British Heart Journal, 1977, 39, 242-254

A study of systolic time intervals during uninterrupted exercise[1]

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A method has been developed for obtaining measurements of the systolic time intervals during uninterrupted graded exercise in the upright position on a bicycle ergometer.

The method has been applied to 112 subjects divided into 4 groups: two of normal subjects below and above the age of 40, respectively (mean ages 30 and 48 years), and two of patients (mean ages for each about 50 years), both with coronary insufficiency, but one without and the other with abnormality of left ventricular function as shown by ventriculography. The measurements obtained yield linear relations between total electromechanical systole (QS_2) and heart rate, between pre-ejection period (PEP) and RR interval for each subject. The average standard deviation about the regression is less than 6 ms for all three regression lines; the average correlation coefficient is greater than 0·93.

The younger group of normal subjects have a significantly shorter PEP compared to the older group. Indices have been derived which separate the patient groups from each other and from the normal subjects. Using these indices 86 per cent of all the subjects were correctly classified according to the group to which they belonged. It is concluded that measurements of STI during uninterrupted exercise offer valuable information in the assessment of cardiac patients.

Non-invasive techniques have become increasingly important in the evaluation of cardiovascular dynamics and myocardial performance in man. The clinical application of systolic time intervals (STI) has recently received more attention (Weissler, *et al.,* 1972). It has been shown that there are differences in STI between normal subjects and patients with cardiac disorders (Toutouzas *et al.,* 1969; Samson, 1970; Sultan Ahmed *et al.,* 1972; Fabian *et al.,* 1972b; Johnson *et al.,* 1972; Armstrong *et al.,* 1973; De Monchy *et al.,* 1973; Beneken *et al.,* 1974). For recent reviews of STI see Wayne (1973) and Harris (1974). For detection of coronary artery disease the results have been disappointing because of statistical overlap with normal subjects (Weissler *et al.,* 1969; Aronow *et al.,* 1971; Buyukozturk *et al.,* 1971; Whitsett and Naughton, 1971; Clerens *et al.,* 1973). Several studies, however, have shown the left ventricular ejection time to be a useful index of cardiac function (Schoenfeld *et al.,* 1967; Wayne, 1968; Diamant and Killip, 1970; Inoue *et al.,* 1970; Heikkilä *et al.,* 1971; Hamosh *et al.,* 1972). At rest, the systolic ratios seem to be the best single index of ventricular function, correlating well with reduced ejection fraction (Meng *et al.,* 1975). The best results have been reported with the ratio ejection time/isovolumetric contraction time; the ratio ejection time/pre-ejection time was considered inferior (Pouget *et al.,* 1971; McDonald and Hobson, 1974).

Systolic time intervals can be obtained at rest, during or after exercise in the supine, sitting, or standing position. Weissler (1972) and McConahay (1972) pointed out that for exercising normal subjects regression equations should preferably be developed, because the relations between intervals and heart rate found during exercise differ widely from those established at rest for the same subjects. 'Correcting for heart rate', using Weissler *et al.*'s (1969) regression formula, derived from subjects at rest, cannot be applied suitably to results obtained

[1]Part of this study is supported by a grant from the Netherlands Heart Foundation.

Received for publication 19 July 1976

from measurements during exercise. This has been confirmed by us in an earlier study (Van der Hoeven *et al.*, 1973).

Exercise studies thus far have not improved the diagnostic value of systolic time intervals, which seems to be partly because measurements were made after interruption of upright exercise and changing to the recumbent position (Whitsett and Naughton, 1971; Pouget *et al.*, 1971) or by measuring intervals in the supine position after supine exercise (McConahay *et al.*, 1972). In an earlier study in which we tried to obtain objective evidence concerning the effect of coronary bypass surgery on left ventricular performance, we used an invasive technique to measure ejection times *during* exercise and found these to be rather long before bypass surgery and considerably shorter after surgery (Vonk *et al.*, 1971). We have now developed a technique for obtaining STI measurements during uninterrupted exercise in the sitting position on a bicycle ergometer and have derived individual values of the STI as a function of the heart rate, obtained from two groups of normal subjects and two groups of patients with coronary arterial disease.

This study was designed to answer the following two questions:
(a) What are the changes of STI of normal subjects and of patients with ischaemic heart disease when subjected to a standardised exercise test?
(b) What are the differences in response for the different groups of healthy subjects and patients, and is it possible to find a set of values on the basis of the exercise STI by which an individual subject may be identified as a member of one or the other groups?

Subjects

Measurements were performed on two groups of normal adults (N) and two groups of patients (P).
(1) 18 young subjects ($N_{<40}$) between 21 and 38 years old (mean 29·5 years).
(2) 33 older subjects ($N_{>40}$) between 41 and 66 years old (mean 48·0 years). Both groups of normal subjects consisted of healthy laboratory workers, hospital personnel or subjects referred to outpatient departments for cardiac examination. These subjects received a complete physical examination, including 12-lead electrocardiogram, exercise test, chest *x*-ray, and serum lipid level determination No evidence of cardiovascular disorder was found. All normal subjects were asymptomatic and none took any form of medication. (There was one woman in each group.)
(3) 36 patients (P_1) between 36 and 63 years old (mean 50·4 years). Patients with classical angina pectoris, subjected to coronary arteriography and left ventriculography with one-, two-, or three-vessel disease with stenosis > 75 per cent but with a normal ventriculogram.
(4) 25 patients (P_2) between 34 and 57 years old (mean 48·6 years). As group P_1 but with an abnormal ventriculogram showing local hypokinesia, akinesia, or dyskinesia.

Table 1 *Subdivision of patient groups according to criteria of the New York Heart Association*

Patient group	*Total No.*	*Class*			
		I	*II*	*III*	*IV*
P_1	36	8	24	4	0
P_2	25	3	14	8	0

Abbreviations see Table 2.

The severity of the anginal complaints in the two groups of patients can be seen in Table 1 where the functional class according to the criteria of the New York Heart Association is given. The exercise tolerance of the subjects in the four groups is given in Table 2. The normal subjects were divided into two subgroups to provide a group of older normal subjects, with an age distribution comparable to that of the patient groups. The exercise tolerance of the $N_{>40}$ group is more comparable to the patient groups as shown in Table 2.

Methods

EXERCISE PROCEDURE

To obtain the systolic time intervals during exercise, the subjects pedalled on either a Muller[1] or a Lode[2] bicycle ergometer. The load on both bicycles was continuously adjustable. The procedure was started

[1]Zentrallwerkstatt GmbH, Göttingen, Germany; Type Nr. 67009.
[2]Lode's Instrumenten N.V., Groningen, The Netherlands; Type 'Lanooy'.

Table 2 *Exercise tolerance of subjects in all classes*

Group	*Total No.*	*No. of subjects reaching maximal load of (Watts)* < 70	70–90	100–120	130–150	> 150
$N_{<40}$	18	0	0	1	3	14
$N_{>40}$	33	0	6	13	14	0
P_1	36	3	13	16	3	1
P_2	25	1	10	12	2	0

$N_{<40}$ normal subjects, age less than 40; $N_{>40}$ normal subjects, age over 40; P_1 cardiac patients with coronary insufficiency but normal ventriculogram; P_2 cardiac patients with coronary insufficiency and abnormal ventricular contraction pattern.

at zero load with a pedal rate of 60 revolutions per minute; this rate was held constant throughout the test. After 1 minute the load was increased 10 Watts each minute. The condition of the subject (fatigue, dyspnoea) or changes in the electrocardiogram (ST depression or ventricular premature beats) determined the termination of the exercise.

