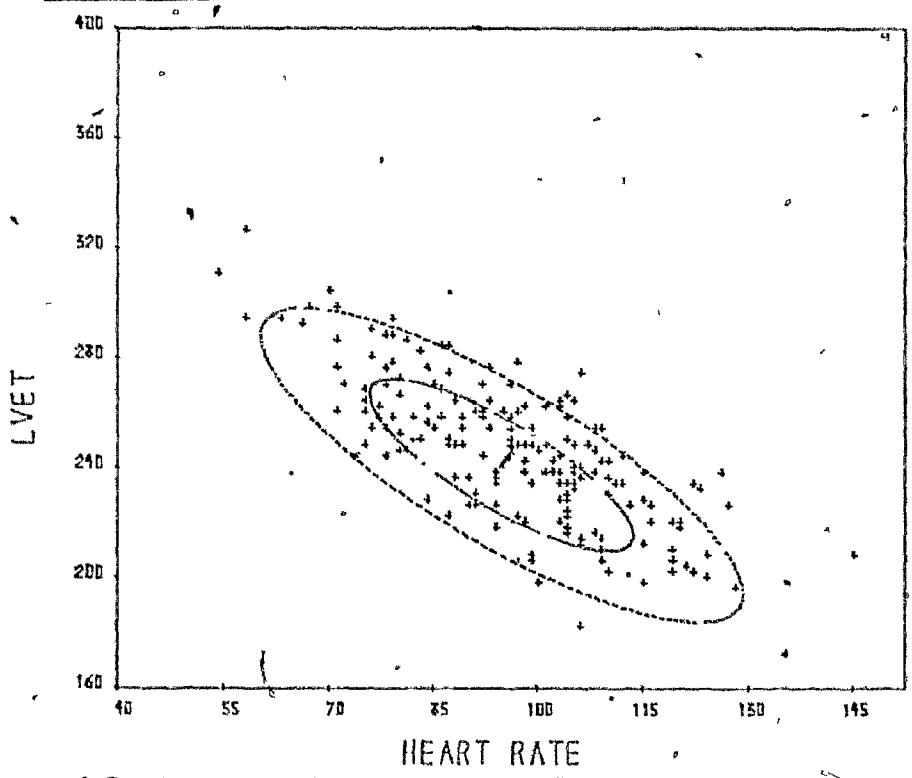


Figure 4.7 - Post-exercise scattergram of LVET vs HR for 178 subjects with hypertension. See Figure 4.1 legend for details.

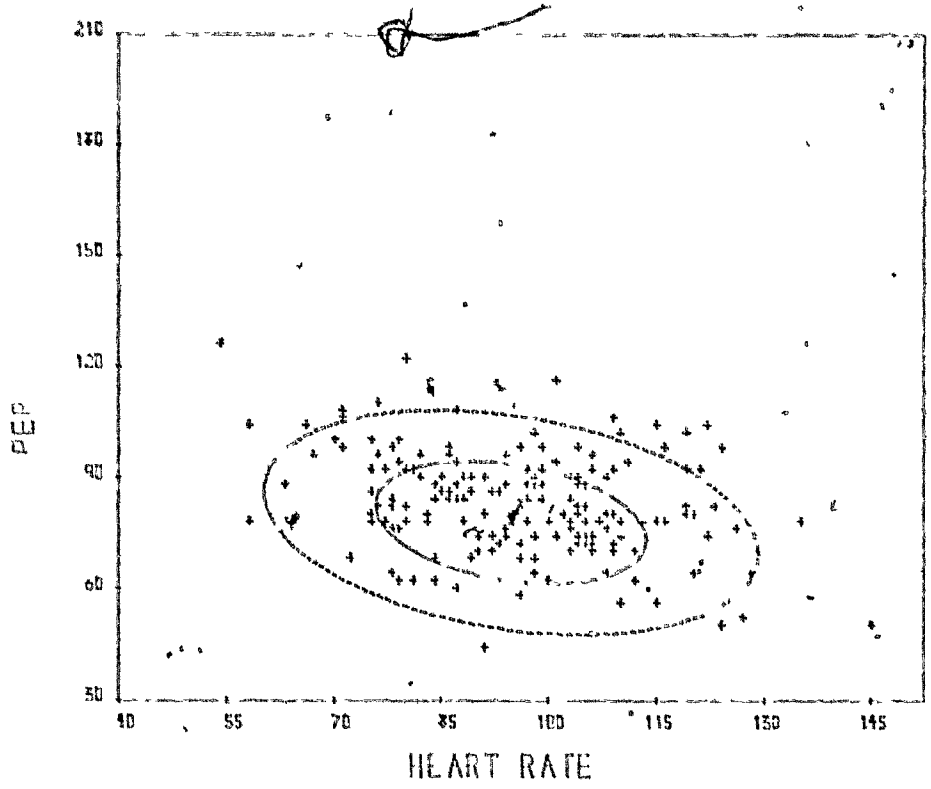


Figure 4.8 - Post-exercise scattergram of PEP vs HR for 178 subjects with hypertension. See Figure 4.1 legend for details.

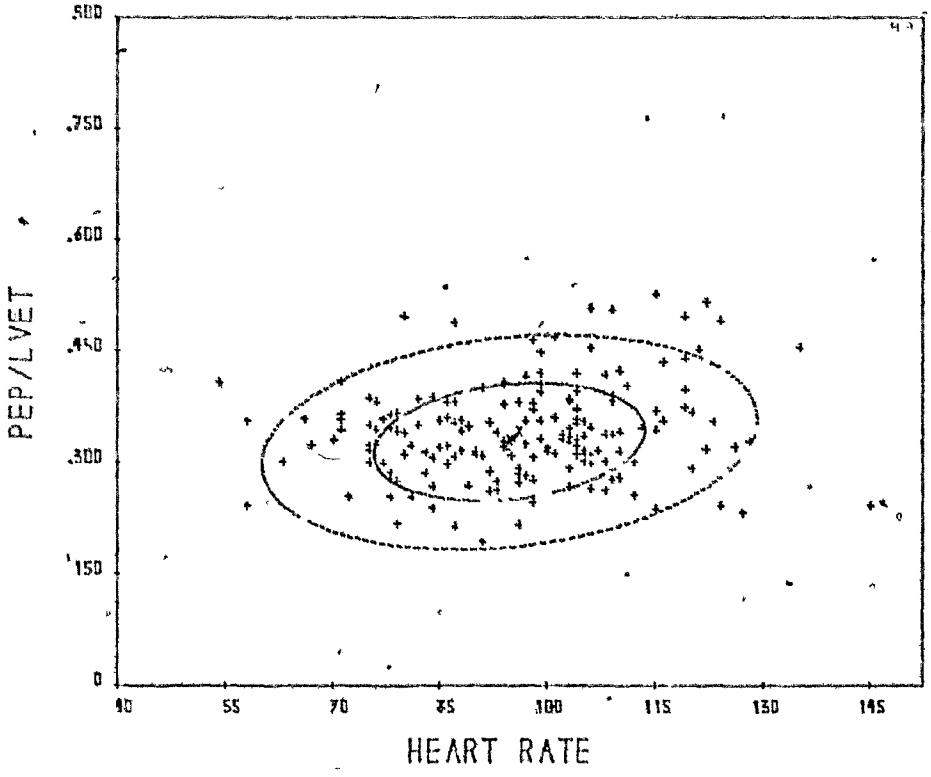


Figure 4.9 - Post-exercise scattergram of PEP/LVET vs HR for 178 subjects with hypertension. See Figure 4.1 legend for details.

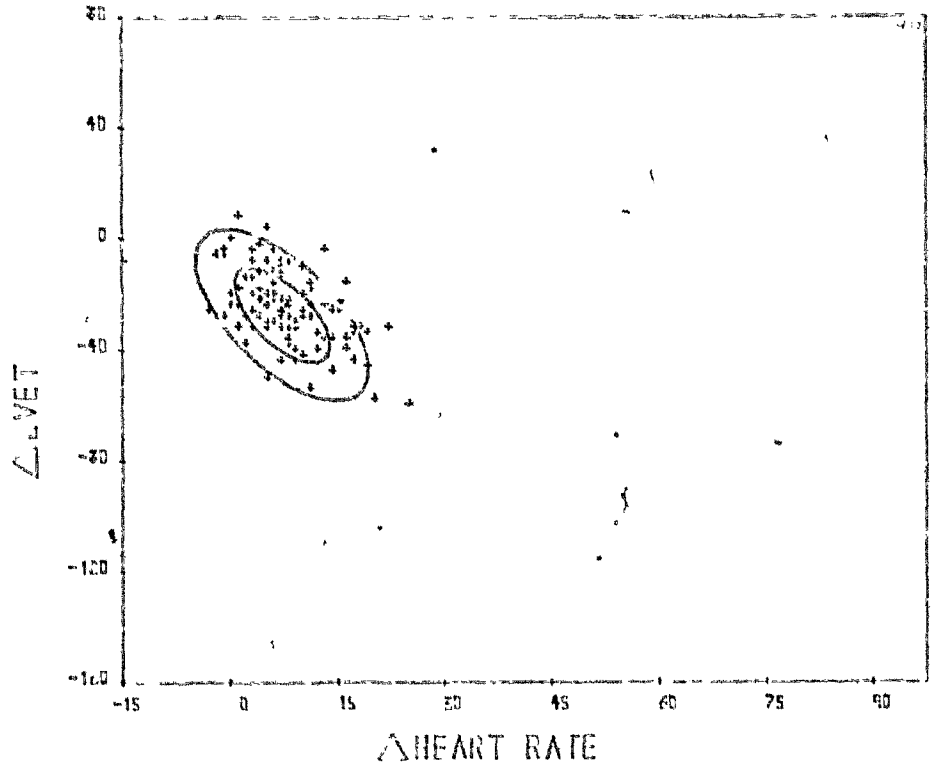


Figure 4.10 - Scattergram of change in LVET vs change in HR from resting supine to resting upright in 100 subjects with hypertension.

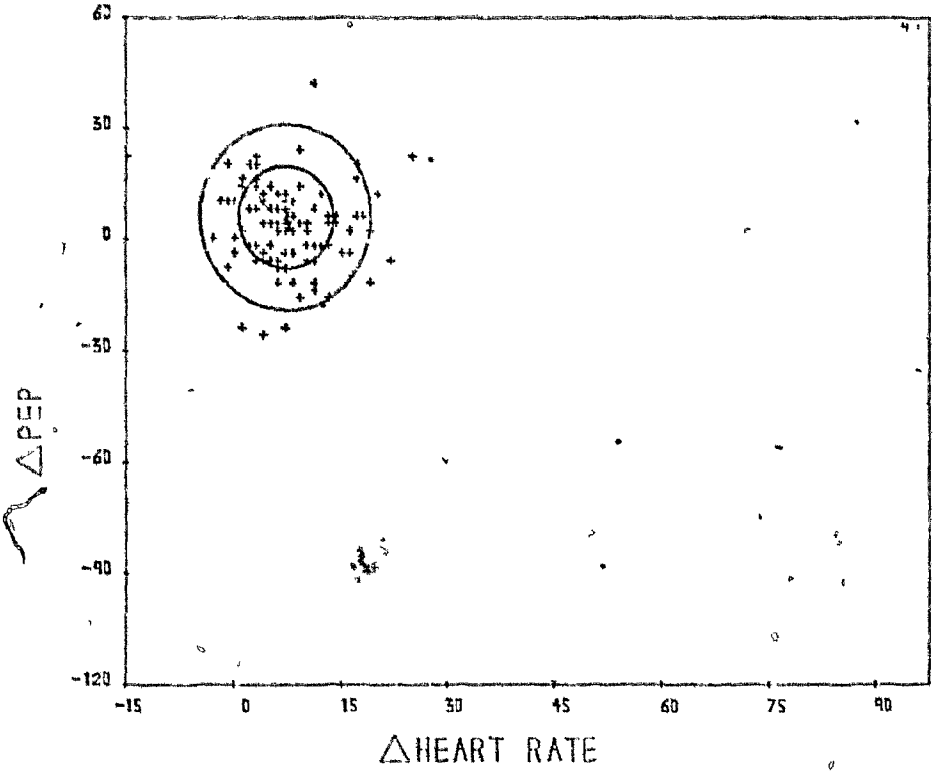


Figure 4.11 - Scattergram of change in PEP vs change in HR from resting supine to resting upright in 100 subjects with hypertension.

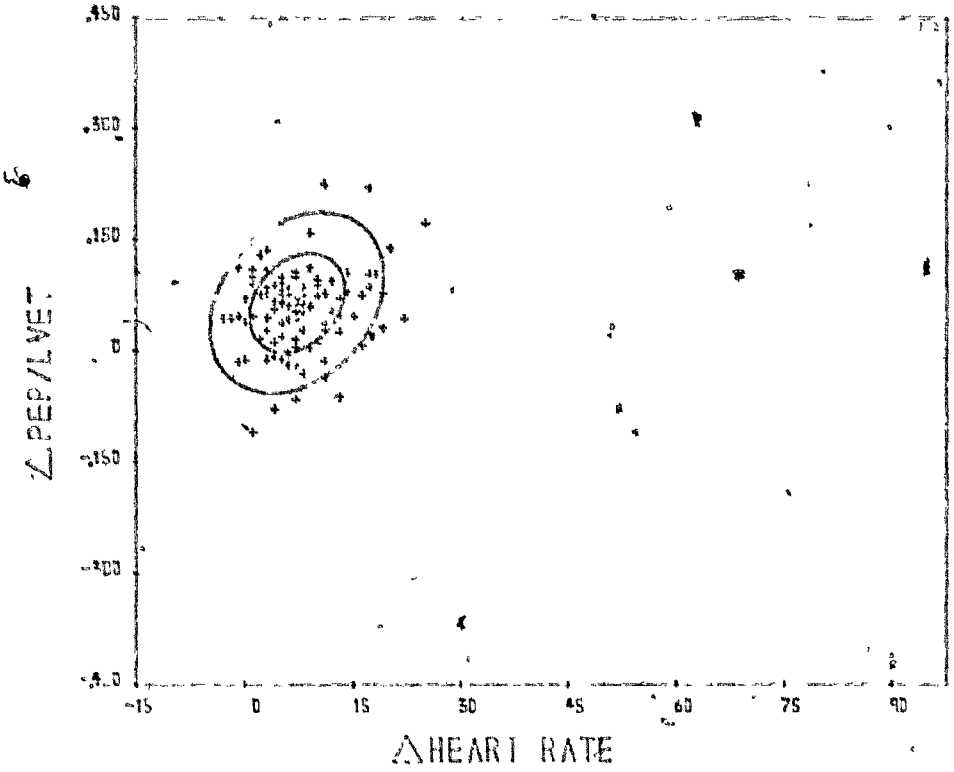


Figure 4.12 - Scattergram of change in PEP/LVET vs change in HR from resting supine to resting upright in 100 subjects with hypertension.

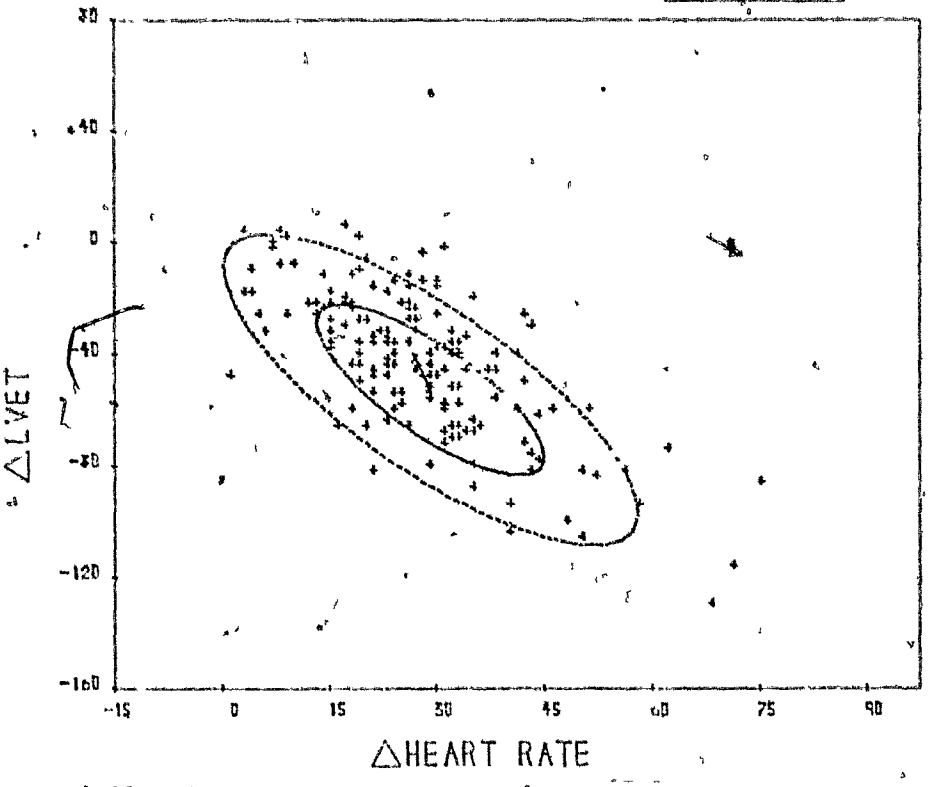


Figure 4.13 - Scattergram of change in LVET vs change in HR from resting supine to post-exercise in 163 subjects with hypertension.

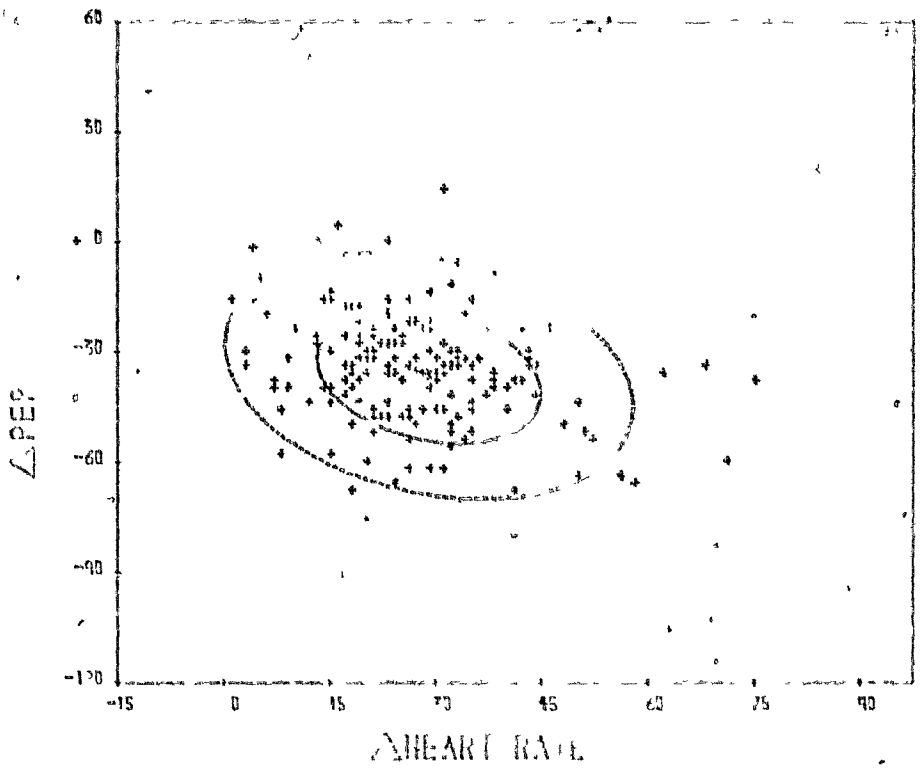


Figure 4.14 - Scattergram of change in PEP vs change in HR from resting supine to post-exercise in 163 subjects with hypertension.

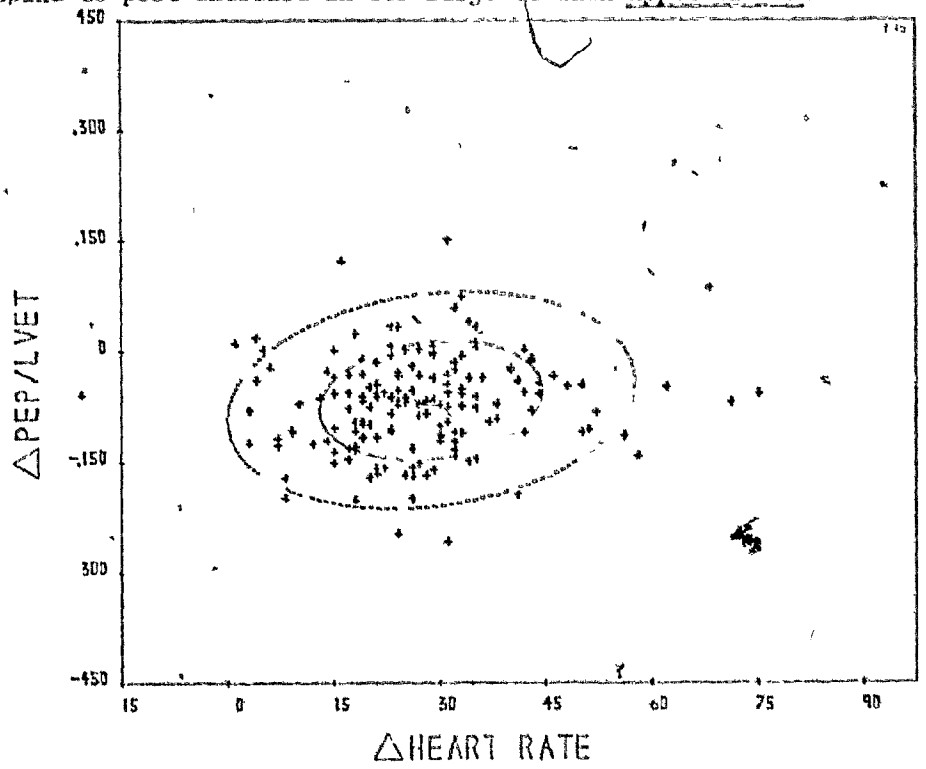


Figure 4.15 - Scattergram of change in PEP/LVET vs change in HR from resting supine to post-exercise in 163 subjects with hypertension.

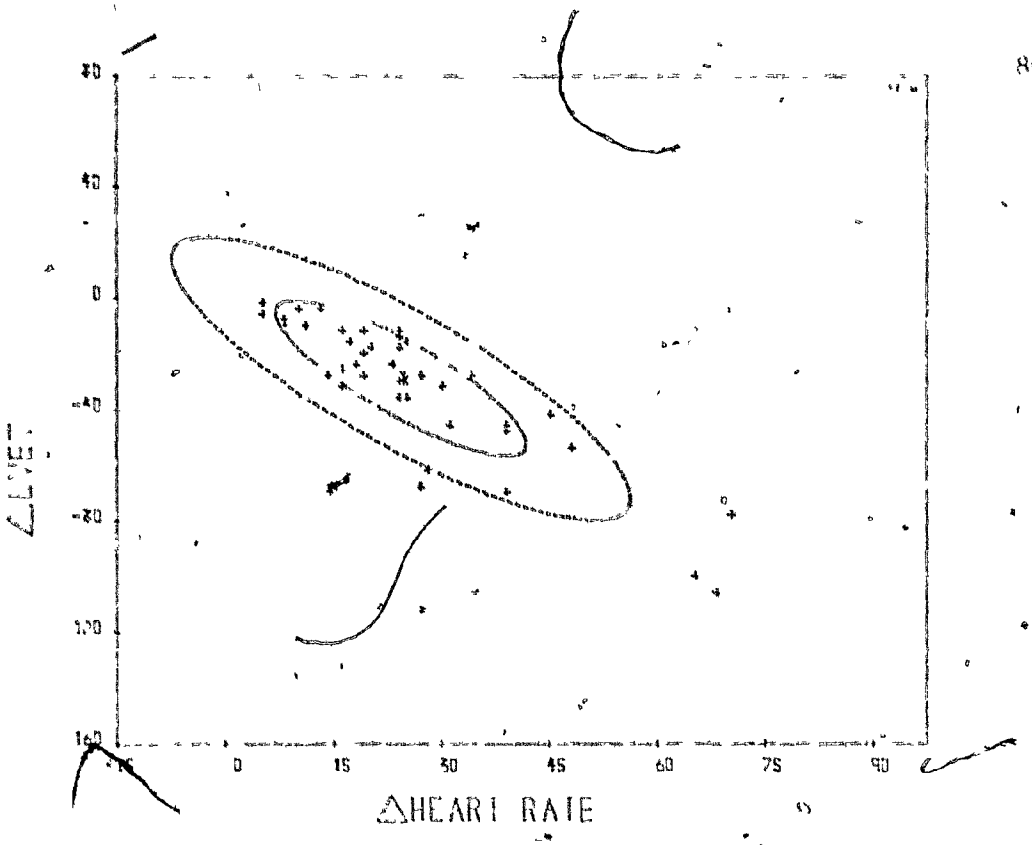


Figure 4.16 - Scattergram of change in LVET vs change in HR from resting upright to post-exercise in 40 subjects with hypertension.

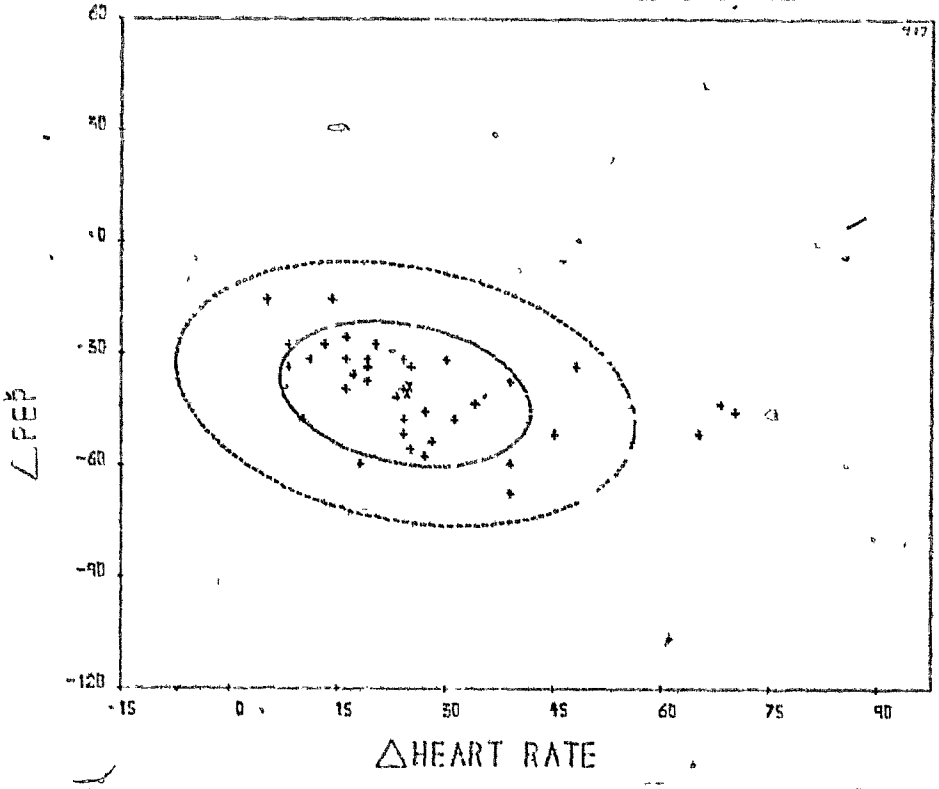


Figure 4.17 - Scattergram of change in PEP vs change in HR from resting upright to post-exercise in 40 subjects with hypertension.

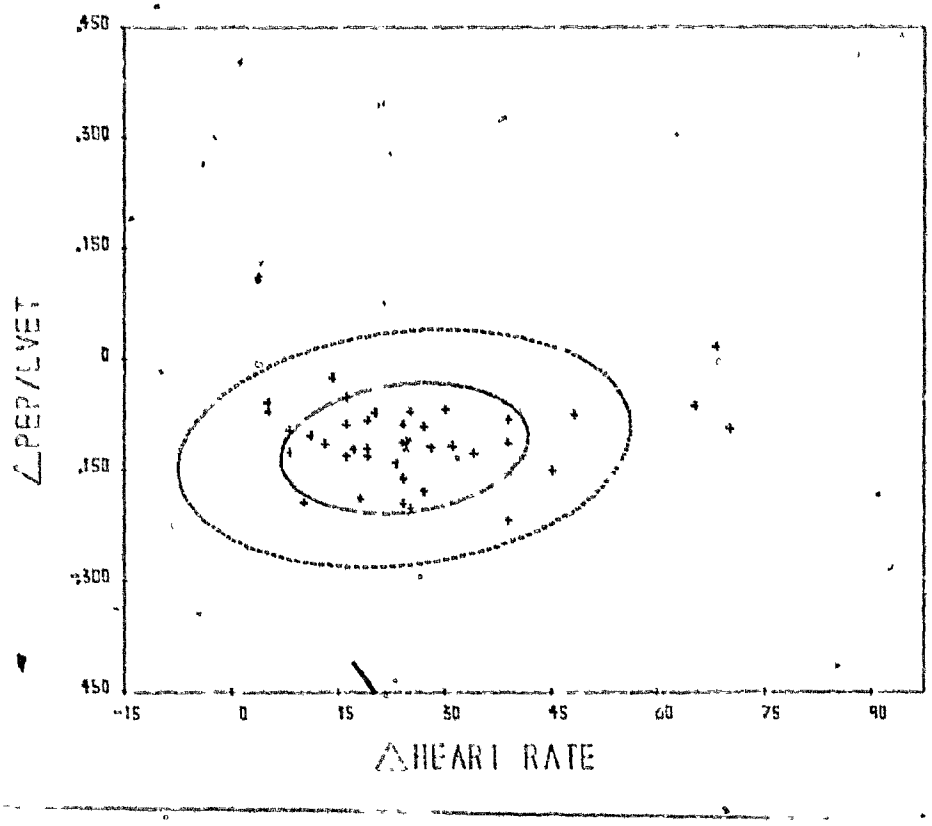


Figure 4.18 - Scattergram of change in PEP/LVET vs change in HR from resting upright to post-exercise in 40 subjects with hypertension. See Figure 4.1 legend for details.

In practice, however, the fact that resting upright records were only available from the Policemen study (which was also a "healthier" group) limited the sample size severely and this pairing was only done for the hypertensive group. In this case, there were only 40 subjects (it is important to realize that to obtain a means vector and covariance matrix for 8 variables implies the estimation of 44 parameters). The scattergrams are shown in Figures 4.16 to 4.18. The average response is seen to be almost identical to that for the normal group, which would indicate that there is no particular advantage in considering both states together (over simply considering each state separately). The multivariate tests yielded a χ^2 of 87.4 on 44 d.f. ($p < .01$) for the combined test of means and covariance and 61.0 on 36 d.f. for the test of covariances only. D^2 was .798 with a F value of 3.37 on 8 and 295 d.f. ($p < .01$). Outlier counts were 6 (15%), 4 (10%) and 4 (10%) and the generalized count is 6 (15%). These could have arisen by chance in a normal population, considering the numbers involved.

2.2 Sustained Hypertension

Resting records were obtained for 292 subjects with hypertension at the time of both studies. Mean blood pressures on the second occasion were 104.3 ± 11.3 mm Hg diastolic and 176.1 ± 19.7 mm Hg systolic. The regression data are in Table 4.3 and the relevant scattergrams are in Figures 4.19 to 4.21. As with the first group studied, the mean difference from normal, except for the difference in PEP, are largely due to the regression relationships with heart rate, which was increased significantly above normal values. The combined test of means and covariances yielded a χ^2 of 477.3 on 14 d.f. ($p < .001$) and the test of

the covariances alone gave a χ^2 of 361.4 on 10 d.f. ($p < .001$). D^2 for the means is 0.405 with an F value of 29.9 on 4 and 1744 d.f. ($p < .001$). Outlier counts were 78 (26.7%), 58 (19.9%) and 63 (21.6%), due largely (as with the simple hypertensive group) to increased heart rates. The "generalized count" was 68 (23.3%).

There were 57 upright records from this group. Regression data is again in Table 4.3 and the scattergrams are in Figures 4.22 to 4.24. The same general observations apply as to the supine records. χ^2 for the combined means-covariance test was 114.0 on 14 d.f. ($p < .001$) and for the covariance test alone 76.7 on 10 d.f. ($p < .001$). D^2 was 0.717 with an F of 9.5 on 4 and 842 d.f. ($p < .001$). Outlier counts were 10 (17.5%), 10 (17.5%) and 11 (19.3%), again related largely to increased heart rates. The 4-dimensional count was 14 (24.6%).

Data on 85 exercise records is summarized also in Table 4.3 and in Figures 4.25 to 4.27. Here we see increases in both LVET and PEP, with a slight increase in their ratio, not particularly related to a slight increase in heart rate. The combined test yields a χ^2 of 66.9 on 14 d.f. ($p < .001$), while the test for covariance matrices alone gives a value of 17.1 on 10 d.f. which is not significant. A multivariate test for equality of the means (which requires that the covariances be equal) gives a χ^2 of 49.8 on 4 d.f. ($p < .001$). This corresponds to a D^2 of 0.700 with an F of 12.9 on 4 and 650 d.f. ($p < .001$). The outlier counts were 16 (18.8%), 9 (10.6%) and 7 (8.2%), indicating perhaps that LVET is the most useful discriminator. The generalized count was 15 (17.6%). As with the exercise records for the non-sustained hypertensive group, HR was not a contributing factor in the outlier counts. This would be expected since the exercise tests were performed at a target heart rate.

There were 49 subjects in the group with both resting supine and resting upright records available, and the scattergrams of the changes in the variables are Figures 4.28 to 4.30. As with the previous group, the response to this state change differs little from the response of the normal group. The combined multivariate test (8 variables) for both means and covariance yields a χ^2 of 288.0 on 44 d.f. ($p < .001$). The portion of this χ^2 due to the difference in the covariance-matrices is 238.3 on 36 d.f. ($p < .001$). D^2 is 1.121 with an F of 6.36 on 8 and 747 d.f. ($p < .001$). The outlier counts on the "change" graphs are 6 (12.2%), 5 (10.2%) and 6 (12.2%) which are not different from what would be expected in a normal group of this size. The 8-dimensional generalized count is 11 (22.4%), which is still not as good as the result obtained from resting records alone.

There were 79 subjects with both resting supine and post-exercise records. The scattergrams of the changes are in Figures 4.31 to 4.33. The mean response is somewhat more different from normal than in the supine to upright test above, with only the change in LVET deviating from the normal regression line. The combined multivariate test gives χ^2 of 261.6 on 44 d.f. ($p < .001$) and the test of covariances alone gives a χ^2 of 197.7 on 36 d.f. ($p < .001$). D^2 is 0.984 with an F ratio of 8.34 and 588 d.f. ($p < .001$). The outlier counts on the response scattergrams are 14 (17.7%), 5 (6.3%) and 7 (8.9%). Only ΔLVET appears useful in this case as a discriminator. The generalized count is slightly less than this, at 13 (16.5%).

The sample size for the combined resting upright and post-exercise pair was too small to be considered useful, and on the basis of the results for the non-sustained hypertensive group, this pairing was not examined for any other of the groups in this study.

TABLE 4.3

Systolic Time Intervals In Sustained Hypertension:

Mean Values and Heart Rate Regressions

	Mean Values		Regression With Heart Rate				
Variable	Mean	S.D.	Intercept	Slope	S.D.	Correlation	P
A - Resting Supine. N = 292							
HR	72.3	13.8					
LVET	284.2	29.5	400.1	-1.60	19.3	-.754	<.001
PEP	116.9	15.9	142.6	- .35	15.1	-.309	<.001
PEP/LVET	.416	.070	.330	.00118	.068	.233	<.001
B - Resting Upright. N = 57							
HR	82.3	14.2					
LVET	253.7	23.5	364.1	-1.34	13.9	-.808	<.001
PEP	120.3	13.8	138.9	- .23	13.4	-.233	n.s.
PEP/LVET	.478	.074	.340	.00167	.071	.320	<. 05
C - Post-Exercise. N = 85							
HR	96.8	15.4					
LVET	247.0	25.4	362.5	-1.19	17.6	-.722	<.001
PEP	83.7	12.9	111.3	- .28	12.2	-.339	<.005
PEP/LVET	.342	.064	.283	.00062	.063	.149	n.s.

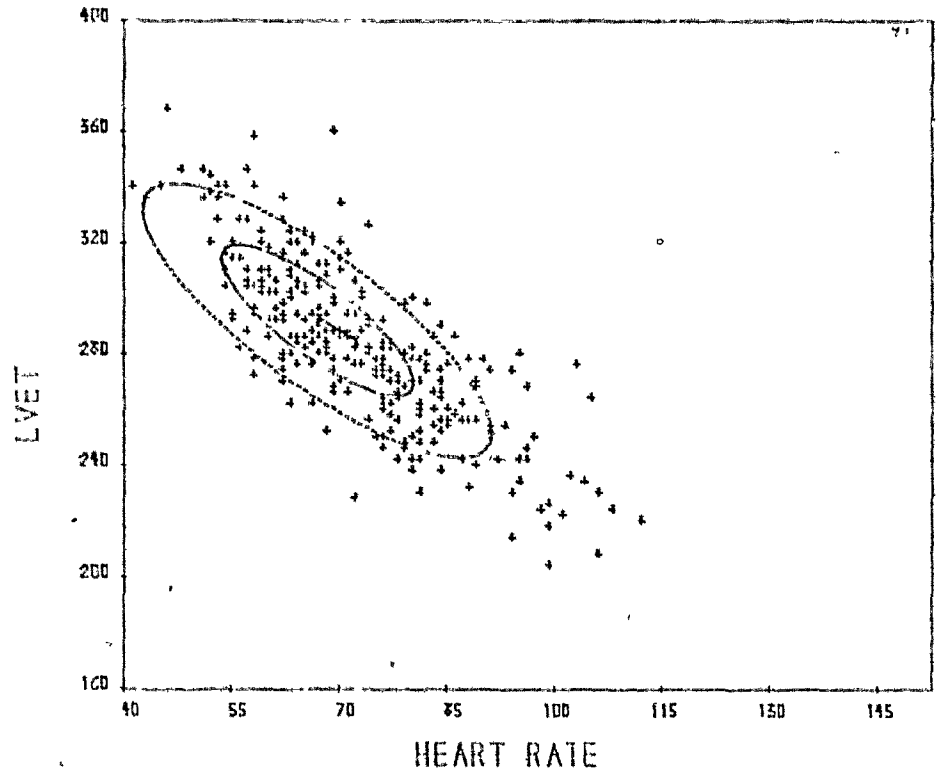


Figure 4.19 - Resting supine scattergram of LVET vs HR for 292 subjects with sustained hypertension. See Figure 4.1 legend for details.

