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Apex cardiogram and systolic time intervals in acute myocardial infarction and effects of practolol

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Systolic time intervals and the ratio of the height of the a wave on the apexcardiogram to the total height of the apexcardiographic deflection (a/H) derived from simultaneous electrocardiogram, phonocardiogram, carotid pulse tracing, and apex cardiogram were recorded in 20 patients with uncomplicated acute myocardial infarction and 6 patients with chest pain without acute myocardial infarction over a period of 5 days. Fifteen normal subjects were investigated on one occasion.

The pre-ejection period and the isometric contraction time were shortened during the first 2 days of acute myocardial infarction with a stepwise prolongation during the following days to values seen in the normal subjects. The a/H ratio was constantly raised in the patients with acute myocardial infarction compared to controls with chest pain and normal subjects. The left ventricular ejection time index corrected for heart rates in msec (LVETI and relative left ventricular ejection time in per cent (rel. LVET)) of patients with and without acute myocardial infarction decreased during the 5 days of observation.

Fourteen patients with acute myocardial infarction and recurrent chest pain and two patients with status anginosus were studied before and 30 minutes after intravenous injection of the cardioselective beta-adrenergic blocking agent practolol (average 18·2 mg). An almost immediate and pronounced relief of pain was observed in all patients and no signs of impaired left ventricular function appeared. The product of systolic blood pressure and heart rate was much decreased by the practolol injection. Pre-ejection period and isometric contraction time increased to normal values and no changes were seen in LVETI and a/H ratio.

It is suggested that an inappropriate sympathetic stimulation is an important factor in provoking recurrent pain in acute myocardial infarction. Cardioselective beta-adrenergic blockade resulted in relief of pain because of reduction of heart work in these patients and it might decrease the severity of myocardial ischaemia and limit the area of infarction.

The size of the myocardial infarction after coronary occlusion depends on a number of factors. Among these are the localization and degree of coronary artery occlusion, the extent of arteriosclerotic disease in nonoccluded collateral vessels, perfusion pressure, length of diastole, oxygen saturation of the arterial blood, heart work, and the oxygen and energy demand of the myocardium (Gorlin, 1971; Hood, 1971; Ross, 1971; Schaper, 1971).

Therapeutic measures designed to limit the area of infarction should be taken immediately after the onset of chest pain typical of acute myocardial infarction. The severity and extent of myocardial ischaemic injury may possibly be reduced by appropriate treatment given several hours after the coronary occlusion (Libby *et al.*, 1973). The introduction of beta-adrenergic blocking agents offered a mode of therapy that theoretically should diminish myocardial ischaemia by the reduction of heart work and oxygen and energy demand. Furthermore, the increased length of diastole should be beneficial for coronary flow in patients with tachycardia. Recent studies in dogs have shown that tachycardia and isoprenaline increased, and propranolol and practolol decreased, the area of experimental myocardial infarction (Maroko *et al.*, 1971; Libby *et al.*, 1973). However, the use of beta-adrenergic blocking drugs in the treatment of acute myocardial infarction is controversial, since these drugs might aggravate cardiac decompensation and precipitate cardiogenic shock (Stephen, 1966; Balcon *et al.*, 1966).

This work was performed in order to study myo-

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cardial function during the early stage of acute myocardial infarction in man with and without the effects of the cardioselective beta-adrenergic blocking agent practolol. The technique of apex cardiography and systolic time interval measurements was used. Firstly, the changes in these non-invasive measurements were followed for five consecutive days in patients with acute myocardial infarction. Secondly, the effect of practolol on these parameters and on the degree of chest pain during the first day of acute myocardial infarction was studied. Patients with angina pectoris and subjects without known cardiovascular disease served as controls.