MEASURING TECHNIQUE

The carotid pulse wave (CPW), the phonocardiogram (PCG), and a single lead electrocardiogram (ECG) were recorded on a Hellige multichannel strip chart recorder Type 9400 or 9900/4, at a paper speed of 100 mm/s. To record the carotid pulse wave during exercise, we used the specially developed transducer, described by Van der Hoeven and Beneken (1970). Our transducer senses the carotid arterial vessel wall displacement by a feeler pin, which is attached to a leaf spring. A semiconductor strain-gauge is fixed to this leaf spring. This transducer has been tested in dog experiments and the signal produced shown to represent very accurately the time course of the intravascular pressure wave.

The transducer was attached to the subject's neck above the right carotid artery, using a foam-padded aluminium strip and a rubber band. The subject was asked to stretch his neck region by keeping his chin slightly raised and turned to the left, while he watched a dial that indicated his cycling rate. In this manner, it was possible to obtain carotid pulse waves during pedalling at different load levels, without having to interrupt the procedure temporarily to take the measurements. In an earlier study the reliability of the external determination of the left ventricular ejection time (LVET) obtained from the carotid pulse wave was tested (Van der Hoeven *et al.*, 1973). Comparison of internally and externally measured LVET values showed that the accuracy was well within the range needed for this study. The resulting regression equation was:

LVET (external) $= 0{\cdot}98$ LVET (intra-arterial) $+3$ ms; correlation coefficient $= 0{\cdot}99$; standard deviation about regression $= 1{\cdot}5$ ms.

The phonocardiogram was obtained from an acceleration microphone[3] applied to the left third intercostal space at the position where the aortic component of the second heart sound appeared maximally. The microphone was fixed in position with double-sided adhesive tape and, in order to secure good contact with the chest wall, a 3 cm wide rubber band was wrapped around the microphone and chest. This did not interfere with the subject's respiration. The signal was filtered using the high-pass Maass-Weber (1952) phonofilter Mm 1, with a slope of –24 db/oct (the –20 db point at 70 cps).

The electrocardiogram was recorded using disturbance-free skin electrodes[4], consisting of silver cups, filled with conducting jelly, in a rigid housing. Linen gauze was attached to the housing and glued to the skin (Boter *et al.*, 1966). A good Q wave without artefacts from muscle activity was obtained with the CM5 lead (electrodes in position V5 and on the manubrium). To eliminate any electrical shock hazard, either the electrocardiogram was telemetered via a battery-powered transmitter, or the leads were insulated by an isolation amplifier. Systolic blood pressures were measured with a normal arm cuff; pressures were measured only for monitoring and not recorded.

DEFINITIONS OF SYSTOLIC TIME INTERVALS

Fig. 1 shows the definitions of the systolic time intervals: total electromechanical systole (QS_2); left ventricular ejection time (LVET); pre-ejection period (PEP).

The definitions follow the description as given by Weissler *et al.* (1969). Fig. 2 illustrates the electrocardiogram, phonocardiogram, and the carotid artery pulsation signal at increasing load levels, obtained from a normal subject during uninterrupted exercise on the bicycle ergometer. Normally, the data points were obtained from the recording, during the final 10 seconds of each minute, just before the next load step except that below 20 Watts, at the beginning of the test, no measurements were made because of the effects of the transition between rest and exercise. The number of data points available for calculating the regression lines for each subject varied for the following reasons:

(1) The duration of the test varied according to the maximal exercise tolerance of the subject.

(2) In about 5% of cases it was not possible to assess all sections of the recordings, because of bad quality.

The average number of data points available for the normal groups was 11 (SD $= 2{\cdot}1$) and $8{\cdot}8$ (SD $= 2{\cdot}4$) for both patient groups.

PROCESSING OF INDIVIDUAL DATA

The processing of the STI, obtained during an exercise test, is illustrated by the results obtained on Subject 1 (normal group $N_{<40}$). The values of QS_2, LVET, the RR interval for each load, obtained for this subject are shown in Table 3A. Every value in this table is an average over at least five consecutive heart beats at the pertinent load level.

[3]Type EMT 25B Elema-Schönander, Solna, Sweden.

[4]Dépex N.V., The Netherlands.

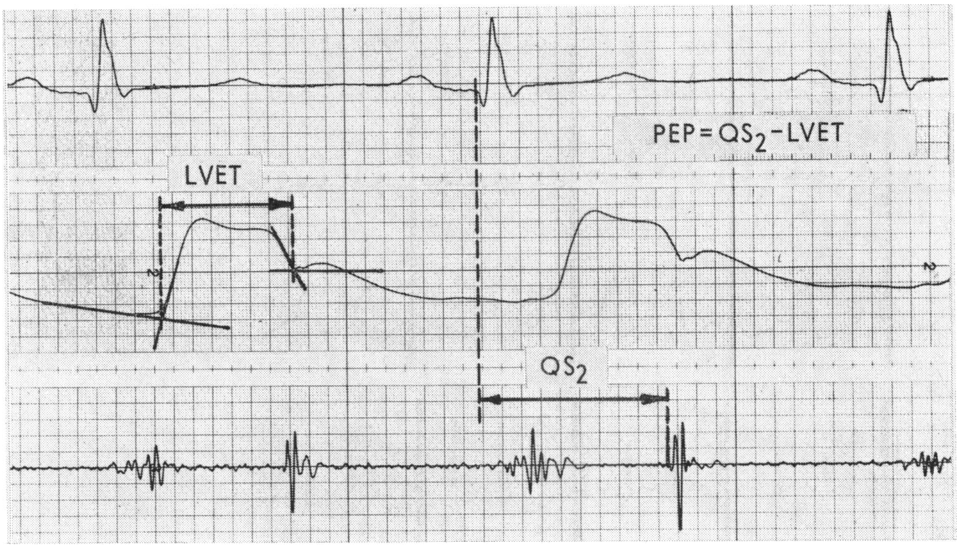

Fig. 1 *A sample of a continuous recording from which the systolic time intervals were measured. From top to bottom: electrocardiogram, external carotid artery pulse wave, and phonocardiogram. The tangents shown in the tracings indicate the procedure to determine beginning of upstroke and incisura.*

From previous studies (Van der Hoeven *et al.*, 1973) and from the analysis of the results of this study (see Discussion) it appears that there are linear relations between QS_2 versus HR, the LVET versus HR, and the PEP versus the RR interval. The individual regression lines calculated, using the method of least squares, from the data of Table 3A are given in Table 3B and Fig. 3.

Each of the three regression lines (QS_2 versus HR, LVET versus HR, PEP versus RR interval) may be described by the equation

$$y = mx + n$$

where m represents the inclination or slope of the line and n its intersection with the y-axis at x=0. To compare the regression lines of the individual subjects, the slopes (m) and the values of y at a standardised x value, close to the average heart rate, may be used. The average heart rates of the patients are usually lower compared with normals, because of the limited exercise tolerance of the patients. Therefore, we chose 2 standard values for the heart rate (x=100 and x=130 bpm) to calculate the corresponding ordinate values: $y_{(100)} = 100m + n$ and $y_{(130)} = 130m + n$. For the regression line PEP versus RR interval, a heart rate of 100 bpm corresponds to an RR interval of 600 ms and 130 bpm corresponds to 462 ms. So, $PEP_{(100)}$ is calculated by $PEP_{(100)} = 600m + n$.