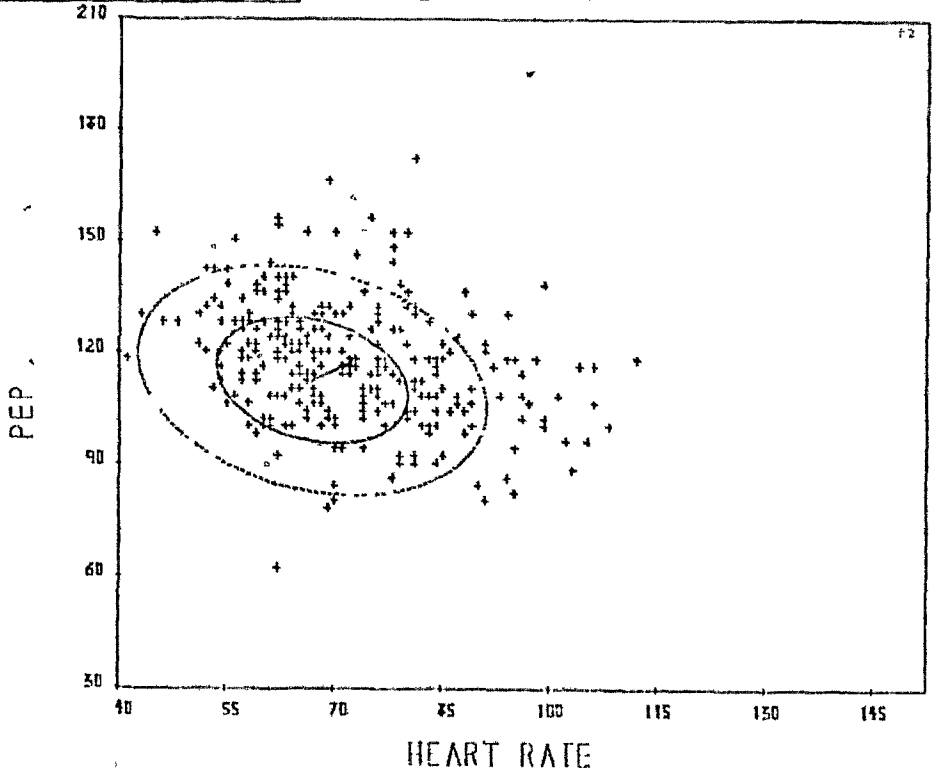


Figure 4.20 - Resting supine scattergram of PEP vs HR for 292 subjects with sustained hypertension. See Figure 4.1 legend for details.

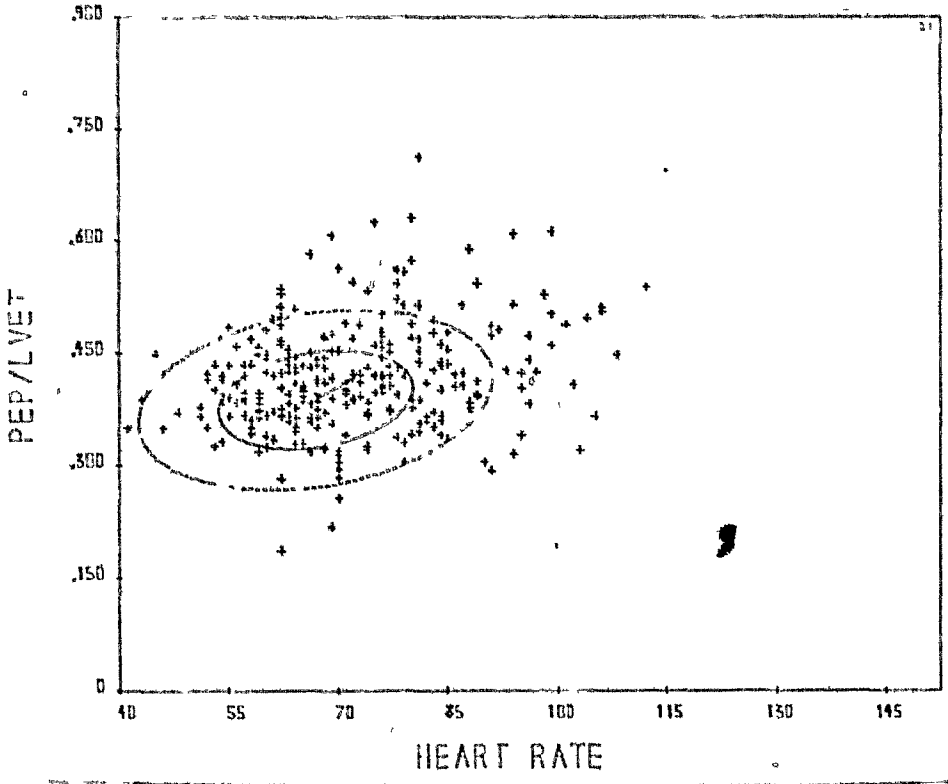


Figure 4.21 - Resting supine scattergram of PEP/LVET vs HR for 292 subjects with sustained hypertension. See Figure 4.1 legend for details.

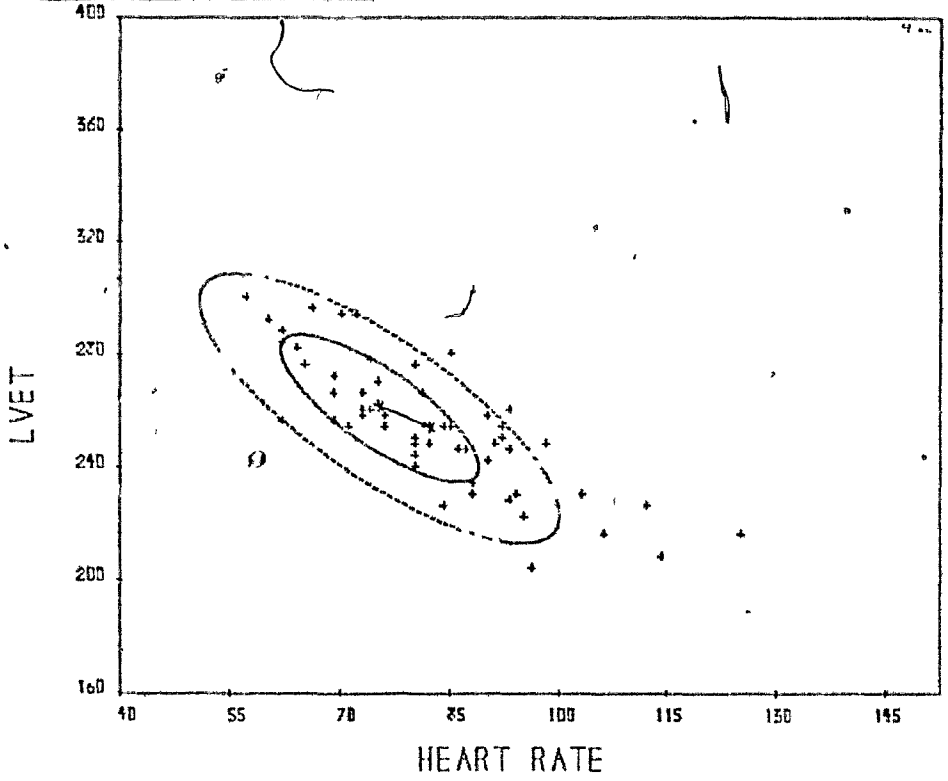


Figure 4.22 - Resting upright scattergram of LVET vs HR for 57 subjects with sustained hypertension. See Figure 4.1 legend for details.

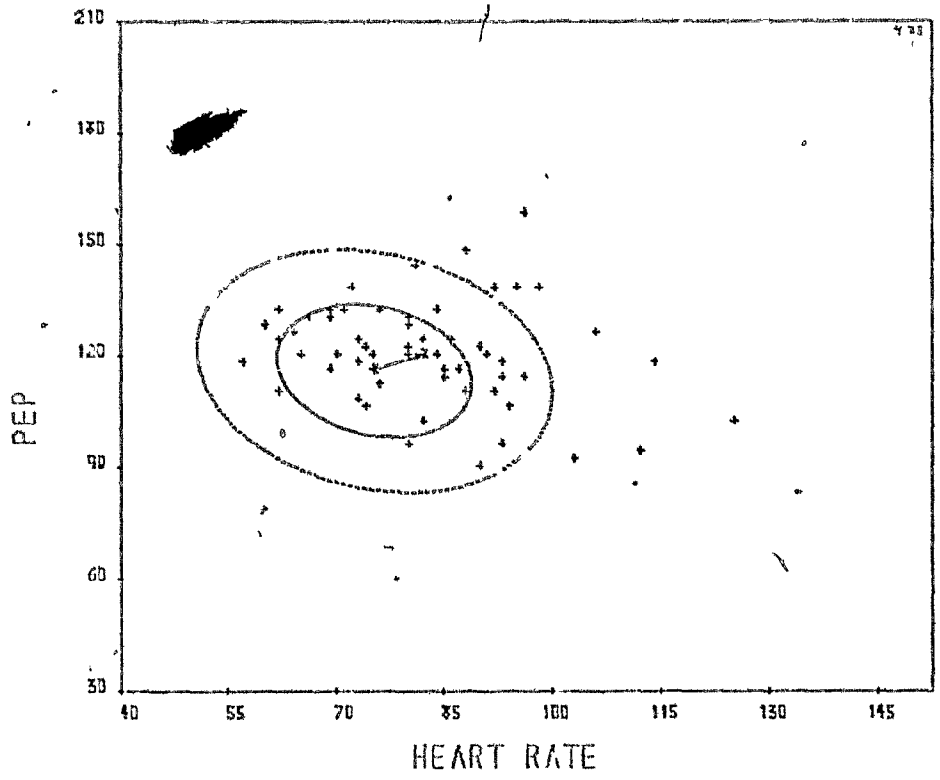


Figure 4.23 - Resting upright scattergram of PEP vs HR for 57 subjects with sustained hypertension. See Figure 4.1 legend for details.

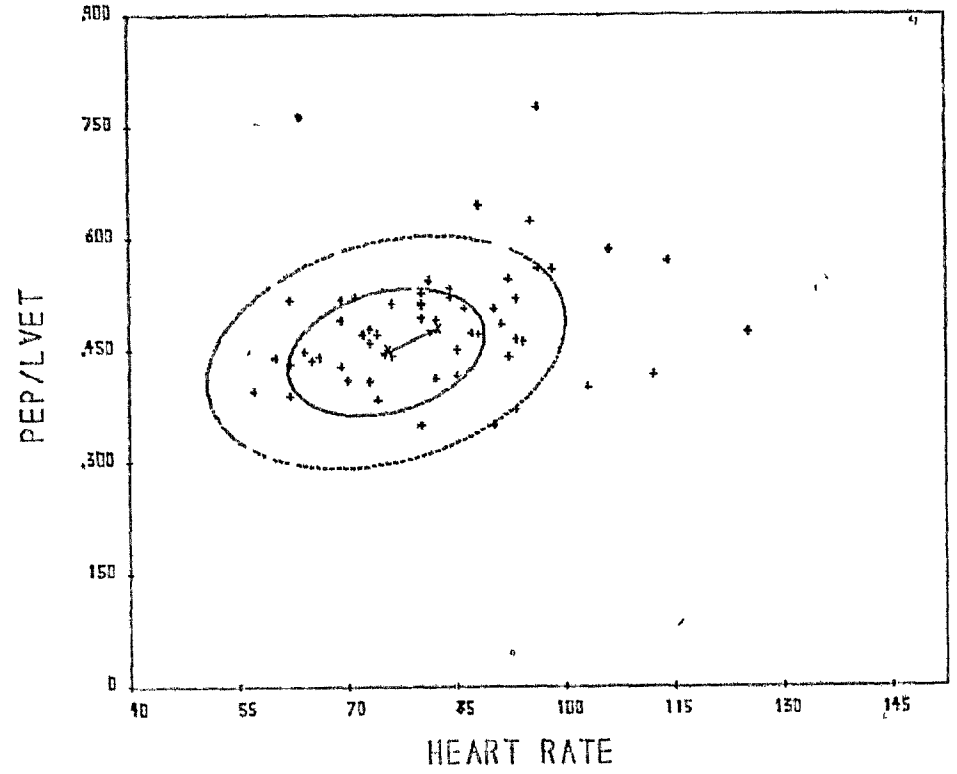


Figure 4.24 - Resting upright scattergram of PEP/LVET vs HR for 57 subjects with sustained hypertension. See Figure 4.1 legend for details.

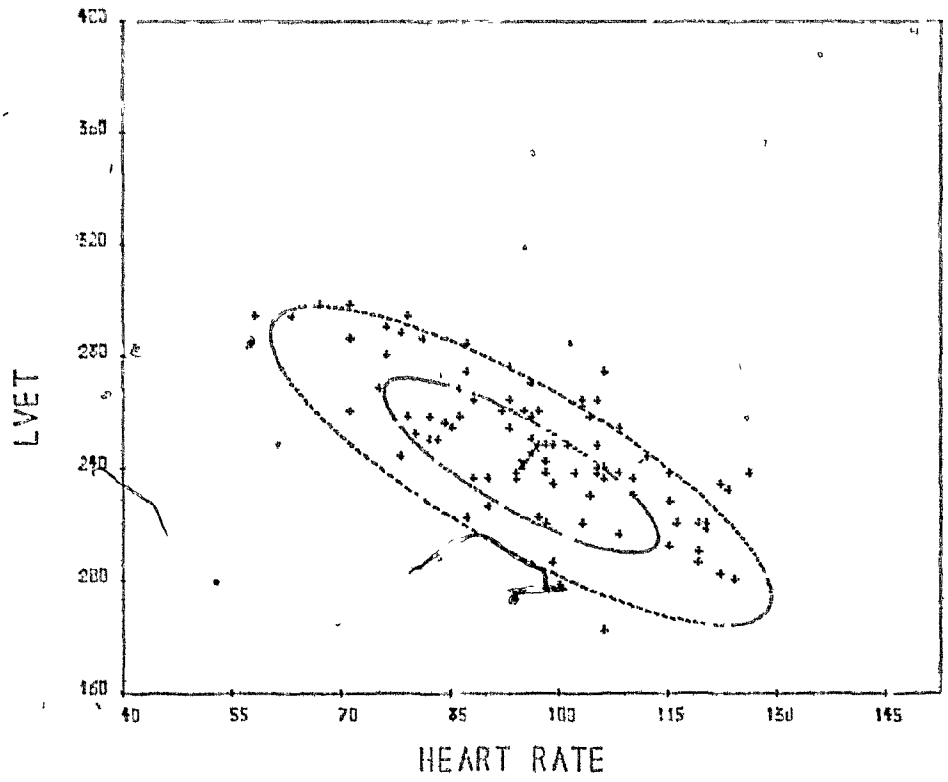


Figure 4.25 - Post-exercise scattergram of LVET vs HR for 85 subjects with sustained hypertension. See Figure 4.1 legend for details.

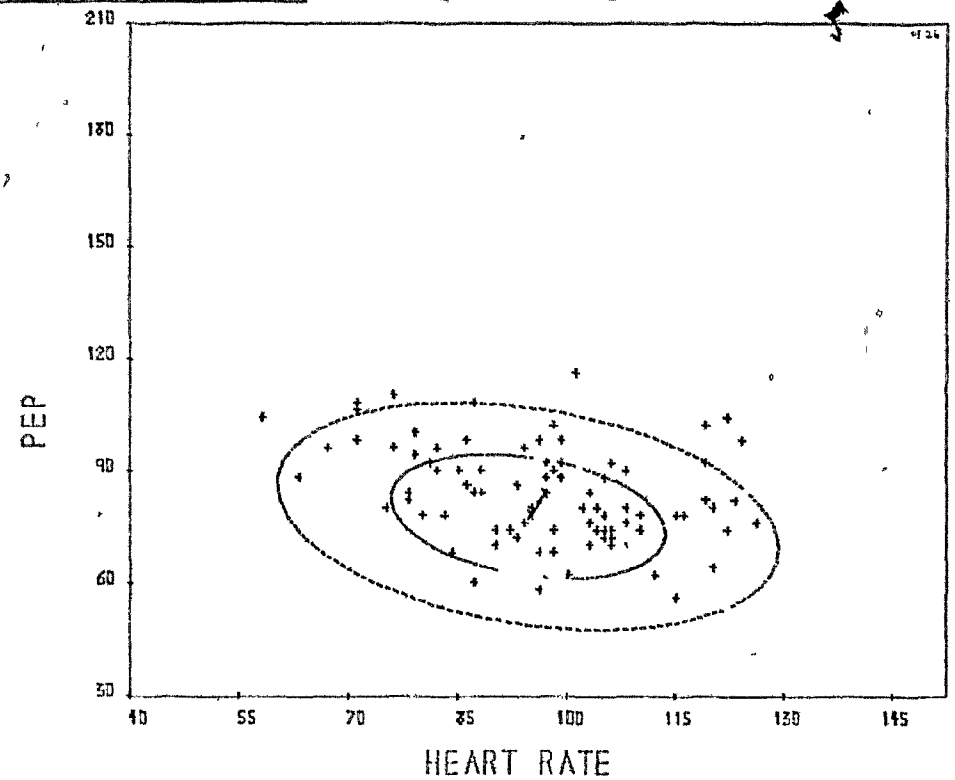


Figure 4.26 - Post-exercise scattergram of PEP vs HR for 85 subjects with sustained hypertension. See Figure 4.1 legend for details.

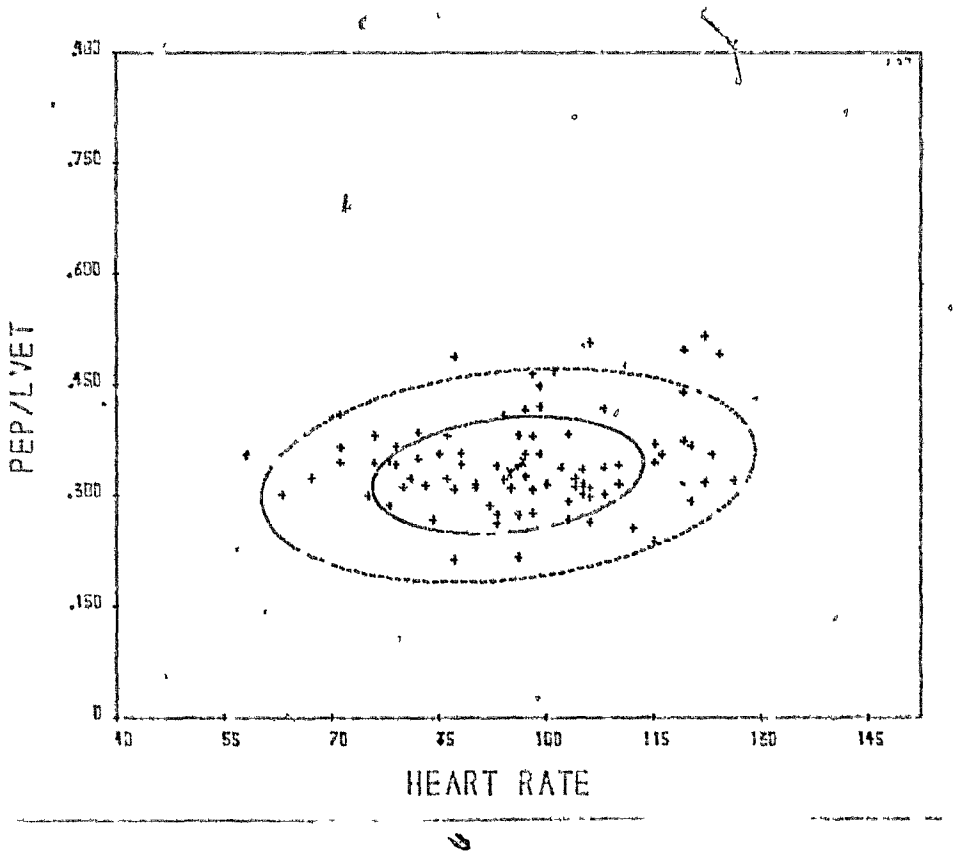


Figure 4.27 - Post-exercise scattergram of PEP/LVET vs HR for 85 subjects with sustained hypertension. See Figure 4.1 legend for details.

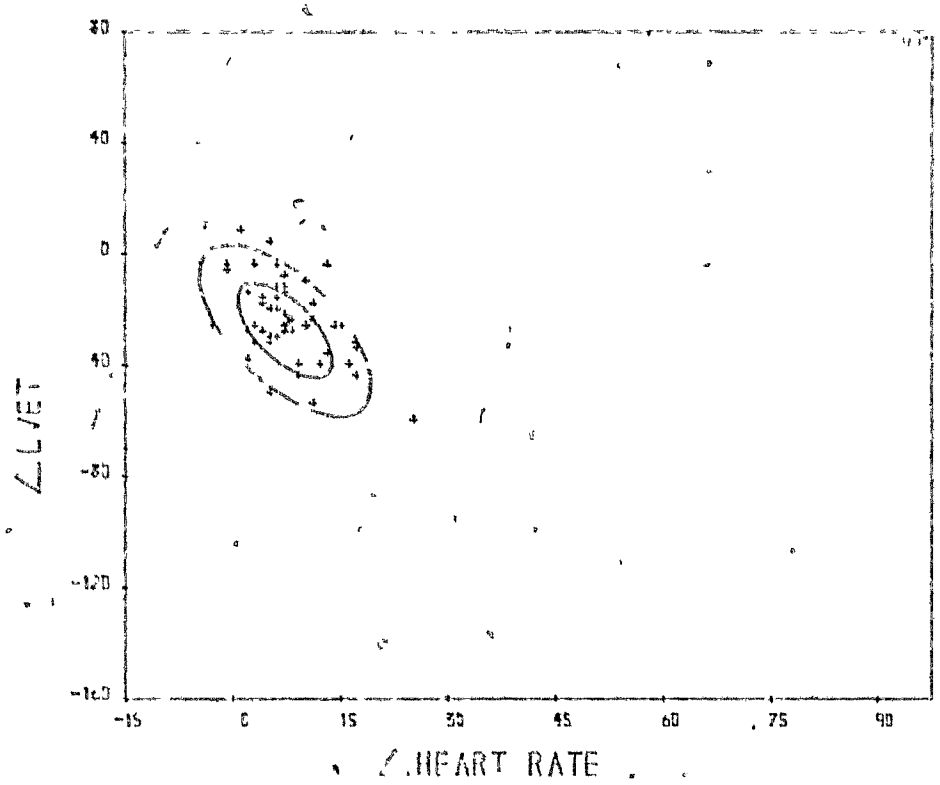


Figure 4.28 - Scattergram of change in LVET vs change in HR from resting supine to resting upright in 49 subjects with sustained hypertension.

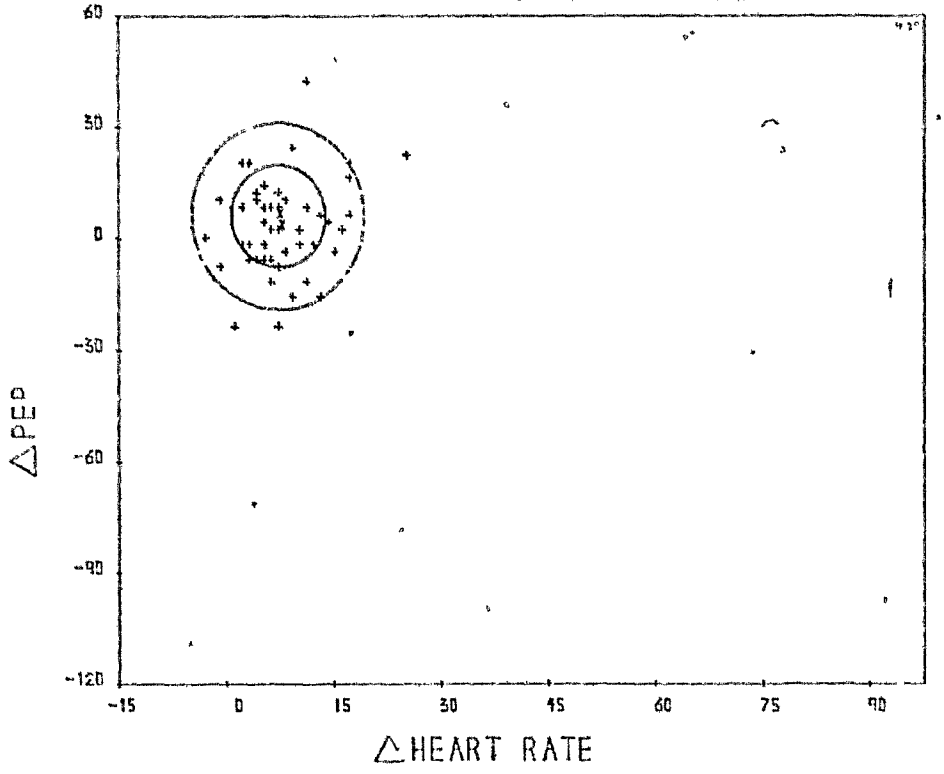


Figure 4.29 - Scattergram of change in PEP vs change in HR from resting supine to resting upright in 49 subjects with sustained hypertension.

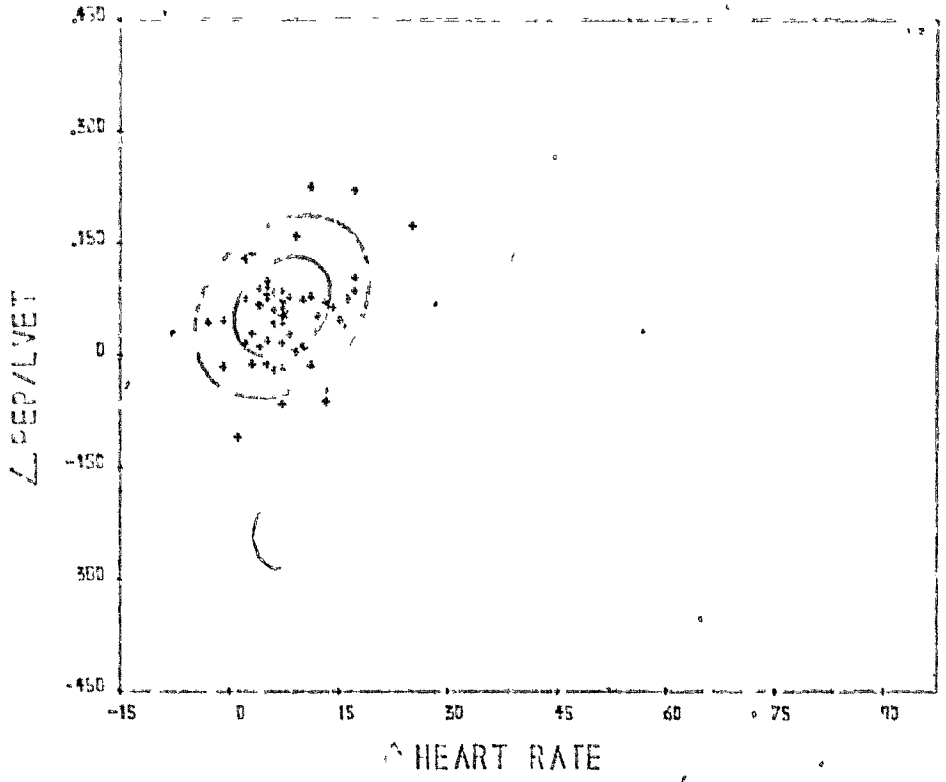


Figure 4.30 - Scattergram of change in PEP/LVET vs change in HR from resting supine to resting upright in 49 subjects with sustained hypertension.

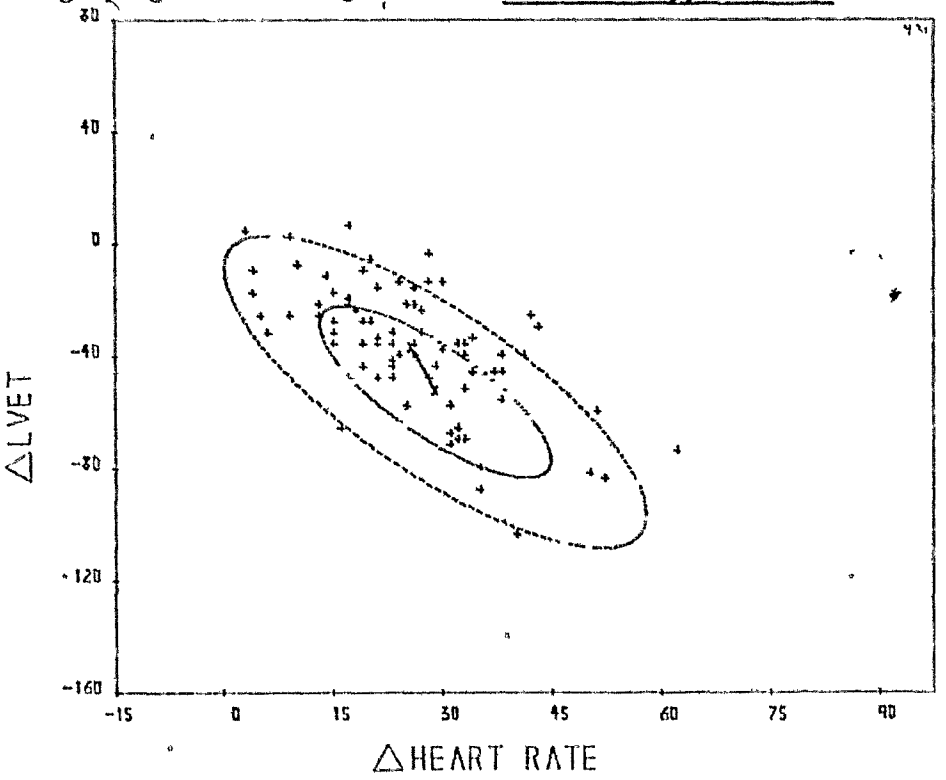


Figure 4.31 - Scattergram of change in LVET vs change in HR from resting supine to post-exercise in 79 subjects with sustained hypertension.

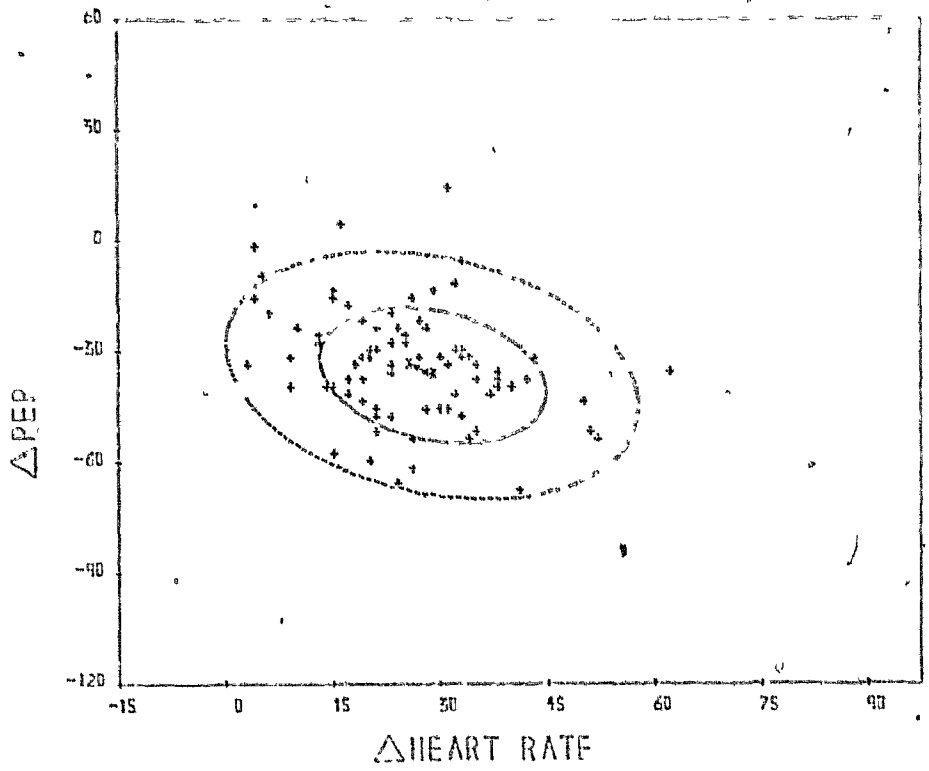


Figure 4.32 - Scattergram of change in PEP vs change in HR from resting supine to post-exercise in 79 subjects with sustained hypertension.

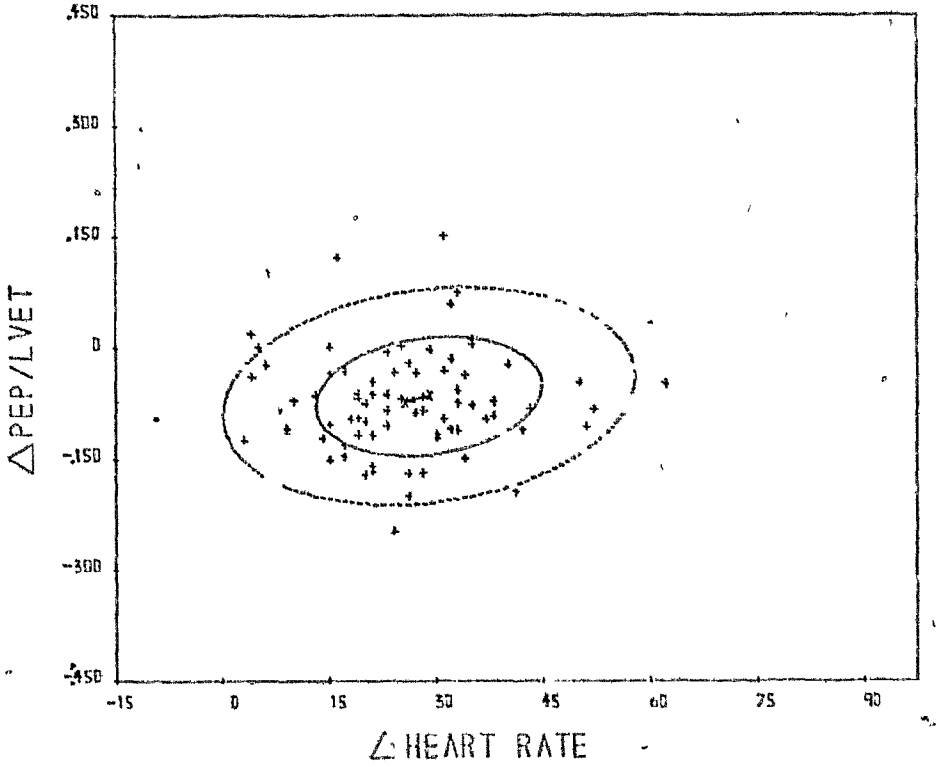


Figure 4.33 - Scattergram of change in PEP/LVET vs change in HR from resting supine to post-exercise in 79 subjects with sustained hypertension.

2.3 Confirmed Hypertensive Heart Disease

Ninety-nine resting supine records were obtained from subjects with confirmed hypertensive heart disease (HHD). Mean blood pressures for this group were 103.1 ± 13.4 mm Hg diastolic and 173.3 ± 21.6 mm Hg systolic. The regression data for this group is in Table 4.4 and the three scattergrams are Figures 4.34 to 4.36. Mean HR is seen to be increased by about 4.4 beats per minute with a decrease in LVET due almost entirely to the regression. There is an increase in PEP and PEP/LVET which is somewhat more than that due to regression. The combined test of means and covariance matrices gives a χ^2 of 221.8 on 14 d.f. ($p < .001$), while the test on the covariance matrices gives a value of 147.5 on 10 d.f. ($p < .001$). D^2 is 0.821 with an F of 19.0 on 4 and 1551 d.f. ($p < .001$). Outlier counts are 33 (33.3%), 24 (24.2%) and 26 (26.3%), due largely to a group of subjects with elevated heart rates. It is interesting to note that the LVET graph shows the greatest number of outliers, even though the mean on this graph lies practically on the normal regression line. The computed generalized outlier count was 23 (23.2%).

Figures 4.37 to 4.39 show resting upright data for 57 subjects from this group and the regression equations are again in Table 4.4. A slight elevation in mean HR is accompanied by a small increase in PEP and PEP/LVET with a negligible increase in LVET. χ^2 is 118.2 on 14 d.f. ($p < .001$) for the combined test and 88.2 on 10 d.f. ($p < .001$) for a test on the covariance matrices. D^2 is 0.573 with an F of 7.58 on 4 and 842 d.f. ($p < .001$). Outlier counts are 12 (21.1%), 10 (17.5%) and 9 (15.8%) with almost half due to elevated heart rates. The generalized count is 12 (21.1%).

Data on 30 subjects after exercise can be seen in Figures 4.40 to 4.42 and in Table 4.4. The means are shifted in much the same way as in the upright records. The two χ^2's are 57.3 on 14 d.f. ($p < .001$) and 37.6 on 10 d.f. ($p < .001$). D^2 is 0.703 with an F ratio of 4.98 on 4 and 595 d.f. ($p < .001$). The outlier counts are 5 (16.7%), 5 (16.7%) and 4 (13.3%) and are not attributable to elevated heart rates, which is consistant with the findings in the two hypertensive groups. The generalized count is 5 (16.7%).

Combined resting supine - resting upright data for 51 subjects can be seen in Figures 4.43 to 4.45. The mean response of all four variables is seen to be somewhat less than in normal subjects. The multivariate χ^2's are 131.6 on 44 d.f. and 93.6 on 36 d.f. (both $p < .001$), and D^2 (8 variables) is 0.819 with an F of 4.82 on 8 and 749 d.f. ($p < .001$). Outlier counts are 5 (9.8%), 4 (7.8%) and 5 (9.8%) which are all within the normal range. The generalized count is 8 (15.7%). As with the previous two groups, this is still not an improvement over the use of resting records

Similar results for the combination of resting supine and post-exercise data for 27 subjects are shown in Figures 4.46 to 4.48. Again we see a slightly smaller response in our test group relative to normals. The two χ^2 tests (8 variables) yield 102.3 on 44 d.f. and 82.2 on 36 d.f. (both $p < .001$) and the computed D^2 is 0.809 with an F of 2.56 on 8 and 536 d.f. ($p < .01$). This F ratio is marginally significant, which might be expected given the sample size. The generalized outlier count is 4 (14.8%) and the individual outlier counts are 5 (18.5%), 3 (11.1%) and 2 (7.4%) with only the first (ΔLVET) being out of the normal range, if such a statement is appropriate with a sample of 5 points. Because of this problem with

TABLE 4.4

Systolic Time Intervals In Hypertensive Heart Disease:
Mean Values and Heart Rate Regressions

	Mean Values		Regression With Heart Rate				
Variable	Mean	S.D.	Intercept	Slope	S.D.	Correlation	P
A - Resting Supine: N = 99							
HR	71.4	14.7					
LVET	282.4	30.8	403.9	-1.70	18.1	-.809	<.001
PEP	117.5	15.0	123.3	- .82	14.9	-.080	n.s.
PEP/LVET	.422	.076	.257	.00231	.068	.446	<.001
B - Resting Upright. N = 57							
HR	77.8	16.6					
LVET	261.8	30.0	384.9	-1.58	14.3	-.879	<.001
PEP	120.5	12.1	121.1	- .01	12.1	-.011	n.s.
PEP/LVET	.467	.079	.236	.00298	.061	.630	<.001
C - Post-Exercise. N = 30							
HR	100.0	16.1					
LVET	236.7	29.8	386.6	-1.50	17.6	-.808	<.001
PEP	85.4	13.6	92.4	- .07	13.5	-.083	n.s.
PEP/LVET	.367	.080	.137	.00231	.071	.462	<. 01

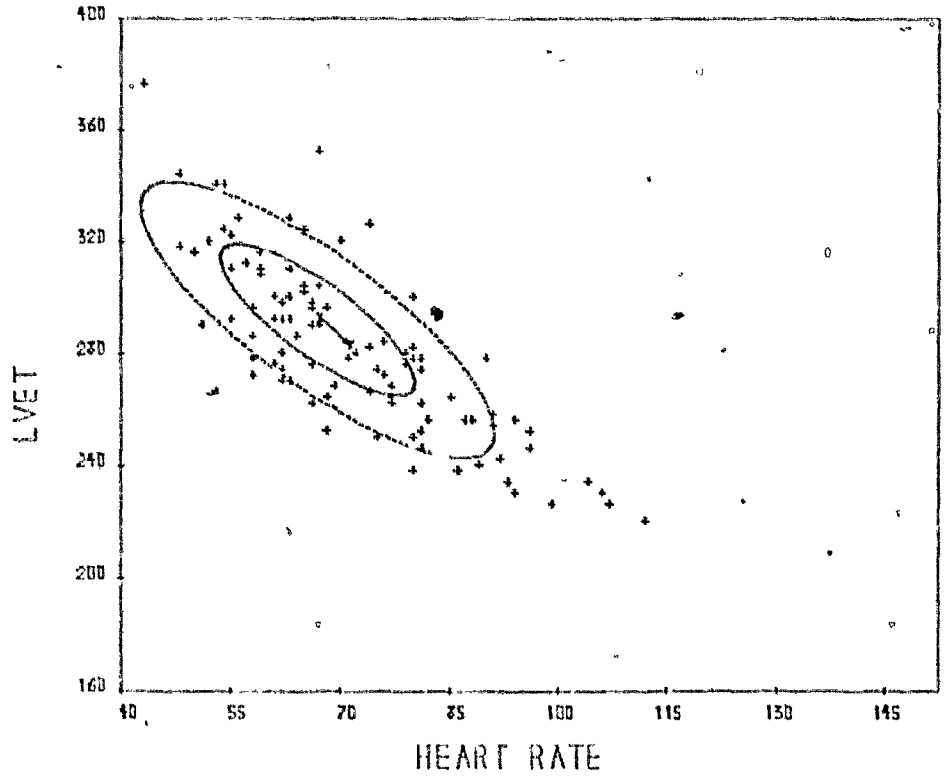


Figure 4.34 - Resting supine scattergram of LVET vs HR for 99 subjects with hypertensive heart disease. See Figure 4.1 legend for details.