Subjects

Patients with chest pain and suspected acute myocardial infarction were studied in the coronary care unit as soon as possible after arrival and not later than 48 hours after the onset of chest pain, apex cardiogram, carotid pulse tracing, phonocardiogram, and electrocardiogram were recorded simultaneously in 61 patients. To be included in the study the patients had to fulfil the following criteria: 1) no previous acute myocardial infarction; 2) well-defined onset of chest pain; 3) no clinical evidence of heart failure (no râles, no third heart sound, systolic blood pressure not lower than 100 mmHg); 4) heart rate not lower than 45/min; 5) no arrhythmias that required therapy (atrial fibrillation, more than 5 ventricular extrasystoles/min); 6) no atrioventricular block; 7) no treatment with digitalis, diuretics, catecholamines, beta-blockers, atropine, or antiarrhythmic drugs other than lignocaine (4 patients were given lignocaine); 8) no QRS duration above 0·1 sec. The patients admitted to the coronary care unit fulfilling the criteria and 15 patients without known cardiovascular disease from other hospital wards were divided into the following 4 groups.

1: Time course in patients with uncomplicated acute myocardial infarction

The aim of this part of the study was to follow patients with acute myocardial infarction with noninvasive techniques for 5 days. During the first two days 25 patients were excluded from the study for various reasons: 5 patients did not fulfil the WHO criteria of acute myocardial ischaemia and 20 because they failed the above criteria in one way or another. Twenty patients with acute myocardial infarction were studied 5 times at 24-hour intervals. These patients were divided into 2 groups: group A, studied within 24 hours after the onset of chest pain, group B studied 24 to 48 hours after the onset of pain (Tables 1 and 2). The recordings were performed as soon as possible after the onset of severe chest pain indicating development of acute myocardial infarction. In group B, 6 patients arrived at the hospital one day after the onset of chest pain and 4 patients were hospitalized in the evening or in the night and could not be studied until 24 hours after the onset of chest pain.

2: Time course in patients with chest pain without acute myocardial infarction

These patients were admitted to the coronary care unit with suspected acute myocardial infarction and were studied 5 times at 24-hour intervals (Tables 1 and 3). Three patients had angina pectoris, 1 patient suffered from cholelithiasis, and 2 patients from myalgia. None of the patients had acute myocardial infarction.

3: Effect of practolol on noninvasive parameters and chest pain in patients with acute myocardial infarction

In 10 patients with acute myocardial infarction and recurrent chest pain (Tables 1 and 4), recordings of noninvasive parameters were made before and 30 minutes after intravenous injection of practolol (Eraldin, ICI). In addition 6 patients with chest pain (4 classified acute myocardial infarction and 2 status anginosus) were given practolol on 9 occasions (Table 5). The average intravenous dose of practolol was 18·2 mg and doses of 5 to 30 mg were given. 5 or 10 mg practolol was injected rapidly at a time and this was repeated after one minute, if necessary. Analgesics were not given for 60 minutes before the injection of practolol on 11 occasions. Practolol was given on 8 occasions as a supplement to analgesics. The time lag between the injections of analgesics and practolol was at least 30 minutes for an intravenous dose and 60 minutes for an intramuscular dose.

4: Noninvasive parameters in patients with no heart disease

Noninvasive parameters were recorded in 15 patients hospitalized in wards of the Departments of Urology and Oto-rhino-laryngology (Table 4). These patients were fully mobilized and were studied on one occasion. The physical examination and histories did not indicate heart or lung disease. Blood pressures and electrocardiogram were normal.