Further studies are required to determine which standardised heart rate provides the best values for a correct classification of patients and normals.

To describe the results we took three quantities into the analysis for each regression line: m, $y_{(100)}$, and $y_{(130)}$, which resulted in 9 values for each subject. These nine are not completely independent.

Results

Table 4 gives the mean and standard error of the mean for each set of values in each class. Averaging the individual regression coefficients results in an average regression equation for each systolic interval and for each group. These regression equations are presented in Table 5 and in graphical form in Fig. 4. The significant differences of the desired parameters compared with those of $N_{>40}$ as the control group are indicated in Table 4. In addition, the significant differences between the values for the P_1 and P_2 group are given. Even though there is a significant difference between the mean values of two sample distributions, it is often not possible to classify the individual members correctly because of a large overlap of the distributions. None of the parameters, as listed in Table 4, is adequate for the classification of normals and patients, the number of false positives and false negatives being too large. Therefore, we have to look for a combination, linear or non-linear, of the values, such that the resulting set of new values will

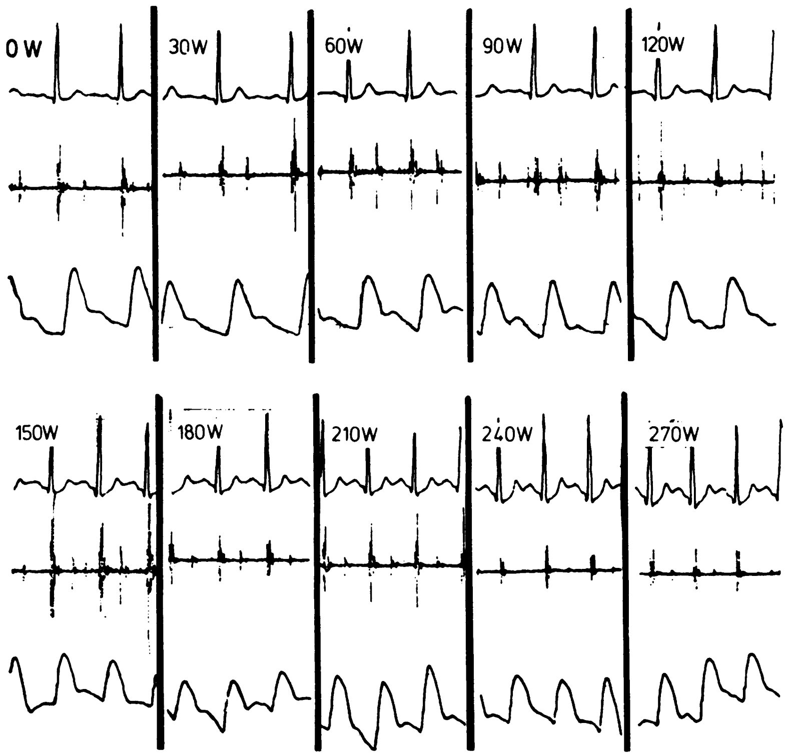

Fig. 2 *Samples of recordings at different loads obtained from a normal adult during uninterrupted exercise. The load, in Watts, at which the samples were taken is indicated.*

give a better separation between the clusters of normals and patients.

Analysing the individual values two indices were found, which are defined as follows:

$$\text{Index } 1 = \frac{QS_{2(130)} - 230}{-m_{LVET}} \text{ (bpm)}$$

$$\text{Index } 2 = \frac{PEP_{(100)}}{LVET_{(100)}}$$

The individual indices for each subject are plotted in Fig. 5. As shown in the figure, P_1 patients are characterised by a relatively high value of $QS_{2(130)}-230/-m_{LVET}$ and P_2 patients are characterised by a high index $PEP_{(100)}/LVET_{(100)}$.

The average values and the SEM of the indices

Table 3A *Mean systolic time intervals at increasing load levels obtained from Subject 1 (group $N_{<40}$)*

Sample (No.)	*Load (Watt)*	*HR (bpm)*	*QS_2 (ms)*	*LVET (ms)*	*PEP (ms)*
1	20	79	376	272	104
2	30	85	370	272	98
3	40	83	369	272	97
4	50	84	375	275	100
5	70	84	355	268	87
6	80	97	351	260	91
7	90	94	354	271	83
8	100	100	335	256	79
9	120	108	322	254	68
10	130	113	312	244	68
11	140	115	310	244	66
12	150	117	306	244	62
13	170	131	289	226	63
14	190	136	276	225	51
15	210	145	267	215	52
16	230	153	257	215	52
17	250	160	254	206	48

Table 3B *Regression equations obtained from data in Table 3A*

Regression equation	s_m	s_{yx}	*r*
$QS_2 = 501 - 1{\cdot}61$ HR	0·062	6·5	−0·99
$LVET = 346 - 0{\cdot}88$ HR	0·033	3·4	−0·99
$PEP = -11 + 0{\cdot}15$ RR	0·009	4·5	+0·97

HR, heart rate in bpm; RR, RR interval (ms); QS_2, electromechanical systole; LVET, left ventricular ejection time; PEP, pre-ejection period; s_m, standard error of the slope m; s_{yx}, standard error about regression; r, correlation coefficient.

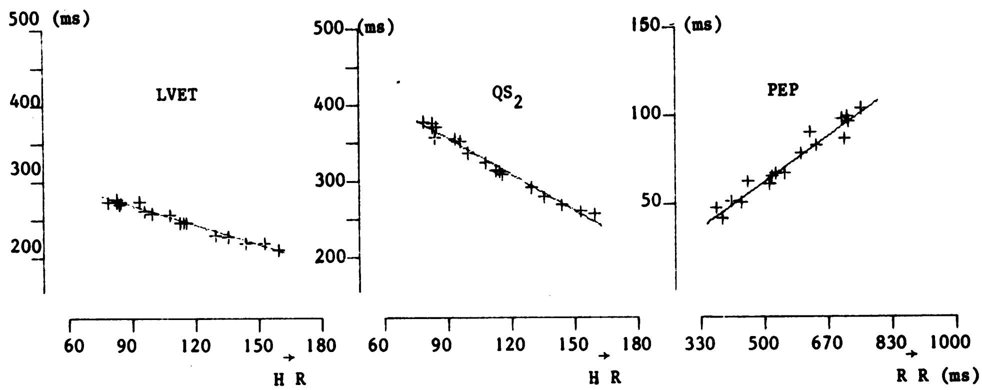

Fig. 3 *LVET versus HR, QS_2 versus HR, and PEP versus RR interval for one normal subject during uninterrupted exercise on a bicycle ergometer. Data points, indicated by crosses, are tabulated in Table 3. Observe the nice fit of the data points by a linear regression line.*

Table 4 *Ejection fraction, and 9 STI measurements obtained during exercise for each group (mean $\pm$ SEM)*