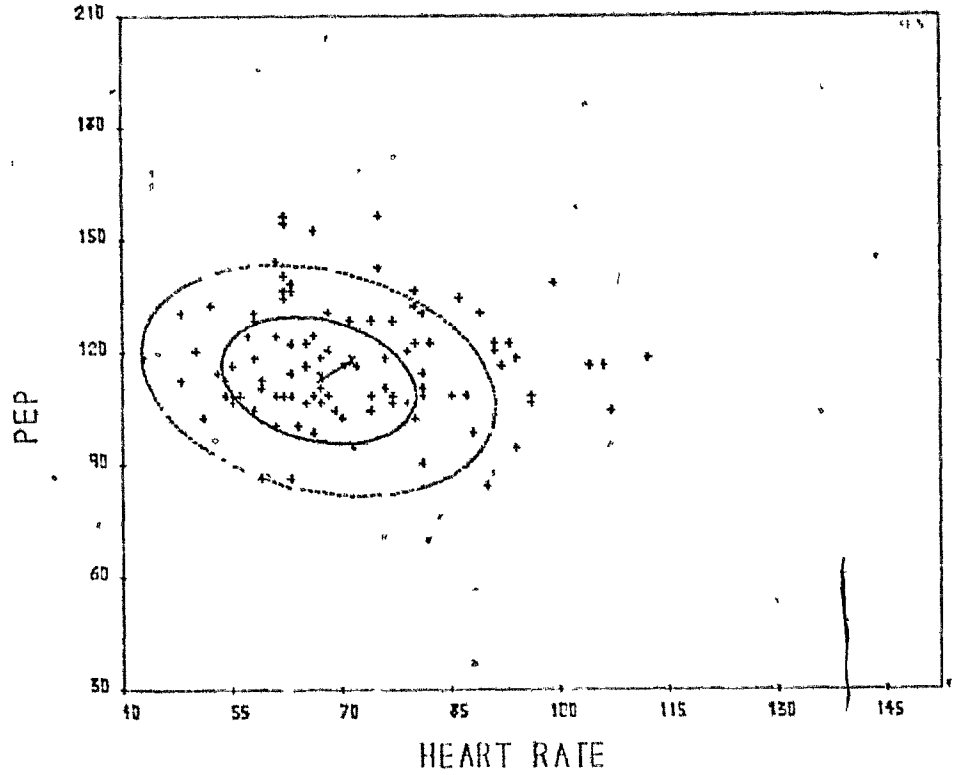


Figure 4.35 - Resting supine scattergram of PEP vs HR for 99 subjects with hypertensive heart disease. See Figure 4.1 legend for details.

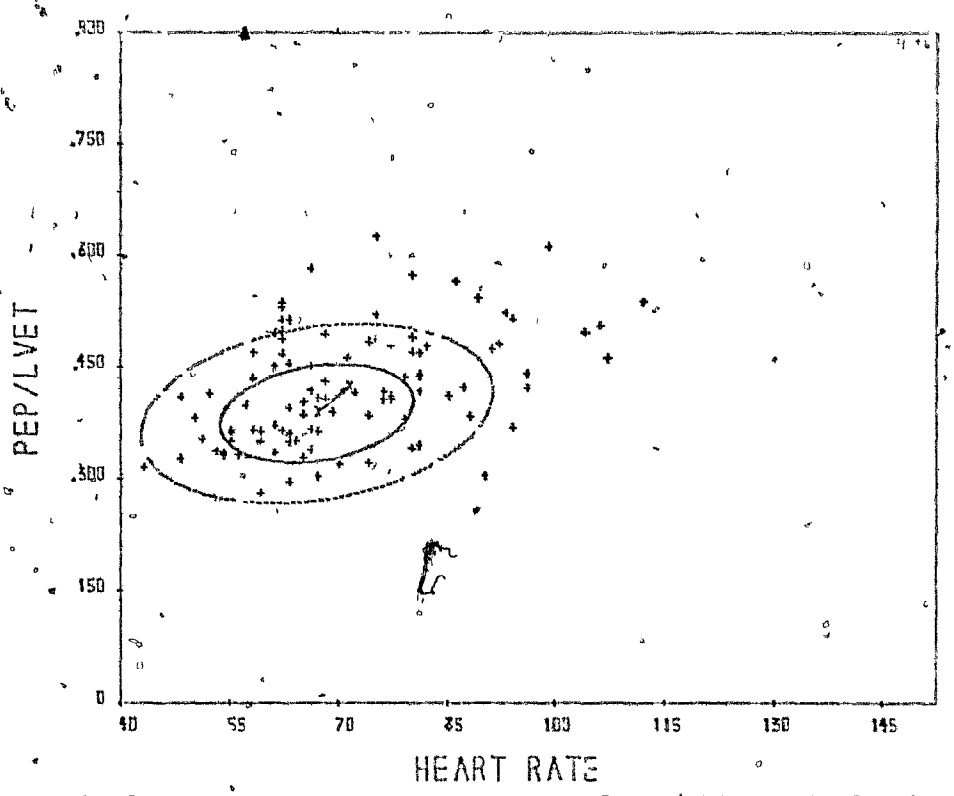


Figure 4.36 - Resting supine scattergram of PEP/LVET vs HR for 99 subjects with hypertensive heart disease. See Figure 4.1 legend for details.

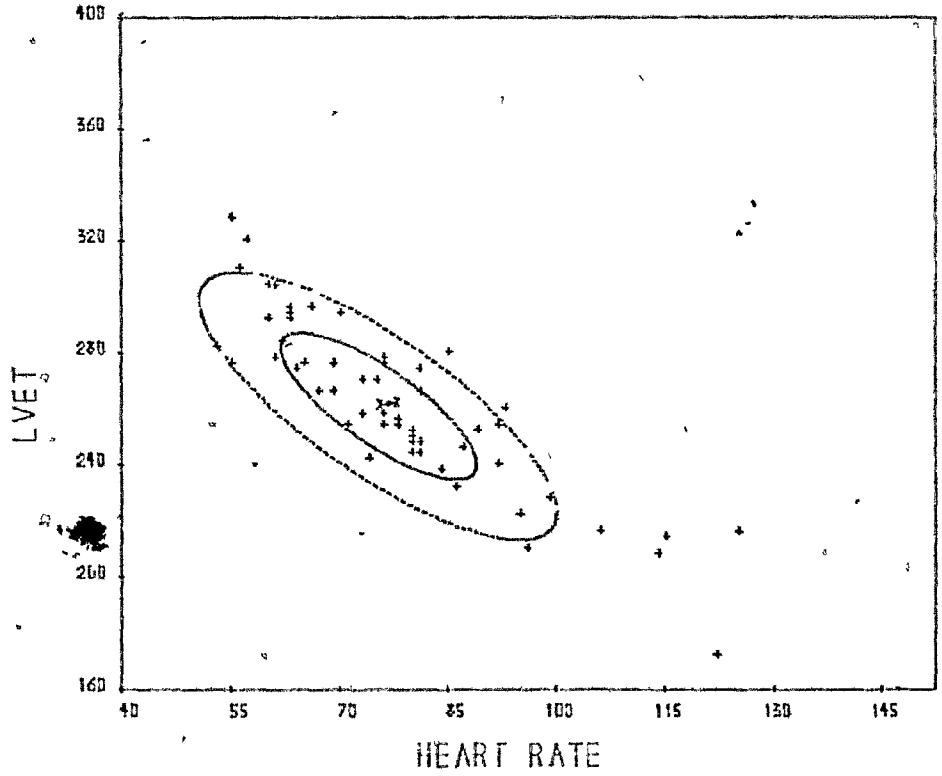


Figure 4.37 - Resting upright scattergram of LVET vs HR for 57 subjects with hypertensive heart disease. See Figure 4.1 legend for details.

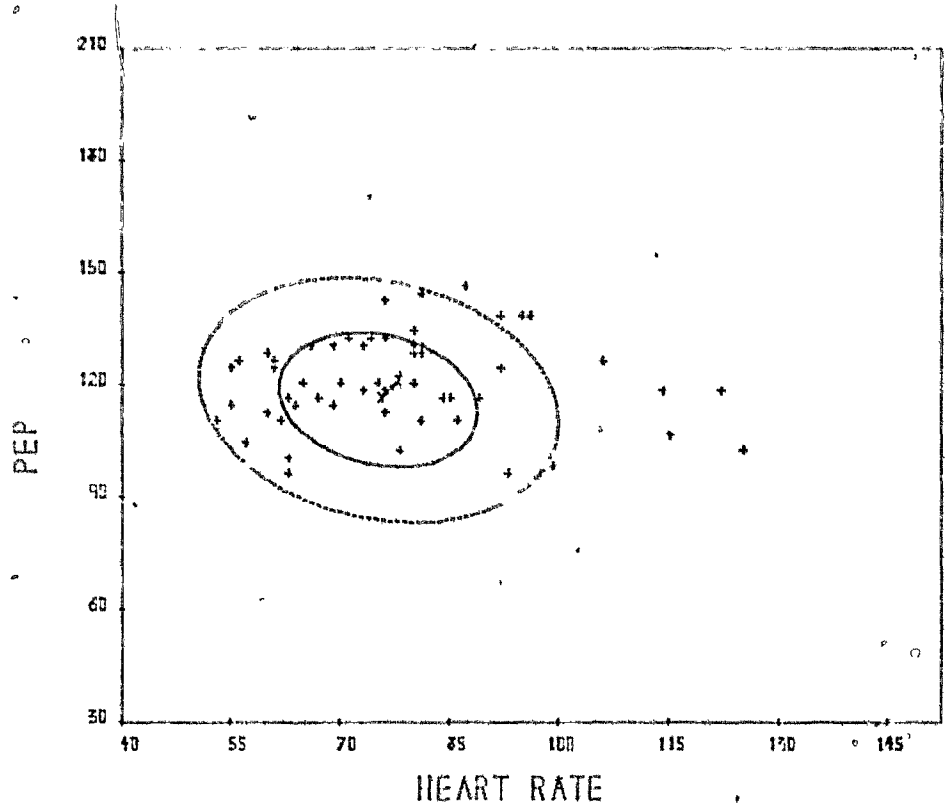


Figure 4.38 - Resting upright scattergram of PEP vs HR for 57 subjects with hypertensive heart disease. See Figure 4.1 legend for details.

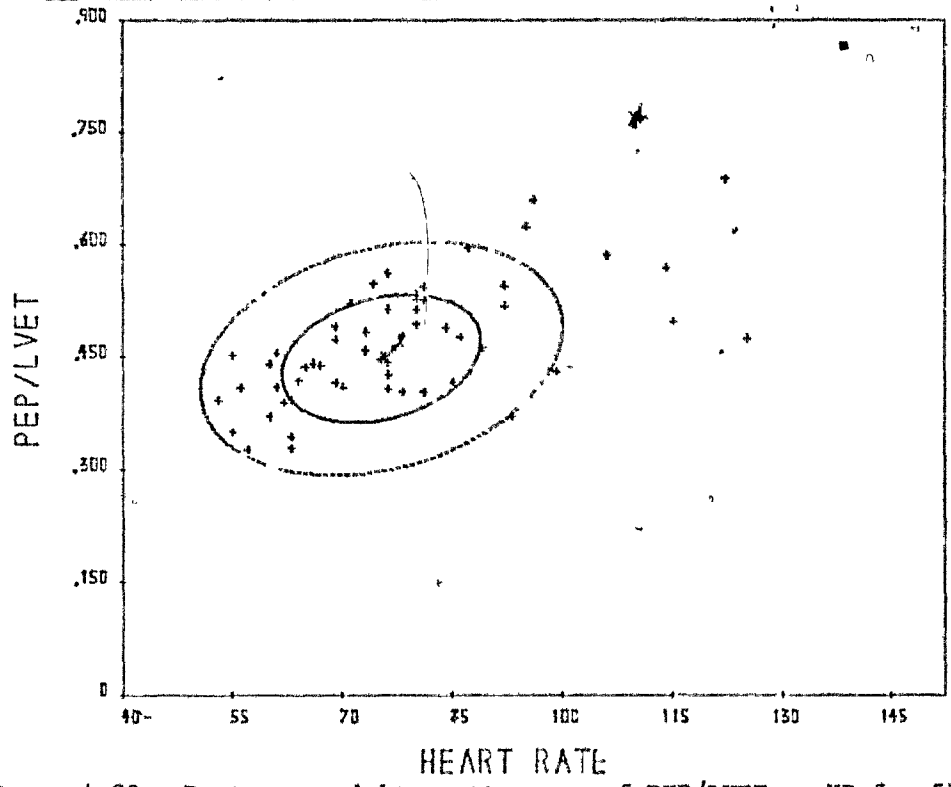


Figure 4.39 - Resting upright scattergram of PEP/LVET vs HR for 57 subjects with hypertensive heart disease. See Figure 4.1 legend for details.

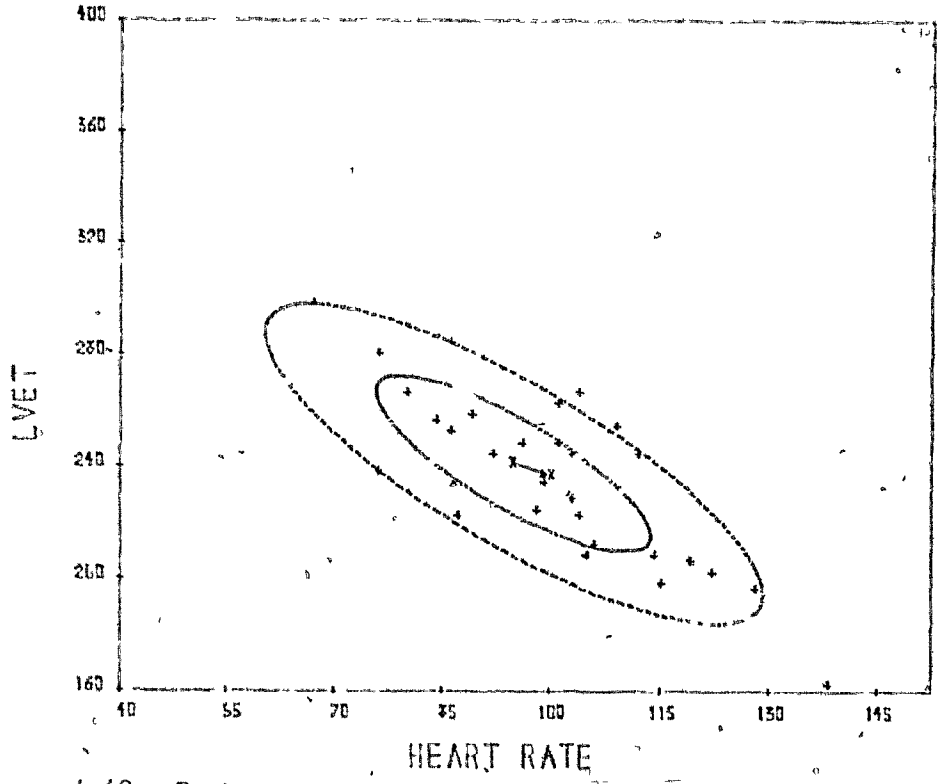


Figure 4.40 - Post-exercise scattergram of LVET vs HR for 30 subjects with hypertensive heart disease. See Figure 4.1 legend for details.

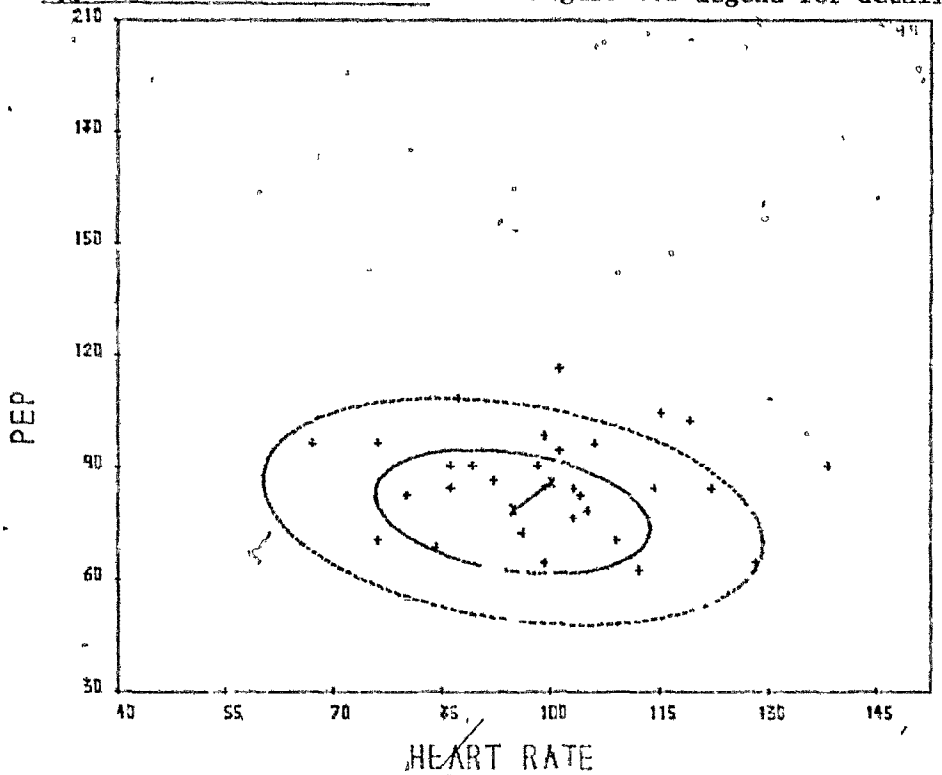


Figure 4.41 - Post-exercise scattergram of PEP vs HR for 30 subjects with hypertensive heart disease. See Figure 4.1 legend for details.

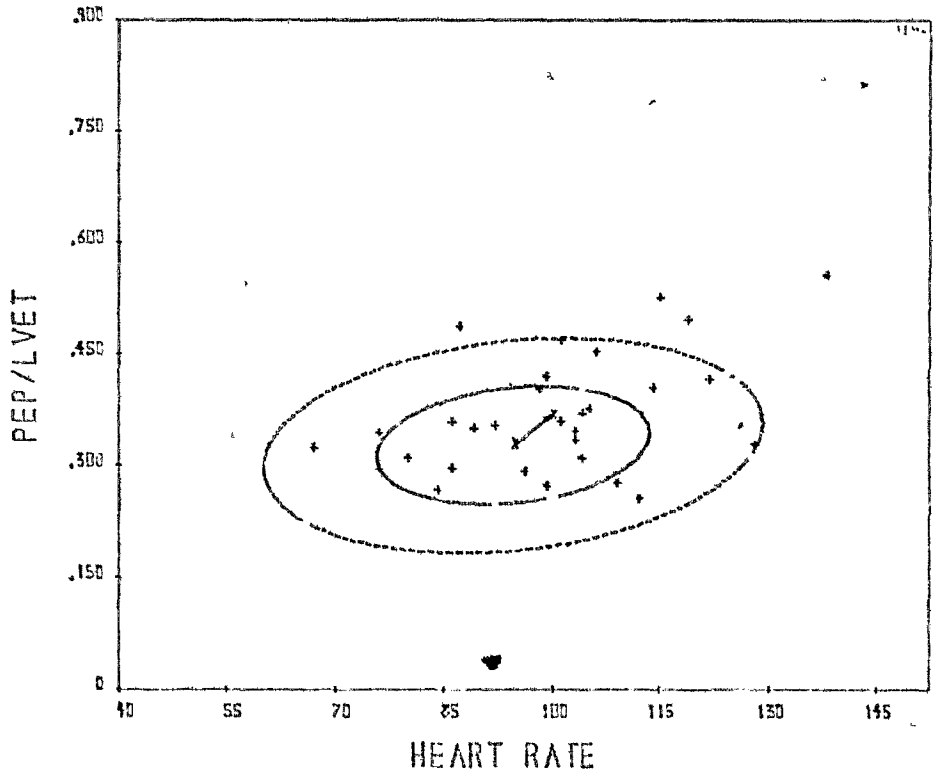


Figure 4.42 - Post-exercise scattergram of PEP/LVET vs HR for 30 subjects with hypertensive heart disease. See Figure 4.1 legend for details.

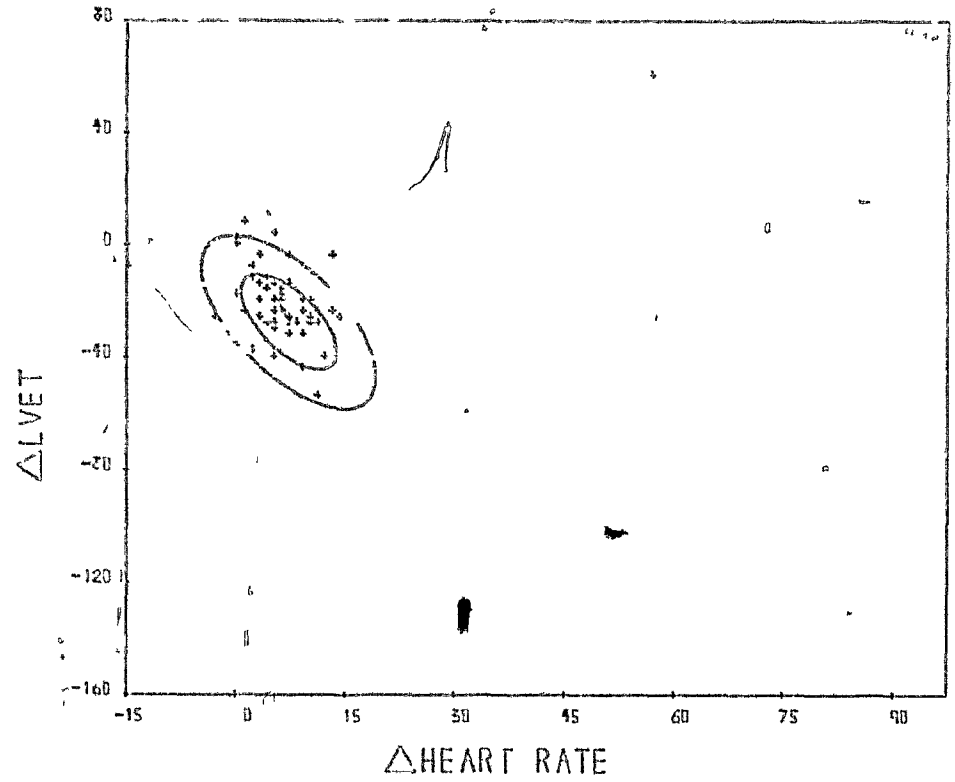


Figure 4.43 - Scattergram of change in LVET vs change in HR from resting supine to resting upright in 51 subjects with hypertensive heart disease.

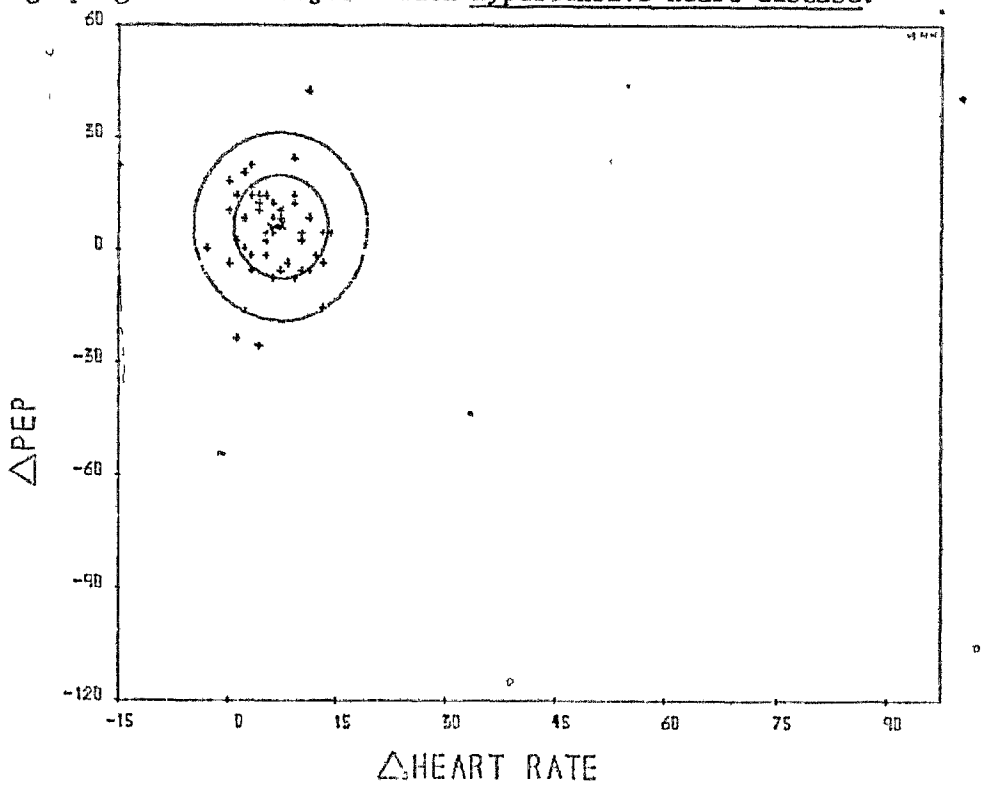


Figure 4.44 - Scattergram of change in PEP vs change in HR from resting supine to resting upright in 51 subjects with hypertensive heart disease.

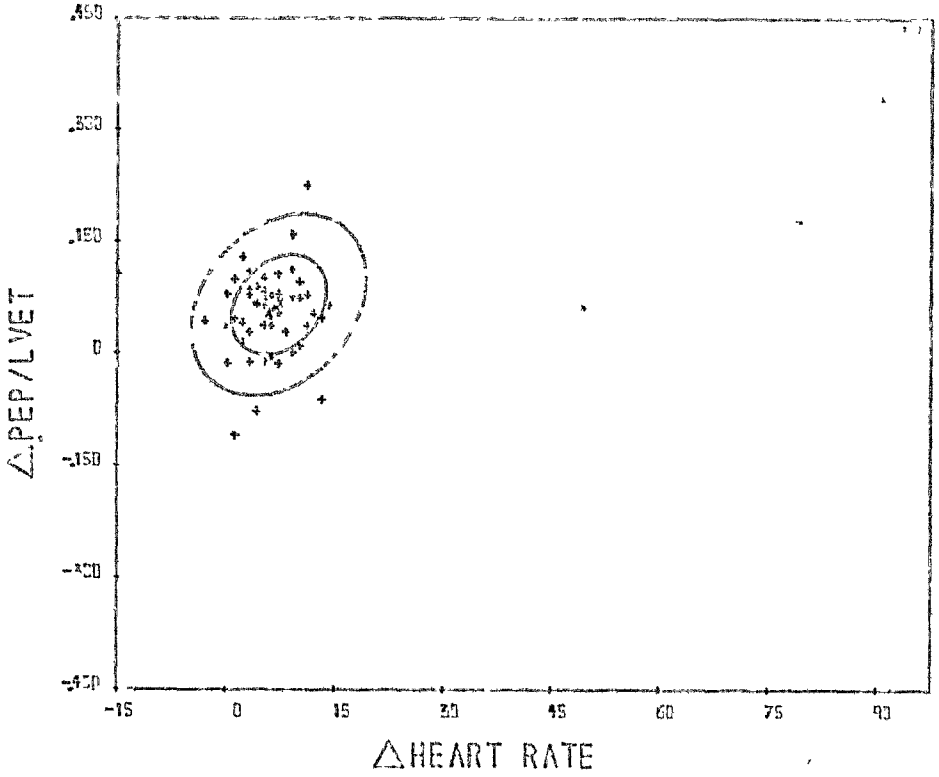


Figure 4.45 - Scattergram of change in PEP/LVET vs change in HR from resting supine to resting upright in 51 subjects with hypertensive heart disease.

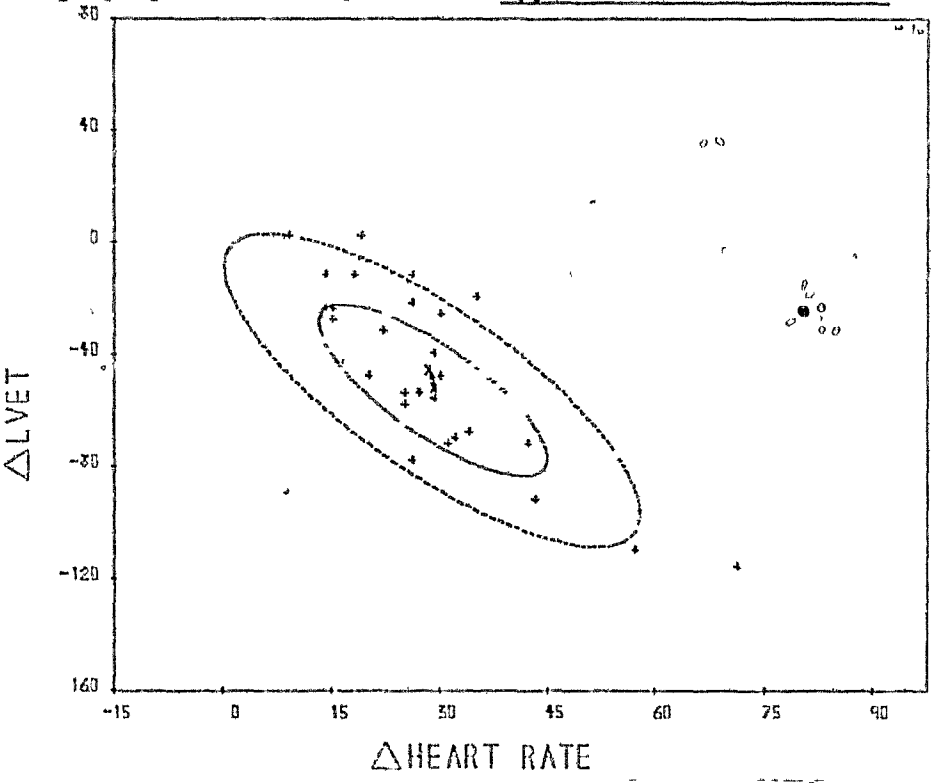


Figure 4.46 - Scattergram of change in LVET vs change in HR from resting supine to post-exercise in 27 subjects with hypertensive heart disease.

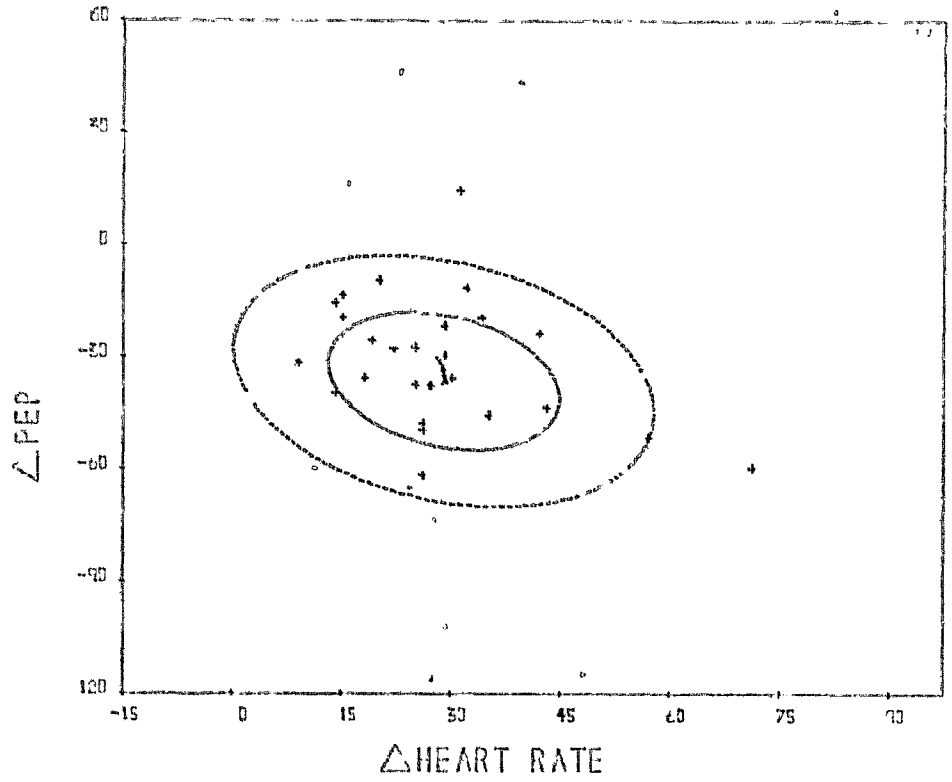


Figure 4.47 - Scattergram of change in PEP vs change in HR from resting supine to post-exercise in 27 subjects with hypertensive heart disease.

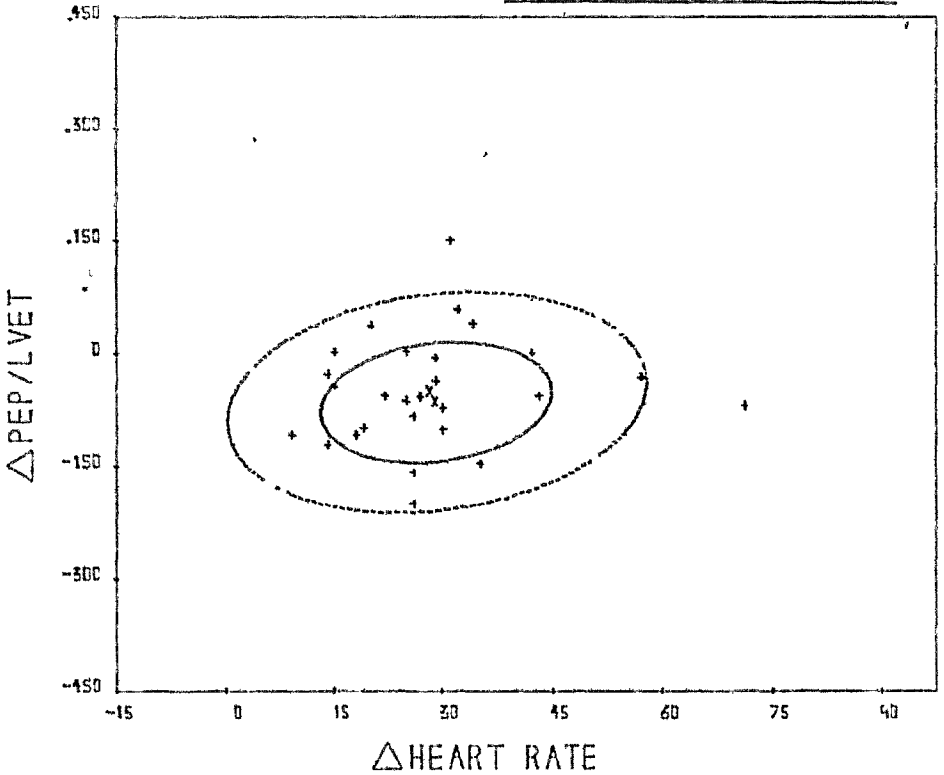


Figure 4.48 - Scattergram of change in PEP/LVET vs change in HR from resting supine to post-exercise in 27 subjects with hypertensive heart disease.

sample sizes, the two-state combinations were not studied in any further groups.

2.4 Cardiac Enlargement

There were 152 subjects with notably increased cardiac enlargement (CE) over the 5 year period and the regression data for each of the three states studied is in Table 4.5. All of these subjects are from the Helsinki Policemen Study. The resting scattergrams are in Figures 4.49 to 4.51. In this data we see a mean heart rate increase of 2.4 beats per minute, with the mean value of LVET, PEP and PEP/LVET lying practically on the normal regression lines. The multivariate tests give χ^2 values of 203.2 on 14 d.f. and 180.2 on 10 d.f. ($p < .001$), while D^2 is only 0.169 with an F of 5.79 on 4 and 1604 d.f. ($p < .001$). The outlier counts are 26 (17.1%), 29 (19.1%) and 26 (17.1%) which are above the expectation for normals, largely because of a number of subjects with elevated heart rates. In addition, there are a fair number of outliers both above and below the regression lines, which is supported by the large χ^2 seen in the test for equality of the covariance matrices (the scatter is obviously much greater in this group). Twenty-five subjects (16.4%) lie outside of 4-dimensional generalized normal limit.

The scattergram for 142 resting upright records are seen in Figures 4.52 to 4.54. In this case, the mean values differ very little from normal. χ^2 for the combined test is 55.4 on 14 d.f. ($p < .001$) and for the covariance test is 45.7 on 10 d.f. ($p < .001$). D^2 is only 0.081 with an F ratio of 2.43 on 4 and 927 d.f., which is barely significant ($p < .05$). The outlier counts, however, are 23 (16.2%), 20 (14.1%) and 17 (12.0%), again reflecting the increased scatter of points for this group. In con-

TABLE 4.5

Systolic Time Intervals In Cardiac Enlargement:

Mean Values and Heart Rate Regressions

	Mean Values		Regression With Heart Rate				
Variable	Mean	S.D.	Intercept	Slope	S.D.	Correlation	P
A - Resting Supine. N = 152							
HR	69.4	12.3					
LVET	288.5	25.8	406.2	-1.70	15.1	-.812	<.001
PEP	112.1	15.7	108.0	.06	15.7	.047	n.s.
PEP/LVET	.393	.074	.204	.00272	.066	.452	<.001
B - Resting Upright. N = 142							
HR	75.4	14.0					
LVET	263.5	25.9	380.1	-1.55	14.4	-.832	<.001
PEP	117.1	14.2	127.8	- .14	14.0	-.139	n.s.
PEP/LVET	.449	.073	.285	.00218	.067	.415	<.001
C - Post-Exercise. N = 55							
HR	99.1	20.1					
LVET	232.9	28.0	349.0	-1.17	15.1	-.842	<.001
PEP	78.1	14.1	90.2	- .12	13.9	-.175	n.s.
PEP/LVET	.340	.076	.210	.00131	.071	.348	<. 01

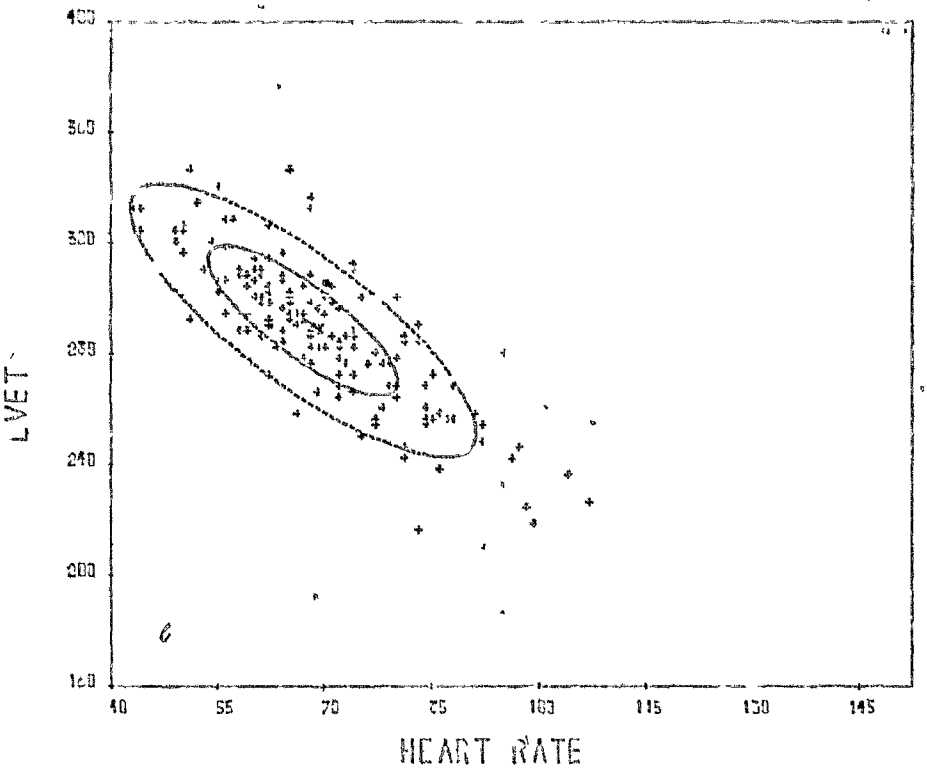


Figure 4.49 - Resting supine scattergram of LVET vs HR for 152 subjects with cardiac enlargement. See Figure 4.1 legend for details.