Methods

The duration of the phases of systole (systolic time intervals) and a/H ratio were measured from simultaneously recorded electrocardiogram, phonocardiogram carotid pulse tracing, and apex cardiogram. A direct writing four-channel ink-jet Mingograph 34 with a paper speed of $100 \pm 0{\cdot}5$ mm/sec was used. Electrocardiogram lead II was always used. A piezoelectric microphone (Elema-Schönander) was placed at the left sternal border in such a position as to obtain the best recording of the second heart sound. The signal was passed through a filter giving a response from 12·5 to 800 Hertz, with relative damping of the lower frequencies to identify the initial part of the aortic closure sound more accurately. The carotid pulse tracing and apex cardiogram were recorded by a special funnel-shaped 'perspex' pick-up (Wikstrand, Wallentin, and Nilsson, to be published) connected with an air-containing rigid latex tubing of an Elema-Schönander-EMT 510 C crystal transducer. The system had a fre-

TABLE 1 *Description of patients with uncomplicated acute myocardial infarction or chest pain*

	Untreated acute myocardial infarction		*Practolol-treated acute myocardial infarction*	*Chest pain without acute myocardial infarction*
	Group A	*Group B*		
No. of patients	10	10	10	6
Age (yr)	54·6 ± 1·9	53·9 ± 1·8	56·0 ± 2·5	56·5 ± 2·8
GOT_{max}	127 ± 28*	96 ± 16*	108 ± 17*	16 ± 1·6
GTP_{max}	26 ± 4·5*	25 ± 4·1*	19 ± 2·8*	11 ± 2·4
SR_{max}	37 ± 11	65 ± 9·2*	59 ± 12*	24 ± 7·0
$Temp_{max}$	38·1 ± 0·17*	38·4 ± 0·14*	38·4 ± 0·2*	37·6 ± 0·2
Days with elevated morning temperature	6·2 ± 1·6	6·8 ± 1·3	7·4 ± 1·8	0
Heart size in ml/body surface area m^2	452 ± 26	466 ± 17	515 ± 26	435 ± 46

Laboratory data, body temperature, and chest *x*-ray findings in three groups of patients with acute myocardial infarction, two untreated and one treated with practolol, and in one group with chest pain without acute myocardial infarction. Normal values for GOT and GPT ≤ 17 units and normal heart size ≤ 450 ml/m^2.
All values are means ± SEM.
*Significantly different from the group without acute myocardial infarction ($P < 0·05$).

TABLE 2 *Noninvasive measurements in the patients with untreated acute myocardial infarction*

Group A

	Day 1	*Day 2*	*Day 3*	*Day 4*	*Day 5*
Heart rate	67 ± 3·8	78 ± 5·5*	78 ± 5·6	79 ± 5·2	71 ± 4·5
Syst. BP (mmHg)	129 ± 7·2	124 ± 6·2	121 ± 5·7	121 ± 7·6	121 ± 4·9
Diast. BP (mmHg)	82 ± 3·5	79 ± 2·4	76 ± 2·6	74 ± 3·7	78 ± 3·1
Syst. BP × HR × 10^{-2}	85·1 ± 6·3	95·2 ± 4·9	92·4 ± 5·0	93·9 ± 7·1	84·8 ± 5·0
PEP	106·6 ± 4·2	107·4 ± 3·2	110·9 ± 2·8	112·8 ± 4·3	114·6 ± 3·6†
PEPI	133·5 ± 3·2	138·7 ± 2·3	142·1 ± 3·4	143·7 ± 4·1	143·0 ± 4·6*
ICT	68·4 ± 5·7	66·5 ± 4·8	78·6 ± 4·1	78·0 ± 4·5	80·5 ± 3·9†
PEP/LVET	0·372 ± 0·014	0·429 ± 0·010	0·461 ± 0·016	0·460 ± 0·027	0·442 ± 0·21†
LVETI	398 ± 3·8	387 ± 3·7	374 ± 4·6	380 ± 3·9	381 ± 3·2†
Rel. LVET	96·0 ± 1·2	87·8 ± 0·9	85·7 ± 1·3	87·3 ± 1·7	89·9 ± 1·2†
a/H ratio	14·8 ± 2·2	20·4 ± 3·3*	14·0 ± 1·6	14·7 ± 1·4	17·6 ± 2·7

