Value of systolic and diastolic time intervals *Studies in normotensive and hypertensive 50-year-old men and in patients after myocardial infarction*

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SUMMARY Systolic and diastolic time intervals were studied non-invasively in a group of untreated hypertensives ($n = 19$) and a reference group ($n = 36$), all derived from a random population sample of 50-year-old men, and in a myocardial infarct group ($n = 67$) representative of men aged 48 to 57 years surviving infarction. The results showed that only the electromechanical interval, pressure rise velocity, and the interval between the aortic component of the second heart sound (A_2) and the O-point in the apex cardiogram were useful discriminants between the three groups. There were no significant differences in systolic time intervals between the groups and the systolic time intervals were of limited diagnostic value as signs of impaired left ventricular function.

The infarct patients had a significantly longer electromechanical interval (34 ms) than individuals in the reference group (27 ms), indicating delayed start of the systolic contraction in the infarction group. The pre-ejection period predicted the isovolumetric contraction time with great uncertainty in the infarct group.

Increased pressure rise velocity (resting diastolic blood pressure/isovolumetric contraction time ≥ 1200 mmHg/s) was seen in 38 per cent of the infarct patients and 67 per cent of the hypertensives, compared with 4 per cent in the reference group, indicating more powerful contraction in infarct patients and hypertensives as compared with subjects in the reference group. The difference could not be explained by a difference in preload as judged from the a-wave in the apex cardiogram.

The A_2O interval was significantly prolonged (≥ 150 ms) in 74 per cent of the infarct patients and 56 per cent of the hypertensives, as compared with 3 per cent in the reference group, indicating prolonged relaxation or prolongation of the early filling phase of the left ventricle in hypertensives and infarct patients. This was mainly related to factors other than heart rate and blood pressure.

Non-invasively derived systolic time intervals for assessment of left ventricular function such as the left ventricular ejection time (LVET) and the pre-ejection period (PEP) have been extensively studied. PEP comprises the isovolumetric contraction time (ICT) and the interval from the beginning of depolarisation to the start of the systolic contraction, i.e. the electromechanical interval (EMI); it has been pointed out that the ICT should provide a better measure of left ventricular function than the PEP (Kumar and Spodick, 1970).

Prolongation of the PEP and shortening of the

LVET with consequent prolongation of the PEP/LVET ratio have been ascribed to impaired contractility of the left ventricle. These changes in PEP and LVET have also been found to correlate well with contractility and measures of pump function (Garrard *et al.*, 1970; Ahmed *et al.*, 1972). Despite this, many authors have doubted the value of the systolic time intervals (Hodges *et al.*, 1972; Parker and Just, 1974).

Several authors have used apex cardiography to measure the interval between the aortic component of the second heart sound (A_2) and the O-point in the apex cardiogram in order to study isovolumetric relaxation (Tavel *et al.*, 1965; Benchimol and Ellis,

1967; Kumar and Spodick, 1970). Transducers with short low frequency time constants have often been used. These transducers, however, shorten the A_2O interval and tend to smooth out differences between a prolonged and a normal A_2O interval (Johnson *et al.*, 1971; Wikstrand *et al.*, 1977).

Most of the above-mentioned studies were carried out in small selected groups of hospital patients. The aim of the present study was to investigate the value of non-invasively registered time intervals in representative groups of untreated hypertensives and postinfarction patients, and to establish the normal limits for these intervals in 50-year-old men.

Groups studied

All subjects of a random population sample of 50-year-old men in Göteborg, Sweden (Wilhelmsen *et al.*, 1972), with untreated essential hypertension were allocated to a hypertensive group ($n=35$). Essential hypertension was defined by casual blood pressure above 175 mmHg systolic or 115 mmHg diastolic on two separate occasions and a negative diagnostic examination for secondary hypertension (Wilhelmsen *et al.*, 1973).

A reference group ($n=73$) with casual blood pressure below 175 mmHg systolic and 115 mmHg diastolic was obtained from the same population by drawing a 10 per cent subsample at random. The way in which these groups were selected (Fig. 1, upper panel) has been described in detail elsewhere (Wikstrand *et al.*, 1976). The infarct group ($n=67$) consisted of men living in Göteborg, born between 1916 and 1924, who suffered a hospital verified myocardial infarction during a 12-month period (15 July 1972 to 14 July 1973) and survived for at least 3 months (Fig. 1, lower panel). The non-invasive investigations were carried out in a randomised half of the reference group ($n=36$) and of the hypertension group ($n=19$) (Fig. 1) and in all infarct patients ($n=67$).