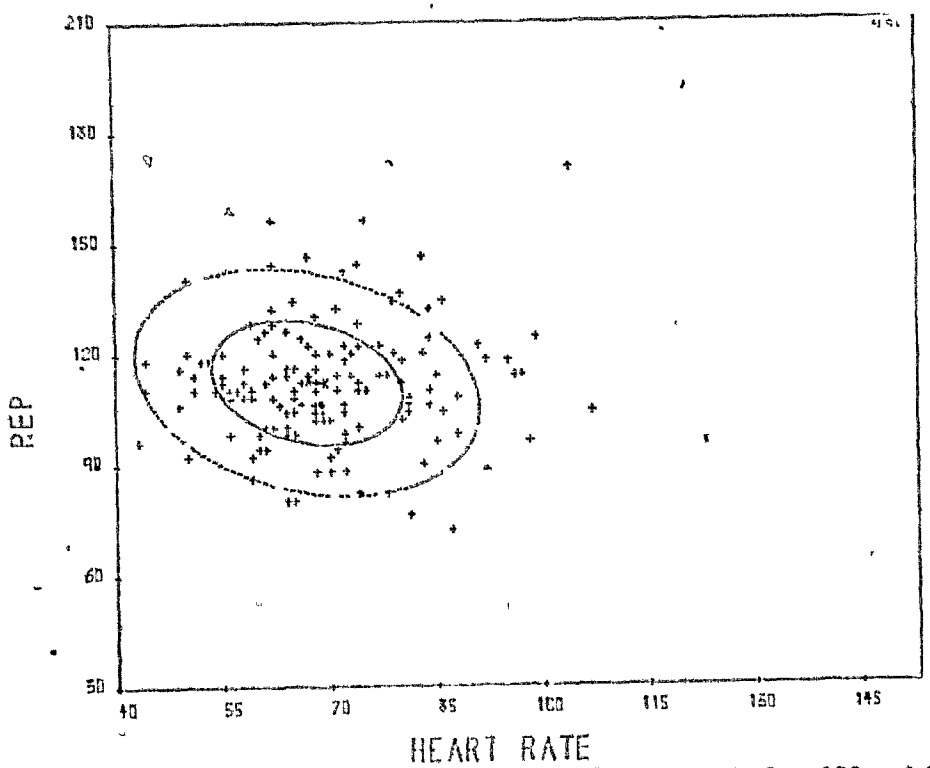


Figure 4.50 - Resting supine scattergram of PEP vs HR for 152 subjects with cardiac enlargement. See Figure 4.1 legend for details.

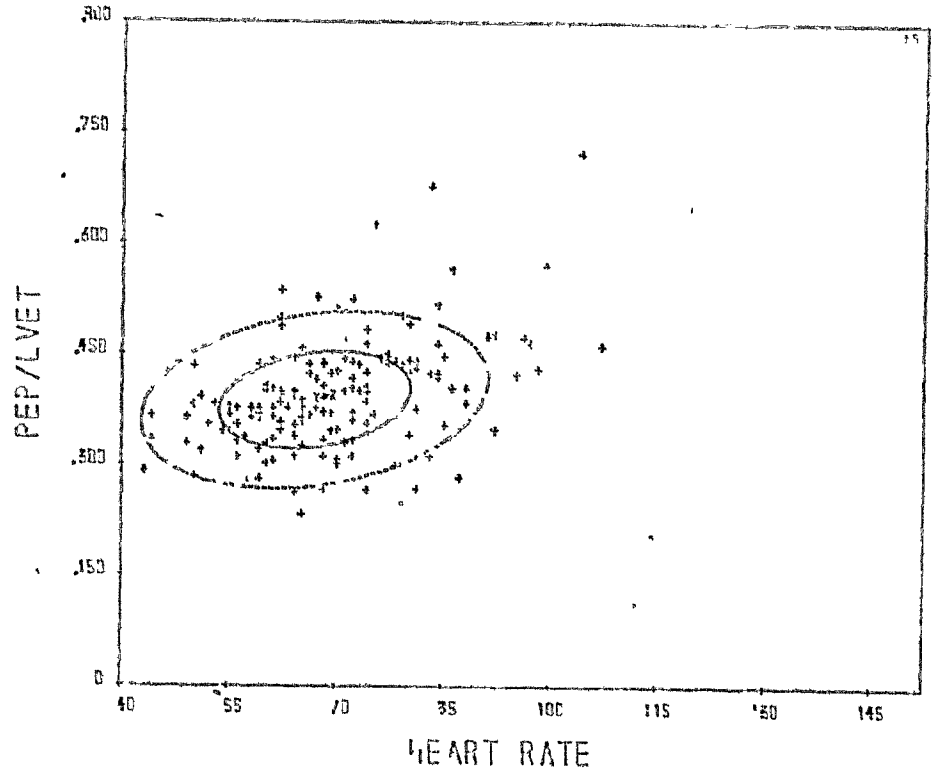


Figure 4.51 - Resting supine scattergram of PEP/LVET vs HR for 152 subjects with cardiac enlargement. See Figure 4.1 legend for details.

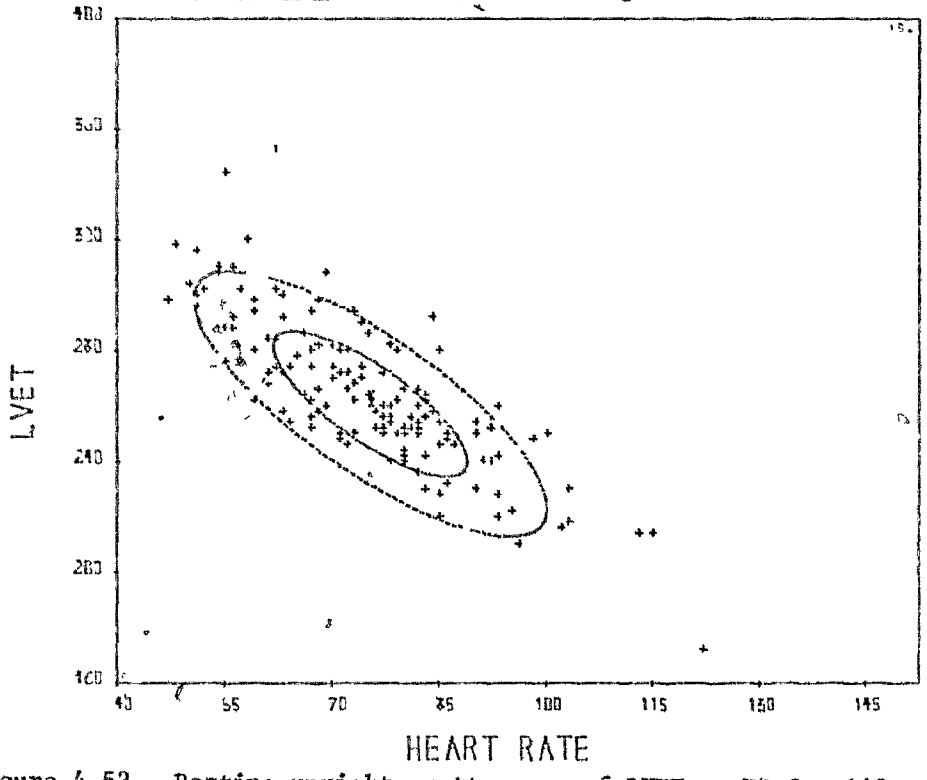


Figure 4.52 - Resting upright scattergram of LVET vs HR for 142 subjects with cardiac enlargement. See Figure 4.1 legend for details.

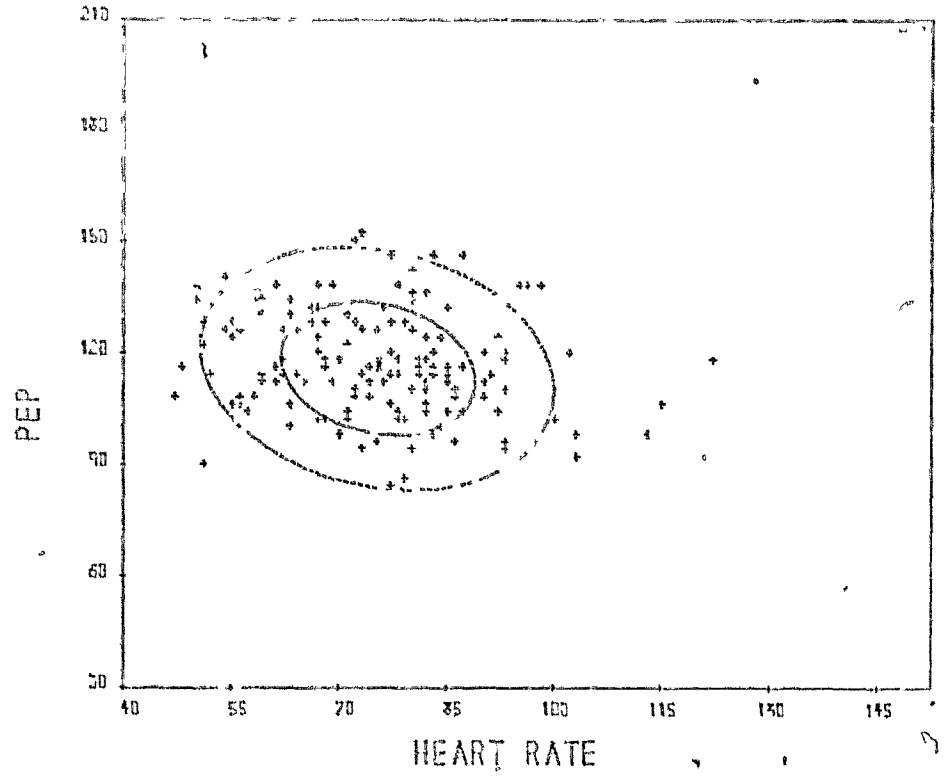


Figure 4.53 - Resting upright scattergram of PEP vs HR for 142 subjects with cardiac enlargement. See Figure 4.1 legend for details.

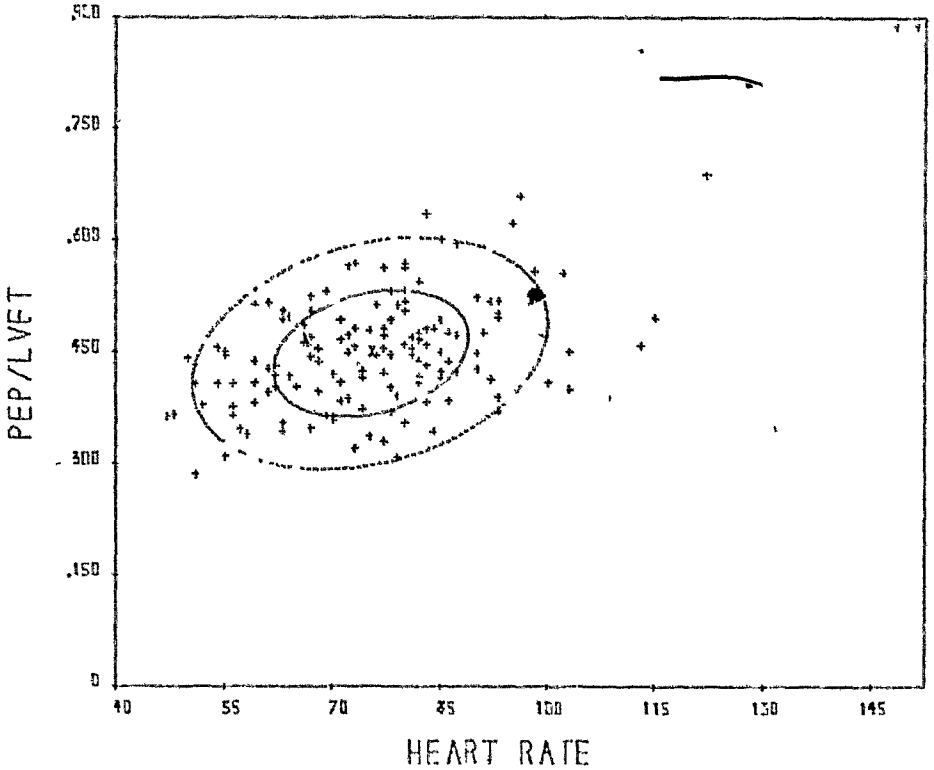


Figure 4.54 - Resting upright scattergram of PEP/LVET vs HR for 142 subjects with cardiac enlargement. See Figure 4.1 legend for details.

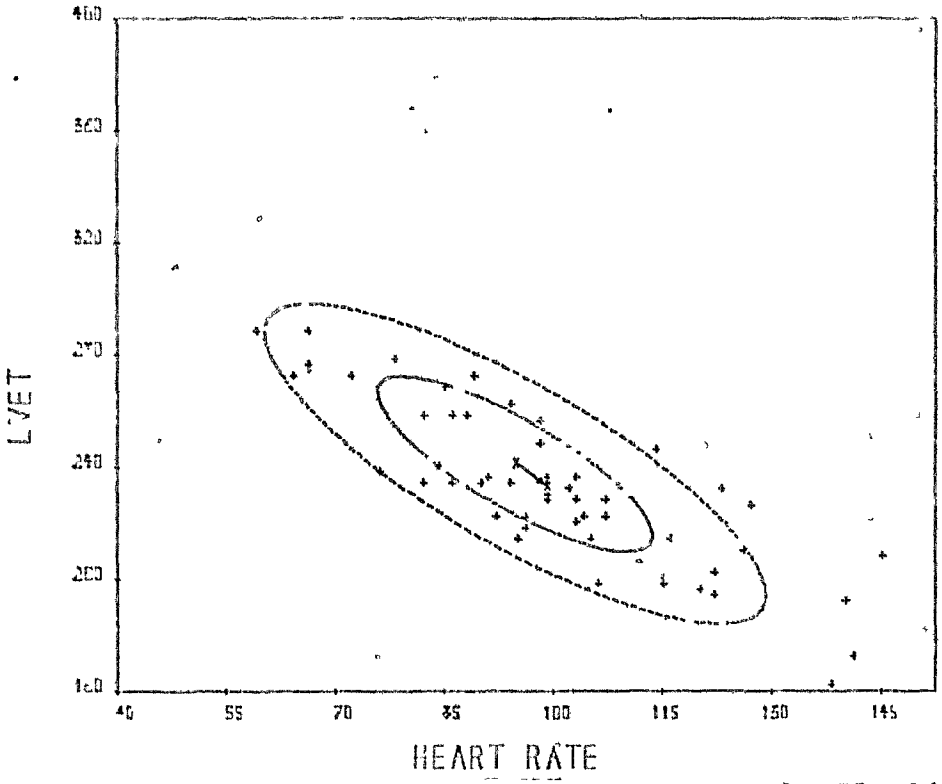


Figure 4.55 - Post-exercise scattergram of LVET vs HR for 55 subjects with cardiac enlargement. See Figure 4.1 legend for details.

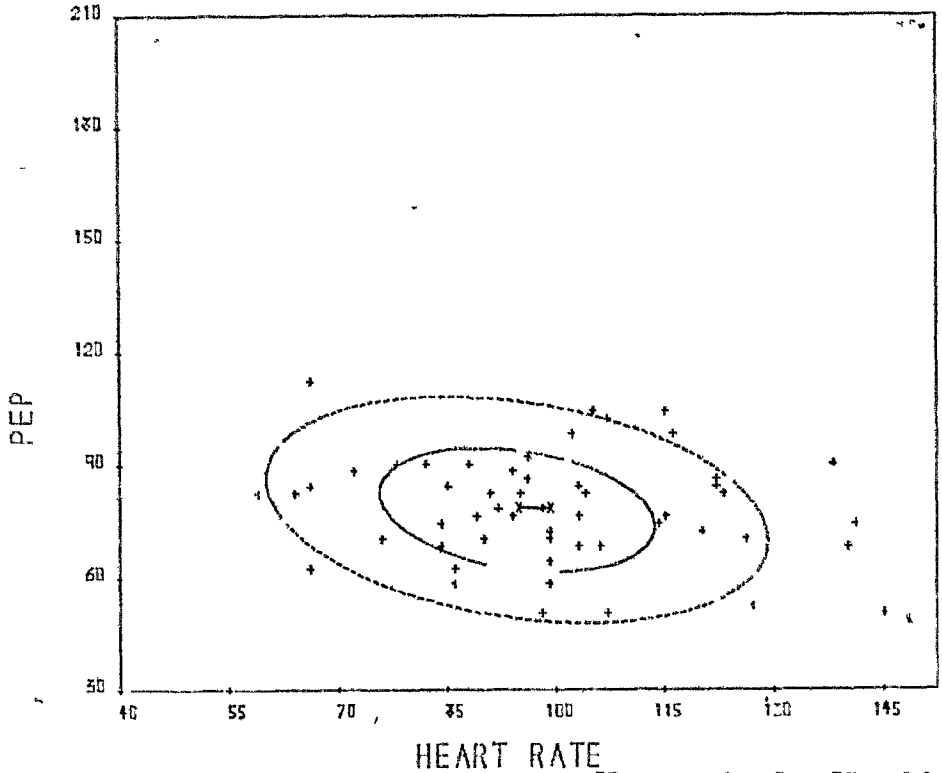


Figure 4.56 - Post-exercise scattergram of PEP vs HR for 55 subjects with cardiac enlargement. See Figure 4.1 legend for details.

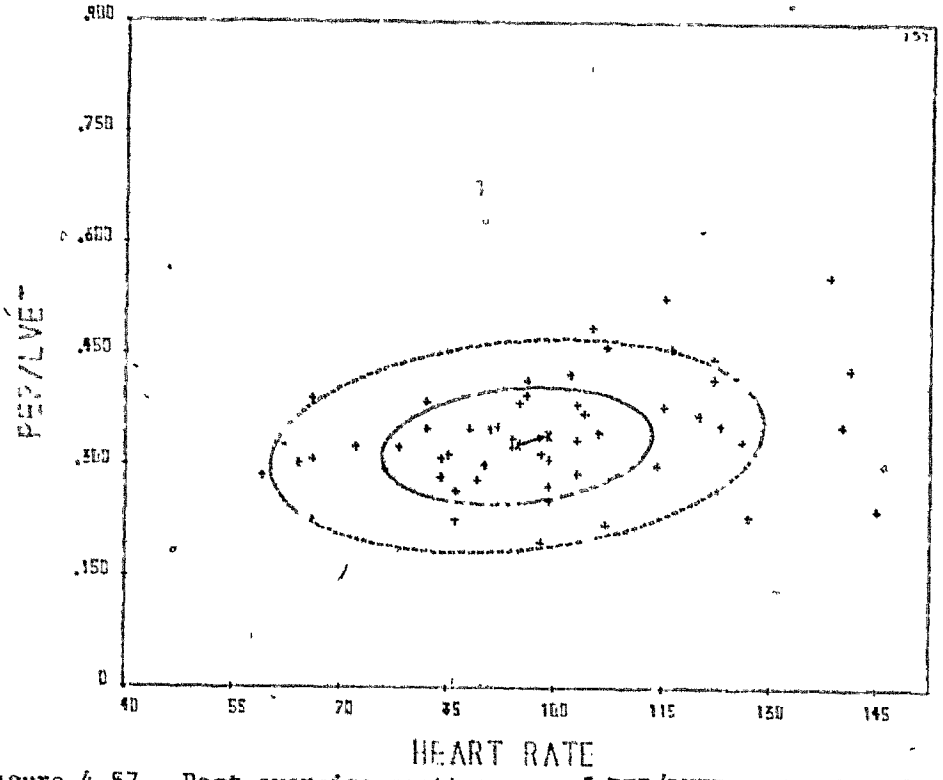


Figure 4.57 - Post-exercise scattergram of PEP/LVET vs HR for 55 subjects with cardiac enlargement. See Figure 4.1 legend for details.

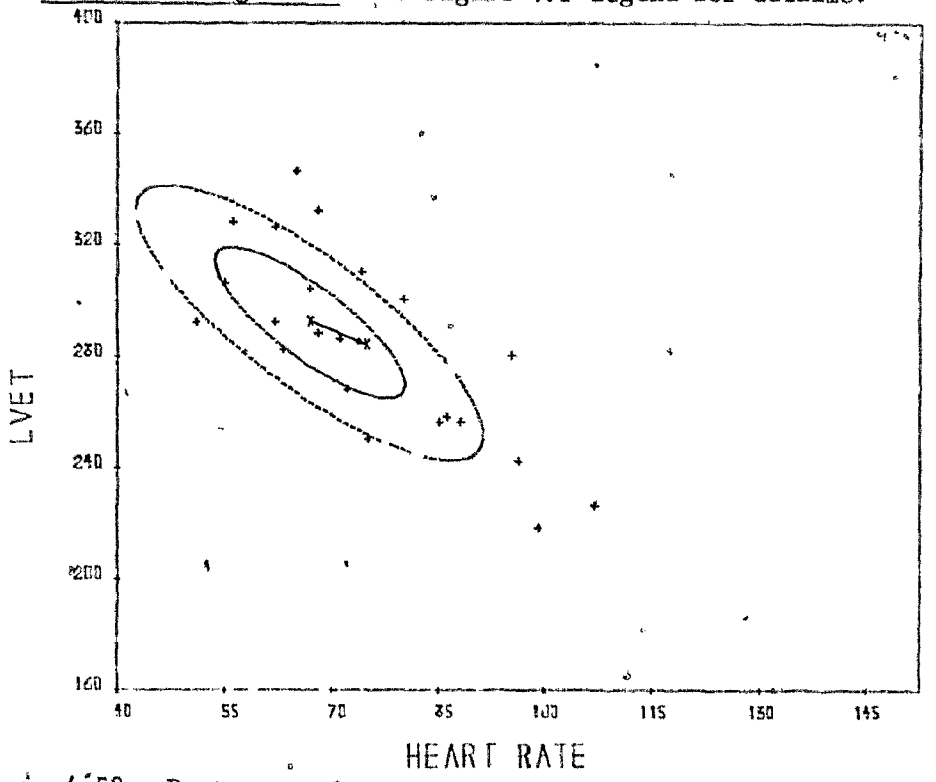


Figure 4.58 - Resting supine scattergram of LVET vs HR for 22 subjects with cardiac enlargement and hypertension. See Figure 4.1 legend for details.

trast with the resting data, there are an equal number of outliers with decreased and elevated heart rates and few of the points fall below the regression lines. The generalized outlier count for this group is 21 (14.8%).

Figures 4.55 to 4.57 show the data for 55 subjects after exercise. In comparison with the normals, the shift in the means is essentially the same as at rest: heart rate is increased with the other three variables close to the normal regression lines. The multivariate tests give χ^2 values of 44.9 on 14 d.f. and 39.2 on 10 d.f. ($p < .001$). D^2 is 0.122 with an F of 1.40 on 4 and 620 d.f., which is not significant. The outlier counts, which are 8 (14.6%), 12 (21.8%) and 11 (20.0%), again reflect a high degree of scatter and include a group of subjects with elevated heart rates. The generalized outlier count is 9 (16.4%).

2.5 Cardiac Enlargement With Hypertension

Of the 152 subjects in the CE group, 22 were hypertensive at the time of the first study and the regression data for all three states is in Table 4.6. The scattergrams in Figures 4.58 to 4.60 show that the means are shifted in the same direction as (but considerably more than) the RHV group. Mean heart rate is elevated by 7.8 beats per minute, and the other three variables are essentially on the normal regression lines. The values of χ^2 are 120.4 on 14 d.f. and 84.5 on 10 d.f. ($p < .001$). Mahalanobis D^2 is 1.676 with an F of 9.06 on 4 and 1474 d.f. ($p < .001$). Outlier counts are 10 (45.5%), 7 (31.8%) and 9 (40.9%) and almost half of these are due to elevated heart rates. The generalized count is 9 (40.9%).

TABLE 4.6

Systolic Time Intervals In Cardiac Enlargement With Hypertension: Mean Values and Heart Rate Regressions

	Mean Values		Regression With Heart Rate				
Variable	Mean	S.D.	Intercept	Slope	S.D.	Correlation	P
1. CE with Non-Sustained Hypertension							
A - Resting Supine. N = 22							
HR	74.8	15.4					
LVET	283.9	34.5	411.6	-1.71	22.4	-.761	<.001
PEP	110.8	19.0	114.0	- .04	19.0	-.034	n.s.
PEP/LVET	.398	.094	.217	.00243	.087	.396	n.s.
B - Resting Upright. N = 20							
HR	85.7	16.0					
LVET	252.8	26.8	379.0	-1.47	12.7	.880	<.001
PEP	115.9	16.6	142.9	- .32	15.8	-.304	n.s.
PEP/LVET	.462	.076	.340	.00143	.072	.302	n.s.
C - Post-Exercise. N = 8							
HR	102.8	16.1					
LVET	236.5	24.4	367.6	-1.28	13.2	-.840	<. 01
PEP	83.5	10.2	76.8	.06	10.2	.102	n.s.
PEP/LVET	.357	.063	.125	.00226	.052	.576	n.s.
2. CE with Sustained Hypertension							
A - Resting Supine. N = 9							
HR	80.1	12.0					
LVET	272.4	21.0	351.6	- .99	17.4	-.564	n.s.
PEP	118.7	22.1	188.2	- .87	19.5	-.472	n.s.
PEP/LVET	.438	.091	.566	-.00159	.088	-.211	n.s.
B - Resting Upright. N = 9							
HR	90.6	8.1					
LVET	247.3	18.4	368.8	-1.34	14.8	-.593	n.s.
PEP	117.8	16.5	169.7	- .57	15.8	-.282	n.s.
PEP/LVET	.479	.081	.456	.00025	.081	.025	n.s.

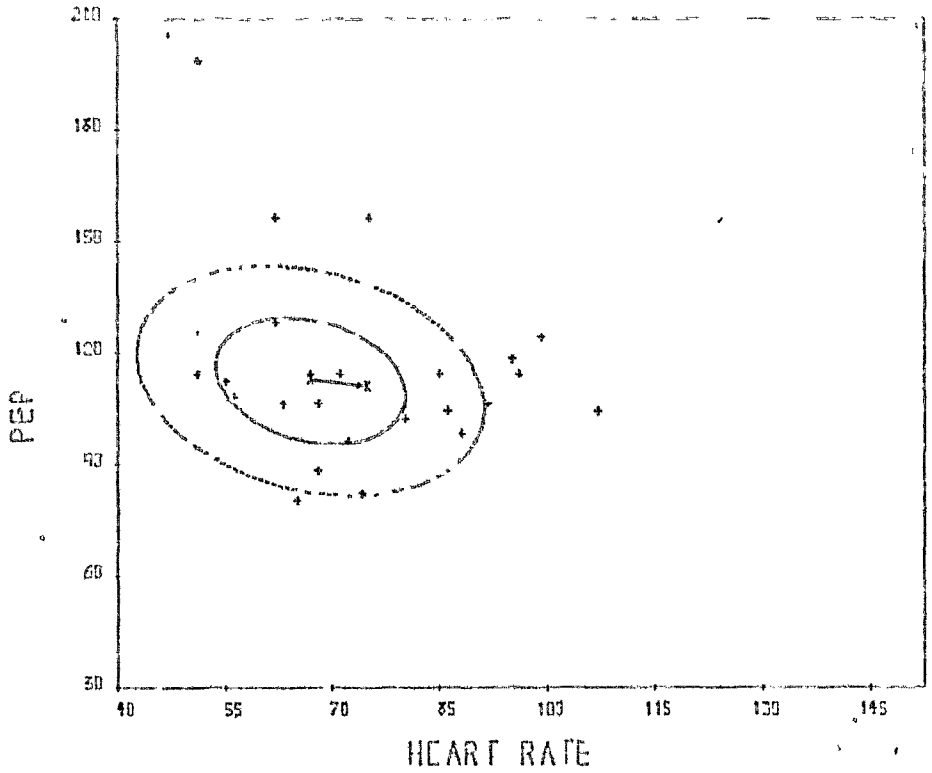


Figure 4.59 - Resting supine scattergram of PEP vs HR for 22 subjects with cardiac enlargement and hypertension. See Figure 4.1 legend for details.

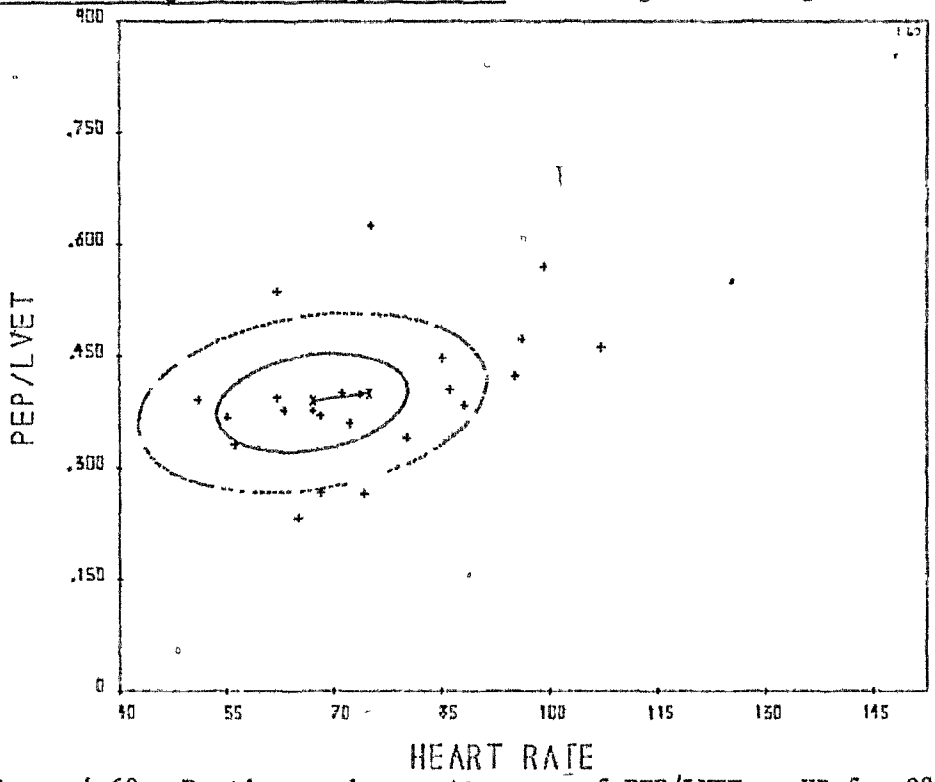


Figure 4.60 - Resting supine scattergram of PEP/LVET vs HR for 22 subjects with cardiac enlargement and hypertension. See Figure 4.1 legend for details.

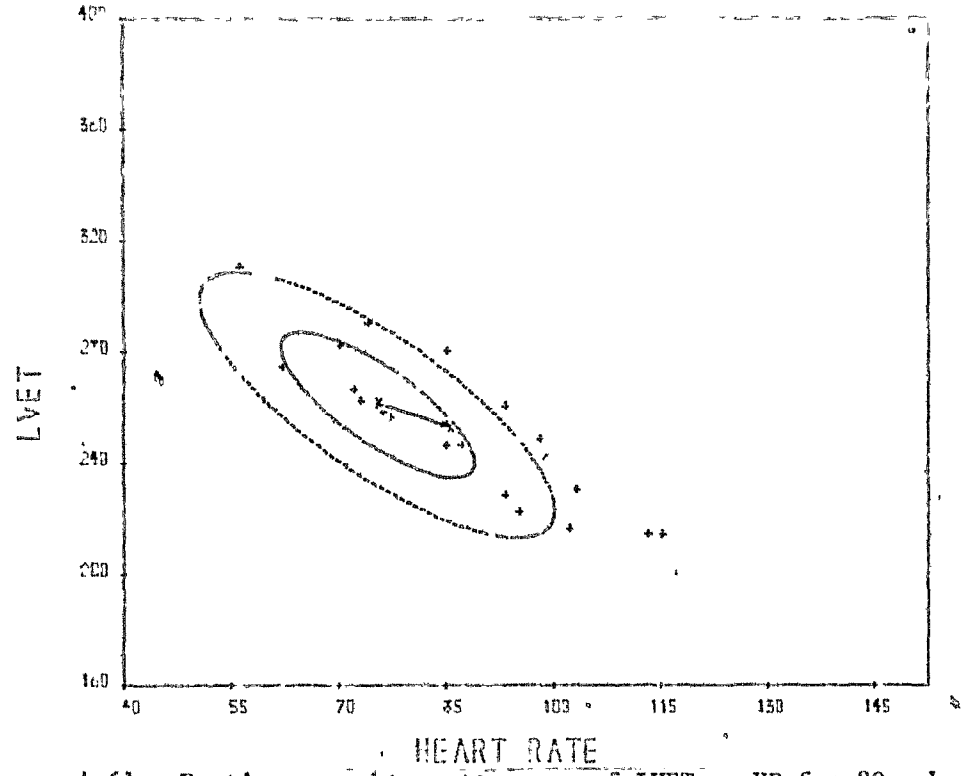


Figure 4.61 - Resting upright scattergram of LVET vs HR for 20 subjects with cardiac enlargement and hypertension. See Figure 4.1 legend for details.

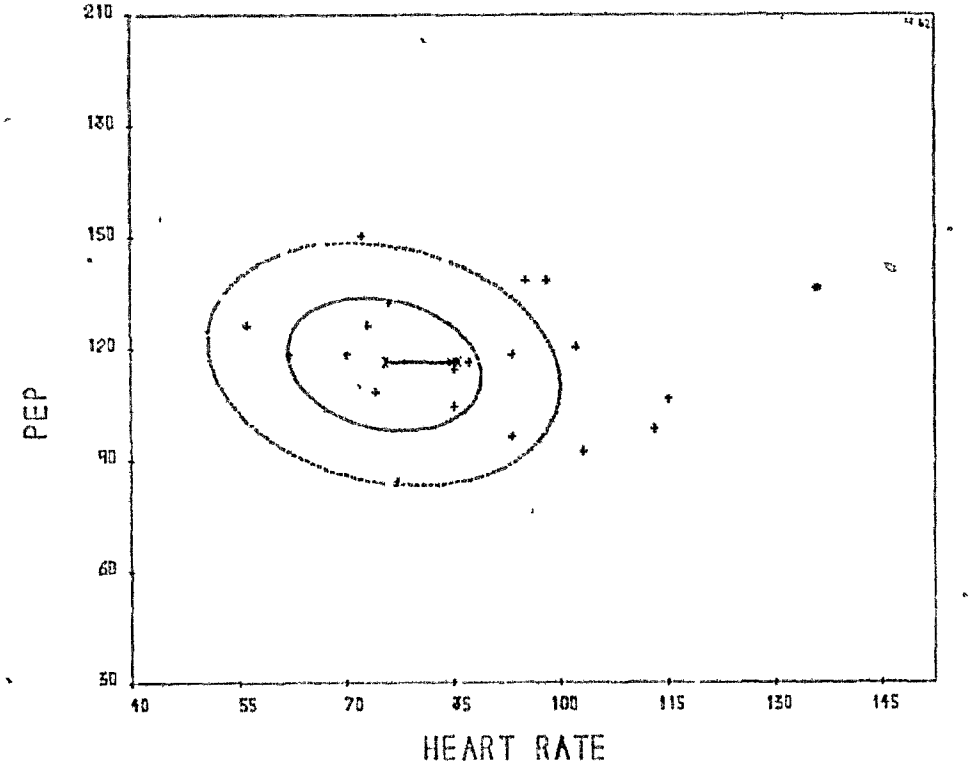


Figure 4.62 - Resting upright scattergram of PEP vs HR for 20 subjects with cardiac enlargement and hypertension. See Figure 4.1 legend for details.

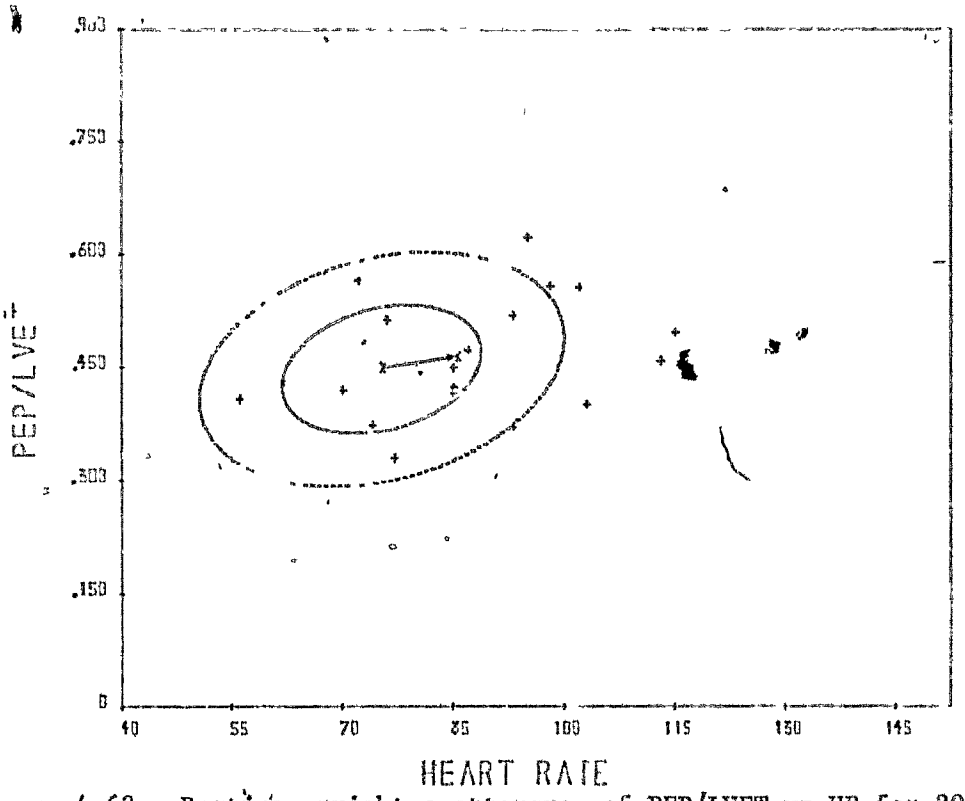


Figure 4.63 - Resting upright scattergram of PEP/LVET vs HR for 20 subjects with cardiac enlargement and hypertension. See Figure 4.1 legend for details.