Group B

	Day 2	*Day 3*	*Day 4*	*Day 5*	*Day 6*
Heart rate	79 ± 3·4	78 ± 4·4	77 ± 3·5	75 ± 3·5	70 ± 2·7†
Syst. BP (mmHg)	159 ± 14	129 ± 7·2	126 ± 7·6	124 ± 7·6	122 ± 8·4†
Syst. BP × HR × 10^{-2}	119·0 ± 9·1	101·0 ± 6·0	99·9 ± 3·8	91·2 ± 4·7	83·5 ± 3·6†
Diast. BP (mmHg)	95 ± 6·3	83 ± 4·8	78 ± 4·4	77 ± 4·0	77 ± 4·1†
PEP	100·2 ± 5·4	115 ± 6·1	112 ± 4·3	114·3 ± 4·8	115·6 ± 5·0†
PEPI	131·6 ± 5·2	146·3 ± 5·5	143·4 ± 4·3	141·1 ± 5·2	143·1 ± 1·5·0†
ICT	57·7 ± 5·3	74·0 ± 4·7	69·0 ± 4·9	68·8 ± 3·8	76·1 ± 2·2†
PEP/LVET	0·392 ± 0·021	0·478 ± 0·023	0·467 ± 0·019	0·471 ± 0·020	0·456 ± 0·020†
LVETI	386 ± 4·9	371 ± 3·7	369 ± 3·4	369 ± 5·0	369 ± 4·6†
Rel. LVET	92·0 ± 1·9	85·4 ± 0·8	86·9 ± 1·2	86·0 ± 1·7	87 ± 1·6†
a/H ratio	19·9 ± 2·4	16·9 ± 2·5	16·7 ± 1·8	20·5 ± 2·7	19·5 ± 2·4

Heart rate (beats/min), blood pressure (mmHg), SPB × HR (product of systolic blood pressure and heart rate), PEP (pre-ejection period in msec), PEPI (pre-ejection period index = pre-ejection period corrected for heart rate in msec according to Weissler), ICT (isometric contraction time in msec), PEP/LVET (pre-ejection period and left ventricular ejection time uncorrected for heart rate), LVETI (left ventricular ejection time index in msec), rel. LVET (relative left ventricular ejection time in per cent) and a/H ratio (in %) were measured over a period of 5 days. All values are means ± SEM.
*Significantly different from day 1 ($P < 0·005$); †Significantly different from 1st or 2nd day value ($P < 0·05$).

TABLE 3 *Noninvasive measurements in 6 patients with chest pain without acute myocardial infarction*

	Day 1	*Day 2*	*Day 3*	*Day 4*	*Day 5*
Heart rate	65·7±3·3	63·2±3·7	65·5±5·9	68·3±5·7	66·3±3·8
Syst. BP (mmHg)	142±7·0	133±4·6*	128±5·1*	131±5·5*	133±7·4
Diast. BP (mmHg)	88±6·0	82±2·8	85±3·7	84±4·0	88±4·0
SBP × HR × 10^{-2}	93·3±7·1	83·8±6·4*	83·9±8·0	89·2±9·8	87·3±5·1
PEP	114±2·4	119·5±3·5	121·0±3·6	115±5·0	119·0±4·8
PEPI	138·7±2·2	145·3±3·9	144·0±7·1	145·5±5·2	145·7±5·2
ICT	82·2±2·4	87·5±5·0	88·7±4·8	80·0±4·2	86·2±4·0
PEP/LVET	0·400±0·009	0·435±0·020	0·459±0·032	0·446±0·031	0·443±0·012*
LVETI	397±7·4	383±5·9	380±6·4	384±5·0	381±8·3*
Rel. LVET	99·4±2·9	92·4±1·9	90·3±2·0*	92·0±1·2*	93·0±2·5*
a/H ratio	10·6±1·6	9·5±1·6	10·2±2·0	9·5±1·6	9·6±1·6

*Significantly different from first day value ($P < 0·05$).