Sahlgren's Hospital takes care of practically all patients sustaining a myocardial infarct in Göteborg. Suspected cases of myocardial infarction were recorded by the staff responsible for the Myocardial Infarction Register in Göteborg. Acute myocardial infarction was considered to have occurred when at least two of the three criteria—central chest pain, transient rise of serum aspartate transaminase, or electrocardiographic abnormalities—were fulfilled. The patients so identified have been shown to constitute at least 90 per cent of the total number of surviving myocardial infarction patients in the population of Göteborg (Elmfeldt *et al.*, 1975a). They were systematically cared for after discharge

from hospital at the Post-Myocardial Infarction Clinic by physicians trained together to achieve a standardised treatment regimen (Elmfeldt *et al.*, 1975b).

During an observation period of one year 100 acute myocardial infarcts were recorded. Before 31 December 1972, 18 patients were selected by means of a random number table to participate in another study. These patients were not followed up at the Post-Myocardial Infarction Clinic and were excluded from our study. Twelve patients died within three months of onset of infarction and two patients were excluded from the analysis, one because of mitral stenosis and one because of aortic valvular disease. One patient who had had a cerebrovascular stroke was unable to participate. The mean age for the infarct group was 53½ years (range 48 to 57). Fifty-nine patients had primary infarcts and 8 patients suffered from reinfarction. During the period of acute care in hospital 14 patients had signs of cardiogenic shock, defined as a systolic blood pressure below 100 mmHg with cold sweaty skin, or left ventricular failure, defined as basal râles over the lungs persisting after cough or evidence of congestion on a chest x-ray film. At the time of the non-invasive examination 21 patients were on digitalis therapy, 7 on β -blockers, and a further 4 on both digitalis and β -blockers. Two years after the non-invasive investigation 9 of the patients in the infarct group had died from ischaemic heart disease, verified at necropsy in all cases.

Methods

Conventional electrocardiograms, carotid pulse tracings, apex cardiograms, phonocardiograms, and resting blood pressures were all recorded on a direct writing ink-jet 7-channel mingograph (EM 81, Siemens-Elema AB, Sweden) with a linear frequency response from 0 to 500 Hz and 30 per cent amplitude reduction at 650 Hz. The phonocardiograms were recorded using a phonopreamplifier (EMT 22) with electrical filters that together with a piezoelectric microphone (EMT 25 C) gave six frequency ranges including one aural frequency range. The pulse tracings and apex cardiograms were obtained using crystal transducers (EMT 510 C) with low frequency time constants between 1.9 and 4.6 s (depending on a capacitance-resistance product, decided by the individual amplification used for each curve) and connected by a 25 to 40 cm rubber tube to a specially designed capillary-damped funnel pick-up, 2.5 cm in diameter, giving a frequency response of at least 0.08 (at low frequency time constant 1.9 s) to 65 Hz (−3dB) (Wikstrand *et al.*, 1977). The paper speed

Fig. 1 Groups studied. Upper panel: schematic representation of the selection of the hypertensive and reference groups. Lower panel: schematic representation of how the infarction group was derived.

Systolic and diastolic time intervals

was 50 mm/s for the electrocardiogram and for the other tracings 100 mm/s.

Blood pressure was measured with a 12 cm broad and 26 cm long rubber cuff. Cuff inflation was rapid, cuff deflation approximately 3 beats/10 mmHg. Diastolic pressure was recorded as phase 5, i.e. when the sounds disappeared. *Casual* blood pressure at the screening examination was measured in the seated position with a mercury manometer and stethoscope. *Resting* blood pressure was measured after one hour's rest, during which the non-invasive tracings were recorded, in the supine position in a sound-protected room with an automatic device for cuff inflation and deflation (Boucke-Brecht), with a microphone (EMT 25 C) placed over the right brachial artery and with simultaneous recording of cuff pressure, Korotkoff sounds, and electrocardiogram. Resting blood pressure was, for technical reasons, lacking for 4 subjects in the reference group. Resting heart rate was measured from the resting blood pressure recordings.

Simultaneous recordings of electrocardiogram lead II, a phonocardiogram from the third left intercostal space parasternally, a carotid pulse tracing or apex cardiogram were recorded during the resting period preceding the measurement of resting blood pressure. The carotid pulse tracing was recorded in the supine position and the apex cardiogram in the left lateral position, both during relaxed expiratory apnoea.