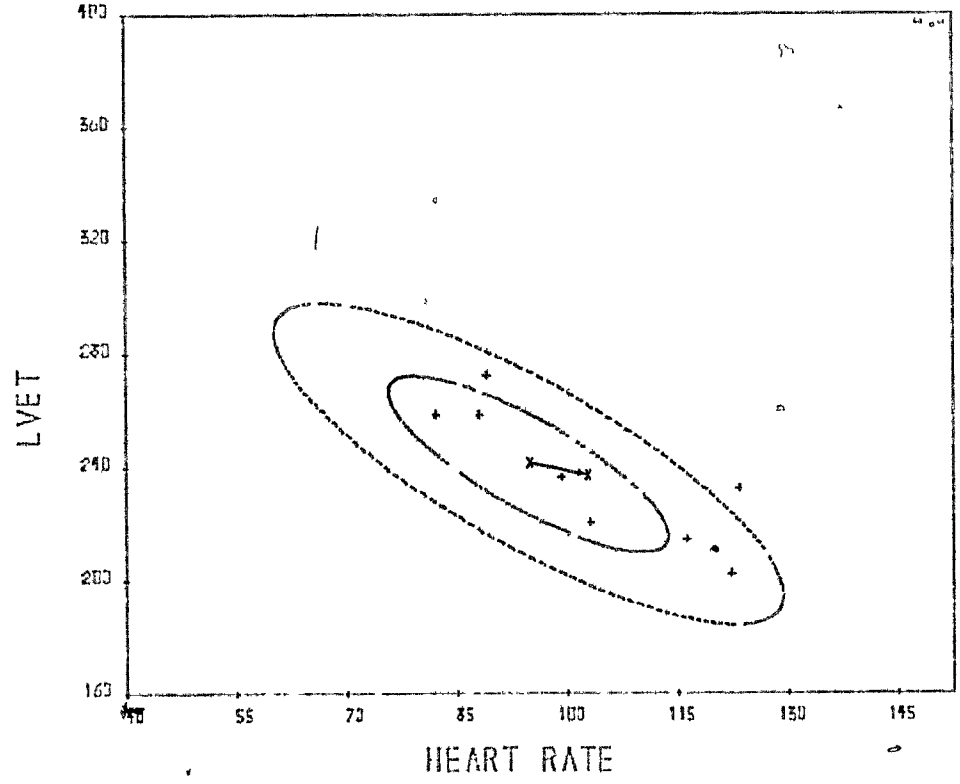


Figure 4.64 - Post-exercise scattergram of LVET vs HR for 8 subjects with cardiac enlargement and hypertension. See Figure 4.1 legend for details.

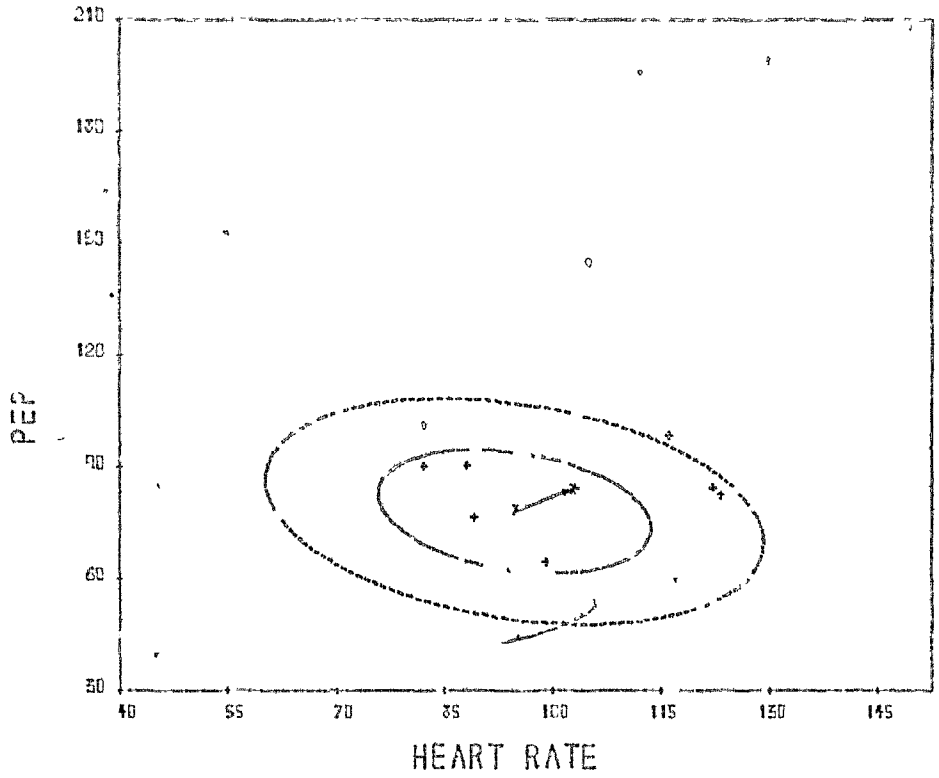


Figure 4.65 - Post-exercise scattergram of PEP vs HR for 8 subjects with cardiac enlargement and hypertension. See Figure 4.1 legend for details.

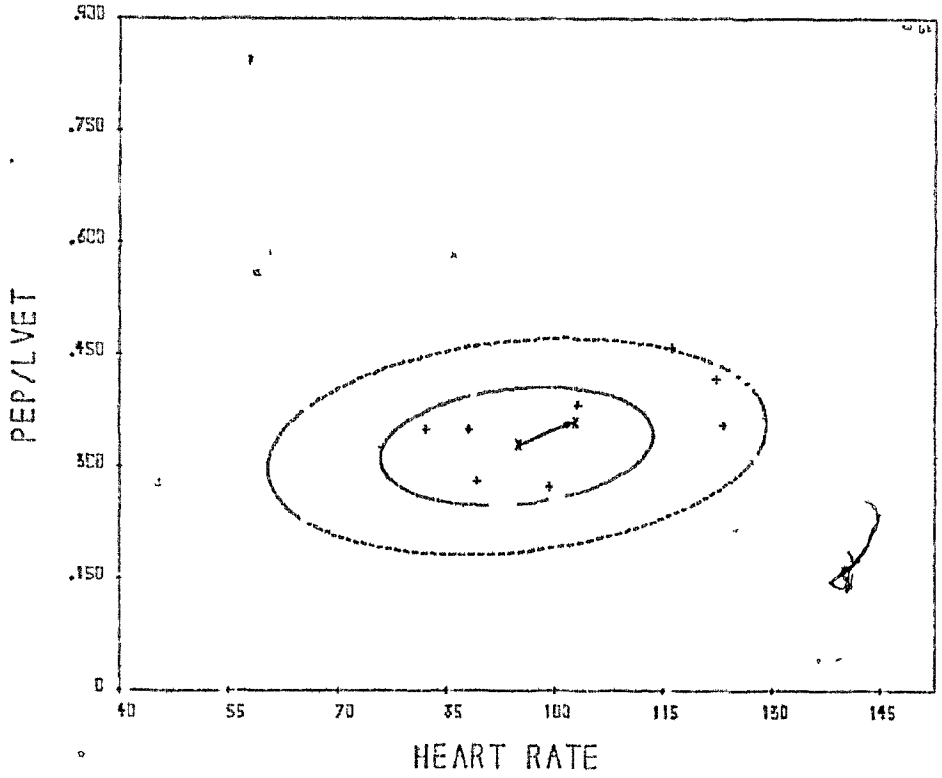


Figure 4.66 - Post-exercise scattergram of PEP/LVET vs HR for 8 subjects with cardiac enlargement and hypertension. See Figure 4.1 legent for details.

The data for 20 subjects in the resting upright state is shown in Figures 4.61 to 4.63. Again there is a large increase in mean heart rate (10.3 beats per minute) and two of the other three variables are close to the normal regressions, with LVET elevated about 8 msec. above the line. χ^2 for the combined test is 37.6 on 14 d.f. ($p < .001$) while it is only 12.9 on 10 d.f. for a test of the covariance matrices, which is not significant. Assuming the covariance matrice to be the same (as the normal group), χ^2 for a test of the difference of the means is 24.7 on 4 d.f. ($p < .001$). D^2 is 1.288 with an F of 6.26 on 4 and 805 d.f. ($p < .001$). Outlier counts are 8 (40%), 7 (35%) and 7 (35%), largely due to increased heart rates. The generalized count is 7 (35%).

There were only 8 exercise records available from this group and their scattergrams are shown in Figures 4.64 to 4.66. Mean HR is increased by 8 beats per minute and mean LVET, PEP and PEP/LVET are all elevated above the normal regressions. None of the χ^2 values are significant and D^2 is 0.861 with an F of 1.69 on 4 and 573 d.f., which is not significant. There is only 1 outlier (12.5%) on each graph, and only 1 lies outside the generalized 4-dimensional normal limit.

2.6 Cardiac Enlargement With Sustained Hypertension

Only 9 of the CE group had hypertension at the time of both studies and the means and standard deviations are included with the regression data for the previous group in Table 4.6. Figures 4.67 to 4.69 show the resting scattergrams. Mean HR is increased by 13 beats per minute and both PEP and PEP/LVET are elevated above the normal regressions. The combined χ^2 is 47.0 on 14 d.f. ($p < .001$) and χ^2 for the covariance test is 27.8 on 10 d.f. ($p < .01$). The Mahalanobis D^2 is 2.161 with an F of

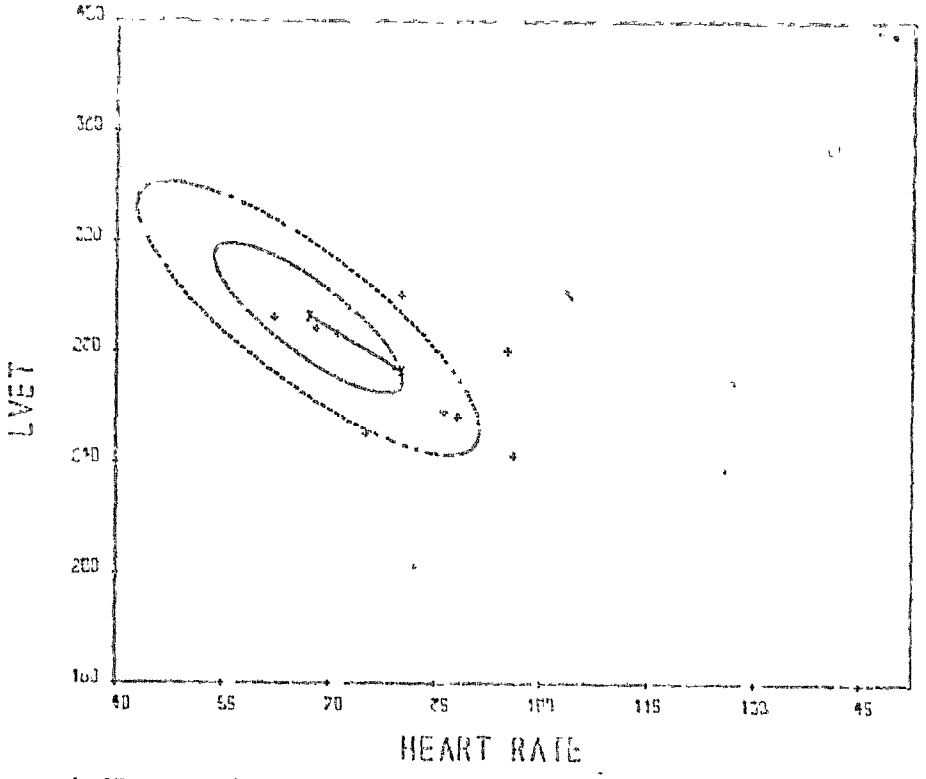


Figure 4.67 - Resting supine scattergram of LVET vs HR for 9 subjects with cardiac enlargement and sustained hypertension.

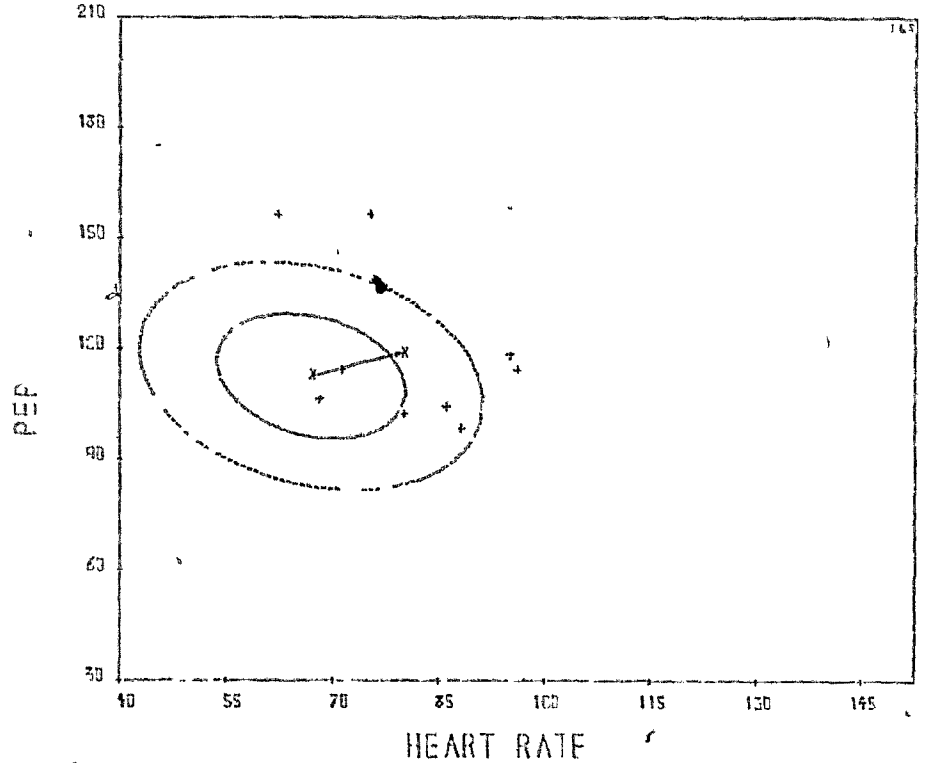


Figure 4.68 - Resting supine scattergram of PEP vs HR for 9 subjects with cardiac enlargement and sustained hypertension.

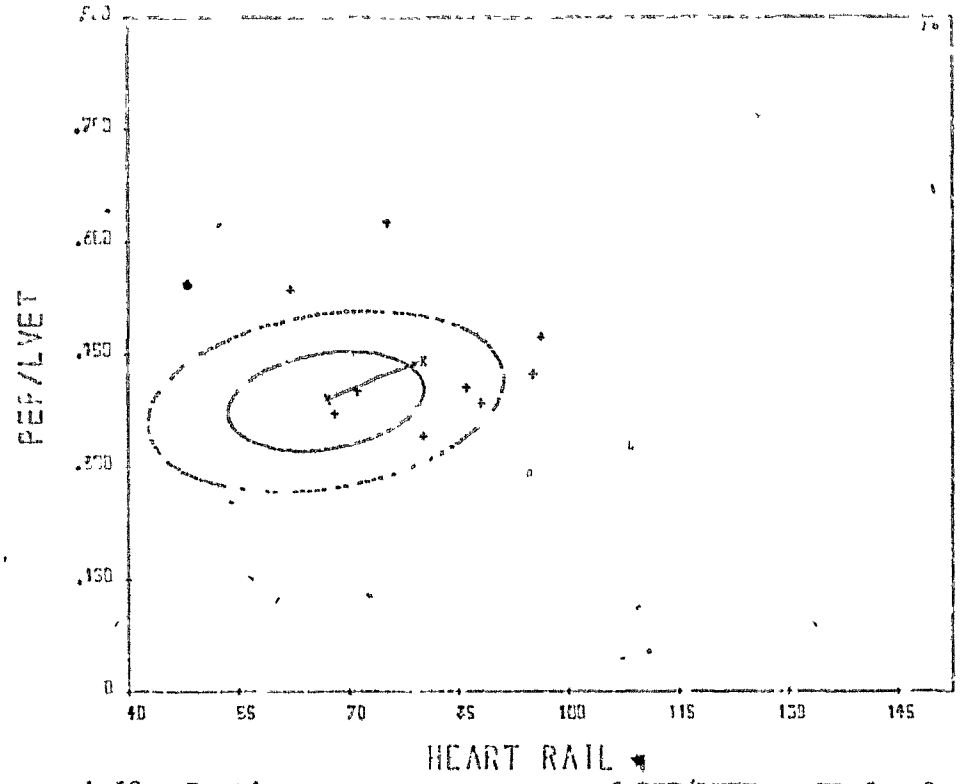


Figure 4.69 - Resting supine scattergram of PEP/LVET vs HR for 9 subjects with cardiac enlargement and sustained hypertension.

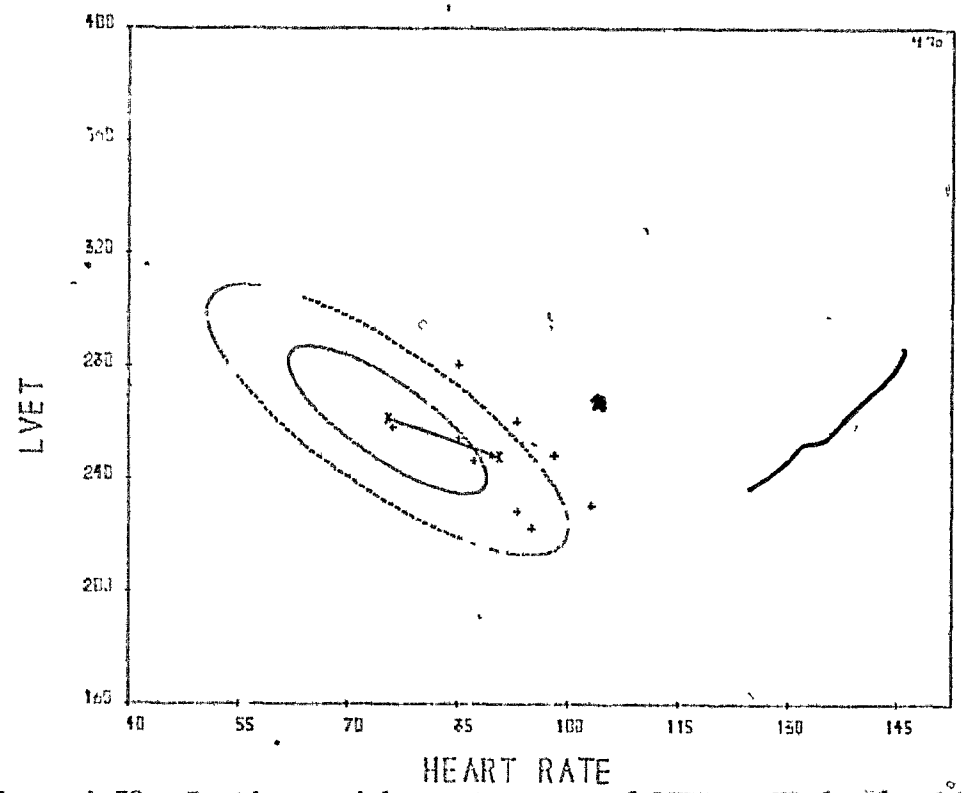


Figure 4.70 - Resting upright scattergram of LVET vs HR for 9 subjects with cardiac enlargement and sustained hypertension.

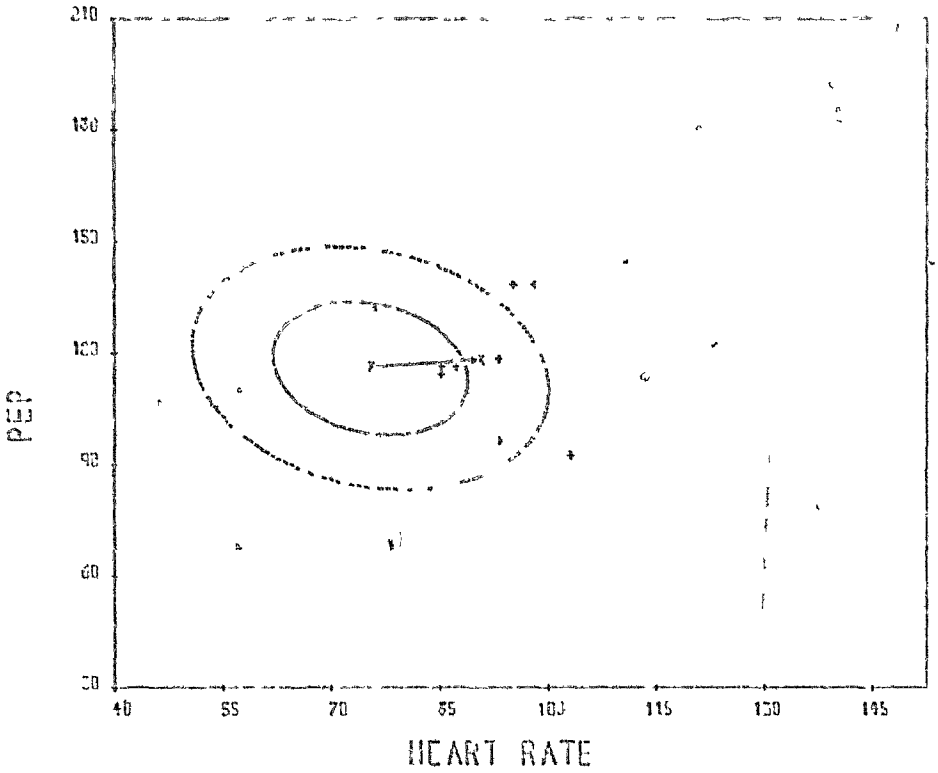


Figure 4.71 - Resting upright scattergram of PEP vs HR for 9 subjects with cardiac enlargement and sustained hypertension.

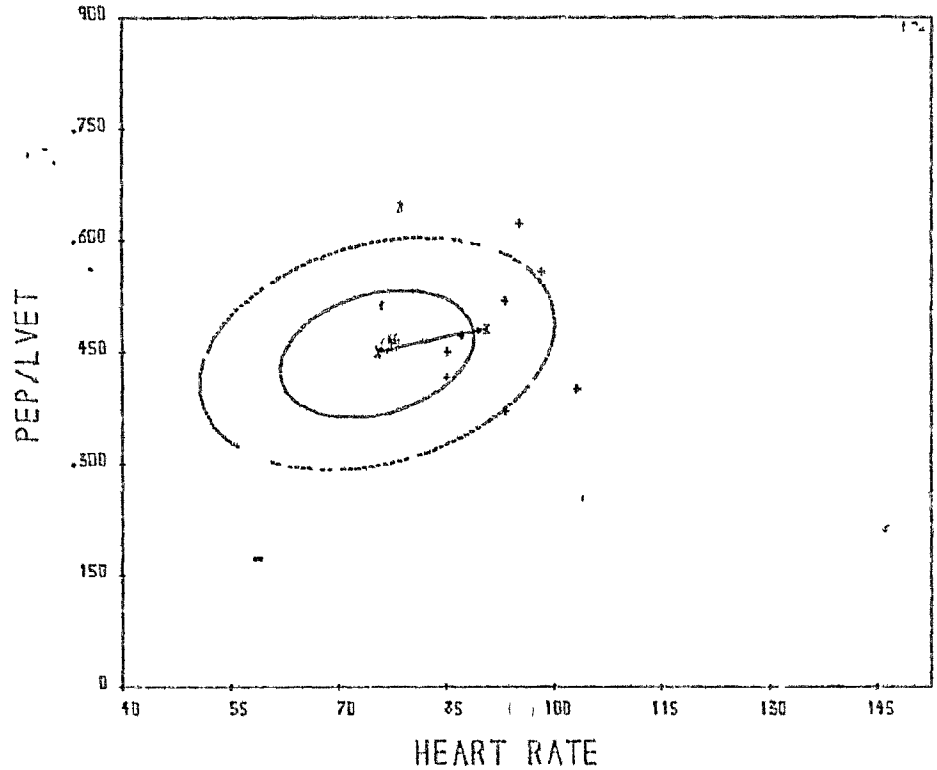


Figure 4.72 - Resting upright scattergram of PEP/LVET vs HR for 9 subjects with cardiac enlargement and sustained hypertension.

4.82 on 4 and 1461 d.f. ($p < .001$). The outlier count is 4 (44.4%) on all three graphs, and the generalized count is also 4.

There were also 9 upright records, shown in Figures 4.70 to 4.72. Mean HR is increased by 15 beats per minute and LVET and PEP are well above the normal regressions. PEP/LVET is elevated, but not above the regression line. χ^2 for the combined test is 37.2 on 14 d.f. ($p < .001$), but is only 12.9 on 10 d.f. (not significant) for the test of the covariances. A test for the difference of the means gives a χ^2 of 24.2 on 4 d.f. ($p < .001$). D^2 is 2.768 with an F of 6.13 on 4 and 794 d.f. ($p < .001$). The outliers number 4 (44.4%), 3 (33.3%) and 4 (44.4%), and the generalized count is 4 (44.4%).

C. Systolic Time Intervals In Coronary Heart Disease

1. Description of Groups

Four groups were studied with varying manifestations of ischemic heart disease. Two of these were extracted from the general data pool and the other two were assembled as separate studies.

The first of these groups were selected on the basis of S-T depression in the Frank-lead exercise electrocardiogram. The "most ischemic lead" was determined by computing the projections of S-T vectors on lead vectors of bipolar leads contained within a 50° cone in the direction of the anterior-inferior left octant. The vector algebra involved is described elsewhere (41b). A parameter known as the "S-T depression integral" was computed from this lead. The integral is essentially the total area below the zero volt axis in a defined section of the S-T segment, and subjects were selected for this group if the value of this integral exceeded 15 uVs. Subjects on cardioactive medication were excluded, leaving a group

of 70 subjects.

The second group consisted of those subjects from the pool with clinically diagnosed angina pectoris. Again, subjects taking medications (with the exception of nitroglycerine) at the time of the study were excluded and the resulting group had 245 subjects.

The third group consisted initially of 100 patients from Helsinki with documented old myocardial infarction. The patients were ambulant and out of hospital at the time of the study and 50 of them had participated in a controlled exercise program during the year since their infarctions, the other 50 having been used as a control. The mean STI did not differ between the two sub-groups and they were combined for the purpose of this thesis. Good resting records were obtained from 79 of these patients.

The fourth group, which was further subdivided into three sub-groups, consisted initially of 20 patients admitted to the Coronary Care Unit of the Victoria General Hospital in the spring of 1971. Acute myocardial infarction was eventually diagnosed in 18 of these and 2 were dropped from the study because they were taking digitalis, leaving a final group of 16 subjects. STI were recorded from these patients in the semi-recumbent position every morning for the first week of hospitalization, once a week for the next 3 weeks and once a month for the next 2 months, following their release from hospital. At the time of each observation, the attending physician assigned a score based on the presence of clinical signs of congestive heart failure. The patients were classified as "Grade 0" if there was no sign of failure, "Grade I" if 3rd or 4th heart sounds were observed on auscultation or "Grade II" if 3rd or 4th sounds were observed, with basal rales and/or X-ray evidence of pulmonary

congestion. The STI records obtained were assigned to one of three sub-groups on the basis of this score. It should be noted that as a consequence of this procedure, each of the three sub-groups contains repeated observations from the same subjects and that subjects generally appear in at least two of these sub-groups as their clinical state changes. An abstract summarizing the initial results from this clinical group was published previously (21).

2. Results

2.1 S-T Interval Depression ("Ischemic" ST Response)

Regression data for the S-T depression group for all three states is in Table 4.7. The scattergrams of the 70 resting records are in Figures 4.73 to 4.75 and it is easily seen that the mean values do not differ significantly from normal. The usual χ^2 values are 9.6 on 14 d.f. and 6.5 on 10 d.f. and χ^2 for a test of the means is 3.0 on 4 d.f. Mahanalobis D^2 is 0.046 with an F value of 0.76 on 4 and 1522 d.f. (none of these statistics are significant at $p < 0.1$). The outlier counts are 5 (7.1%), 4 (5.7%) and 5 (7.1%) which are within normal expectations. The generalized count is 9 (12.9%).

Thirty-nine resting upright records are shown in Figures 7.76 to 7.78. Again the observed means do not differ from normal. The (3) χ^2 values are 8.0 on 14 d.f., 7.3 on 10 d.f. and 0.7 on 4 d.f. D^2 is 0.049 with an F of 0.18 on 4 and 824 d.f. Outlier counts are 3 (7.7%), 2 (5.1%) and 3 (7.7%) and the generalized count is 4 (10.3%). Again, none of the statistics are significant.

The data for 31 post-exercise records is shown in Figures 4.79 to 4.81. In this case a slight decrease in mean HR is accompanied by a 10

TABLE 4.7

Systolic Time Intervals In Subjects With ST Depression:
Mean Values and Heart Rate Regressions

	Mean Values		Regression With Heart Rate				
Variable	Mean	S.D.	Intercept	Slope	S.D.	Correlation	P
A - Resting Supine. N = 70							
HR	66.5	10.5					
LVET	292.9	23.4	413.8	-1.82	13.4	-.818	<.001
PEP	111.2	15.1	122.2	- .17	15.0	-.115	n.s.
PEP/LVET	.383	63.5	.257	.00189	.060	.314	<. 01
B - Resting Upright. N = 39							
HR	74.3	10.4					
LVET	262.3	21.7	380.0	-1.59	14.1	-.759	<.001
PEP	115.6	14.0	117.6	- .03	14.0	-.020	n.s.
PEP/LVET	.445	.072	.244	.00270	.067	.389	<. 05
C - Post-Exercise. N = 31							
HR	92.5	21.3					
LVET	251.3	29.2	356.0	-1.13	16.3	-.829	<.001
PEP	76.5	13.4	100.4	- .27	12.2	-.411	<. 05
PEP/LVET	.307	.058	.271	.00039	.058	.143	n.s.

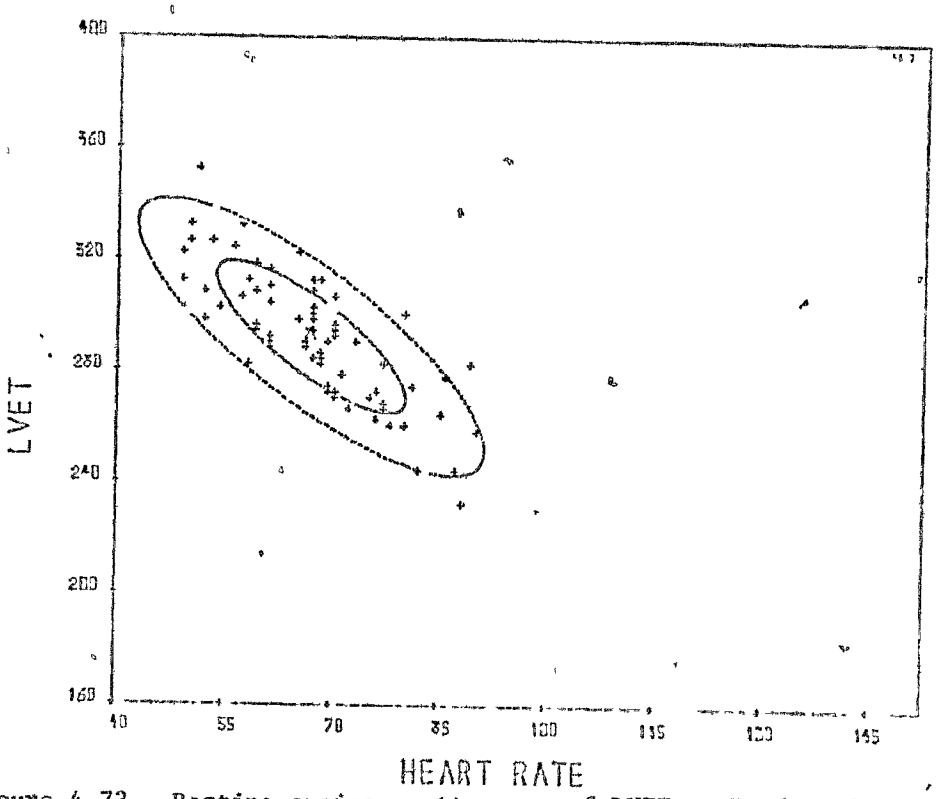


Figure 4.73 - Resting supine scattergram of LVET vs HR for 70 subjects with S-T depression. See Figure 4.1 legend for details.

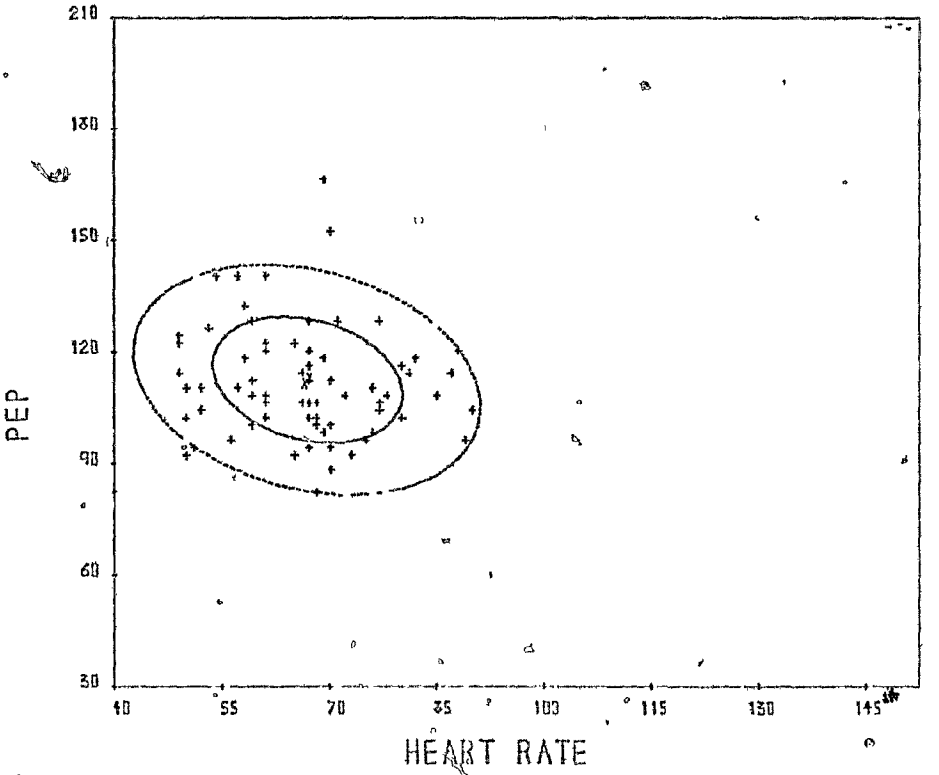


Figure 4.74 - Resting supine scattergram of PEP vs HR for 70 subjects with S-T depression. See Figure 4.1 legend for details.

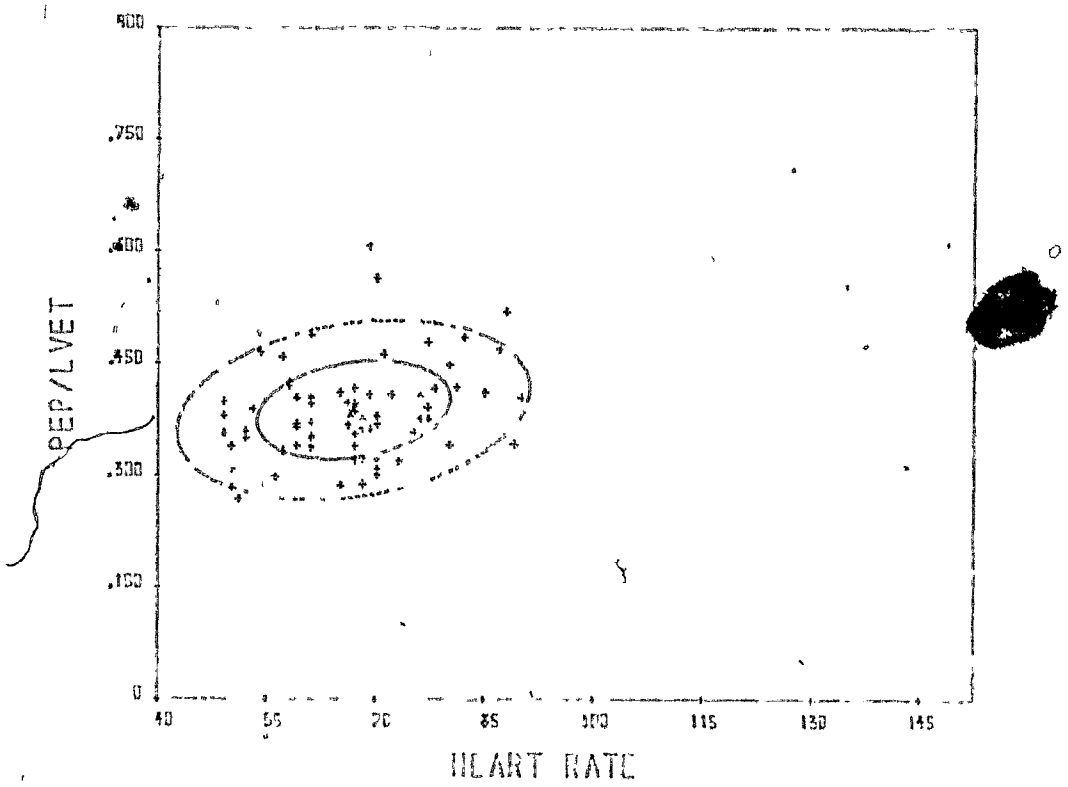


Figure 4.75 - Resting supine scattergram of PEP/LVET vs HR for 70 subjects with S-T depression. See Figure 4.1 legend for details.

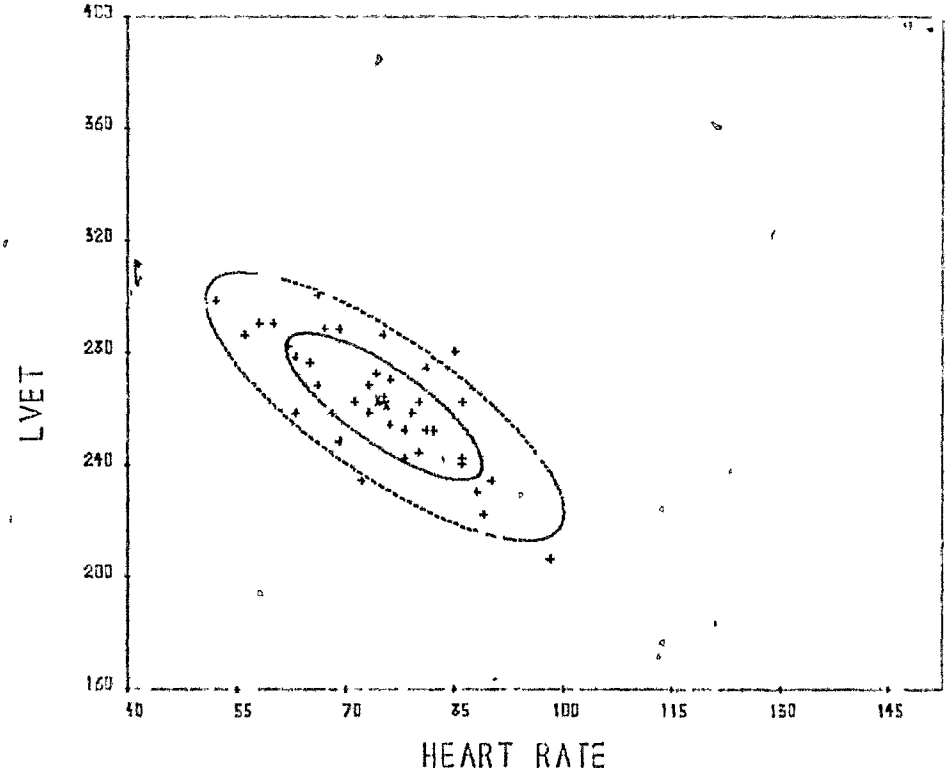


Figure 4.76 - Resting upright scattergram of LVET vs HR for 39 subjects with S-T depression. See Figure 4.1 legend for details.