TABLE 4 *Noninvasive measurements in normals and in the patients with acute myocardial infarction before and after practolol*

	Normal controls	*Acute myocardial infarction*	
		Before practolol	*After practolol*
No. of patients	15	10	10
Age (yr)	53·4±2·7	56·0±2·5	56·0±2·5
Heart rate	73±1·2	80±5·9	72±4·1*
Syst. BP (mmHg)	133±3·7	148±4·8	132±4·0*
Diast. BP (mmHg)	88±2·0	95±3·6	96±3·0
Syst. BP × HR × 10^{-2}	97·6±3·3	117·4±8·7	93·8±6·3*
PEP	113±2·8	107±3·8	116±3·6*
PEPI	141·8±3·2	138·6±4·4	144·3±4·1*
ICT	83·2±2·2	69·0±3·6	82·4±4·4*
PEP/LVET	0·382±0·015	0·406±0·024	0·424±0·073*
LVETI	406±4·2	400±5·4	397±7·4
Rel. LVET	100±1·5	96·8±2·0	96·3±2·1
a/H ratio	7·9±0·045	19·7±2·3	18·2±1·5

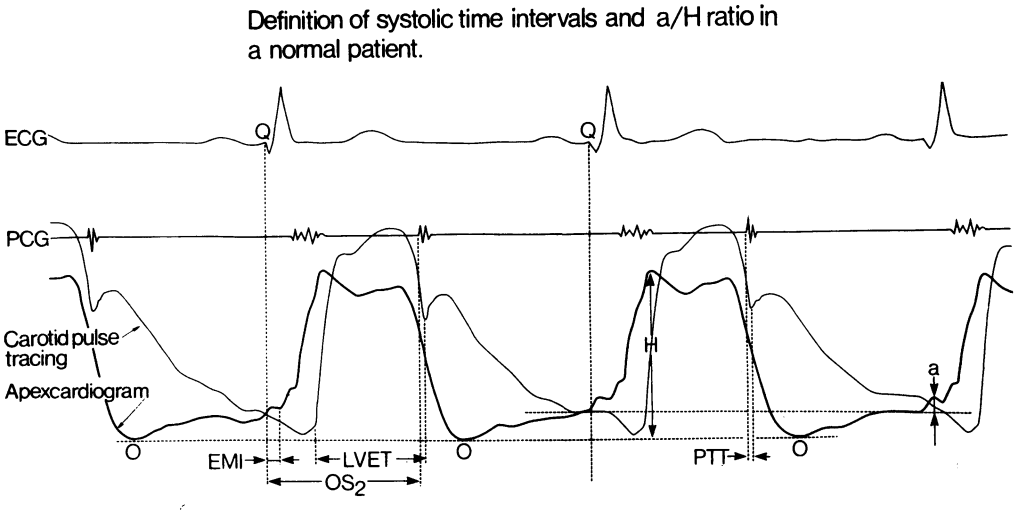
* Significantly different from values before practolol ($P < 0·005$) and not significant from normal values.

quency-response from 0·08 to 60 Hertz (3 dB) and a time constant of 1·9 to 3·8 sec depending on the amplification.

The recordings were made with the patient in the left lateral position with the left arm abducted. The pick-ups were firmly pressed against the right common carotid artery and the point of maximal praecordial movement. All recordings were made during apnoea after a normal expiration. The Valsalva manoeuvre was avoided. Only records showing a well-defined upstroke and incisure in the carotid pulse tracing and a well-defined O point, a wave, and systolic upstroke in the apex cardiogram were used. Care was taken to obtain curves of comparable amplitude from one time to the next in order to avoid distortions. When using a transducer with a minimum time constant close to 2 sec there was no reduction of time intervals as compared to those obtained with a DC response (Johnson, Siegel, and Blomqvist, 1971).