Simultaneous recordings of the carotid pulse tracing, apex cardiogram, electrocardiogram lead II, and the phonocardiogram in the left lateral position were carried out in a randomised half of the reference group and in 56 infarct patients in order to perform regression analysis with ICT and heart rate, and ICT/LVET and heart rate. Except for the purpose of this correlation analysis, all data were obtained from recordings made separately.

All channels were corrected for coincidence, the deviations being calculated as the mean value of the difference in upstroke in 4 consecutive mV tests induced simultaneously in the 7 channels. Correction was also made for the time delay (4 ms) in the recording system (Wikstrand *et al.*, 1977). Definitions of the measurement points on the electrocardiogram, phonocardiogram, carotid pulse tracing, and apex cardiogram have been presented in detail elsewhere (Wikstrand, thesis 1976, available on request). The measurement points were determined in relation to 4 arbitrary reference lines (Fig. 2) and plotted on a stencil, the time interval being determined by addition of the various component intervals before, between, and after the reference lines which made up each individual time

interval. This procedure was used in order to simplify the extensive calculations and to avoid bias by the observer when calculating consecutive beats. In each curve the time was obtained in ms by means of a simultaneously recorded stable time signal with one impulse/s calibrated with the aid of a time generator (Type 1192-B/Z, General Radio Company, USA). This time signal was used because the paper speed was not constant, probably because of fluctuations in the electricity supply to the equipment.

The time intervals studied (Fig. 2, lower panel) were as follows: (1) Total electromechanical systole from the beginning of the QRS complex to the beginning of the aortic component of the second heart sound (QA_2). In 2 infarct patients A_2 could not be identified with certainty. (2) The electromechanical interval from the beginning of the QRS complex to the systolic upstroke of the apex cardiogram (EMI).¹ In 4 subjects (11%) in the reference group, 1 hypertensive subject (5%), and 1 patient in the infarct group (1.5%) an acceptable apex cardiogram could not be recorded, and in another 2 subjects in the reference group and 1 in the infarct group the upstroke of the apex cardiogram could not be identified with certainty. (3) The left ventricular ejection time from the beginning of the systolic upstroke of the carotid pulse tracing to the incisura (LVET). The LVET was also expressed as a percentage of the expected value for the given heart rate calculated from the regression equation between LVET and heart rate in the reference group (LVET%). (4) The pre-ejection period ($PEP = QA_2 - LVET$). (5) The isovolumetric contraction time ($ICT = PEP - EMI$). (6) The $PEP/LVET$ ratio. (7) The $ICT/LVET$ ratio. (8) The interval between A_2 and the point on the downstroke of the apex cardiogram at which the curve fell to 10 per cent of the total height of the curve ($A_2 - 90\%$ amplitude reduction). (9) The interval between the aortic component of the second sound and the O-point of the apex cardiogram (A_2O). In 3 subjects in the reference group the O-point could not be identified with certainty.

In left bundle-branch block or $QRS \geq 0.12$ s (not caused by right bundle-branch block; Minnesota Code 7:1 or 7:4) in 1 hypertensive individual and 6 infarct patients the values for QA_2 and EMI were not included in the distribution or mean values since these conduction defects cause delayed activation of the left ventricle (Baragan *et al.*, 1968). The

¹No significant difference was found between values of mean EMI calculated from recordings made separately and simultaneously. Measurements of EMI made by two independent observers from recordings obtained one hour apart agreed closely (correlation coefficient 0.91, $n=86$).

Fig. 2 Simultaneous recording of the apex cardiogram, carotid pulse tracing, phonocardiogram, and electrocardiogram in one of the infarct patients. Upper panel: paper speed 100 mm/s. Lower panel: time intervals are, for practical reasons, marked on this recording at a paper speed of 250 mm/s. Four reference lines (marked in lower panel) were used when the time intervals were measured (see Methods). The a-wave (a) and the total height (H) of the apex cardiogram are also marked in the lower panel (abbreviations, see Methods).

values have, however, been used for calculation of ICT ($ICT = QA_2 - EMI - LVET$).

The a-wave (a) percentage amplitude of the total deflection of the apex cardiogram (H) was calculated.

Time intervals and the a/H ratio were calculated as the mean of measurements from 5 consecutive beats.