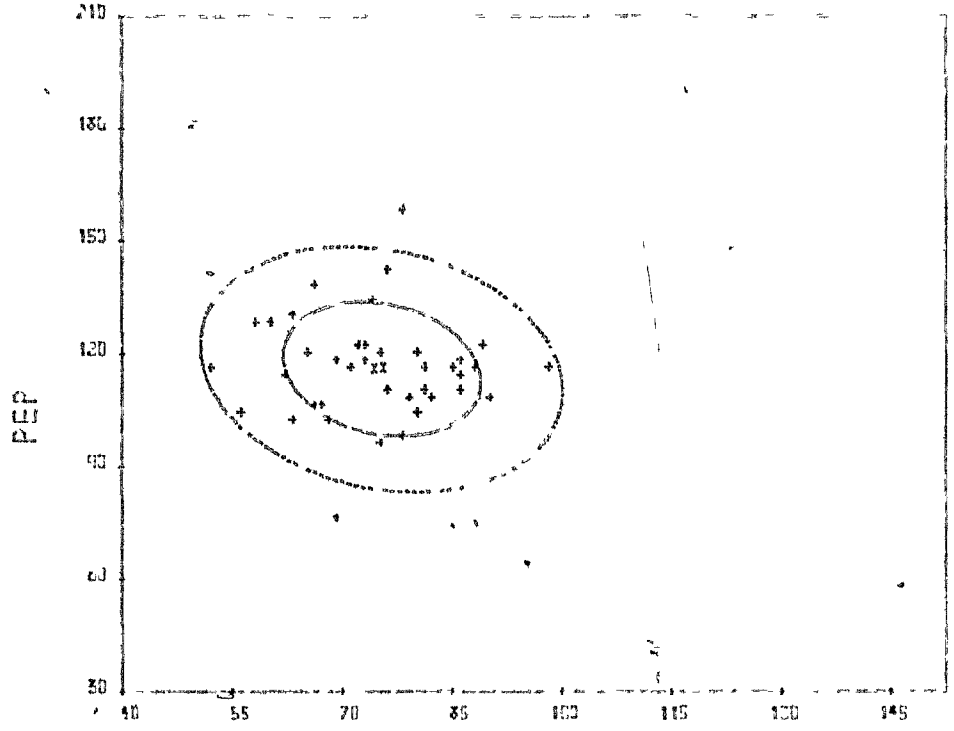


Figure 4.77 - Resting upright scattergram of PEP vs HR for 39 subjects with S-T depression. Figure 4.1 legend for details.

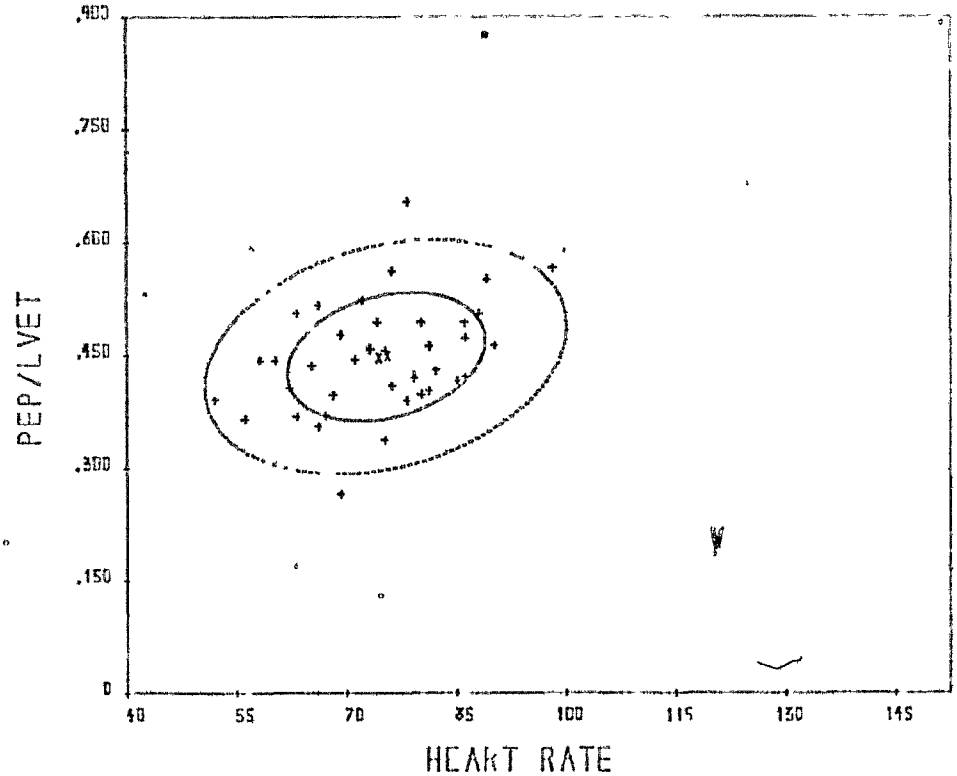


Figure 4.78 - Resting upright scattergram of PEP/LVET vs HR for 39 subjects with S-T depression. See Figure 4.1 legend for details.

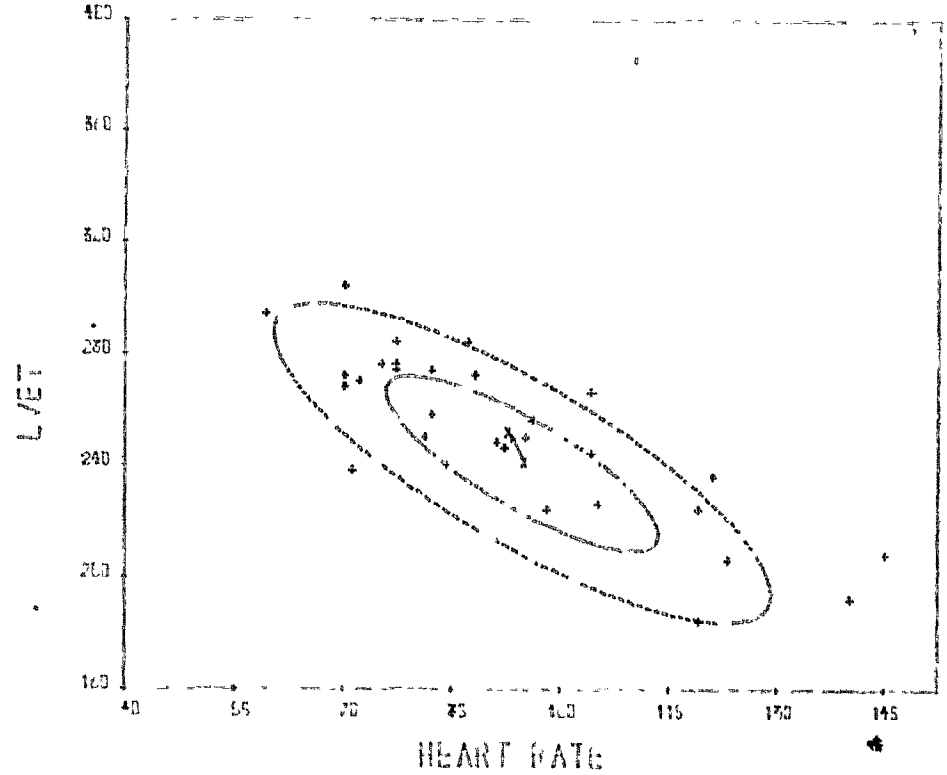


Figure 4.79 - Post-exercise scattergram of LVET vs HR for 31 subjects with S-T depression. See Figure 4.1 legend for details.

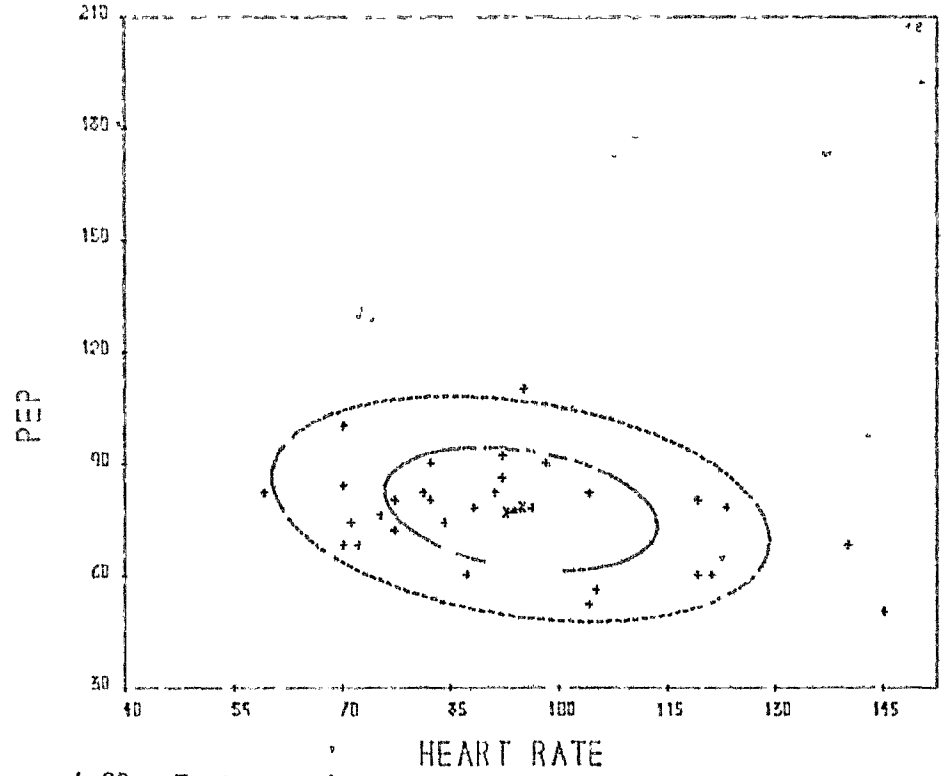


Figure 4.80 - Post-exercise scattergram of PEP vs HR for 31 subjects with S-T depression. See Figure 4.1 legend for details.

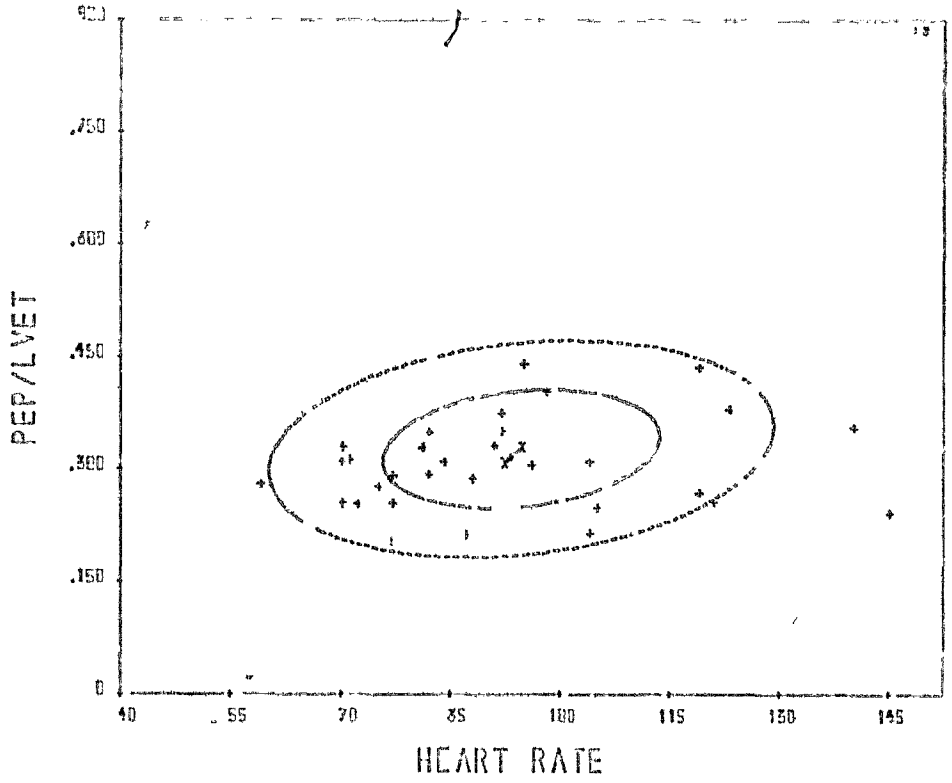


Figure 4.81 - Post-exercise scattergram of PEP/LVET vs HR for 31 subjects with S-T depression. See Figure 4.1 legend for details.

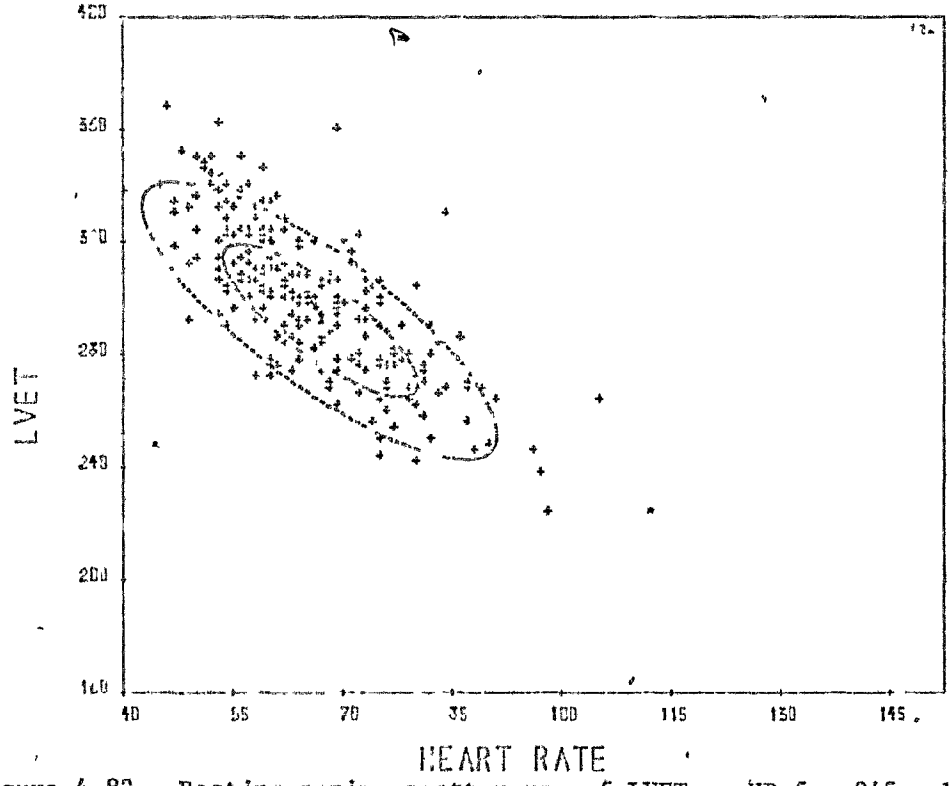


Figure 4.82 - Resting supine scattergram of LVET vs HR for 245 subjects with angina pectoris. See Figure 4.1 legend for details.

ms. increase in mean LVET, with a relatively small change in PEP and PEP/LVET. The combined χ^2 test gives a value of 23.1 on 14 d.f., which is almost significant at $p = .05$. The χ^2 for the test of the covariance matrix is 15.8 on 10 d.f. (not significant) and a test of the means gives a χ^2 of 7.3 on 4 d.f. (not significant). D^2 is 0.250 with an F of 1.83 on 4 and 596 d.f., which is also not significant. The outlier counts are 9 (29.0%), 4 (12.9%) and 4 (12.9%). Of these, only the count on the LVET graph is much above the expectant number for a normal population. The generalized count is 7 (22.6%).

2.2 Angina Pectoris

Table 4.8 contains the regression data for the angina group in all three states and the resting supine data (N = 245) is shown in Figures 4.82 to 4.84. Mean heart rate is decreased by about 1.5 beats per minute, accompanied by increases of about 7 msec. in LVET and PEP. PEP/LVET is also raised slightly. The combined χ^2 is 184.8 on 14 d.f. ($p < .001$) and the score for the covariance matrix test is 103.7 on 10 d.f. ($p < .001$). D^2 is 0.396 with an F ratio of 20.7 on 4 and 1697 d.f. ($p < .001$). The outlier counts are 42 (17.1%), 33 (13.5%) and 37 (15.1%), all above the expectant number for normals and attributable to the increased scatter of the data points. The generalized count is 46 (18.8%) which is higher than any of the 2-dimensional counts.

There are only 30 resting upright records for this group. The data is shown in Figures 4.85 to 4.87. A slight decrease in mean heart rate is accompanied by a small increase in PEP and PEP/LVET. The combined multivariate test gives a χ^2 of 26.5 on 14 d.f. ($p < .05$) and the covariance test gives 16.3 on 10 d.f. (not significant). The test on the

TABLE 4.8

Systolic Time Intervals In Angina Pectoris:

Mean Values and Heart Rate Regressions

	Mean Values		Regression With Heart Rate				
Variable	Mean	S.D.	Intercept	Slope	S.D.	Correlation	p
A - Resting Supine. N = 245							
HR	65.3	11.0					
LVET	299.1	25.7	414.1	-1.76	16.9	-.754	<.001
PEP	119.1	16.4	143.9	- .38	15.8	-.255	<.001
PEP/LVET	.401	.068	.322	.00121	.067	.197	<.005
B - Resting Upright. N = 30							
HR	77.1	14.5					
LVET	261.8	23.3	362.9	-1.31	13.6	-.814	<.001
PEP	121.0	15.0	131.6	- .14	14.9	-.132	n.s.
PEP/LVET	.466	.075	.323	.00186	.070	.358	n.s.
C - Post-Exercise. N = 56							
HR	90.0	15.2					
LVET	250.2	31.6	406.9	-1.74	17.3	-.837	<.001
PEP	83.5	14.7	105.9	- .25	14.2	-.257	n.s.
PEP/LVET	.339	.073	.215	.00137	.070	.285	<. 05

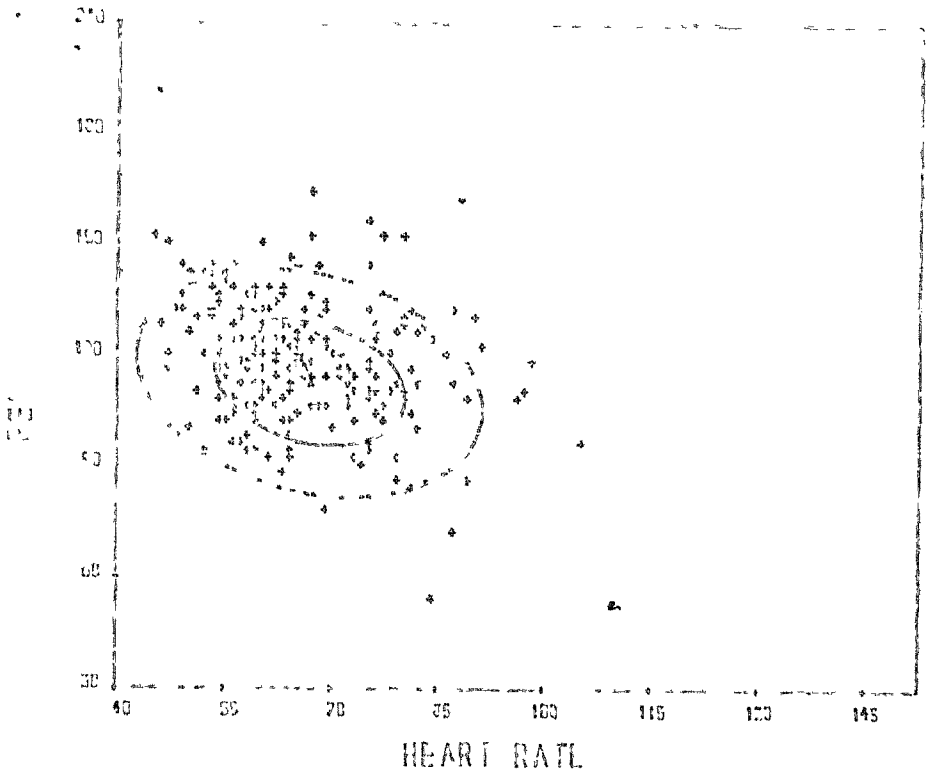


Figure 4.83 - Resting supine scattergram of PEP vs HR for 243 subjects with angina pectoris. See Figure 4.1 legend for details.

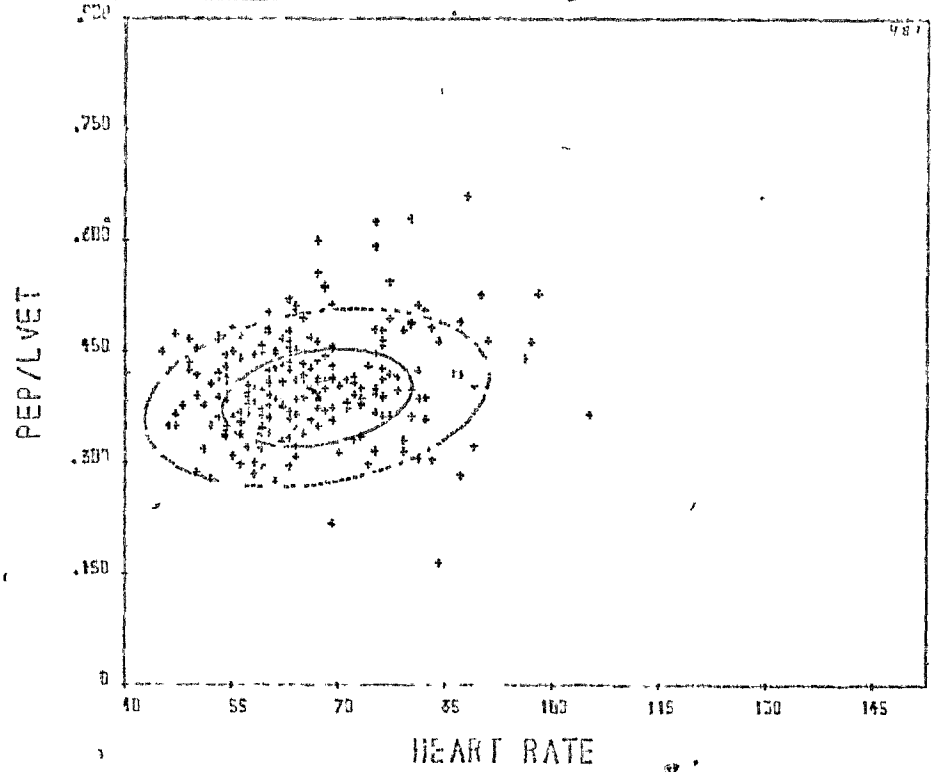


Figure 4.84 - Resting supine scattergram of PEP/LVET vs HR for 245 subjects with angina pectoris. See Figure 4.1 legend for details.

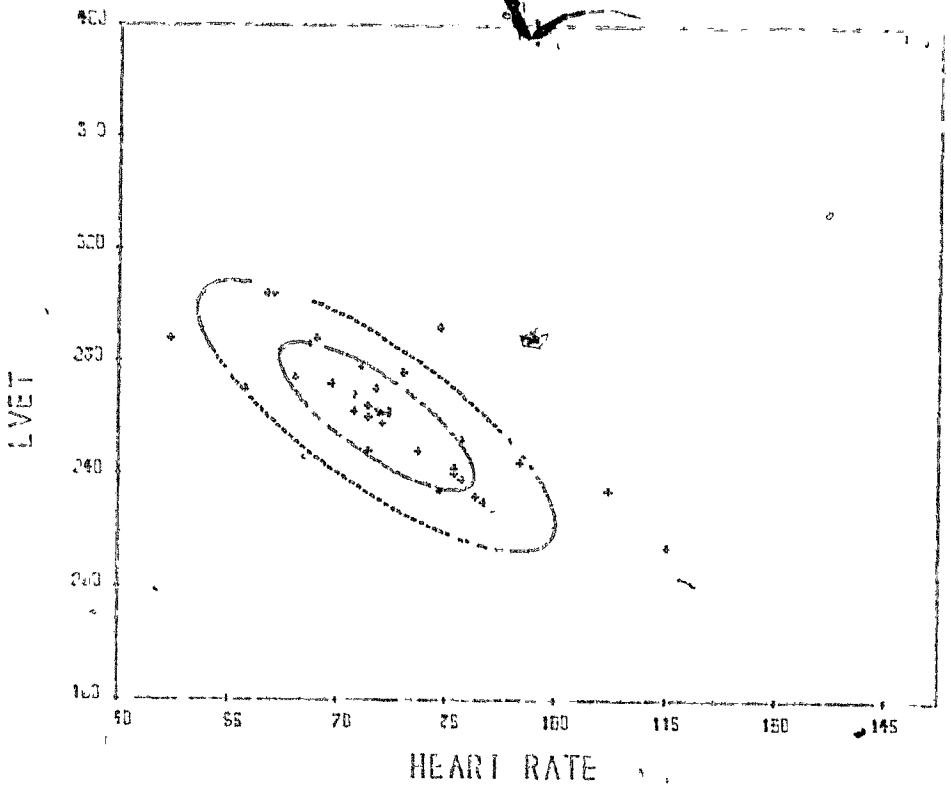


Figure 4.85 - Resting upright scattergram of LVET vs HR for 30 subjects with angina pectoris. See Figure 4.1 legend for details.

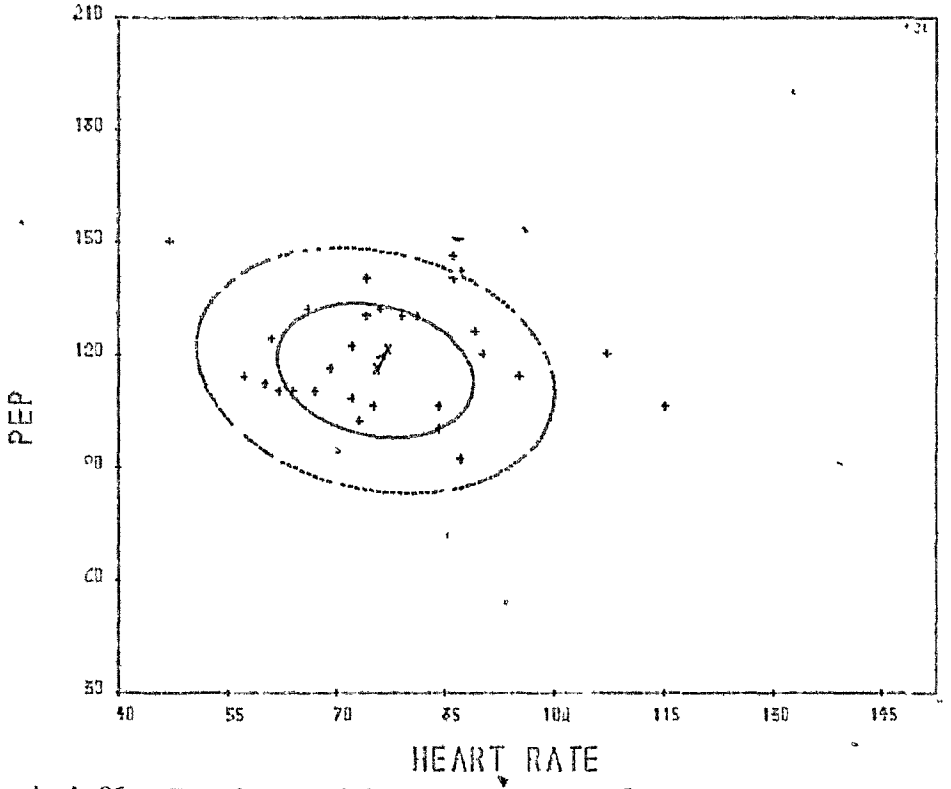


Figure 4.86 - Resting upright scattergram of PEP vs HR for 30 subjects with angina pectoris. See Figure 4.1 legend for details.

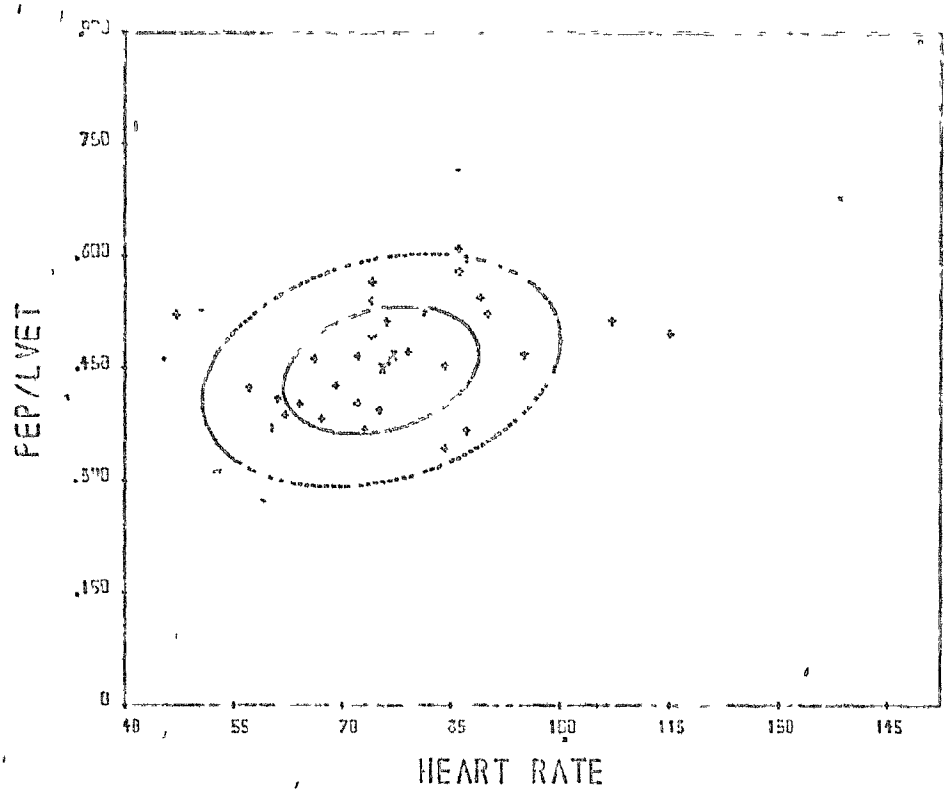


Figure 4.87 - Resting upright scattergram of PEP/LVET vs HR for 30 subjects with angina pectoris. See Figure 4.1 legend for details.

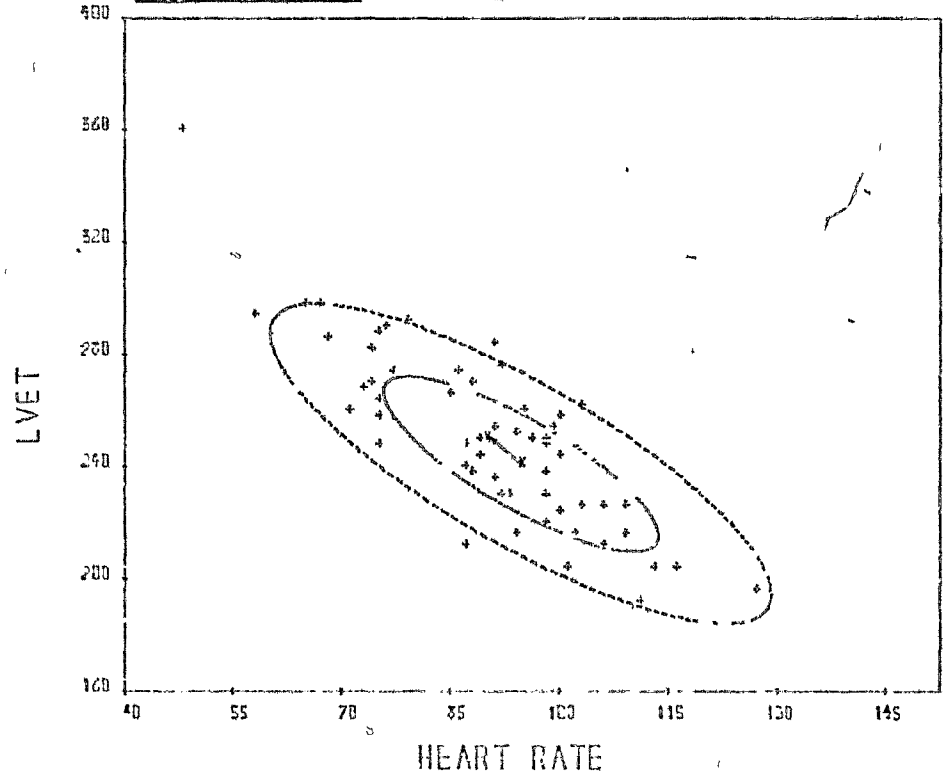


Figure 4.88 - Post-exercise scattergram of LVET vs HR for 31 subjects with angina pectoris. See Figure 4.1 legend for details.

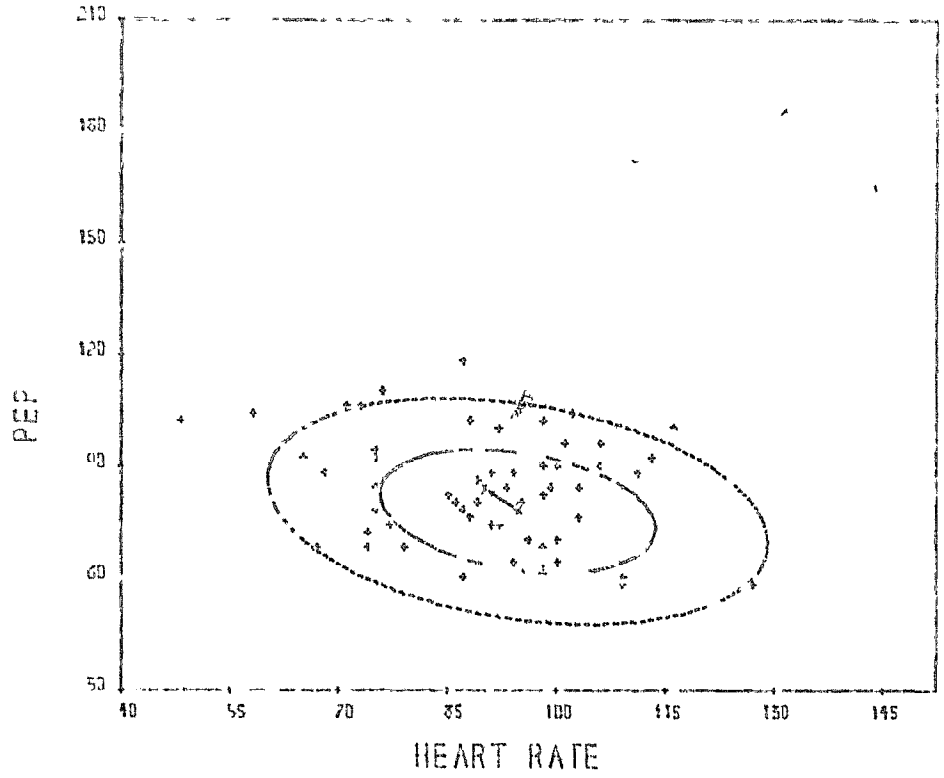


Figure 4.89 - Post-exercise scattergram of PEP vs HR for 31 subjects with angina pectoris. See Figure 4.1 legend for details.

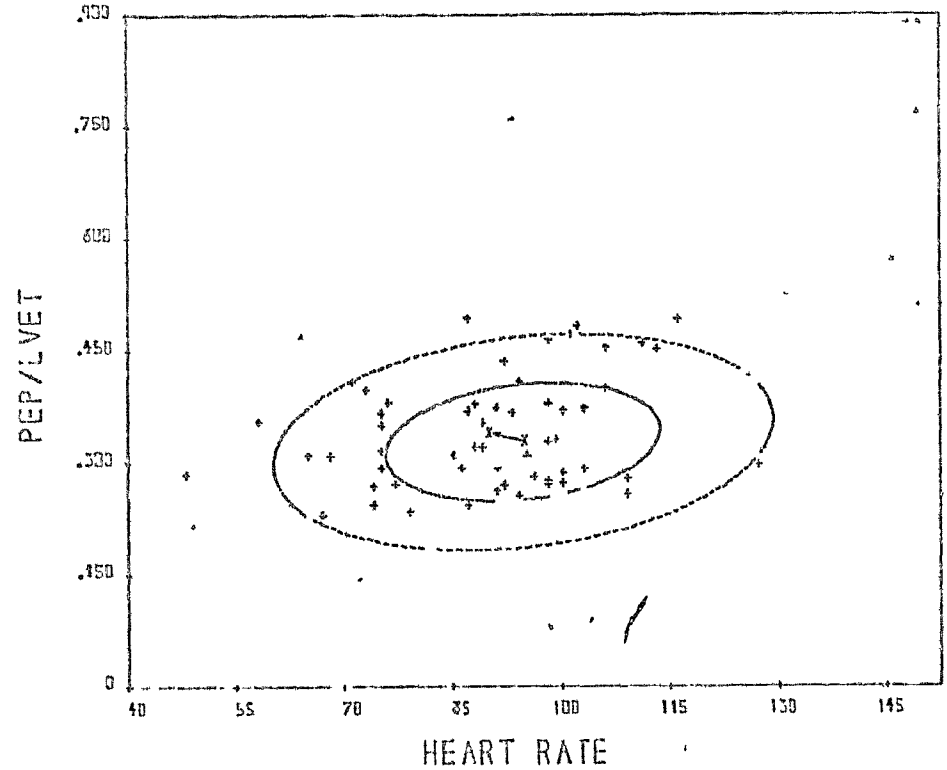


Figure 4.90 - Post-exercise scattergram of PEP/LVET vs HR for 31 subjects with angina pectoris. See Figure 4.1 legend for details.

means gives $\chi^2 = 10.2$ on 4 d.f. ($p < .05$). D^2 is 0.354 with $F = 2.55$ on 4 and 815 d.f. ($p < .05$). The outlier counts are 4 (13.3%), 5 (16.7%) and 4 (13.3%), and the generalized count is 4 (13.3%).

A number of the subjects with angina did not participate in the exercise test. The data for 56 subjects with exercise records is shown in Figures 4.88 to 4.90. Mean heart rate is decreased by about 5 beats per minute, but the three STI measurements lie pretty close to their normal regression lines. The combined χ^2 is 25.0 on 14 d.f. ($p < .05$) but the test of the covariances gives a value of 11.0 on 10 d.f. (not significant). A test of the means gives a χ^2 of 14.0 on 4 d.f. ($p < .01$). D^2 is 0.277 with an F of 3.52 on 4 and 621 d.f. ($p < .01$). The outliers number 8 (14.3%), 8 (14.3%) and 7 (12.5%), slightly more than the expectant for normals. The generalized outlier count is 9 (16.1%).