		Group				
		$N_{>40}$	$N_{<40}$	P_1	P_2	
No.		33	18	36	25	
Mean age (yr)		48	30	50	49	
Ejection fraction		—	—	0·62 ±0·02	0·45 ±0·02	(*)
$QS_{2(100)}$	(ms)	332 ±2·0	321 ±2·9*	347 ±2·9*	328 ±2·6	(*)
$QS_{2(130)}$	(ms)	282 ±2·4	277 ±2·6	303 ±3·1*	283 ±2·8	(*)
m_{QS_2}	(ms/bpm)	−1·68 ±0·04	−1·45 ±0·04*	−1·45 ±0·05*	−1·50 ±0·09**	
$LVET_{(100)}$	(ms)	241 ±1·6	238 ±2·9	249 ±2·2*	220 ±2·2*	(*)
$LVET_{(130)}$	(ms)	210 ±1·5	211 ±2·5	227 ±2·6*	194 ±2·2*	(*)
m_{LVET}	(ms/bpm)	−1·03 ±0·03	−0·91 ±0·03**	−0·71 ±0·05*	−0·86 ±0·06**	(**)
$PEP_{(100)}$	(ms)	91 ±1·3	82 ±2·2*	98 ±1·9*	108 ±2·5*	(*)
$PEP_{(130)}$	(ms)	72 ±1·2	65 ±1·7*	79 ±1·4*	90 ±3·1*	(*)
m_{PEP}		0·13 ±0·006	0·12 ±0·01	0·14 ±0·01	0·13 ±0·01	

*$P < 0·005$, **$P < 0·05$ with $N_{>40}$ as control group.
Between parentheses (last column) the significance of the differences between group P_1 and group P_2. Abbreviations as in Tables 2 and 3. Indices in first column indicate the heart rates (100 and 130 bpm) at which the STI are computed.

Table 5 *Mean regression equations for four groups*

Group	*Regression equation*	*R*	S_{yx}
$N_{>40}$	QS_2 = 500−1·68 HR	−0·98	6·0
$N_{<40}$	QS_2 = 466−1·45 HR	−0·98	5·6
P_1	QS_2 = 492−1·45 HR	−0·96	5·3
P_2	QS_2 = 478−1·50 HR	−0·96	5·2
$N_{>40}$	LVET = 344−1·03 HR	−0·98	3·5
$N_{<40}$	LVET = 329−0·91 HR	−0·96	5·6
P_1	LVET = 320−0·71 HR	−0·88	3·8
P_2	LVET = 306−0·86 HR	−0·95	3·6
$N_{>40}$	PEP = 13+0·13 RR	0·94	4·1
$N_{<40}$	PEP = 10+0·12 RR	0·94	4·5
P_1	PEP = 14+0·14 RR	0·94	3·9
P_2	PEP = 30+0·13 RR	0·85	3·5

R, mean correlation coefficient of the individual regression lines; S_{yx}, mean standard deviation about regression (ms). Other abbreviations as in Tables 2 and 3.

are indicated in the figure. A rationale for the choice of the two indices is presented in the discussion.

EJECTION FRACTIONS

All patients underwent cardiac catheterisation and from 29 P_1 and 22 P_2 patients the ejection fraction could be estimated reliably from the ventriculogram in the right oblique position, using the method of Sandler and Dodge (1968). Average values and SEM of the ejection fractions for the two patient groups are given in Table 4.

Discussion

SOURCES OF ERROR

The average regression coefficients as presented in Table 4 are known with a limited accuracy, partly

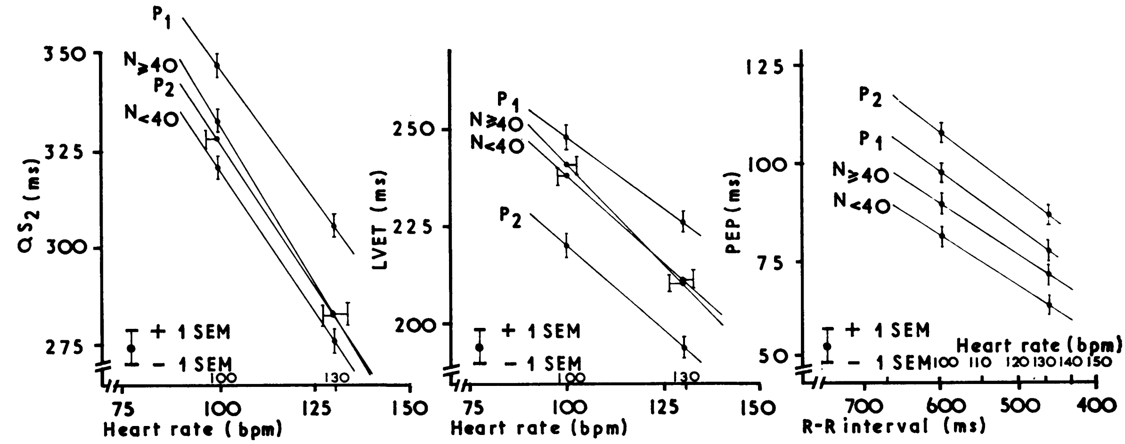

Fig. 4 *Graphical representation of the relation between QS_2 and HR, LVET and HR, and PEP and RR interval, for the 4 groups of subjects. Lines are drawn as given by the data in Tables 4 and 5.*

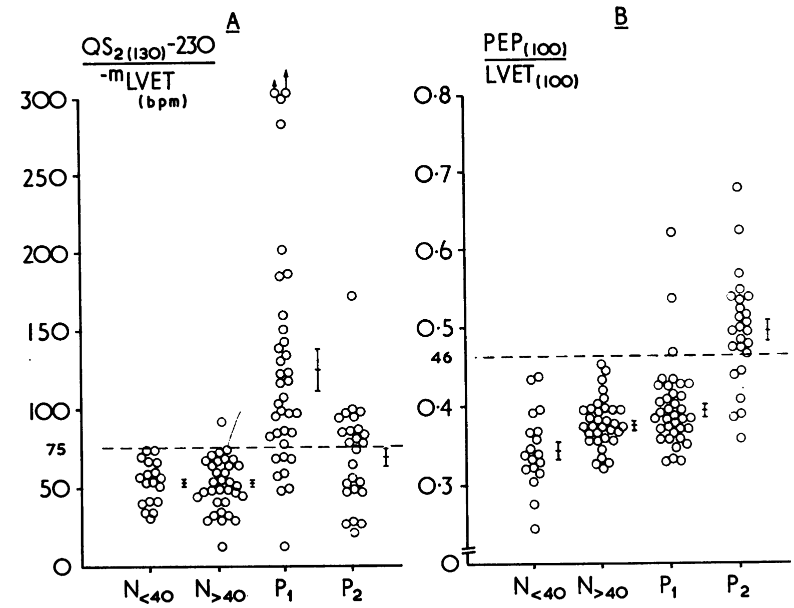

Fig. 5 *Panel A: Index 1=$(QS_{2(130)}-230)/-m_{LVET}$ for all subjects in each group. Mean values ±1 SEM are indicated. Abbreviations as in Tables 2 and 3. A horizontal line at Index 1=75 separates P_1 subjects from normal subjects. One value (at Index 1=2300) for a P_1 subject is excluded from the computation of the mean and SEM. This value is extremely high because of an almost zero value of m_{LVET}.*
Panel B: Index 2=$PEP_{100}/LVET_{100}$ for all subjects in each group. A horizontal line at Index 2=0·46 separates P_2 subjects from normal subjects.

expressed by their standard deviation. There are several possible sources of inaccuracy:

(a) Inaccuracy of individual data points: Our experience is that individual time intervals may be estimated within 3 ms of the true value, which is in accordance with the value given by Aronow *et al.* (1971). Since five or more beats were taken for the calculation of one data point, the inaccuracy of data points is of the order of 1 to 2 ms.