An a/H ratio above 15 per cent was considered abnormal (Voigt and Friesinger, 1970; Wikstrand *et al.*, 1976). Limits for abnormal time intervals were arbitrarily set at the second highest or lowest value in the reference group, depending on whether a high or low value of the variable concerned was of pathological significance. If the two highest (or lowest) values in the reference group were identical, the limit was set at the highest (or lowest) value. On this basis pathological values were defined as: $EMI \geq 40$ ms, $PEP \geq 130$ ms, $ICT \geq 100$ ms, $LVET \leq 90$ per cent, $ICT/LVET > 0.35$, $PEP/LVET > 0.45$, A_2 to 90 per cent amplitude reduction ≥ 105 ms, and $A_2O \geq 150$ ms. The diastolic resting blood pressure was divided by the ICT and in a corresponding manner a diastolic blood pressure/ICT ≤ 775 mmHg/s was defined as pathologically low. The limit for elevation of this variable was set at 1200 mmHg/s.

Analysis of each variable was performed without knowledge of the results of the other examinations or to which group the subject belonged.

Standard methods were used for calculation of the mean ($\bar{x}$), the standard deviation (s_x), the linear bivariate, and partial correlation coefficients (r). The hypothesis of no differences in means was tested with the Wilcoxon Rank Sum Test for two samples. The hypothesis of no differences in proportions between two groups was tested with Fisher's exact test. The hypothesis of no differences in proportions when examining one group of subjects with two separate methods was tested with McNemar's test for correlated proportions (Remington and Schork 1970). Only two-tailed tests were used and differences were considered significant for P values of 0.05 or less.

Results

RESTING BLOOD PRESSURE

The resting blood pressure in the hypertensive group ($\bar{x} = 154/96$ mmHg) was higher ($P < 0.01$) than in the reference group ($\bar{x} = 123/77$ mmHg) and in the infarct group ($\bar{x} = 124/81$ mmHg).

ELECTROMECHANICAL INTERVAL (EMI)

EMI was longer ($P < 0.01$) in the infarct group ($\bar{x} = 34$ ms) than in the reference group ($\bar{x} = 27$ ms), Table 1, and the proportion of patients in the infarct group with $EMI \geq 40$ ms (25%) was also

greater ($P < 0.05$) than in the reference group, 3 per cent (Fig. 3). The individual in the reference group who had EMI above 40 ms had a pathological a-wave ($a/H = 33\%$) and angina pectoris with pathological ST and T changes on the electrocardiogram.

ISOVOLUMETRIC CONTRACTION TIME (ICT) AND PRE-EJECTION PERIOD (PEP)

There were no significant differences in means between the groups with respect to ICT or PEP (Table 1).

ICT was negatively correlated to heart rate in the infarct group but not in the reference group. PEP was negatively correlated to heart rate in the hypertensive group but not in the reference or infarct groups. Trivariate regression analysis with resting diastolic blood pressure, ICT, and heart rate gave no significant correlation between diastolic blood pressure and ICT.

A linear correlation analysis between ICT and PEP gave $r = 0.92$ in the reference group, $r = 0.73$ in the infarct group, and $r = 0.84$ in the hypertensive group.

LEFT VENTRICULAR EJECTION TIME (LVET)

LVET was negatively correlated to heart rate. The equation for the regression line in the reference group was $LVET = 390 - 1.51 \times \text{heart rate}$.

Fig. 3 Distribution of the electromechanical interval (EMI), and the proportion of subjects with $EMI \geq 40$ ms, the means ($\bar{x}$), and the standard deviations (s_x) in the 3 groups.

There was no difference in the mean value for LVET between the three groups.

Trivariate regression analysis with resting systolic blood pressure, LVET, and heart rate gave no significant correlation between systolic blood pressure and LVET.

COMBINATION OF SYSTOLIC TIME INTERVALS
Altogether 10 per cent of the patients in the infarct group and 11 per cent of the hypertensives had values of ICT ≥ 100 ms or LVET ≤ 90 per cent which are not significantly higher than in the reference group, 3 per cent (Table 2). The dis-