The patients were examined carefully before all recordings and after injection of practolol. Auscultation of the lungs was performed to check for râles and an apical phonocardiogram was recorded for possible third and fourth heart sounds. Patients were questioned concerning dyspnoea and chest pain. If necessary, a bedside chest *x*-ray was taken. To estimate the heart size all patients had a chest *x*-ray taken after mobilization in the standing position.

From simultaneous electrocardiogram, phonocardiogram, carotid pulse tracing, and apex cardiogram the following measurements were obtained (see Fig. 1). The left ventricular ejection time (LVET) is the interval from the carotid upstroke to the incisure notch. The pre-ejection period (PEP) is QS_2-LVET, where S_2 begins with the initial high frequency vibration of the aortic closure sound. The pulse transmission time (PTT) is the interval from S_2 to incisure notch, which is suggested to be the same at the beginning and end of the ejection period. The electromechanical interval (EMI) is the interval from Q to the upstroke of the systolic part of the apex cardiogram. The isometric contraction time (ICT) is PEP-EMI (Inoue *et al.*, 1970; Willems, De Geest, and Kesteloot, 1971). The a/H ratio is the ratio between the



QS_2 = total electromechanical systole.
LVET = left ventricular ejection time.
EMI = electromechanical interval
QS_2-LVET = PEP = preejection period.
PEP-EML = ICT = isometric contraction time.
PTT = pulse transmission time.
O = o-point = opening point.
a = height of the a-wave.
H = total height of apexcardiogram.
$100 \times \frac{a}{H}$ = a/H ratio in %.

FIG. 1 *Simultaneous tracings of electrocardiogram, phonocardiogram, carotid pulse tracing, and apex cardiogram with definitions of systolic time intervals and a/H ratio.*

height of the a wave and the total height of the apex cardiogram (H) measured in per cent. In most cases it was easy to determine the systolic upstroke. In a few cases the a wave was very close to the systolic upstroke of the apex cardiogram and the point after the a wave showing the lowest angle of the tangent was used as the beginning of isometric contraction.

LVET was corrected for heart rate in two ways: 1) the LVET index was calculated, i.e. based on the fact of a linear relation between LVET and heart rate according to Weissler *et al.* 1969; and 2) according to Meiners' diagram (Meiners, 1958) which is based on an exponential relation between LVET and heart rate (relative LVET). A better regression line coefficient was found for the exponential compared to the linear function (Meiners, 1958; Willems and Kesteloot, 1967). PEP was given both as an absolute value and corrected for heart rate (Harris, Schoenfeld, and Weissler, 1967; Talley, Meyer, and McNay, 1971; Weissler *et al.*, 1965). ICT was given without correction. All values are means of those derived from 5 consecutive heart beats. The heart rate was calculated from the electrocardiogram.

Results

Noninvasive measurements during 5 days in patients with and without acute myocardial infarction

Noninvasive measurements were recorded on 5 consecutive days in 20 patients with acute myocardial infarction and in 6 patients with chest pain without acute myocardial infarction (Table 1). Depending on the time of arrival in the coronary care unit, 10 patients (group A) were studied for 24 hours and 10 patients (group B) for 24 to 48 hours after the onset of severe chest pain which could indicate initiation of acute myocardial infarction.

Heart rates were significantly higher on the second day of infarction compared to the last day in both groups with infarction, while no changes were observed in patients without infarction (Tables 2 and 3 and Fig. 2). The patients in group B had higher systolic and diastolic blood pressures, which decreased during the 5 days of observation. This was not found in group A or in the patients without infarction (Tables 2 and 3). The product of systolic blood pressure and heart rate, which is considered to be an index of heart work (Robinson, 1967), was higher on day 2 compared to day 5 in all patients with infarction (Table 2 and Fig. 2). This change from day 2 to day 5 was also significant in group A and B when calculated separately.