(b) The use of a linear model to fit the data points: We have used linear models for the relation between the systolic intervals and heart rate (or RR interval for the PEP). These models are validated by the individual values of the linear correlation coefficient, which is larger than 0·85 in 95 per cent of all cases. Average values of the correlation coefficients are given in Table 5. These results confirm earlier investigations (Van der Hoeven *et al.*, 1973). Higher order regression lines did not reduce the residual least squares error significantly.

(c) Inaccuracy of the derived values: The accuracy of the slope m is directly related to the correlation coefficient, and related to both the range and number of x-values from which the regression line is calculated. We found, as an average, that the inaccuracy of the slopes of all individual regression lines within a group is a factor 4 to 5 less than the standard deviation of the total population of that group. Therefore, we may disregard the error in the individual values of m.

The same reasoning applies to the error in the values $y_{(100)}$ and $y_{(130)}$. The mean residual errors about regression are in the range 3 to 6 ms (see Table 5) and the standard deviations of the systolic intervals within all classes is in the range 7 to 19 ms (see Table 4). Since the average heart rate is always in the range 100 to 130 bpm a possible error in the slope will not contribute much to the error of $y_{(100)}$ or $y_{(130)}$. This would be the case if we had chosen a standardised heart rate far outside the average heart rate (say, at $x=0$ bpm).

(d) Interindividual differences within each class of subjects: The mean parameter values presented in Table 4 are calculated by simply adding all individual values. When there were large interindividual differences in the accuracies of the values, weighting factors should have been applied. We have tested this possibility, and the results were essentially the same, indicating that no large interindividual differences exist. Another reason is that individual errors are much less than the standard deviation of the population of a group, so we may conclude that the estimate of the individual values is good enough to find representative values of the class-values, and that no individual weighting of values is necessary.

REGRESSION EQUATIONS

Most investigators combine all individual data points and compute only one regression line for each class of subjects, for example, the regression line relating LVET and heart rate as published by Weissler *et al.* (1969) gives a quantitative relation between the LVET at a certain heart rate of one individual and those of a large group of other subjects at various heart rates. However, this regression line gives no information about how the LVET of that individual will change if his own heart rate changes as a result of drugs or exercise, for example. Our mean regression lines indicate how a certain systolic time interval will change as a function of heart rate for the average subject within a class.

QS_2 VERSUS HR

In this study, the QS_2 measurements of the normal subjects show an inverse relation with HR. A linear regression equation has been used, though the individual data suggest a slightly non-linear relation. This departure from the linear was so small over the relevant range (HR=90–140 beats/min) that a second order regression line gave no significant improvement. Kesteloot *et al.* (1968) came to the same conclusion, from their measurements on 267 normals, carried out in supine position at rest. Their regression equation ($QS_2=493-1{\cdot}5$ HR) does not differ essentially from our results. Using phonocardiography, Strandell (1964) obtained regression lines between the interval S_1–S_2 (interval between the first and second heart sound) and HR during exercise in a sitting position. Though S_1–S_2 is a different time interval from the QS_2, which we used, there is a remarkable agreement with our findings: during exercise in the sitting position with stepwise increased work loads, S_1–S_2 at first decreased approximately linearly with increased HR but a slightly non-linear relation was found at higher rates.

LVET VERSUS HR

The LVET obtained from normals shows that the individual LVET relation was inversely linear to HR. This corresponds with the results of a great number of other investigators who also found such linear relations for groups of normals in the supine position at rest. Weissler *et al.* (1969), who carried out measurements in 121 normal male subjects in a supine position, found a mean regression line: LVET$=-1{\cdot}7$ HR $+413$ (ms). Willems *et al.* (1970) found: LVET$=-1{\cdot}65$ HR$+419$ (ms) as a mean regression line in 72 normals in the supine position at rest. A notable difference between Weissler's results obtained at rest and ours during exercise in the upright position is that the LVET is found to decrease less with rising heart rate. No subject in our normal groups shows an individual slope (m_{LVET}) steeper than −1·4, and the mean slope is −1·0 (±0·15). Maher *et al.* (1974) obtained regression equations relating STI to heart rate during submaximal supine exercise in a small group (10) of young physically active men. They found that the slopes for the LVET (also QS_2) with the increase in heart rate were nearly identical to the regression equations of Weissler. It seems probable that the differences in results obtained by Maher *et al.* and our group are caused by the difference in position (supine or upright) of the normal subjects. This requires further investigation.

PEP VERSUS RR

An important observation based on the measured data is the linearity of individual relations when PEP is plotted as a function of RR interval. This simplifies the data handling as compared with the necessity of calculating a second order regression line if PEP is given as a function of HR. This result confirms a preliminary investigation (Van der Hoeven *et al.*, 1973). Fabian *et al.* (1972a) calculated an equation for PEP versus HR through data points obtained from 50 normal subjects, in the supine position at rest; the coefficients were of the same order as Weissler's findings. However, Fabian indicated a very poor correlation (−0·30) between PEP and HR, while Weissler gave no information on this item. Our data show a distinct relation between PEP and RR interval for each individual with a high mean correlation coefficient of 0·92.

VARIANCE IN MEASUREMENTS

The individual regression lines as presented in this study are characterised by a high mean correlation coefficient and relatively low standard deviations about regression. Other work suggests that the measuring circumstances may influence such results drastically; in particular, data obtained at rest are very dependent on physical and physiological factors. When measurements have been taken during breaks in an exercise period, the results of a number of studies indicate a relatively large individual spread. Pouget *et al.* (1971) found, for 20 normals after exercise at a heart rate of 87 beats/min, a group standard deviation in LVET of $\sqrt{20} \times 5{\cdot}7 = 25$ ms; the present investigation yields a group standard deviation of only 9 to 13 ms for $LVET_{(100)}$. The results of McConahay *et al.* (1972) and Agress *et al.* (1965) on measurements taken several seconds after exercise show such a large spread that those workers conclude that their results cannot be used to separate patients from normals. Using a method, comparable to ours, Pigott *et al.* (1971) found a spread which is about the same as that of our present study.