Table 1 Time intervals, resting blood pressure, and heart rate in 3 groups

Measurement		Reference group	Hypertensive group	Infarct group
QA _s (ms)	n	36	18	61
	$\bar{x}$	397	397	410
	s _x	23 (17)	28 (17)	30 (17)
	r	-0.68 (P < 0.001)	-0.82 (P < 0.001)	-0.82 (P < 0.001)
HR	$\bar{x}$	64	64	61
	n	30	17	59
	$\bar{x}$	27	31	34
	s _x	5.5	8.2	11
EMI (ms)	r	0.40 (P < 0.05)	0.08 (NS)	0.33 (P < 0.05)
	$\bar{x}$	61	64	60
PEP (ms)	n	36	18	61
	$\bar{x}$	104	104	107
	s _x	13	13 (12)	13
	r	0.00 (NS)	-0.52 (P < 0.05)	-0.01 (NS)
HR	$\bar{x}$	64	64	61
ICT (ms)	n	30	18	63
	$\bar{x}$	77	74	73
	s _x	14	15	17 (16)
	r	-0.14 (n = 16, NS)	-0.50 (n = 18, P < 0.05)	-0.39 (n = 56, P < 0.01)
HR	$\bar{x}$	62	64	61
LVET (ms)	n	36	19	67
	$\bar{x}$	293	293	300
	s _x	19 (12)	21 (14)	30 (17)
	r	-0.79 (P < 0.001)	-0.76 (P < 0.001)	-0.82 (P < 0.001)
HR	$\bar{x}$	64	64	62
ICT/LVET	n	30	18	63
	$\bar{x}$	0.263	0.253	0.243
	s _x	0.056	0.049	0.061
	r	0.24 (n = 16, NS)	-0.16 (n = 18, NS)	-0.06 (n = 56, NS)
HR	$\bar{x}$	62	64	61
PEP/LVET (ms)	n	36	18	61
	$\bar{x}$	0.355	0.357	0.356
	s _x	0.052 (0.050)	0.046	0.061 (0.052)
	r	0.35 (P < 0.05)	-0.10 (NS)	0.53 (P < 0.001)
HR	$\bar{x}$	64	64	61
A _s O (ms)	n	29	18	65
	$\bar{x}$	133	153	160
	s _x	9.0	24 (22)	21 (17)
	r	0.09	-0.46 (P < 0.05)	-0.43 (P < 0.001)
HR	$\bar{x}$	61	65	61
Resting SBP (mmHg)	n	32	19	67
	$\bar{x}$	123	154	124
	s _x	13	23	17
	$\bar{x}$	77	96	81
Resting DBP (mmHg)	s _x	10	15	10
	$\bar{x}$	60	61	61
	s _x	8	8	12
	$\bar{x}$			

The correlation coefficients (r) between the different time intervals and heart rate are given together with the standard deviation around the regression line (in brackets after the s_x). For correlation analysis between ICT and ICT/LVET, respectively, and heart rate the heart rate in the hypertension group was taken from the carotid pulse tracing (abbreviations: see Methods).

crimination was not improved if the variable ICT/LVET was added and no patient with normal values for ICT, LVET, or ICT/LVET had an abnormal PEP/LVET value. There were no significant differences in means between the groups with respect of ICT/LVET or PEP/LVET (Table 1).

PRESSURE RISE VELOCITY AND A/H RATIO

Fig. 4 shows on the horizontal axis the a/H ratio from the apex cardiogram and on the vertical axis the pressure rise velocity in the left ventricle calculated by dividing the diastolic blood pressure at

Table 2 Proportion of subjects with isovolumetric contraction time $ICT \geq 100$ ms, left ventricular ejection time $LVET \leq 90$ per cent, and $ICT/LVET > 0.35$ in the 3 groups

	Reference group		Hypertensive group		Infarct group	
	n	%	n	%	n	%
$ICT \geq 100$ ms	1/30	3	1/18	6	4/63	6
$LVET \leq 90\%$	0/36	0	1/19	5	4/67	6
$ICT/LVET > 0.35$	1/30	3	1/18	6	2/63	3
Cumulative total	1/36	3	2/19	11	7/67	10

Fig. 4 Distribution of resting diastolic blood pressure/isovolumetric contraction time (DBP/ICT) and a/H ratio from the apex cardiogram and the relation between these variables in the 3 groups. Left: Reference group ($n=36$), $a/H > 15\%$ = $2/32=6\%$. $DBP/ICT \leq 775$ mmHg/s = $1/26=4\%$; ≥ 1200 mmHg/s = $1/26=4\%$. Middle: Hypertension group ($n=19$), $a/H > 15\%$ = $7/18=39\%$. DBP/ICT , —, ≥ 1200 mmHg/s = $12/18=67\%$. Right: Infarction group ($n=67$), $a/H > 15\%$ = $29/66=44\%$. $DBP/ICT \leq 775$ mmHg/s = $4/63=6\%$, ≥ 1200 mmHg/s = $24/63=38\%$. Note that only one infarcted patient had both $DBP/ICT < 775$ mmHg/s and a/H ratio > 15 per cent concomitantly, and that the a/H ratio discriminates better between the reference and infarct group than does a shortened DBP/ICT.

rest by the ICT. An abnormal a/H ratio was found in 39 per cent in the hypertensives and 44 per cent in the infarct group, which was more ($P < 0.05$, $P < 0.01$, respectively) than in the reference group (6%).