The systolic time intervals, PEP and ICT, were significantly longer on the last day of registration as compared to the first day in both groups of patients with myocardial infarction (Table 2). This was also true when pre-ejection period was corrected for heart

TABLE 5 *Effect of practolol on degree of chest pain*

Case No.	*Diagnosis*	*Dose of practolol (mg)*	*Grade of pain before practolol*	*Grade of pain 10 minutes after practolol*	*Time to maximal relief of pain (min)*	*Dose of analgesics in equivalents 6 hr before practolol*
1	Acute myocardial infarction	20	4	0	3	0
2	" " "	20	2	0	2	0
3[I]	" " "	20	4	1	2	0
3[II]	" " "	20	4	1	3	2
4	" " "	20	4	0	3	3
5[I]	" " "	15	2	0	2	3
5[II]	" " "	10	4	2	10	2
6	SA	20	3	0	5	2
7	Acute myocardial infarction	30	3	0	10	0
8	" " "	20	4	2	10	2
9	" " "	20	4	0	2	3
10	" " "	20	3	0	3	2
11	" " "	5	5	0	3	5
12	" " "	20	4	1	10	2
13	" " "	20	5	0	2	3
14	SA	20	5	0	2	3
15[I]	Acute myocardial infarction	10	5	2	4	7
15[II]	" " "	15	5	1	2	9
16	" " "	20	5	5	5	2
	Mean ± SEM of 19 pts	18·2 ± 1·2	3·94 ± 0·22	0·78 ± 0·29	4·37 ± 0·72	2·63 ± 0·53
	Mean ± SEM of 10 pts[1]	19·5 ± 1·6	3·40 ± 0·26	0·60 ± 0·26	5·40 ± 1·25	1·70 ± 0 39

Grading of pain

Grade 0 No pain.
Grade 1 Retrosternal oppression.
Grade 2 Easy constant retrosternal pain without radiation not requiring analgesics.
Grade 3 Moderate constant retrosternal pain without radiation requiring analgesics. The patient does not show any signs of pain.
Grade 4 Intense constant retrosternal pain with radiation. The patient shows signs of pain.
Grade 5 Very intense retrosternal pain with radiation. The patient is pale, cool, sweating, frightened, often screaming and restless.

Analgesics in equivalents

1 ml morphine = 10 mg morphine chloride = 3 analgesic equivalents
1 ml pethidine = 50 mg pethidine chloride = 2 analgesic equivalents
1 ml Cliradon = 5 mg ketobemidone chloride = 3 analgesic equivalents
1 ml Spasmofen = 6·6 mg morphine chloride, 0·4 mg codeine chloride, 3 mg noscapine chloride, 0·15 mg methyl scopalamine nitrate, 20 mg papaverine chloride, 5 mg chlorbutol = 2 analgesic equivalents

[1] Pts who were noninvasively investigated.
I = first investigation.
II = second investigation.
SA = Status anginosus.

rate (PEPI). The mean values of these measurements recorded in all the patients on day 2 and 5 of infarction also show this prolongation (Fig. 2). In the two groups of infarction, LVET corrected for heart rates (relative LVET and LVETI) decreased considerably during the 5 days of observation and a slight reduction was seen in patients without infarction (Tables 2 and 3). The ratio of uncorrected PEP and LVET, which has been found to correlate well with the contractile index and the ejection fraction (Ahmed *et al.*, 1972; Garrard, Weissler, and Dodge, 1970) was much increased in both groups of acute myocardial infarction (Fig. 3) during the 5 days.

It has been suggested that increases in the a/H ratio of the apex cardiogram reflect rises in left ventricular filling pressure (Willems *et al.*, 1971). In the groups of acute myocardial infarction this ratio

Dose of analgesics in equivalents 1 hr before practolol	*Dose of analgesics in equivalents 1 hr after practolol*	*Dose of analgesics in equivalents 3 hr after practolol*
0	0	2
0	0	0
0	0	0
0	0	0
0	0	1
0	0	2
0	0	2
0	0	0
0	0	0
0	0	0
0	0	0
2	0	0
1	0	0
2	0	0
1	0	1
3	0	0
3	2	3·5
2	1·5	1·5
2	1	1
0·84 ± 0·26	0·24 ± 0·59	0·74 ± 0·24
0·40 ± 0·26	0·00 ± 0·00	0·50 ± 0·26

was significantly raised compared to the patients with chest pain and those without known cardiovascular disease (Tables 2 and 3 and Fig. 2).