The length of the LVET is determined by various factors, such as preload, afterload, myocardial inotropy, and heart rate (Shaver *et al.*, 1968; Sultan Ahmed *et al.* 1972). During a subject's transition from exercise to rest, all these factors will change, thus contributing to large variations in the LVET. Continuous recording during and after exercise indicated that during the first minute after exercise the heart rate in a group of normal subjects fell at a rate between 0·25 and 1·1 bpm/s. However, the LVET decreases at a relatively much faster rate. This is illustrated in Fig. 6, which gives LVET as a function of HR for two subjects A and B. The upper regression lines are calculated according to the procedure described in this paper. At the end of the exercise test the subjects stopped pedalling but the recording continued. The lower re-

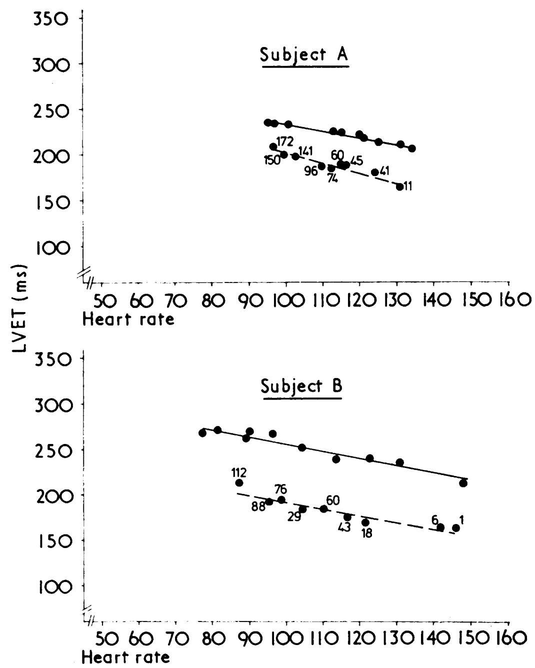

Fig. 6 *LVET as a function of HR for two subjects A and B. The upper lines in each plot are calculated through all data points obtained during increasing exercise load. The lower lines are calculated through the data points obtained during the transition from exercise to rest. Next to the data points is indicated the time in seconds elapsed since pedalling was stopped. Observe the almost immediate drop in LVET and the gradual return of HR back to resting values.*

gression lines are calculated through the data points obtained during this exercise-to-rest transition period; the time in seconds which elapsed after pedalling was stopped is indicated for each point. The regression lines derived after exercise are shifted downwards significantly. The LVET shortens rapidly after cessation of the exercise; moreover, a considerable difference between the shortening in the two subjects is apparent (40 and 60 ms). In the study of STI in relation to exercise, therefore, it is recommended that only data obtained during *uninterrupted* exercise be used.

Other factors which will contribute to a uniform response, with small intra-individual variations are as follows: increase of exercise load at a low rate so that the measurements are obtained virtually during a steady state; decrease of beat-to-beat variations in RR interval at heart rates above 100 bpm, which will reduce the beat-to-beat variations in the STI values; stroke volume, which is one of the determining factors of LVET, will reach a maximum at heart rates of approximately 110 bpm (Åstrand *et al.*, 1964). This stabilisation will decrease the beat-to-beat variations in LVET.

DIFFERENCES BETWEEN GROUPS

In Table 4 the significance of the differences between the values of different groups is indicated.

The most striking difference between the two normal groups is given by the QS_2 values, which is probably the result of a difference in PEP, the young normal subjects having a PEP which is 10 ms shorter. Using the S_1–S_2 interval, Strandell (1964) established similar differences between his older and younger groups. In addition, the differences between the two patient groups are striking. This is specially true of the relation between LVET and HR which turns out to be important in separating patients with coronary insufficiency but normal ventriculograms (P_1) from those with an abnormal left ventriculogram (P_2). The P_1 group has longer LVET corrected for heart rate, but the P_2 group has a considerably shorter LVET as compared with the normal groups.

In both patient groups we found a considerable lengthening of the PEP, the P_2 group showing the longest PEP. In the P_2 group the short LVET is compensated by a long PEP, resulting in almost normal QS_2 values. Only the slope m_{QS2} of the P_2 group differs significantly from that of the older group of normals ($N_{>40}$) (see also Fig. 4).

CORRELATION WITH EJECTION FRACTION

The ejection fraction (EF) is considered to be a measure of left ventricular function, and it is relatively easy to calculate this fraction from the left ventriculogram. In Fig. 7 the EF is plotted as a function of $PEP_{(100)}/LVET_{(100)}$ for those patients for which the EF could be estimated. The ejection fraction of the P_2 group is found to be significantly lower than that of the P_1 group ($P<0{\cdot}001$). If both groups are combined, a statistically significant correlation of $-0{\cdot}51$ between $PEP_{(100)}/LVET_{(100)}$ and the EF is found. In the same subjects the correlation of the systolic ratio $PEP_{(100)}/LVET_{(100)}$ with end-diastolic volume or with stroke volume was much lower.

These results confirm those reported by Vonk and Clerens (1974), who, in addition, found an average EF of 0·67 (SEM=0·05) for a small group of 8 normal subjects.

From the results given in Table 4, the following conclusions may be drawn concerning the differentiation of the subjects in the various groups:

(A) P_2 SUBJECTS

P_2 subjects are characterised by a low value of $LVET_{(100)}$ and a high value of $PEP_{(100)}$, so that the ratio $PEP_{(100)}/LVET_{(100)}$ of the P_2 subjects is high. Indeed, all but 6 P_2 patients have a ratio higher than 0·46; all the normal subjects, both old and young, and all but 3 P_1 patients have a ratio lower than 0·46 (Fig. 5). Since the correlation within groups between $PEP_{(100)}$ and $LVET_{(100)}$ is low, both characteristics (raised $PEP_{(100)}$ and depressed $LVET_{(100)}$) have to be present for a subject to be classified as a P_2 subject.

Only 16 per cent of all normal subjects have a ratio of $PEP_{(100)}/LVET_{(100)}$ higher than 0·40; 88

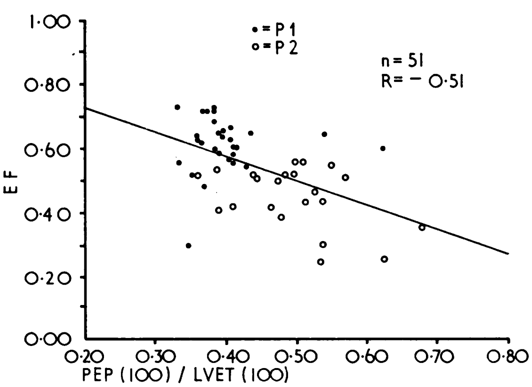

Fig. 7 *Relation between PEP/LVET at a heart rate of 100 and the ejection fraction at rest. Data points are from the 51 subjects of the P_1 and P_2 patient groups. Correlation equals $-0{\cdot}51$, and differs significantly from zero with $P<0{\cdot}0005$*

per cent of all P_2 subjects and 40 per cent of P_1 subjects exceed that value. We may conclude that a ratio over 0·46 suggests coronary insufficiency and that a ratio over 0·45 is related to ventricular dysfunction which results in a poor contraction pattern with long PEP values and a reduced ejection time. The high mean value of $PEP_{(100)}/LVET_{(100)}$ for the P_2 group coincides with a low mean ejection fraction at rest.

(B) P_1 SUBJECTS

P_1 patients are characterised by a relatively high value of $LVET_{(100)}$ and a low value of $-m_{LVET}$, so that the index $LVET_{(100)}/m_{LVET}$ is high for P_1 subjects. For all but 10 P_1 subjects the value $LVET_{(100)}/-m_{LVET}$ exceeds 280 bpm[1].