Only 4 infarct patients (6%) had pressure rise velocities below 775 mmHg/s. Only one patient had an abnormal a/H ratio simultaneously with a pressure rise velocity below 775 mmHg/s.

The mean pressure rise velocity was higher ($P < 0.01$) in the hypertensive group ($\bar{x}=1323$ mmHg/s) than in the reference group ($\bar{x}=1044$ mmHg/s). In the infarct group the mean value was 1168 mmHg/s. Sixty-seven per cent of the men in the hypertensive group and 38 per cent of the infarct patients had pressure rise velocities ≥ 1200 mmHg/s, which was more ($P < 0.01$) than in the reference group (4%). When infarct patients who were taking digitalis or β -blockers were excluded from this analysis 34 patients remained. Thirty-two per cent of these patients showed values of pressure rise velocity above 1200 mmHg/s, which was still more ($P < 0.02$) than in the reference group. The a/H ratio for these patients was 13.5 per cent, which

Fig. 5 Distribution of the interval between the aortic component of the second heart sound and the O-point in the apex cardiogram (A_2O), and the proportion of subjects with $A_2O \geq 150$ ms, the means ($\bar{x}$), and the standard deviation (s_x) in the 3 groups.

was not significantly higher than for infarct patients who were not receiving digitalis or β -blockers ($\bar{x}=10.9\%$) and who had pressure rise velocities <1200 mmHg/s.

A₂O INTERVAL

The A₂O interval was longer ($P<0.01$) in both the hypertensive group ($\bar{x}=153$ ms) and the infarct group ($\bar{x}=160$ ms) than in the reference group ($\bar{x}=133$ ms). The proportion of patients with A₂O interval ≥ 150 ms was also higher ($P<0.01$) in the hypertensive group (56%) and the infarct group (74%) than in the reference group, 3 per cent (Fig. 5). The man in the reference group with a prolonged A₂O interval had the highest diastolic pressure in the reference group at the screening examination (110 mmHg), but the pressure was normal (89 mmHg) when the apex cardiogram was registered. Eighty-eight per cent of all subjects in the hypertensive and infarct groups with prolonged A₂O interval also had prolongation of the interval between A₂ and 90 per cent amplitude reduction of the apex cardiogram.

The A₂O interval was negatively correlated to heart rate in the infarct group ($r=-0.43$, $n=65$, $P<0.01$) and in the hypertensive group ($r=-0.46$, $n=18$, $P<0.05$) but not in the reference group ($r=0.09$). Trivariate regression analysis with resting systolic blood pressure, A₂O, and heart rate gave a significant positive correlation between resting systolic blood pressure and A₂O in the hypertensive group, $r=0.56$ ($P<0.05$) but not in the reference or infarct groups. The corresponding analysis for diastolic resting blood pressure gave a significant correlation in the infarct group, $r=0.27$ ($P<0.05$) but not in the hypertensive or reference groups.

TIME INTERVALS IN PATIENTS WITH AND WITHOUT DIGITALIS THERAPY

The mean value for LVET per cent was lower ($P<0.01$) in patients receiving digitalis ($\bar{x}=98\%$, $s_x=5.7$, $n=21$) than in the infarct patients not on digitalis ($\bar{x}=103\%$, $s_x=6.2$, $n=35$), but there were no significant differences in means with respect to ICT, PEP, ICT/LVET, the A₂O interval, resting blood pressure, or heart rate.

PROGNOSIS IN INFARCT GROUP IN RELATION TO SYSTOLIC TIME INTERVALS

Of the 14 patients in the infarct group who exhibited cardiogenic shock or left ventricular failure during the acute illness, 3 (21%) had pathological systolic time intervals 3 months after onset of infarction. Of the 67 infarct patients, 9 (13%) died within 2 years after the non-invasive examination and 3 of these (33%) had had pathological systolic

time intervals at the non-invasive investigation (LVET=90%, and ICT=101 ms and 102 ms, respectively).