2.3 Myocardial Infarction

Figures 4.91 to 4.93 show the scattergrams for the resting records obtained from the 79 subjects with one-year old myocardial infarction. The corresponding regression data is in Table 4.9. A slight increase in mean HR is accompanied by a 9.2 msec. shortening of LVET and a 6.7 msec. increase in PEP with a corresponding increase of 0.040 in PEP/LVET. The combined multivariate test gives a χ^2 of 246.9 on 14 d.f. ($p < .001$) and the test of the covariance matrix alone gives a χ^2 of 181.2 on 10 d.f. ($p < .001$). D^2 is 0.896 with an F value of 16.7 on 4 and 1531 d.f. ($p < .001$). Outlier counts are 15 (19.0%), 11 (13.9%) and 18 (22.8%). Four of these outliers (on each graph) are due to elevated heart rates, while the rest of them are well away from the normal regression lines. The generalized outlier count is 17 (21.5%). There were no upright or

TABLE 4.9

Resting Supine Systolic Time Intervals In Myocardial Infarction: Mean Values and Heart Rate Regressions

	Mean Values		Regression With Heart Rate				
Variable	Mean	S.D.	Intercept	Slope	S.D.	Correlation	P
1. Old Infarctions. N = 79							
HR	68.1	12.2					
LVET	282.9	25.6	394.2	-1.64	16.0	-.782	<.001
PEP	119.3	14.4	113.4	.09	14.4	. 07	n.s.
PEP/LVET	.427	.078	.229	.00291	.069	.458	<.001
2. A.M.I. Without Failure. N = 64							
HR	69.3	10.4					
LVET	269.8	23.0	378.2	-1.57	16.3	-.705	<.001
PEP	117.2	21.2	132.1	- .21	21.1	-.105	n.s.
PEP/LVET	.438	.092	.320	.00171	.090	.193	n.s.
3. A.M.I. With Grade I Failure. N = 25							
HR	78.1	11.6					
LVET	248.0	22.9	343.0	-1.22	18.0	-.616	<.001
PEP	116.0	24.5	178.8	- .80	22.7	-.381	n.s.
PEP/LVET	.471	.102	.535	-.00082	.102	- .09	n.s.
4. A.M.I. With Grade II Failure. N = 16							
HR	91.1	9.7					
LVET	227.0	20.5	346.2	-1.31	16.2	-.617	<. 01
PEP	117.4	19.1	210.9	1.03	16.3	-.520	<. 05
PEP/LVET	.518	.070	.632	-.00125	.069	-.172	n.s.

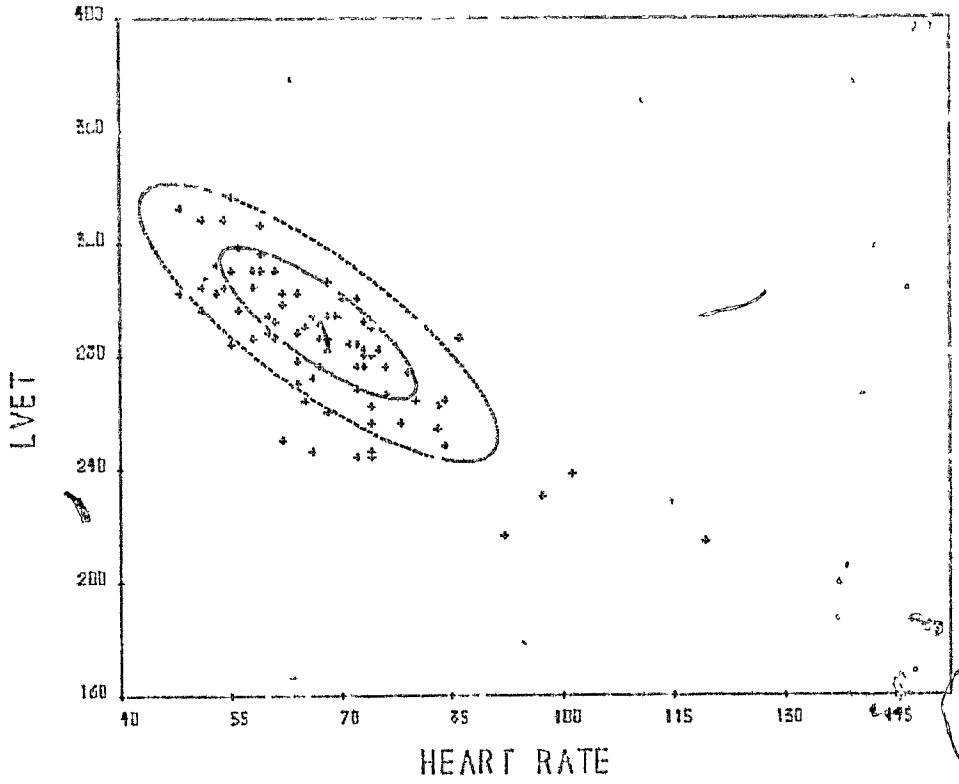


Figure 4.91 - Resting supine scattergram of LVET vs HR for 79 subjects with old myocardial infarction. See Figure 4.1 legend for details.

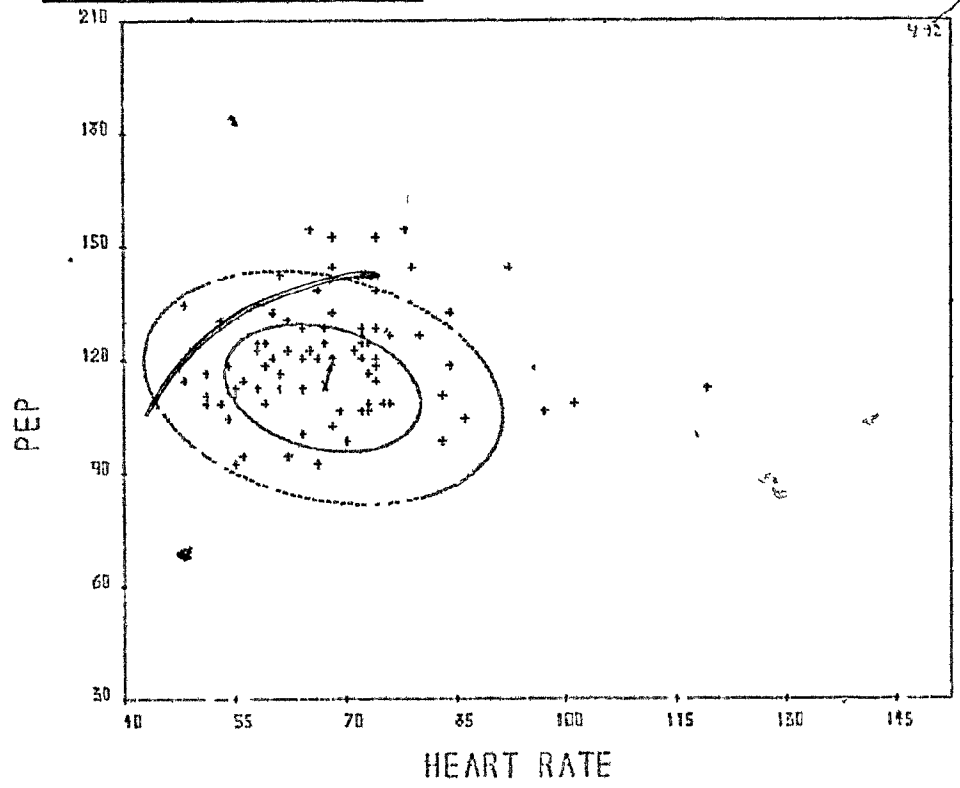


Figure 4.92 - Resting supine scattergram of PEP vs HR for 79 subjects with old myocardial infarction. See Figure 4.1 legend for details.

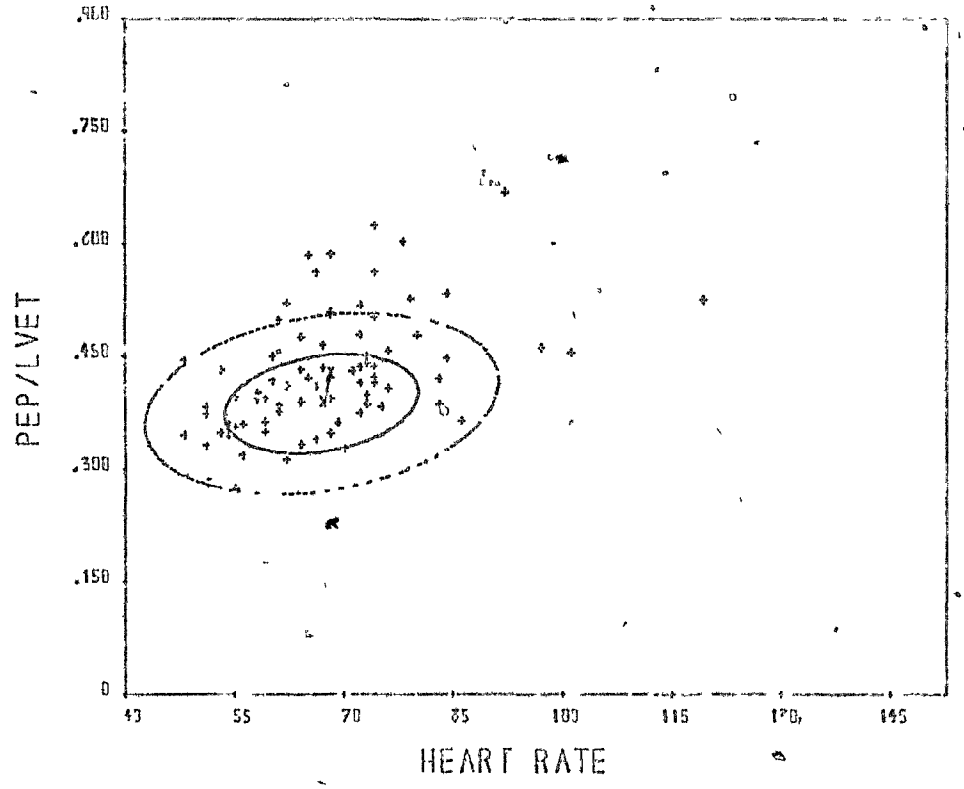


Figure 4.93 - Resting supine scattergram of PEP/LVET vs HR for 79 subjects with old myocardial infarction. See Figure 4.1 legend for details.

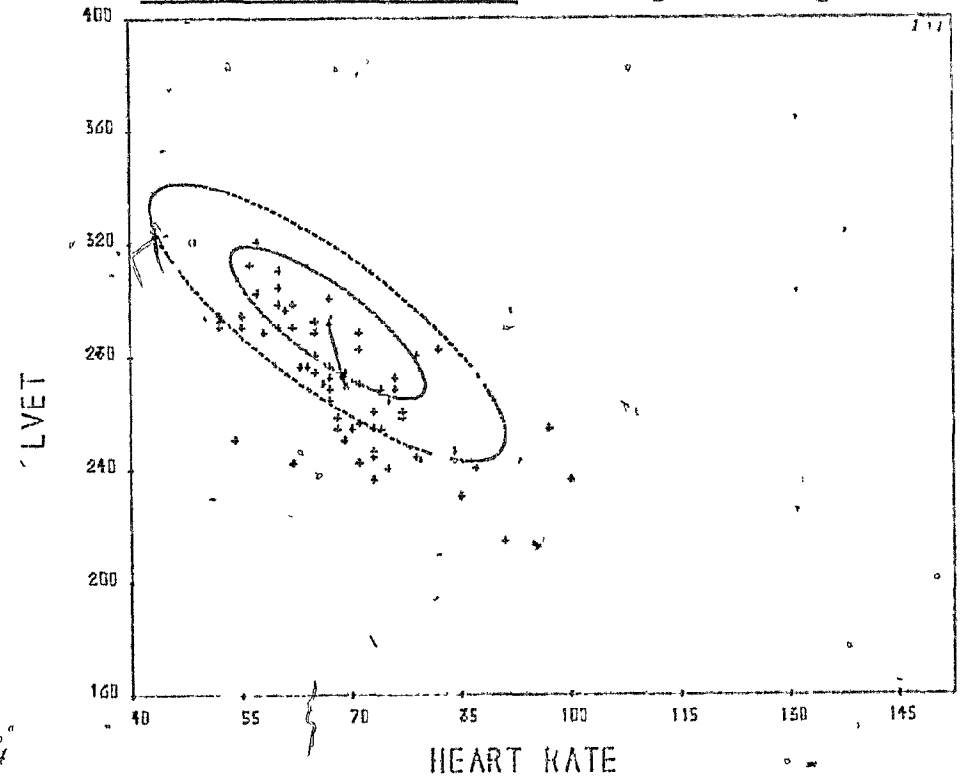


Figure 4.94 - Resting supine scattergram of LVET vs HR for 64 observations of subjects with acute myocardial infarction without failure.

exercise records available from this group.

2.4 Acute Myocardial Infarction

For obvious reasons, only resting records were available from the acute infarction group. There are three sets of data from this group, corresponding to the heart failure scores assigned at the time of each record. The same subjects usually appear in more than one of these sets and each set contains repeated measurements taken from subjects on different days. The regression data for the three sub-groups is in Table 4.9.

The scattergrams for sub-group 0 (no failure) are in Figures 4.94 to 4.96. There were 64 records in this category, including each subject in the group at least once. Although mean HR is only increased by 2.2 beats per minute, LVET is shortened by 22.3 msec. PEP is increased by 4.7 msec., slightly less than in the old infarction group, and PEP/LVET is increased by 0.051. The combined test gives a χ^2 of 362.0 on 14 d.f. ($p < .001$) and the covariance matrix test alone gives a χ^2 of 210.1 on 10 d.f. ($p < .001$). D^2 is 7.605 with an F value of 39.9 on 4 and 1516 d.f. ($p < .001$). The outlier counts are 21 (32.8%), 18 (28.1%) and 20 (31.3%). The generalized outlier count is 26 (40.6%) and seems to be more sensitive in this case than any of the individual 2-dimensional counts.

Figures 4.97 to 4.99 show the 25 samples in sub-group I (mild failure). Most of the 16 subjects are also represented at least once in this sub-group. Mean HR is elevated by 11.1 beats per minute and LVET is decreased by 44.1 msec. PEP is increased by only 3.5 msec. while PEP/LVET is up by 0.084. The combined χ^2 is 418.4 on 14 d.f. ($p < .001$) and χ^2 for the covariance test is 212.1 on 10 d.f. ($p < .001$). D^2 is 9.01 with a

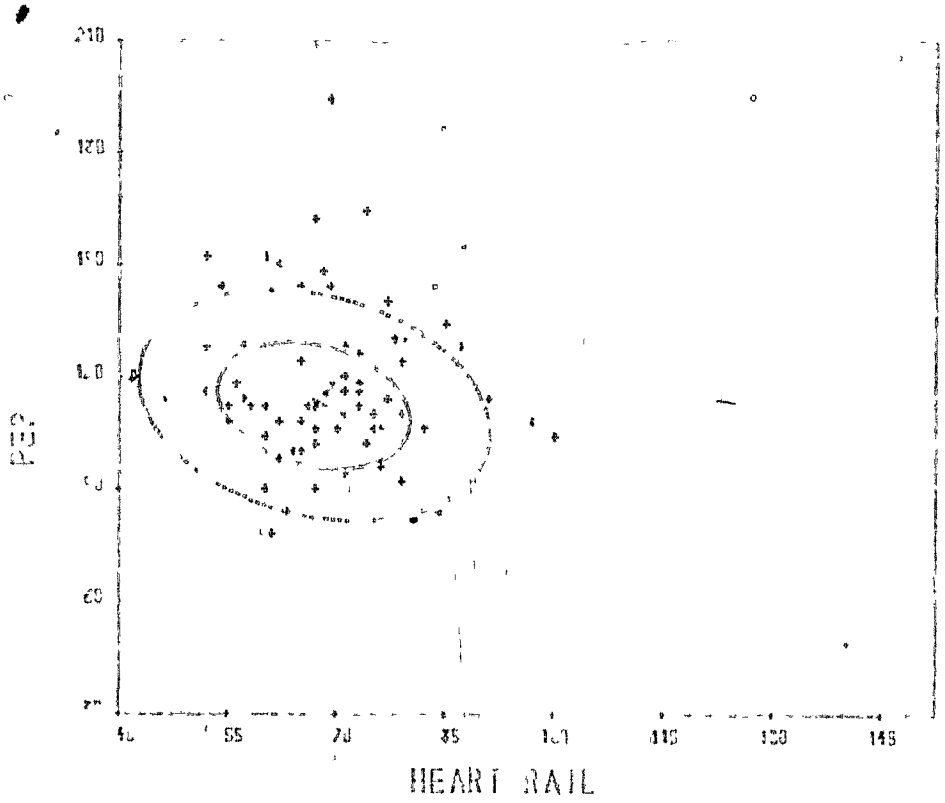


Figure 4.95 - Resting supine scattergram of PEP vs HR for 64 observations of subjects with acute myocardial infarction without failure.

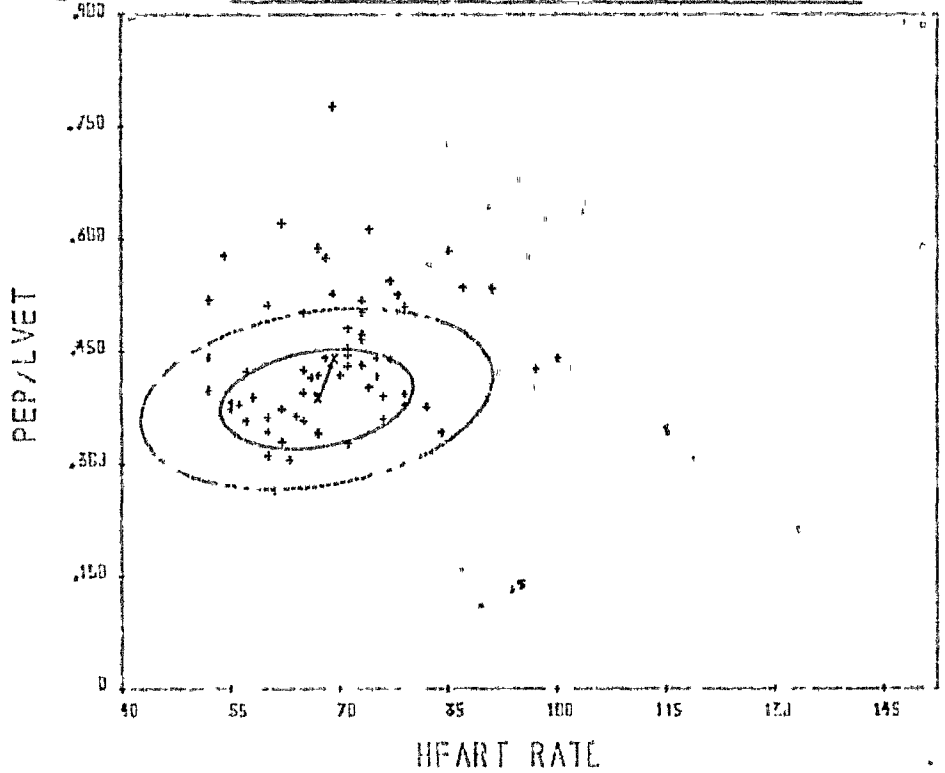


Figure 4.96 - Resting supine scattergram of PEP/LVET vs HR for 64 observations of subjects with acute myocardial infarction without failure.

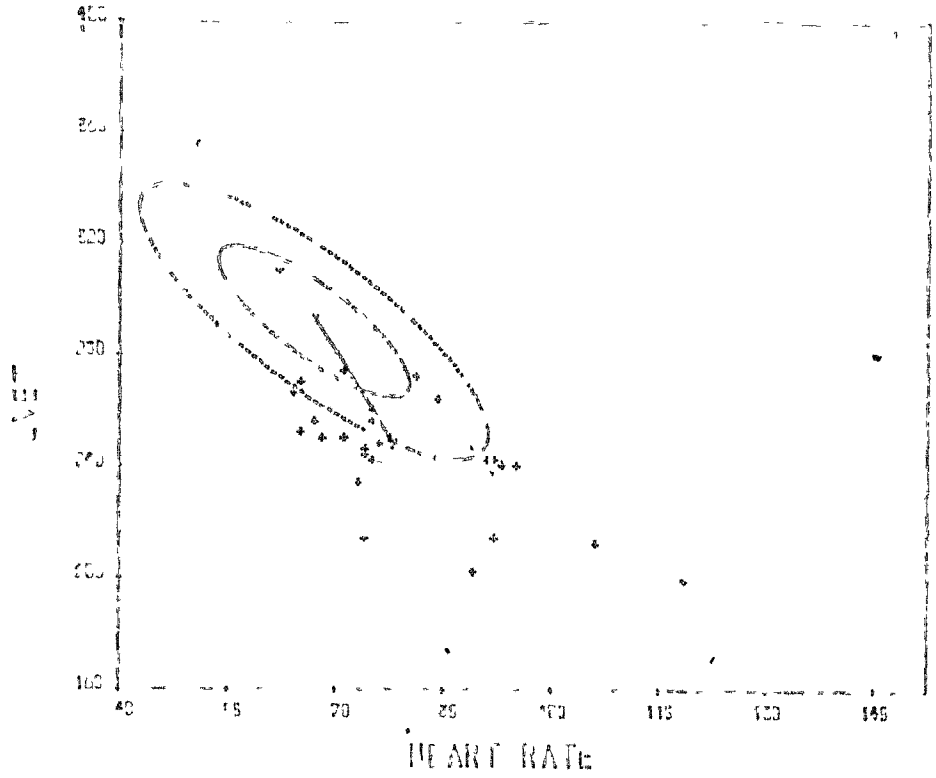


Figure 4.97 - Resting supine scattergram of LVET vs HR for 25 observations of subjects with A.M.I. with failure grade I.

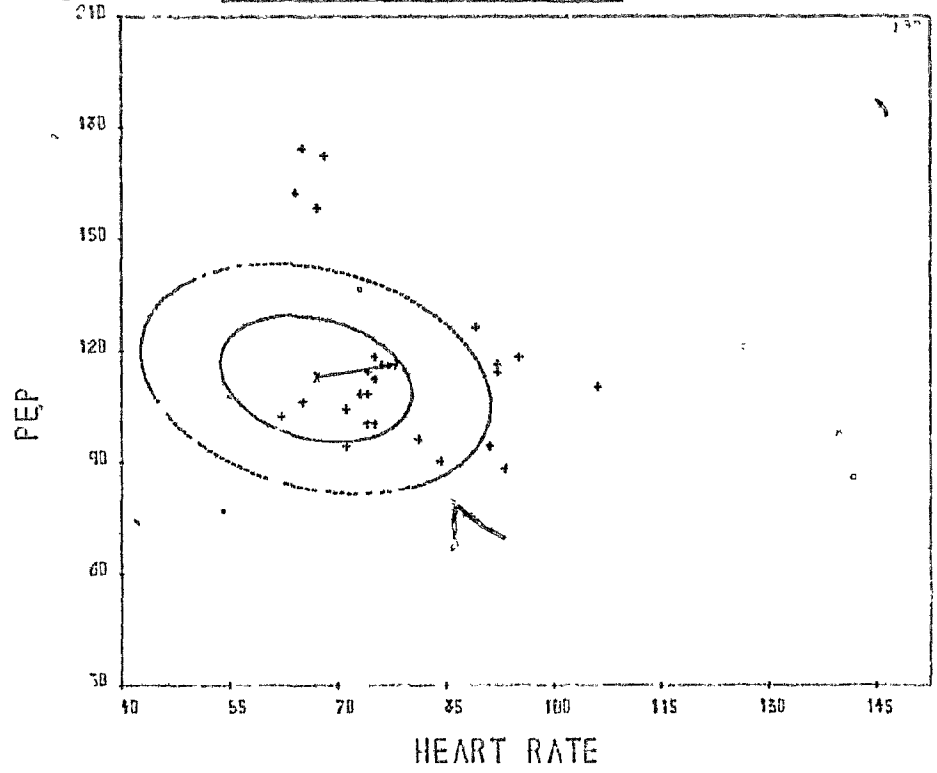


Figure 4.98 - Resting supine scattergram of PEP vs HR for 25 observations of subjects with A.M.I. with failure grade I.

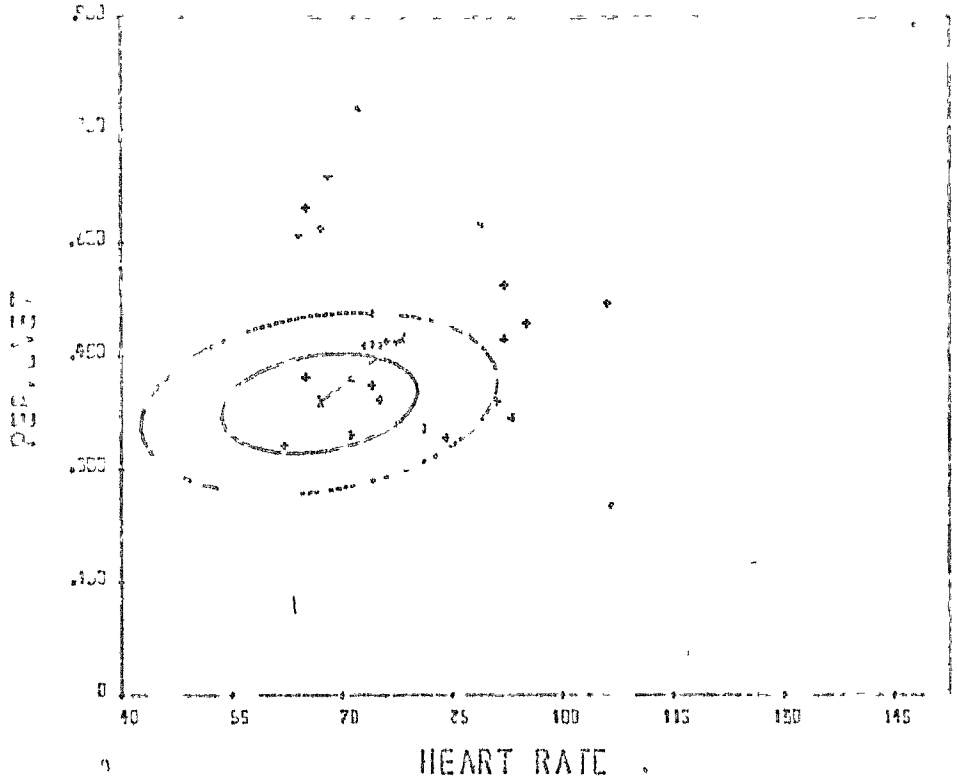


Figure 4.99 - Resting supine scattergram of PEP/LVET vs HR for 25 observations of subjects with A.M.I. with failure grade I.

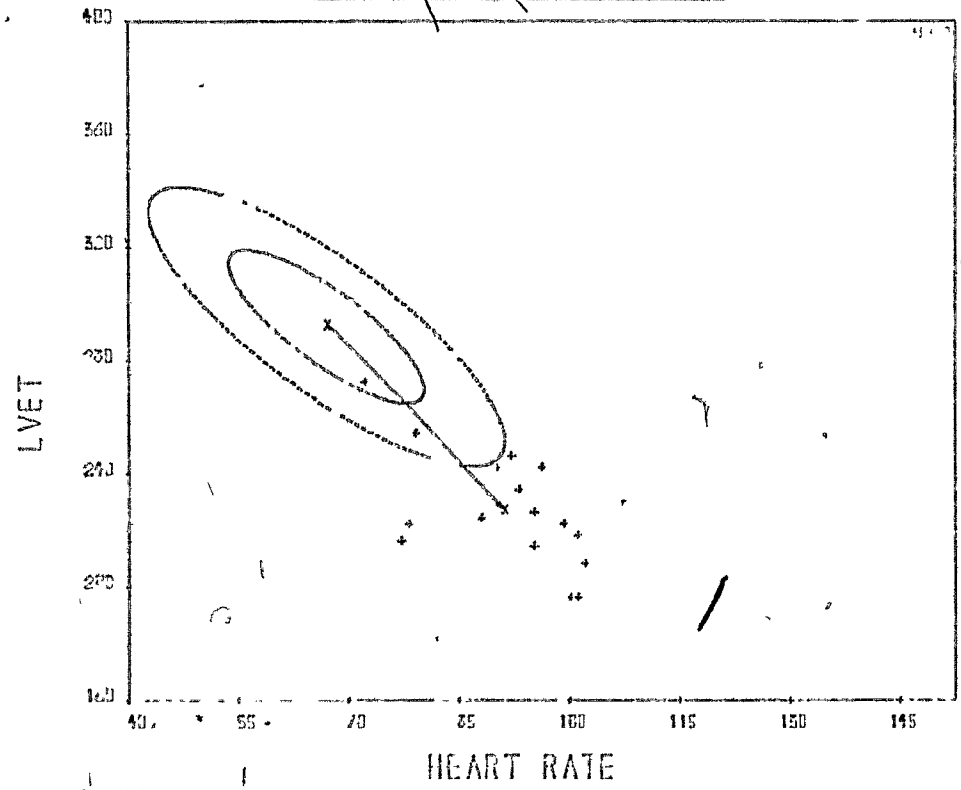


Figure 4.100 - Resting supine scattergram of LVET vs HR for 16 observations of subjects with A.M.I. with failure grade II.

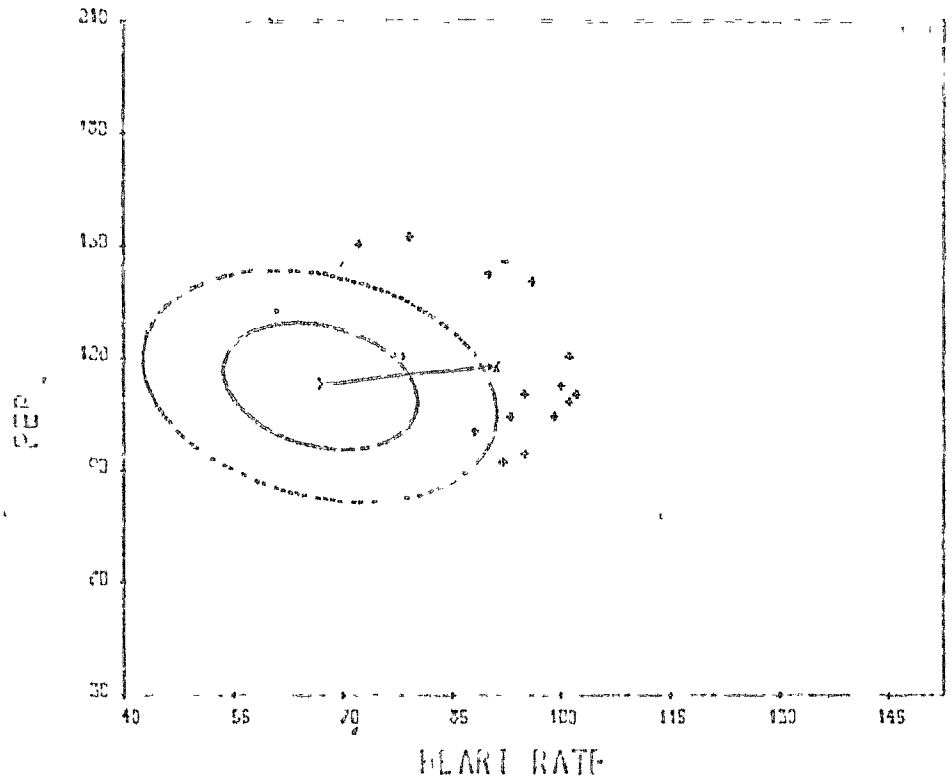


Figure 4.101 - Resting supine scattergram of PEP vs HR for 16 observations of subjects with A.M.I. with failure grade II.

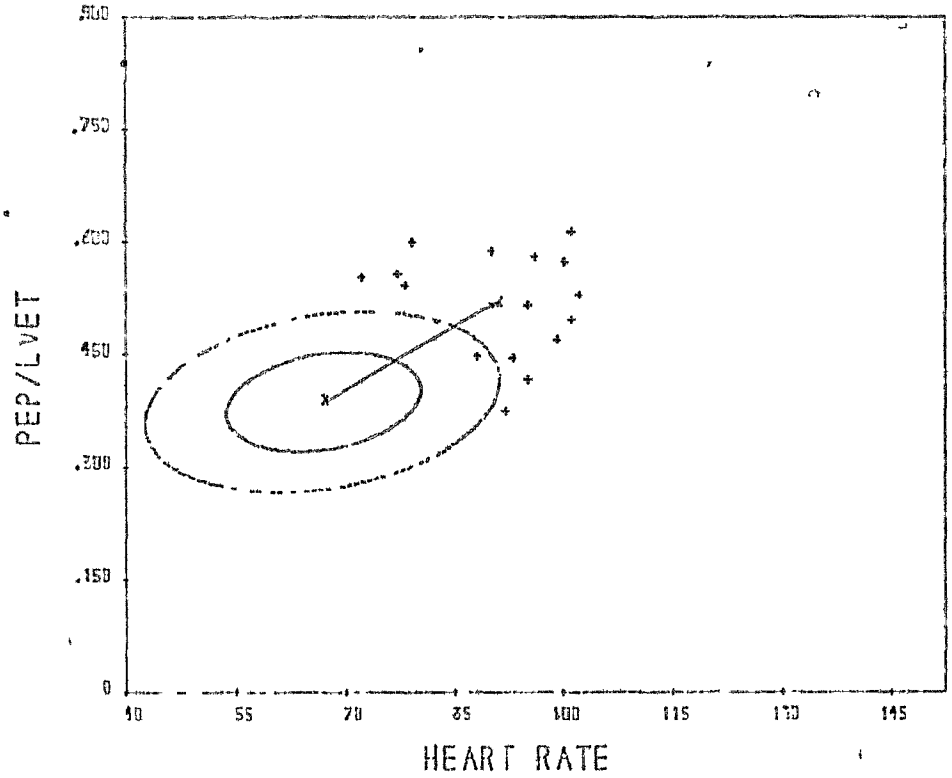


Figure 4.102 - Resting supine scattergram of PEP/LVET vs HR for 16 observations of subjects with A.M.I. with failure grade II.

corresponding F ratio of 55.2 on 4 and 1477 d.f. ($p < .001$). The outlier counts are 18 (72%), 11 (44%) and 11 (44%). About 5 of these in each case reflect elevated heart rates. The generalised count is 18 (72%).

Finally, there were 16 records with failure Grade II representing 7 of the subjects. The scattergrams are Figures 4.100 to 4.102. The means are seen to be shifted in the same general direction as in the milder cases, but to a much greater extent. Mean HR is now elevated by 24.1 beats per minute, with LVET decreased by 65.1 msec. PEP is again slightly elevated (by 4.8 msec.) and PEP/LVET is up by 0.130. The two χ^2 values are 578.1 on 14 d.f. ($p < .001$) and 190.3 on 10 d.f. ($p < .001$). D^2 is 28.0 with an F of 110.7 on 4 and 1468 d.f. ($p < .001$). The outlier counts are 14 (87.5%), 13 (81.3%) and 15 (93.8%). A large proportion of these would be selected on the basis of HR elevation alone, although about half are beyond normal regression limits on at least one graph. The generalized count is 15 (93.8%).

D. Summary

Most of the results are summarised in Tables 4.10 to 4.15 (the two-state combined data is not included in these tables). Tables 4.10 to 4.13 show the means vectors for all of the groups, expressed first in relation to the means vectors for the corresponding normals, and second as a vertical distance from the corresponding normal regression line. This second set of figures is more useful for discussion purposes, since they represent the residual changes in the mean values after the effect of HR has been removed. Changes in this set of figures can be compared with changes in the STI indices proposed by Weissler and others, except that in the present case PEP/LVET has also been heart rate corrected, while

Welsler reported no significant regression of this parameter with heart rate and, therefore, performed no correction for it. Tables 4.11 and 4.14 summarise the χ^2 values for the three hypothesis just discussed, testing the means vectors and covariance matrices for equality with those for the corresponding normals. In addition, the generalised distance D^2 is shown, along with the significance level achieved for the F test just discussed. It must be remembered that, strictly speaking, the values for D^2 and F, and for that matter the χ^2 for hypothesis H_2, are only valid if the covariance matrices are equal. From a practical point of view, in the cases where these matrices are <u>not</u> equal, the figures quoted are computed from a pooled covariance matrix which by virtue of the relative sample sizes is very close to the covariance for the normal control group and they, therefore, represent reasonably valid estimates of the displacement of the means in standard deviation units representative of the normal distributions. Tables 4.12 and 4.15 summarise the outlier counts.