However, it is not only P_1 patients who have a high index $LVET/-m_{LVET}$, as young normal subjects also tend to have an index which is higher compared with the old normal group. We might postulate that young normal subjects compensate for a relatively short ejection time by a high outflow velocity, which is related to a short PEP and a high rate of rise of left ventricular pressure. Therefore, we may incorporate PEP as an extra value, since young normal subjects have a PEP which is significantly lower than the PEP for all other classes. This leads to an attempt to try:

$$\frac{LVET_{(100)}+PEP_{(100)}}{-m_{LVET}} = \frac{QS_{2(100)}}{-m_{LVET}}$$

for its ability to separate the groups. As can be seen in Fig. 4, the difference in QS_2 between the P_1 group and the other groups increases for increasing heart rates, which indicates an influence of the slope m_{QS2}. The difference especially in QS_2 between the old normal subjects and P_1 increases because of steeper slope m_{QS2} for $N_{>40}$.

Incorporating the influence of the slope m_{QS2} is achieved by taking the value $QS_{2(130)}$ instead of $QS_{2(100)}$. Applying linear classification theory to the data points indicates that a suppression of the zero-QS_2 point will improve the separation power. Therefore, the index

$$\frac{QS_{2(130)}-230}{-m_{LVET}}$$

is obtained as an index for separation of P_1 patients from normal subjects. Individual values of this index for all subjects are given in Fig. 5. If this index exceeds the value of 75 bpm, the subject is identified as a P_1 patient.

In order to test the reproducibility of the results, 6 subjects, 4 from the group of young normals, and 2 from the old normal group, repeated their exercise test after a time span from one week to several months. The results in terms of the individual identifying indices are given in Table 6; each subject is assigned to the same (normal) group as before. The number of repeated tests is small; a large group of both patients and normals will have to be investigated in order to determine the reproducibility of identification according to appropriate groups using the indices desired.

The intraclass correlations between the indices $PEP_{(100)}/LVET_{(100)}$ and $QS_{2(130)}-230)/-m_{LVET}$ is for all classes less than 0·41 (average: 0·31), which is sufficiently low to regard these two indices as having an independent information content. The intraclass correlation of $PEP_{(100)}/LVET_{(100)}$ and $PEP_{(130)}/LVET_{(130)}$ is more than 0·76 (average 0·81) for all classes.

This indicates that the choice of a standardised heart rate is not critical, as long as the heart rate does not differ too much from the average heart rate during the exercise test.

Conclusions

Heuristic classification rules were found for the separation of P_1 and P_2 subjects from the normal groups. We may summarise these rules as:

Rule 1: if $PEP_{(100)}/LVET_{(100)}$ exceeds the value 0·46 the subject is identified as a P_2 patient.

Table 6 *Results of repeated exercise tests*

Subject No.	*Age (y)*	*$PEP_{(100)}/LVET_{(100)}$*	*$QS_{2(130)}-230$ / $-m_{LVET}$ (bpm)*
1	37	0·306	69
		0·343	74
3	27	0·329	57
		0·355	65
8	24	0·370	59
		0·362	44
16	22	0·316	67
		0·309	50
36	48	0·382	63
		0·394	68
53	41	0·454	54
		0·400	41

Abbreviations as in Table 3.

[1]This ratio may be interpreted as the change in heart rate required for a 100 per cent change in LVET, since

$$\frac{LVET_{(100)}}{-m_{LVET}} = \frac{LVET_{(100)}}{\left(\frac{\Delta LVET}{\Delta HR}\right)} = \frac{\Delta HR}{\left(\frac{\Delta LVET}{LVET_{(100)}}\right)}$$

For a ratio of 280 bpm, this would mean, by a theoretical extrapolation of the regression line, that LVET will be zero at 100+280= 380 bpm. A high index would indicate a slow adaptation of LVET to increasing heart rates.

For all remaining subjects the second rule applies:

Rule 2: if $(QS_{2(130)}-230)/-m_{LVET}$ exceeds 75 bpm the subject is identified as a P_1 patient.

If both conditions are not fulfilled, the subject is regarded as being normal.

These classification rules are applied to all subjects and the results are given in Table 7. As is indicated, in 86 per cent of all cases a correct classification is made. If we make the simplification of combining the two patient groups and look for the classification 'normal' or 'patient' (whether P_1 or P_2), in 93 per cent a correct classification is made. In the latter case, the 'Index of Merit' equals 0·80[1].

It should be noted that a second, independent, group of patients and normals needs to be analysed in order to test the merits of the above given classification system. Though data from a much larger group than that presented here (from other clinical centres or collected after the closure of this study) is available such a detailed evaluation has yet to be done.

From Table 7 it can be seen that 19 P_2 subjects are classified correctly. If we apply rule 2 (for P_1 classification) to the P_2 subjects, 11 of those 19 subjects have the characteristics of P_1 patients, and 8 subjects are classified as 'normal'. The average ejection fractions of these two subgroups are 0·39 and 0·49, respectively. This might be an indication that there is a relation between the assignment of a subject in one or both classes and the myocardial performance: fulfilling the criteria for both P_1 and P_2 patients is worse than doing so for a P_1 or P_2 patient alone.

The results of this study indicate that exercise systolic time intervals may provide valuable information for the assessment of cardiac patients.

Table 7 *Results of classification method*

Class	*Total No.*	*Classified as*			*Fraction correct negative*
		Normal	P_1	P_2	
$N_{>40}$	33	32	1	0	0·97
$N_{<40}$	18	18	0	0	1·00
					Fraction correct positive
P_1	36	7	26	3	0·72
P_2	25	4	2	19	0·76

Abbreviations as in Table 2.

[1]The 'Index of Merit' is defined as the fraction correct negative + the fraction correct positive −1 = 0·98 + 0·82−1 = 0·80. If the classification follows a random assignment of subjects to two groups, the Index of Merit will be 0·5 + 0·5−1 = 0.

Besides the power of exercise STI to separate normals from patients, it has the ability to distinguish between patients with normal and those with abnormal ejection fractions, a distinction determined usually by means of the invasive method of left ventriculography.

References

Agress, C. M., Wegner, S., Nakakura, S., Lehman, E. H., Jr., and Chait, L. (1965). Comparison of the ejection time-heart rate relationships in normal and ischemic subjects. *Japanese Heart Journal*, **6**, 497.

Armstrong, T. G., Lewis, B. S., and Gotsman, M. S. (1973). Systolic time intervals in constrictive pericarditis and severe primary myocardial disease. *American Heart Journal*, **85**, 6.

Aronow, W. S., Bowyer, A. F., and Kaplan, M. A. (1971). External isovolumic contraction times and left ventricular ejection time/external isovolumic contraction time ratios at rest and after exercise in coronary heart disease. *Circulation*, **43**, 59.

Åstrand, P., Cuddy, T. E., Saltin, B., and Stenberg, J. (1964). Cardiac output during submaximal and maximal work. *Journal of Applied Physiology*, **19**, 268.

Beneken, J. E. W., Van der Hoeven, G. M. A., Clerens, P. J. A., and Donders, J. J. H. (1974). Systolic time intervals during uninterrupted exercise and their diagnostic significance. In *Proceedings of 6th European Congress of Cardiology, Madrid 1972*, p. 358. Editorial Paz Montalvo.

Boter, J., Den Hertog, A., and Kuiper, J. (1966). Disturbance-free skin electrodes for persons during exercise. *Medical and Biological Engineering*, **4**, 91.

Buyukozturk, K., Kimbiris, D., and Segal, B. L. (1971). Systolic time intervals. Relation to severity of coronary artery disease, intercoronary collateralisation and left ventricular dyskinesia. *American Journal of Cardiology*, **28**, 183.