Discussion

When cardiac function has been studied more precisely in hypertensives or infarct patients this has previously been done in small selected groups of hospital patients, the control groups also necessarily being small and selected. To avoid the drawbacks entailed by selection the groups in the present study comprised random population samples. This definition of the groups studied makes it possible to generalise about the results. The results showed that only the electromechanical interval, pressure rise velocity, and A₂O point interval were useful discriminants between the three groups. It is clear that invasive assessment of left ventricular function would have yielded interesting data for correlation with the non-invasive data. Catheterisation and angiocardigraphy were, however, not performed, as it was not considered ethically justifiable to perform these invasive investigations in the symptomless subjects in the reference and hypertensive groups derived by screening, or in several of the infarct patients. Several studies of the correlation between non-invasive variables and invasive indices of left ventricular function have been carried out by other authors in selected groups of subjects (Voigt and Friesinger, 1970; Martin *et al.*, 1971; Van de Werf *et al.*, 1975).

Comparison of the mean values for systolic time intervals in the infarct and hypertensive groups with those in the reference group showed that the pattern was not that which could be expected when left ventricular function was impaired. The prognostic value was difficult to assess since the number of infarct patients who died during follow-up was low and very few infarct patients had divergent systolic time intervals. The prognostic value of the combined non-invasive data is discussed elsewhere, the systolic time intervals having been found in several cases to be quite normal despite the fact that other non-invasive data suggested considerable impairment of left ventricular function (Wikstrand, 1976). Furthermore, 3 of the 4 infarct patients with low LVET were taking digitalis. Digitalis shortens LVET even in patients with heart failure (Weissler and Schoenfeld, 1970) and the significance of a shortened LVET is thus difficult to assess in a patient taking digitalis.

A quarter of the patients in the infarct group had prolonged EMI values, indicating delayed start of the systolic contraction of the left ventricle (Willems *et al.*, 1971; Manolas *et al.*, 1975). An

individual with apparently normal impulse conduction on the electrocardiogram may thus have a prolonged PEP, owing to prolongation of the EMI, which may be erroneously interpreted as indicating a prolonged isovolumetric contraction time. Correlation analysis also showed that a PEP value predicted an ICT value with great uncertainty in the infarct group. These factors and our results make it unlikely that PEP will be a sensitive index of impaired left ventricular function. This is not to be wondered at since even complicated and sophisticated *invasive* isovolumetric indices of left ventricular function have proved to be of doubtful value (Peterson *et al.*, 1974; Kreulen *et al.*, 1975).

It has been found that the diagnostic value of the PEP increases when it is combined with invasively measured pulmonary capillary venous pressure and non-invasively measured diastolic arterial blood pressure for calculation of the pressure rise velocity in the left ventricle (Agress *et al.*, 1972; Diamond *et al.*, 1972). Combination of ICT and resting diastolic arterial blood pressure did not improve discrimination in our study as regards impaired left ventricular function. Correction for the end-diastolic pressure in the left ventricle could not be done, however, as invasive measurements were not performed. One of the reasons why Fig. 4 was constructed was to obtain an indirect measure of preload, the a/H ratio, in relation to pressure rise velocity. Only one infarct patient, however, had an abnormal a/H ratio and a reduced pressure rise velocity concomitantly, which should be a combination indicative of substantially impaired left ventricular function. On the contrary the results regarding pressure rise velocity may be interpreted as showing that ventricular contraction was more powerful in several infarct patients compared with the individuals in the reference group. This finding could not be explained by digitalis therapy. Nor could it be explained by differences in the end-diastolic pressure, as judged from the a/H ratio from the apex cardiogram. Reservation must, however, be made for the fact that patients with greatly increased end-diastolic pressure may have a normal a-wave in the apex cardiogram (Voigt and Friesinger, 1970). Infarct patients exhibit signs of increased sympathetic activity in the acute phase, which can be reduced by β -blockade (Waagstein *et al.*, 1974). Our data regarding pressure rise velocity suggest that the sympathetic activity may be raised in these patients at rest even long after the acute phase. The results showed that the pressure rise velocity during the isovolumetric contraction was also higher in hypertensives than in normotensive individuals. This was at least partly related to left ventricular hypertrophy as judged by

orthogonal electrocardiogram (Wikstrand, 1976).

It has been claimed that arterial pressure must be included as a prime determinant of LVET along with stroke volume, heart rate, and inotropic state in man (Shaver *et al.*, 1968). Our results accord, however, with the findings of Weissler *et al.* (1969), that among patients with chronic arterial hypertension and minimal functional impairment no independent effect of arterial pressure on the systolic time intervals or PEP/LVET ratio can be shown. Braunwald *et al.* (1958) have also shown that when heart rate and stroke volume were maintained constant, increasing aortic pressure did not affect the duration of ejection except at very high mean aortic pressure (175 to 200 mmHg). Cardiac output was not measured in our study. At this stage of hypertension cardiac output is, however, known to be raised or normal (Lund-Johansen, 1967). Since the mean values for LVET were identical in the hypertensive and reference groups, and the pulse pressure was higher in the hypertensive group the figures imply increased rate of ejection in the hypertensive group.