TABLE 4.10

Summary of Mean Changes - Hypertension Series

Group	State	N	Difference From Normal Mean				Difference From Normal Regression		
			HR	LVET	PEP	PEP/LVET	LVET	PEP	PEP/LVET
Hypertension	Supine	615	3.1	- 3.1	4.4	.021	2.9	5.3	.017
	Upright	110	5.8	- 5.0	3.3	.022	3.9	4.7	.012
	Exercise	178	1.4	4.9	4.7	.012	6.8	5.0	.011
Sustained Hypertension	Supine	292	5.2	- 7.9	4.4	.028	0.7	6.0	.022
	Upright	57	6.9	- 7.2	4.4	.030	3.4	6.1	.018
	Exercise	85	2.0	6.0	5.7	.015	8.7	6.2	.013
Hypertensive Heart Disease	Supine	99	4.4	- 9.7	4.9	.034	-2.4	6.2	.029
	Upright	57	2.4	0.9	4.6	.020	4.6	5.2	.016
	Exercise	30	5.2	- 4.4	7.4	.040	2.6	8.6	.033
Cardiac Enlargement	Supine	152	2.4	- 3.6	- .4	.006	0.4	0.3	.003
	Upright	142	0.0	2.6	1.3	.001	2.6	1.3	.001
	Exercise	55	4.4	- 8.1	0.0	.013	-2.2	1.1	.009
Cardiac Enlargement and Hypertension	Supine	22	7.8	- 8.1	-1.7	.011	4.8	0.6	.001
	Upright	20	10.3	- 8.1	0.0	.014	7.7	2.5	.004
	Exercise	8	8.0	- 4.5	5.3	.030	6.3	7.4	.023
Cardiac Enlargement and Sustained Hypertension	Supine	9	13.1	-19.6	6.1	.051	2.1	10.0	.035
	Upright	9	15.1	-13.6	1.9	.031	9.5	5.5	.035

TABLE 4.11

Statistical Summary - Hypertension Series

Group	State	N	H_0 (14 d.f.)	H_1 (10 d.f.)	H_2 (4 d.f.)	D^2	P
Hypertension	Supine	615	439.1	309.3	129.8	.310	<.001
	Upright	110	120.6	69.3	51.4	.547	<.001
	Exercise	178	67.0	10.5	56.5	.433	<.001
Sustained Hypertension	Supine	292	477.3	361.4	115.9	.493	<.001
	Upright	57	114.0	76.7	37.3	.717	<.001
	Exercise	85	66.9	17.1	49.8	.760	<.001
Hypertensive Heart Disease	Supine	99	221.8	147.5	74.3	.821	<.001
	Upright	57	118.2	88.2	29.9	.573	<.001
	Exercise	30	57.3	37.6	19.7	.703	<.001
Cardiac Enlargement	Supine	152	203.2	180.2	23.0	.169	<.001
	Upright	142	55.4	45.7	9.7	.081	<.05
	Exercise	55	44.9	39.2	5.6	.112	<.001
Cardiac Enlargement and Hypertension	Supine	22	120.4	84.5	35.9	1.676	<.001
	Upright	20	37.6	12.9	24.7	1.238	<.001
	Exercise	8	15.2	8.5	6.8	.861	n.s.
Cardiac Enlargement and Sustained Hypertension	Supine	9	47.0	27.8	19.2	2.161	<.001
	Upright	9	37.2	12.9	24.3	2.768	<.001

NOTE: Underlined χ^2 values are not significant at p = .01

TABLE 4.12

Summary of Outlier Counts - Hypertension Series

Number and percent of subjects with D^2 score exceeding upper 90 percent normal limit

Group	State	N	HR Scattergram						Generalized Limit (4 Variables)	
			LVET		PEP		PEP/LVET			
			Count	%	Count	%	Count	%	Count	%
Hypertension	Supine	615	125	20.3	98	15.9	110	17.9	119	19.3
	Upright	110	20	18.2	19	17.3	20	18.2	23	20.9
	Exercise	178	26	14.6	24	13.5	16	9.0	29	16.3
Sustained Hypertension	Supine	292	78	26.7	58	19.9	63	21.6	68	23.3
	Upright	57	10	17.5	10	17.5	11	19.3	14	24.6
	Exercise	85	16	18.8	9	10.6	7	8.2	15	17.6
Hypertensive Heart Disease	Supine	99	33	33.3	24	24.2	26	26.3	23	23.2
	Upright	57	12	21.1	10	17.5	9	15.8	12	21.1
	Exercise	30	5	16.7	5	16.7	4	13.3	5	16.7
Cardiac Enlargement	Supine	152	26	17.1	29	19.1	26	17.1	25	16.4
	Upright	142	23	16.2	20	14.1	17	12.0	21	14.8
	Exercise	55	8	14.6	12	21.8	11	20.0	9	16.4
Cardiac Enlargement and Hypertension	Supine	22	10	45.5	7	31.8	9	40.9	9	40.9
	Upright	20	8	40.0	7	35.0	7	35.0	7	35.0
	Exercise	8	1	12.5	1	12.5	1	12.5	1	12.5
Cardiac Enlargement and Sustained Hypertension	Supine	9	4	44.4	4	44.4	4	44.4	4	44.4
	Upright	9	4	44.4	3	33.3	4	44.4	4	44.4

TABLE 4.10

Summary of Mean Changes - Coronary Heart Disease Series

Group	State	N	Difference From Normal Mean				Difference From Normal Regression		
			HR	LVET	PEP	PEP/LVET	LVET	PEP	PEP/LVET
S-T Depression	Supine	70	- .5	0.8	- 1.4	-.005	0.0	- 1.6	-.004
	Upright	39	- 1.2	1.4	- .2	-.003	- 0.4	- 0.5	-.001
	Exercise	31	- 2.3	10.3	- 1.5	-.020	7.2	- 2.1	-.018
Angina Pectoris	Supine	245	- 1.5	7.0	6.5	.014	4.5	6.1	.016
	Upright	30	1.7	0.9	5.2	.019	3.5	5.6	.016
	Exercise	56	- 4.7	9.2	5.5	.012	2.9	4.4	.016
Myocardial Infarction	Supine	79	1.1	- 9.2	6.8	.040	- 7.4	7.1	.039
A.M.I. Grade 0	Supine	64	2.2	-22.3	4.7	.051	-18.6	5.4	.048
A.M.I. Grade I	Supine	25	11.1	-44.1	3.5	.084	-25.7	6.8	.070
A.M.I. Grade II	Supine	16	24.1	-65.1	4.8	.130	-25.1	12.0	.160

TABLE 4.14

Statistical Summary - Coronary Heart Disease Series

Group	State	N	χ^2 H_0 (14 d.f.)	χ^2 H_1 (10 d.f.)	χ^2 H_2 (4 d.f.)	D^2	P
S-T Depression	Supine	70	9.6	6.5	3.0	.046	n.s.
	Upright	39	8.0	7.3	0.7	.019	n.s.
	Exercise	31	23.1	15.8	7.3	.250	n.s.
Angina Pectoris	Supine	245	184.8	103.7	81.1	.396	<.001
	Upright	30	26.5	16.3	10.2	.354	<.05
	Exercise	56	25.0	11.0	14.0	.277	<.01
Myocardial Infarction	Supine	79	246.9	181.2	65.7	.896	<.001
A.M.I. Grade 0	Supine	64	362.0	210.1	151.9	2.605	<.001
A.M.I. Grade I	Supine	25	418.4	212.1	206.3	9.006	<.001
A.M.I. Grade II	Supine	16	578.1	190.3	387.8	28.032	<.001

NOTE: Underlined χ^2 values are not significant at p = .01

TABLE 4.15

Summary of Outlier Counts - Normals, Coronary Heart Disease Series

Number and percent of subjects with D^2 score exceeding upper 90 percent normal limit

Group	State	N	HR Scattergram LVET Count	LVET %	PEP Count	PEP %	LVET/PEP Count	LVET/PEP %	Generalized Limit (4 variables) Count	Generalized Limit (4 variables) %
Normals	Supine	1457	138	9.5	131	9.0	132	9.1	145	10.0
	Upright	790	87	11.0	76	9.6	80	10.1	79	10.0
	Exercise	570	53	9.3	51	9.0	48	8.4	57	10.0
S-T Depression	Supine	70	5	7.1	4	5.7	5	7.1	9	12.9
	Upright	39	3	7.7	2	5.1	3	7.7	4	10.3
	Exercise	31	9	29.0	4	12.9	4	12.9	7	22.6
Angina Pectoris	Supine	245	42	17.1	33	13.5	37	15.1	46	18.8
	Upright	30	4	13.3	5	16.7	4	13.3	4	13.3
	Exercise	56	8	14.3	8	14.3	7	12.5	9	16.1
Myocardial Infarction	Supine	79	15	19.0	11	13.9	18	22.8	17	21.5
A.M.I. Grade 0	Supine	64	21	32.8	18	28.1	20	31.3	26	40.6
A.M.I. Grade I	Supine	25	18	72.0	11	44.0	11	44.0	18	72.0
A.M.I. Grade II	Supine	16	14	87.5	13	81.3	15	93.4	15	93.8

CHAPTER V

Discussion

The computer analysis procedure developed proved to be reasonably effective when used to measure STI from resting records, but its performance was diminished considerably when presented with exercise records. The measurement success rate was 90.5% with resting supine records and 85.9% with resting upright ones, but was only 39.5% with the exercise runs. It should be noted that the approach taken in the visual verification was to reject records for which the computer measurements were in any doubt. The majority of the measurement failures arose in records in which the amplitude of the second heart sound was low compared to the noise in the signal, particularly in post-exercise records. The recording schedule for these field examinations was very rigid, with 40 subjects or more scheduled for each working day and it was impossible to reschedule subjects with inadequate recordings. Good measurements would have been obtained from some of these by a good visual reader, but in many of the records the second heart sound was barely discernable above the noise. While more sophisticated wave detection logic could probably improve the measurement success rate in the exercise phonocardiogram, a dramatic improvement will probably only be achieved by the development of a methodology which eliminates the use of the [illegible] altogether, at least for the exercise part of the test. Such an approach has been proposed recently by Spodick and Lance (49).

It is difficult to compare the precision of the measurement program with the precision achieved by other techniques, because very few investigators have analysed the precision of their own methods. Good agreement has been reported between STI derived externally and internally from

catheter tracings and this is supported by a similar comparison reported here. Spodick et al (48) reported a standard error of 4.77 msec. in the measurement of LVET in a multiple observer study using paper tracings. This compares well with a residual error of 5.1 msec. in LVET measurement by the present computer program, relative to visual readings from tracings of the same signals. The only other basis for comparison lies in comparing the standard deviations about heart rate regression lines reported for normal groups by various investigators. In particular, the standard deviations for LVET, PEP, and QS_2 reported by Weissler et al (63) are on the average about 3 msec. lower than those reported in this investigation. Let us consider, for instance, LVET regressions. Even if it is assumed that Weissler's measurements are perfect and that the 10 msec. standard deviation he reports is the real physiological scatter, the addition of a 5 msec. random error would only increase the total standard deviation to just over 11 msec. Since the standard deviation for LVET in the present study is 13.2 msec. (Table 3.1), and the measurement error in Weissler's data is probably also of the order of 5 msec., the conclusion is that the additional scatter is probably due to diurnal and respiratory variability, which Weissler took pains to eliminate in his study, or other physiological variability. The measurement precision of the present computer program is probably comparable, therefore, to that of the manual techniques currently used by others in the field. It is important to note, however, that the ratio PEP/LVET is very sensitive to even small measurement errors, particularly in LVET, to the extent that most of the scatter seen in this parameter in normal subjects can be attributed to such errors.

The heart rate regressions computed for the normal subjects at rest are very similar to those obtained by Weissler et al (61) with several minor differences. In the first place, the residual standard deviations about the regression lines are about 3 msec. greater than reported by Weissler. As already mentioned, this is probably related to a combination of respiratory and diurnal effects which Weissler was successful in avoiding. In a large scale study of this type it is not practical to record only early in the morning, so it is difficult to avoid the diurnal effect. It would be possible to eliminate most of the respiratory effect by using a different approach in the measurement process. In any case, the elimination of residual variation is unlikely to have any effect on the regression lines themselves.

The present resting regression lines for LVET and QS_2 are very nearly parallel to those of Weissler et al, but lie below them by approximately 10 msec. The PEP regression line, on the other hand, has a similar intercept as Weissler's but is less steep so that the predicted PEP value for a heart rate around 70 is about 7 msec. greater than predicted by Weissler's equation. The systematic shifts in LVET and QS_2 probably reflect differences in measurement technique. This is not considered to be a serious problem, since it is the stability of a given measurement that is important when comparing results between subjects using the same measurement procedure. The slope of Weissler's regression for PEP is apparently such that the ratio PEP/LVET shows no significant correlation with heart rate, while in the present series (with a sample size over 10 times as large) a significant but relatively weak correlation was found. The magnitude of the heart rate correction suggested by this regression is such that the residual standard error in PEP/LVET is decreased from 0.056

to 0.054 after correction, which is only a slight improvement. The same is true, for that matter, with PEP, for which the residual standard error is decreased from 14.4 to 14.0 msec.

When the technique of multivariate analysis is utilized, the whole discussion about regression lines becomes a moot point, since it is the means vectors and covariance matrices that become important. This is true in the application of discriminant analysis whether the approach taken is linear, or based on multi-dimensional generalized distances, which is the case with both the Bayesian and the "outlier" approach. It is for this reason that the complete covariance matrices for the normal group are included in Chapter III.

It is difficult to compare the regression equations for the upright and post-exercise states with the work of others since very few authors have computed separate equations for these states. In this sense, the present equations should fill a badly needed void, since many authors have tried to use resting regression coefficients to correct exercise data. It is pointed out in Chapter III that the assumption of the upright posture has the primary effect of shifting the regression lines and only a minor effect on the slopes. The obvious flattening of the regression relationships at the higher heart rates encountered after exercise has been noted by others and underlines the importance of using corrections based on normal standards established in the same physiological state.

Weissler and Garrard state in their review article (62) that both PEP and LVET tend to remain within normal limits in patients with chronic hypertensive disease except when failure develops. Shah and Slodki (45) found QS_2 elevated an average of 32.4 msec. in patients with severe systemic hypertension. In the present series (Tables 4.11 to 4.13), rate

corrected PEP was found to be elevated around 5 msec. in the group with hypertension, about 6 msec. in sustained hypertension, and 5 to 9 msec. in the group with hypertensive heart disease both at rest and after exercise. There are smaller (less than 5 msec.) increases in corrected LVET at rest, and increases of about 7 and 9 msec. in hypertension and sustained hypertension after exercise. LVET is decreased slightly in the H.H.D. group in the resting supine state. There is a gradual increasing trend in PEP and PEP/LVET in these three groups, but the trend in LVET is inconsistent. Although these mean changes all lie within normal limits, they are all statistically significant because of the sample size involved. The values for Mahalanobis D^2 for the separation of the sample means from the control group increase consistently through the three groups for both the resting supine and exercise records, but D^2 for the HHD group upright records is less than that observed in sustained hypertension. Even the largest distance observed in this sub-series ($D^2 = 0.821$) is not large enough to make the application of a linear discriminant procedure very useful.

An examination of the χ^2 scores in Table 4.11 shows that in most cases not only the means vectors, but the covariance matrices of the distributions differ considerably from the distributions in normals and a look at the appropriate scattergrams confirms that the extent of the scatter is greater in the hypertensive groups. In such a situation it is possible to do a limited discrimination even in the case of nearly identical means vectors, by classifying a point as abnormal if it falls outside a specified limit established around the normal distribution. In the present case the limit enclosing 90% of normals has been chosen, which leads to a 10% "false positive" indication when normal subjects are tested. The

"outlier counts" for the selected abnormal groups then gave a measure of the "true positive" classification rate. This obviously must be something greater than 10% to be of any use at all. One form of application of this technique is the use of the ellipses plotted on each 2-dimensional scattergram. The sizes of these ellipses were determined from the statistical parameters of the distributions of the normal subjects and the actual false positive rates are seen in Table 4.16 to be slightly different from 10%. In the case of the "generalized" multi-dimensional outlier counts, the limit was set empirically as that value of D^2 (to the normal population center) which yielded exactly a 10% false positive rate. The "generalized outlier count" is preferred by the author, since it considers all variables measured, and it is seen from Table 4.13 that this procedure correctly identifies approximately 23% of the subjects in the sustained hypertension and H.H.D. groups using resting records alone. It was noted in Chapter IV that the use of all 8 variables from the two-state combined sets does not improve on this figure. In all three of the groups being discussed at this point, the exercise test is less sensitive than either of the two resting states for this purpose.

In the group with cardiac enlargement, the means vectors are surprisingly close to the normal reference means. Even more surprising is the obvious poor correlation between the presence of hypertension and the development of cardiac enlargement over a five-year period. Of 152 subjects with a significant increase in heart size (resting supine figures), only 22 were hypertensive at the beginning of the five year project. This was unexpected and several explanations can be offered. There may have been many cases of hypertrophy developing from mild cases of hypertension (for instance, diastolic pressure just under 95 mm Hg.).

There may have been a number of blood pressure readings in error by 5 mm Hg or so and there may have been substantial errors in the measurement of the heart volumes, although the required increase of 60 ml/m^2 represents a relative change of about 15% and most of the enlargements observed were considerably more than this. Since all of the subjects in this group came from the group of policemen, some explanation may lie in above average levels of physical exertion in this group. Finally, there may be a higher than expected level of enlargement due to other non-hypertensive heart disease, such as primary myocardial and coronary heart disease. Aintablian et al (3) and others have noted cardiomegaly in coronary heart disease patients not related to hypertension.

While the mean STI in the cardiac enlargement group are virtually the same as the normal controls, the covariance matrices are different, and it can be seen from the outlier counts that this again is because the scatter is greater.

In the group with cardiac enlargement in conjunction with hypertension, corrected LVET is elevated 5 to 8 msec. in the two resting states, but this is not accompanied by increases in PEP of the size seen in the previous hypertensive groups. The change in PEP/LVET is insignificant. The 7.4 msec. increase in PEP indicated for the exercise state is not significant because of the small sample size. Since the increase in PEP in hypertensive subjects is believed to be due to a delay in aortic valve opening introduced by an elevation in diastolic pressure in conjunction with a normal rate of rise of left ventricular pressure, the absence of an increase in PEP in this case probably reflects the effect of

compensatory hypertrophy. The final group in this series, with sustained hypertension and cardiac enlargement, shows a 10 msec. increase in PEP in the resting supine state and a 10 msec. increase in LVET in the resting upright state, but the small sample sizes make it unwise to attach overdue significance to these figures. The values of D^2 are higher in the two groups with hypertension in combination with enlargement than in the other hypertensive groups, and the outlier counts correctly identify upwards of 40% of the subjects.

In ischemic heart disease several authors have found increases in PEP accompanied by decreases in LVET in resting subjects with varying degrees of functional impairment and have shown correlations between the extent of the changes in the STI and the severity of disease, as evidenced by the number of coronary arteries involved, the severity of symptoms and various other indexes of left ventricular function such as stroke volume. In some cases decreases in QS_2 have been observed and attributed to increased adrenergic activity. At least two authors (41, 28) have noted an increase in LVET after exercise in patients with documented significant coronary artery disease and at least one (35) has not.

In the present series the two groups with ST depression in the exercise ECG and with angina pectoris represent possibly milder forms of ischemic disease not documented by angiographic observations. The group with ST depression had STI statistically indistinguishable from normal, although the outlier counts were somewhat elevated after exercise. The means vector after exercise in this group shows a 7.2 msec. prolongation of corrected LVET although is it not significant statistically. The larger group with angina pectoris shows a slight increase in LVET accompanied by a slightly larger increase in PEP (but still only 6 msec.).

In the resting upright state these increases are not significant. However, in the resting supine and exercise states the observed increase in LVEE, and by inference QS_2, is in contradiction with the results of others (37,35, 28), although the differences involved are small (QS_2 however is prolonged by about 11 msec. at rest). D^2 for this group is small, and the best outlier count is 18.8% for the "generalized" count at rest.

In the group with old infarctions LVET is decreased and PEP is increased by about 7 msec., with a resulting increase of about 0.04 in PEP/LVET. This is in general agreement with the results of others, such as Margolis (33) and Stack et al (50), although there is a scarcity of studies devoted to STI in old infarctions. The result here is statistically highly significant, although D^2 is only about 0.9. The generalized outlier count correctly isolates about 22% of these patients.

The three functional subgroups of patients with acute myocardial infarction show a marked shortening of LVET ranging from 19 to 26 msec., accompanied by progressive increases in heart rate, PEP and PEP/LVET with increasing involvement of failure. This pattern has already been observed by others (42). In the present group QS_2 can be seen by inference to be considerably shortened as well. The work of Lewis et al (28, 27) suggests that this is probably due to high levels of adrenergic activity in these patients. The sample D^2 increases from 2.6 to 28 through the three functional classes. The generalized outlier count isolates respectively 41%, 72% and 94% of the observations in the three classes. The magnitude of the D^2 indicates that an effective linear discrimination could be performed, not only to separate the patients from normals, but also to reach a reasonable separation of those with failure from those without. The potential for such a discrimination can be seen in Figure 5.1

which shows cumulative distributions illustrating the progressive upward shift in PEP/LVET in five subject groups including normals, old infarction patients, and the three functional classes of the A.M.I. group.

Statistically significant trends in STI are apparent with increasing severity of both hypertensive and coronary heart disease. However, the trends observed in the present subject groups are too small to justify any claims of the usefulness of STI measurements in epidemiological and large scale screening studies. In the HHD group, for instance, the D^2 for the separation from the control group is only 0.821, while Cornfield et al achieved a D^2 of over 4 in their group with left ventricular hypertrophy with resting ECG measurements alone (10). In the present groups with cardiac enlargement in conjunction with hypertension, the D^2 values as high as 2.768 are still smaller than can be obtained with the ECG and the two highest D^2 values reported here are based on a very small sample. The suggested use of multi-dimensional "outlier counts" takes some advantage of the increased scatter in the abnormal groups and increases the sensitivity of the attempted discriminations somewhat, but the improvement achieved is by no means large. It is also important to note that the STI results were, in general, not improved in the post-exercise state, although a limited improvement was achieved by considering resting and exercise data simultaneously. While it seems clear that STI measurements in conjunction with a resting ECG would add marginally to the discriminatory power available, it is doubtful that the additional cost would be justified.

Considering coronary heart disease, the STI results in the two groups with ST depression and with angina also appear to be disappointing.

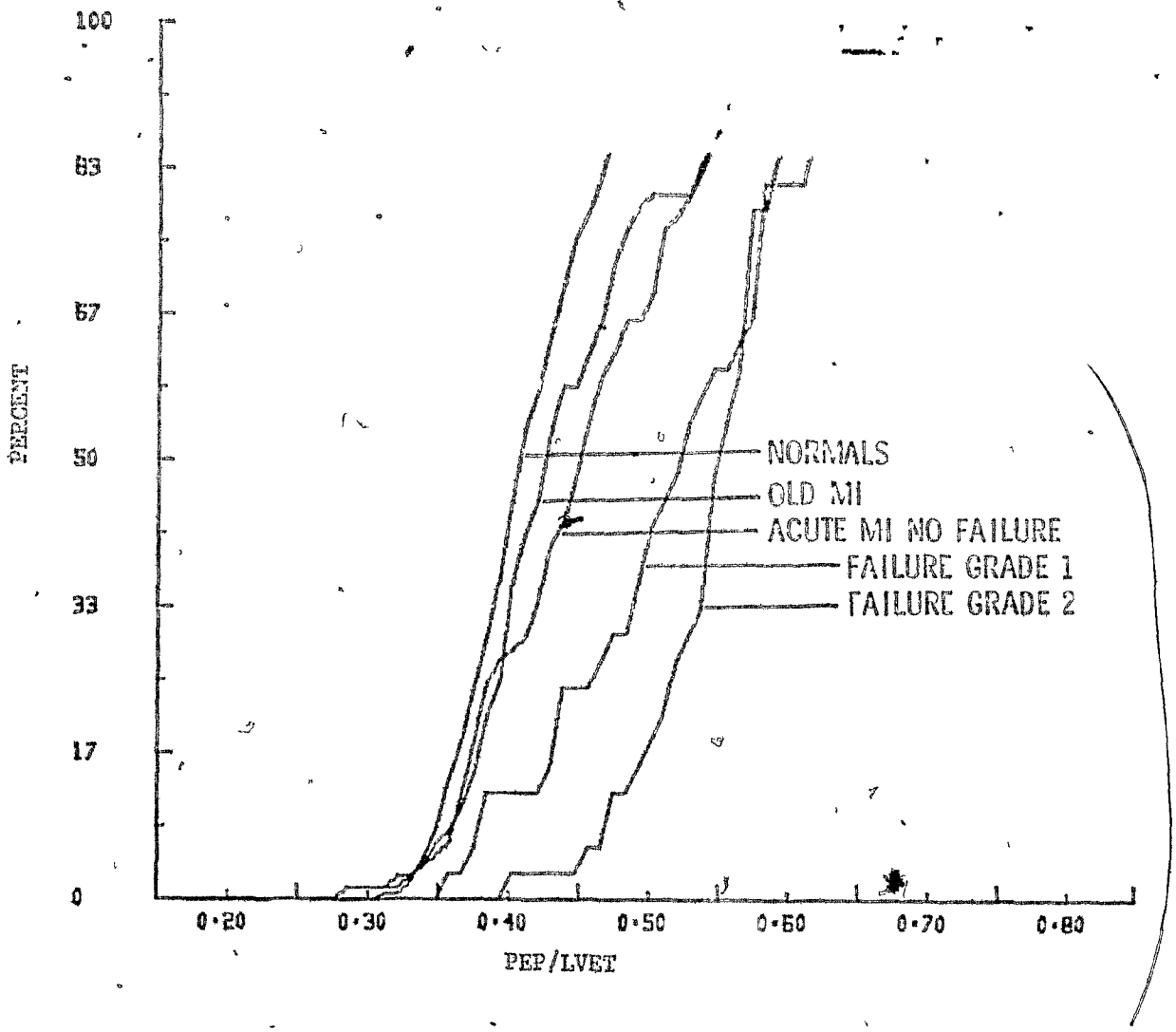


Figure 5.1 Cumulative distributions of PEP/LVET at rest showing the progressive increase in this parameter in groups with old myocardial infarction, acute myocardial infarction without failure, and A.M.I. with Grade I and Grade II failure, compared with a group of normal subjects.

The correlation of STI with ST depression in the exercise ECG is practically non-existent. The D^2 observed in the angina group is less than that observed in non-sustained hypertension, and the prolongation in LVET after exercise in patients with angina or coronary artery disease (41, 28) could not be confirmed in the present study. Other authors have also failed to observe this response (33). The usefulness of STI would seem to be limited mainly to patients with more advanced involvement of the coronary arteries.

In old myocardial infarctions, there are statistically significant shifts of the order of a half of a standard deviation in each of the STI measured giving a total D^2 of 0.896. The limited diagnostic value of a D^2 of this magnitude becomes obvious if it is compared to the results obtained by Cornfield et al from resting ECG's with D^2 values of the order of 12 and greater, not only for differentiation of the MI groups from their normal control group but also in the identification of the location of infarcts. It seems pretty clear that the use of STI in screening studies cannot improve the rate of detection of infarcts over the rate achievable from ECG examination, although it has been shown by others that STI can give a useful indication of functional impairment in these subjects. This, of course, can be valuable in a clinical setting.

The results reported here in acute myocardial infarction support the results of several other authors and reflect the effects of impaired ventricular function in these patients. They also correlate well with the severity of dysfunction during the progress of the acute state of this disease. Although STI provide a good degree of discrimination from normal in these patients, attempts by others have failed to produce a good differential discrimination between acute infarction and acute

coronary insufficiency (40). The identification of acute infarction, for that matter, is not an important consideration except in clinical settings.

Limited measurement accuracy with current non-invasive techniques may contribute to the poor discriminatory power of the STI measurements. It is unlikely, however, that more precise and accurate techniques would produce major changes in the results and conclusions of this study.

CHAPTER VI

Summary and Conclusions

A computer program has been developed to measure the principal systolic time intervals of the cardiac cycle by the digital signal acquisition and analysis of the Frank lead electrocardiogram, phonocardiogram and external arterial pulse. The measurement program identifies the onset of the QRS complex from up to four simultaneous ECG leads, the onsets of the first and second heart sounds, and the initial upstroke and incisura of the arterial pulse. Visual verification results indicate that the program is successful in producing accurate estimates of LVET, PEP, QS_2 and HR from about 90% of resting records and 40% of post-exercise records. Poor quality of the heart sounds in post-exercise records was the primary reason for the fairly large failure rate of the method.

Based on the measurements in large groups of normal subjects obtained from a series of population studies, the statistical distributions of LVET, PEP, PEP/LVET and HR were established for normal male subjects in the resting state in the supine and upright positions, and immediately after submaximal exercise. These distributions are defined as a series of regression relationships with HR as the independent variable, and as means vectors and covariance matrices for the purposes of multivariate statistical and discriminant analysis.

Similar statistical distributions were evaluated for two series of subject groups, one with varying degrees of cardiac involvement due to arterial hypertension, and the other with varying forms of evidence of ischemic heart disease. Although statistically significant trends were observed in systolic time intervals in both series, the magnitudes of the differences in STI compared to the normal group were too small to permit

useful discriminant analysis, except in the series of subjects with acute myocardial infarction.

The results do not support any claims of the usefulness of the STI measurements in epidemiological studies and screening programs. Therefore, it is concluded that although the use of a computer measurement program makes it practical to measure STI on a large scale, the results the present study groups do not indicate that systolic time intervals are sufficiently sensitive indices of early cardiac involvement in either hypertensive or ischemic heart disease.

BIBLIOGRAPHY

1. Agress, C.M., Wegner, S., Nakakura, S., Lehman, E.H. Jr., and Chait, J.
Comparison of the ejection time-heart rate relationships in normal and ischemic subjects
Jap. Heart J. 6:497, 1965

2. Ahmed, S.S., Levinson, G.E., Schwartz, C.J., and Ettinger, P.O.
Systolic time intervals as measures of the contracile state of the left ventricular myocardium in man
Circulation 46:559, 1972

3. Aintablian, A., Hamby, R.I., and Garsman, J.
Correlation of heart size with clinical and hemodynamic findings in patients with coronary artery disease
Am. Heart J. 91:21, 1976

4. Anderson, T.W., and Bahadur, R.R.
Classification into two multivariate normal distributions with different covariance matrices
Annals of Mathematical Statistics 33:420, 1962

5. Aronow, W.S.
Isovolumic contraction and left ventricular ejection times - external measurements at rest and after exercise in normal men
Am. J. Cardiol. 26:239, 1970

6. Benchimol, A., and Dimond, E.G.
The normal and abnormal apexcardiogram
Am. J. Cardiol. 61:485, 1963

7. Blumberger, K.
Die untersuchung der dynamik des herzens beim menschen
Ergebn inn Med. Hinderheilk 62:424, 1942

8. Bowen, W.P.
Changes in heart rate, blood pressure and duration of systole from bicycling
Am. J. Physiol. 11:59, 1904

9. Braunwald, E., Moscovitz, H.L., Amram, S.S., Lasser, R.P., Sapin, S.O., Himmelstein, A., Ravitch, M.M., and Gordon, A.J.
Timing of electrical and mechanical events of the left side of the human heart
J. Appl. Physiol. 8:309, 1955

10. Cornfield, J., Dunn, R.A., Batchlor, C.D., and Pipberger, H.V.
Multigroup diagnosis of electrocardiograms
Comput. Biomed. Res. 6:97, 1973

11. Foley, D.H., and Sammon, J.W. Jr.
An optimal set of discriminant vectors
IEEE Trans. Comput. C-24:281, 1975

12. Fowler, N.O.
Non-invasive methods of cardiac diagnosis
Advances in Internal Medicine 18:283, 1972

13. Franks, D., and Cureton, T.K. Jr.
Orthogonal factors of cardiac intervals and their response to stress
The Research Quarterly 39:524, 1968

14. Freis, E.D., and Kyle, M.C.
Computer analysis of carotid and brachial pulse waves - Effects of age in normal subjects
Am. J. Cardiol. 22:691, 1968

15. Garrard, C.L. Jr., Weissler, A.M., and Dodge, H.T.
The relationship of alterations in systolic time intervals to ejection fraction in patients with cardiac disease
Circulation 42:455, 1970

16. Garrod, A.H.
On cardiographic tracings from the human chest-wall
J. Anat. Physiol. 5:17, 1870

17. Garrod, A.H.
On some points connected with circulation of the blood arrived at from a study of the sphygmograph
Proc. Roy. Soc. London 23:140, 1874/75

18. Hardarson, T., Spiro, S.G., Curiel, R., and Hahn, H.L.
Cardiac function during exercise: A study of systolic time intervals during increasing and constant work rate exercise tests
The American Journal of the Medical Sciences 266:371, 1973

19. Hodges, M., Halpern, B.L., Friesinger, G.C., and Dagenais, G.R.
Left ventricular preejection period and ejection time in patients with acute myocardial infarction
Circulation 45:933, 1972

20. Jones, W.B., and Foster, G.L.
Determinants of duration of left ventricular ejection in normal young men
J. Appl. Physiol. 19(2):279, 1964

21. Jost, A.G., Stewart, J.W., Wang, H.C., Rautaharju, P.M., and Chandler, B.M.
Systolic time interval indices in acute myocardial infarction (abstract)
Proceedings of the 25th Annual Meeting of the Canadian Cardiovascular Society, Toronto, 1972

22. Katz, L.N., and Feil, H.S.
Clinical observations on the dynamics of ventricular systole: I. Auricular fibrillation
Arch. Intern Med. 32:672, 1923

23. Kendall, M.G., and Stuart, A.
The advanced theory of statistics
Charles Griffin & Company Limited, London, 1968

24. Kumar, S., and Spodick, D.H.
Study of the mechanical events of the left ventricle by atraumatic techniques: Comparison of methods of measurement and their significance
Am. Heart J. 80:401, 1970

25. Kyle, M.C., and Freis, E.D.
Computer identification of systolic time intervals
Comput. Biomed. Res. 3:637, 1971

26. Kyle, M.C., Klingeman, J.D., and Freis, E.D.
Computer identification of brachial arterial pulse waves
Comput. Biomed. Res. 2:151, 1968

27. Lewis, R.P., Boudoulas, H., Forester, W.F., and Weissler, A.M.
Shortening of electromechanical systole as a manifestation of excessive adrenergic stimulation in acute myocardial infarction
Circulation 46:856, 1972

28. Lewis, P., Boudoulas, H., Welch, T.G., and Forester, W.F.
Usefulness of systolic time intervals in coronary artery disease
Am. J. Cardiol. 37:787, 1976

29. Lombard, W.P., and Cope, O.M.
The duration of systole in man
Am. J. Physiol. 77:263, 1926

30. Luomanmäki, K., and Heikkilä, J.
Duration of the phases of left ventricular mechanical systole in healthy men aged 45 to 64 years
Annals of Clinical Research 1:156, 1969

31. MacQueen, J.
Some methods for classification and analysis of multivariate observations
Proceedings of the Fifth Berkely Symposium on Mathematical Statistics, page 281-298

32. Maher, J.T., Beller, G.A., Ransil, B.J., and Hartley, L.H.
Systolic time intervals during submaximal and maximal exercise in man
Am. Heart J. 87:334, 1974

33. Margolis, C.
The significance of ejection period/tension period as a factor in the assessment of cardiac function and as a possible diagnostic tool for the uncovering of silent coronary heart disease
Dis. Chest. 46:706, 1964

34. Martin, C.E., Shaver, J.A., Thompson, M.E., Reddy, P.S., and Leonard, J.J.
Direct correlation of external systolic time intervals with internal indices of left ventricular function in man
Circulation 44:419, 1971

35. McConahay, D.R., Martin, C.M., and Cheitlin, M.D.
Resting and exercise systolic time intervals - Correlations with ventricular performance in patients with coronary artery disease
Circulation 45:592, 1972

36. McDonald, I.G., and Hobson, E.R.
A comparison of the relative value of noninvasive techniques - echocardiography, systolic time intervals and apexcardiography - in the diagnosis of primary myocardial disease
Am. Heart J. 88:454, 1974

37. Meng, R., Hollander, G., Liebson, P.R., Teran, J.C., Barresi, V., and Lurie, M.
The use of noninvasive methods in the evaluation of left ventricular performance in coronary artery disease
Am. Heart J. 90:134, 1975

38. Nandi, P.S., Pigott, V.M., and Spodick, D.H.
Sequential cardiac responses during the respiratory cycle: patterns of change in systolic intervals
Chest 63:380, 1973

39. Nandi, P.S., and Spodick, D.H.
Determination of systolic intervals utilizing the carotid first derivative
Am. Heart J. 86:495, 1973

40. Naqvi, S.Z., Chisholm, A.W., and Shane, S.J.
Left ventricular function in ischemic heart disease: assessment by noninvasive techniques
Am. Heart J. 90:312, 1975

41. Pouget, J.M., Harris, W.S., Mayron, B.R., and Naughton, J.P.
Abnormal responses of the systolic time intervals to exercise in patients with angina pectoris
Circulation 43:289, 1971

41a Rao, C.R.
Advanced statistical methods in biometric research
John Wiley & Sons Inc., New York, 1952

41b Rautaharju, P.M., and Wolf, H.K.
Computer interpretation and classification of exercise electrocardiograms, vector cardiographic aspects
In "XIth International Symposium on Vectorcardiography, New York" (I. Hoffman, Ed.) North-Holland, Amsterdam, 1971

42. Robijns, H., Clement, D., Verstreken, G., DeGeest, H., Kesteloot, H., and Joossens, J.V.
Left ventricular systolic time intervals during acute myocardial infarction
Europ. J. Cardiol. 2/4:431, 1975

43. Robinson, D.A.
Quantitative analysis of the control of cardiac output in the isolated left ventricle
Circulation Res. 17:207, 1965

44. Samson, R.
Changes in systolic time intervals in acute myocardial infarction
Br. Heart J. 32:839, 1970

45. Shah, P.M., and Slodki, S.J.
The Q-II Interval - A study of the second heart sound in normal adults and in systemic hypertension
Circulation 29:551, 1964

46. Spodick, D.H., Dorr, C.A., and Calabrese, B.F.
Detection of cardiac abnormality by clinical measurement of left ventricular ejection time
JAMA 209:239, 1969

47. Spodick, D.H., and Kumar, S.
Left ventricular ejection period - measurement of atraumatic techniques: results in normal young men and comparison of methods of calculation
Am. Heart J. 76:70, 1968

48. Spodick, D.H., Kumar, S., Flessar, A.P., Sriratanaban, A.D., Sosler, G., Klints, R.V., and Muench, H.
Relationship of paper speed to precision of pulse wave measurements: a multiple observer study of left ventricular ejection time
Aerospace Medicine 40:707, 1969

49. Spodick, D.H., and Lance, V.Q.
Noninvasive stress testing - methodology for elimination of the phonocardiogram
Circulation 53:673, 1976

50. Stack, R.S., Lee, C.C., Reddy, B.P., Taylor, M.L., and Weissler, A.M.
Left ventricular performance in coronary artery disease evaluated with systolic time intervals and echocardiography
Am. J. Cardiol. 37:331, 1976

51. Stafford, R.W., Harris, W.S., and Weissler, A.M.
Left ventricular systolic time intervals as indices of postural circulatory stress in man
Circulation 41:485, 1970

52. Starmer, C.F., McHale, P.A., and Greenfield, J.C. Jr.
Processing of arterial pressure waves with a digital computer
Comput. Biomed. Res. 6:90, 1973

53. Tavel, E.T., Campbell, R.W., Feignenbaum, H., and Steinmetz, E.F.
The apexcardiogram and its relationship to haemodynamic events within the left heart
Brit. Heart J. 27:289, 1965

54. Thorwald, J.
Science and secrets of early medicine
Thames and Hudson, London, 1962, pp. 238-239

55. Van Bemmel, J.H., Talmon, J.L., Duisterhout, J.S., and Hengeveld, S.J.
Template waveform recognition applied to ECG/VCG analysis
Comput. Biomed. Res. 6:430, 1973

56. Van de Werf, F., Piessens, J., Kesteloot, H., and DeGeest, H.
A comparison of systolic time intervals derived from the central aortic pressure and from the external carotid pulse tracing
Circulation 51:310, 1975

57. Wallace, A.G., Mitchell, J.H., Skinner, N.S., and Sarnoff, S.J.
Duration of the phases of left ventricular systole
Circulation Res. 12:611, 1963

58. Weaver, C.S., Von der Groeben, J., Mantey, P.E., Toole, J.G., Cole, J.A. Jr., Fitzgerald, J.W., and Lawrence, R.W.
Digital filtering with applications to electrocardiogram processing
IEEE Trans Audio and Electroacoustics AU-16:350, 1968

59. Weisdorf, D., and Spodick, D.H.
Duration of diastole versus cycle length as correlates of left ventricular ejection time
Br. Heart J. 38:282, 1976

60. Weissler, A.M.
Noninvasive methods for assessing left ventricular performance in man (Editorial) Am. J. Cardiol. 34:111, 1974

61. Weissler, A.M., and Garrard, C.L. Jr.
Systolic time intervals in cardiac disease (I)
Modern Concepts of Cardiovascular Disease 40:1, 1971

62. Weissler, A.M., and Garrard, C.L. Jr.
Systolic time intervals in cardiac disease (II)
Modern Concepts of Cardiovascular Disease 40:5, 1971

63. Weissler, A.M., Harris, W.S., and Schoenfeld, C.D.
Systolic time intervals in heart failure in man
Circulation 37:149, 1968

64. Weissler, A.M., Harris, W.S., and Schoenfeld, C.D.
Bedside technics for the evaluation of ventricular function in man
Am. J. Cardiol. 23:577, 1969

65. Weissler, A.M., Peeler, R.G., and Roehill, W.H.
Relationships between left ventricular ejection time, stroke volume, and heart rate in normal individuals and patients with cardiovascular disease
Am. Heart J. 62:367, 1961

66. Weissler, A.M., and Schoenfeld, C.D.
Effect of digitalis on systolic time intervals in heart failure
The American Journal of the Medical Sciences 259:4, 1970

67. Wiggers, C.J.
Studies on the consecutive phases of the cardiac cycle II. The laws governing the relative duration of ventricular systole and diastole
Am. J. Physiol. 56:439, 1921

68. Wilks, S.S.
Mathematical Statistics
John Wiley & Sons Inc., New York and London, 1962

69. Willems, J., and Kesteloot, H.
The left ventricular ejection time. Its relation to heart rate, mechanical systole and some anthropometric data
Acta Cardiol. 22:401, 1967

70. Wolf, H.K., MacInnis, P.J., Helppi, R.K., and Rautaharju, P.M.
Computer analysis of rest and exercise electrocardiograms
Comput. Biomed. Res. 5:329, 1972

71. Xenakis, A.P., Quarry, V.M., and Spodick, D.H.
Immediate cardiac response to exercise: physiologic investigation by systolic time intervals at graded workloads
Am. Heart J. 89:178, 1975

72. Zoneraich, S., Zoneraich, O., and Rodenrys, J.
Computerized system for noninvasive techniques
Am. J. Cardiol. 33:643, 1974