Clerens, P. J. A., Vonk, J. T. C., Van der Hoeven, G. M. A., and Beneken, J. E. W. (1973). Systolic time intervals at rest and during exercise—a measure of cardiac function? *Netherlands Journal of Medicine*, **16**, 79.

DeMonchy, C., Van der Hoeven, G. M. A., and Beneken, J. E. W. (1973). Studies on innocent praecordial vibratory murmurs in children. II. Systolic time intervals and pulse wave transmission times in children with an innocent praecordial vibratory murmur. *British Heart Journal*, **35**, 679.

Diamant, B., and Killip, T. (1970). Indirect assessment of left ventricular performance in acute myocardial infarction. *Circulation*, **42**, 579.

Fabian, J., Epstein, E. J., and Coulshed, N. (1972a). Duration of phases of left ventricular systole using indirect methods I. Normal subjects. *British Heart Journal*, **34**, 874.

Fabian, J., Epstein, E. J., Coulshed, N., and McKendrick, C. S. (1972b). Duration of phases of left ventricular systole, using indirect methods. II. Acute myocardial infarction. *British Heart Journal*, **34**, 882.

Hamosh, P., Cohn, J. N., Engelman, K., Broder, M. I., and Fries, E. D. (1972). Systolic time intervals and left ventricular function in acute myocardial infarction. *Circulation*, **45**, 375.

Harris, W. S. (1974). Systolic time intervals in the non-invasive assessment of left ventricular performance in man. In *Cardiac Mechanics*, p. 233. Ed. by I. Mirsky, D. N. Ghista, and H. Sandler. John Wiley, New York.

Heikkilä, J., Luomanmäki, K., and Pyörälä, K. (1971). Serial observations on left ventricular dysfunction in acute myocardial infarction. II. Systolic time intervals in power failure. *Circulation,* **44,** 343.

Inoue, K., Young, G. M., Grierson, S. L., Smulyan, H., and Eich, R. H. (1970). Isometric contraction period of the left ventricle in acute myocardial infarction. *Circulation,* **42,** 79.

Johnson, A. D., O'Rourke, R. A., Karlinger, J. S., and Burian, C. (1972). Effect on myocardial revascularisation on systolic time intervals in patients with left ventricular dysfunction. *Circulation,* **45** and **46,** Suppl. I, 91.

Kesteloot, H., Willems, I., and Joossens, J. V. (1968). A study of some determinants of the QA_2 and Q upstroke interval. In *Proceedings of the 5th European Congress of Cardiology, Athens,* p. 305. Hellenis Society of Cardiology.

McConahay, D. R. (1972). Resting and exercise systolic time intervals. *Circulation,* **46,** 633.

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

McDonald, I. G., and Hobson, E. R. (1974). A comparison of the relative value of non-invasive techniques—echocardiography, systolic time intervals, and apexcardiography, in the diagnosis of primary myocardial disease. *American Heart Journal,* **88,** 454.

Maass, H., and Weber, A. (1952). Herzschallregistrierung mittels differenzierender Filter. Eine Studie zur Herzschallnormung. *Cardiologia,* **21,** 773.

Maher, J. T., Beller, G. A., Ransil, B. J., and Hartley, L. H. (1974). Systolic time intervals during submaximal and maximal exercise in man. *American Heart Journal,* **87,** 334.

Meng, R., Hollander, C., Liebsen, R., Teran, J., Barresi, V., and Lurie, M. (1975). The use of non-invasive methods in the evaluation of left ventricular performance in coronary artery disease. *American Heart Journal,* **90,** 134.

Pigott, V. M., Spodick, D. H., Rectra, E. H., and Khan, A. H. (1971). Cardiocirculatory responses to exercise: physiologic study by noninvasive techniques. *American Heart Journal,* **82,** 632.

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

Samson, R. (1970). Changes in systolic time intervals in acute myocardial infarction. *British Heart Journal,* **32,** 839.

Sandler, H., and Dodge, H. T. (1968). The use of single plane angiocardiograms for the calculation of left ventricular volume in man. *American Heart Journal,* **75,** 325.

Schoenfeld, C. D., Robinson, J. L., Weissler, A. M., and Warren, J. V. (1967). The left ventricular systolic time intervals in myocardial infarction. *Circulation Research,* **15,** 411.

Shaver, J. A., Kroetz, F. W., Leonard, J. J., and Paley, H. W. (1968). The effect of steady-state increases in systemic arterial pressure on the duration of left ventricular ejection time. *Journal of Clinical Investigation,* **47,** 217.

Strandell, T. (1964). Mechanical systole at rest, during and after exercise in supine and sitting position in young and old men. *Acta Physiologica Scandinavica,* **61,** 279.

Sultan Ahmed, S., Levinson, G. E., Schwartz, C. J., and Ettinger, P. O. (1972). Systolic time intervals, as measures of the contractile state of the left ventricular myocardium in man. *Circulation,* **46,** 559.

Toutouzas, P., Gupta, D., Samson, R., and Shillingford, J. (1969). Q-second sound interval in acute myocardial infarction. *British Heart Journal,* **31,** 462.

Van der Hoeven, G. M. A., and Beneken, J. E. W. (1970). A reliable transducer for the recording of the arterial pulse wave. *Progress Report* **2,** *Institute of Medical Physics TNO, Utrecht, The Netherlands,* p. 19.

Van der Hoeven, G. M. A., Beneken, J. E. W., and Clerens, P. J. A. (1973). A new atraumatic technique of recording systolic time intervals at rest and during exercise. *Netherlands Journal of Medicine,* **16,** 70.

Vonk, J. Th. Ch., and Clerens, P. J. A. (1974). Systolische tijdsintervallen. *Hartbulletin,* **5,** 111.

Vonk, J. Th. Ch., Pluym, B. F. M., and Geraedts, E. P. W. (1971). Some subjective and objective results of bypass surgery in coronary artery disease. *Folia Medica Neerlandica,* **14,** 263.

Wayne, H. H. (1968). Serial apexcardiograms, phonocardiograms and carotid tracings in myocardial infarction. *Circulation,* **38,** Suppl. IV, 203.

Wayne, H. H. (1973). *Non-invasive Technics in Cardiology.* Year Book Medical Publishers, Chicago.

Weissler, A. M. (1972). Resting and exercise systolic time intervals. *Circulation,* **46,** 633.

Weissler, A. M., Harris, W. S., and Schoenfeld, C. D. (1969). Bedside technics for the evaluation of ventricular function in man. *American Journal of Cardiology,* **23,** 577.

Weissler, A. M., Lewis, R. P., and Leighton, R. F. (1972). The systolic time intervals as a measure of left ventricular performance in man. In *Progress in Cardiology,* p. 155. Ed. by Paul N. Yu and John F. Goodwin. Lea & Febiger, Philadelphia.

Whitsett, T. L., and Naughton, J. (1971). The effect of exercise on systolic time intervals in sedentary and active individuals and rehabilitated patients with heart disease. *American Journal of Cardiology,* **27,** 352.

Willems, J. L., Roelandt, J., DeGeest, H., Kesteloot, H., and Joossens, J. V. (1970), The left ventricular ejection time in elderly subjects. *Circulation,* **42,** 37.

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