The results regarding the systolic time intervals give the impression that the hypertensive group as well as the infarct group were homogeneous. It is, however, obvious from other non-invasive results in these groups that the nature as well as the severity of heart involvement varies considerably within the groups (Berglund *et al.*, 1976; Wikstrand, 1976; Wikstrand *et al.*, 1976) though the systolic time intervals failed to show this. Signs of systolic left ventricular functional impairment appear at a late stage since the altered filling pattern during diastole, with powerful atrial contractions and increased diastolic filling and hypertrophy of the left ventricle, may for a long time compensate for the impaired left ventricular function, at least during rest (Rackley *et al.*, 1970; Dodge, 1973). When impairment of the left ventricular function is studied at an early stage interest should, therefore, be concentrated mainly on diastole. Several methods are required to identify the majority of patients with left ventricular dysfunction and the systolic time intervals are only a small part of the whole picture. This is also evident from the other non-invasive results in the infarct group (Wikstrand, 1976) and from the fact that the a/H ratio discriminated well between the groups, unlike a decreased pressure rise velocity (Fig. 4).

The A_2O interval was significantly prolonged in more than 50 per cent of the hypertensives and more than 70 per cent of the patients in the infarct group. The finding that not only the A_2O interval but also the interval between A_2 and a point on the diastolic downstroke of the apex cardiogram defined

by the total amplitude of the apex cardiogram discriminates well between the groups, supports the postulate that this phase of the cardiac cycle really was prolonged. One of the reasons why such a striking finding has been so little studied may be the use of transducers with too short low frequency time constants in many previous studies, since transducers with short low frequency time constants not only shorten the A_2O interval but also tend to smooth out differences between an individual with a prolonged, and a person with a normal, A_2O interval (Wikstrand *et al.*, 1977).

The prolongation of the A_2O interval in the infarct group could not be explained by differences in heart rate or arterial blood pressure since the mean values for heart rate and blood pressure were almost identical with those in the reference group. It is difficult to suggest, on the basis of the findings in this study, any form of correction procedure for the A_2O interval for heart rate and blood pressure for routine clinical use, since no significant correlations were found in the reference group and the correlations found in the infarct and hypertensive groups were weak. Nor is it possible to determine the extent to which the weak correlations found between A_2O and arterial blood pressure in the hypertensive group were the result of morphological changes owing to hypertension and not the result of the actual blood pressure level. Prolongation of the A_2O interval could not be related to hypertension in the infarct group (Wikstrand, 1976). It has been shown that the A_2O interval is prolonged by infusion of ouabain (Benchimol and Ellis, 1967). The A_2O difference does not seem to have been influenced by digitalis therapy in our study however.

Previously the A_2O interval has often been used as a synonym for the isovolumetric relaxation time (Benchimol and Ellis, 1967; Harmjan *et al.*, 1971). The A_2O interval, however, comprises two phases, the relaxation phase and a period of the early filling phase of the left ventricle. Since the mean value for this filling phase has been calculated to be 50 ms (Prewitt *et al.*, 1975), the latter may in certain cases represent about one-third of the A_2O interval.

The parallel-coupled elastic elements may, if rigid, owing to reduced elasticity because of, for example, collagen deposits or hypertrophy, recover more slowly, thus prolonging the relaxation period (Harrison *et al.*, 1964). In addition, relaxation is an energy-demanding process (Langer, 1968; Meerson and Kapelko, 1975). If in ischaemia the supply and demand of calcium or ATP are barely balanced during the systolic contraction, a relative deficiency of ATP, with delayed inactivation of calcium might

arise, leading to delayed relaxation (Fogelman *et al.*, 1972; Kovick *et al.*, 1975). It has also been found that the contraction phase and the relaxation phase can be influenced partly independently of one another (Parmley and Sonnenblick, 1969; Cohn *et al.*, 1972; Meerson and Kapelko, 1975). The findings in our study in both the hypertensive and the infarct groups of increased pressure rise velocity, and delayed O point in the apex cardiogram concomitantly thus do not seem contradictory. Further studies are required to elucidate the reasons for the prolongation of the A_2O interval in hypertensives and in postinfarction patients.

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