Heart rate, blood pressure, systolic time intervals and a/H ratio on day 2 and day 5 in 20 patients with uncomplicated acute myocardial infarction.

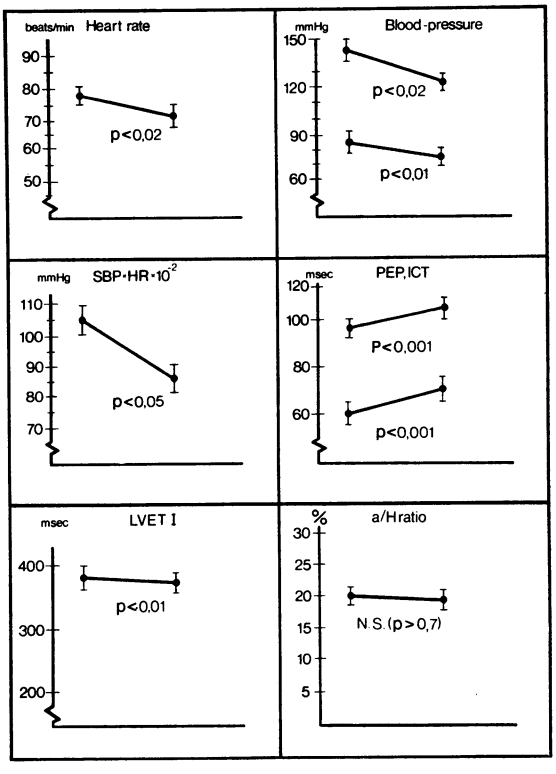


FIG. 2 *Heart rate, blood pressure, product of systolic blood pressure and heart rate, pre-ejection period (PEP), isometric contraction time (ICT), left ventricular ejection time index (LVETI), and a/H ratio on day 2 and 5 after the onset of chest pain in 20 patients with acute myocardial infarction. All values are mean ± SEM.*

Effects of practolol on noninvasive measurements in patients with acute myocardial infarction

In Table 4 data are given from 10 patients with acute myocardial infarction obtained before and 30 minutes after an injection of practolol and from 15 patients without known cardiovascular disease. Practolol was given to reduce chest pain. When satisfactory relief of pain was obtained or a total dose of 30 mg had been given the injection was stopped. It may be seen from Table 4 and Fig. 3 to 5 that practolol given intravenously to patients on the first day of acute myocardial infarction reduced the heart rate and systolic blood pressure and prolonged the PEP and ICT to normal levels. Practolol did not significantly change the diastolic blood pressure, LVETI or the a/H ratio. None of the patients given practolol complained of dyspnoea and no râles or third heart sound appeared. It may be concluded that the injection of practolol reduced heart work and did not seem to aggravate the latent failure of the left ventricle in this group of patients with acute myocardial infarction. It should be stressed that the patients were a selected group and none had manifest heart failure or arrhythmia after the injection of practolol.

Effects of practolol on chest pain

All the 10 patients with acute myocardial infarction in whom noninvasive parameters were recorded had chest pain when practolol was given. Another 4 patients with acute myocardial infarction and two patients with status anginosus were also given practolol to reduce chest pain. These 6 patients were given injections of practolol on 9 occasions. The pain was graded from 0 to 5 as indicated in Table 5. Practolol reduced the pain in all patients, as may be

PEP/LVET ratio in 20 patients with uncomplicated AMI (group A, B, A+B) and 10 patients with AMI before and after i.v. injection of practolol.

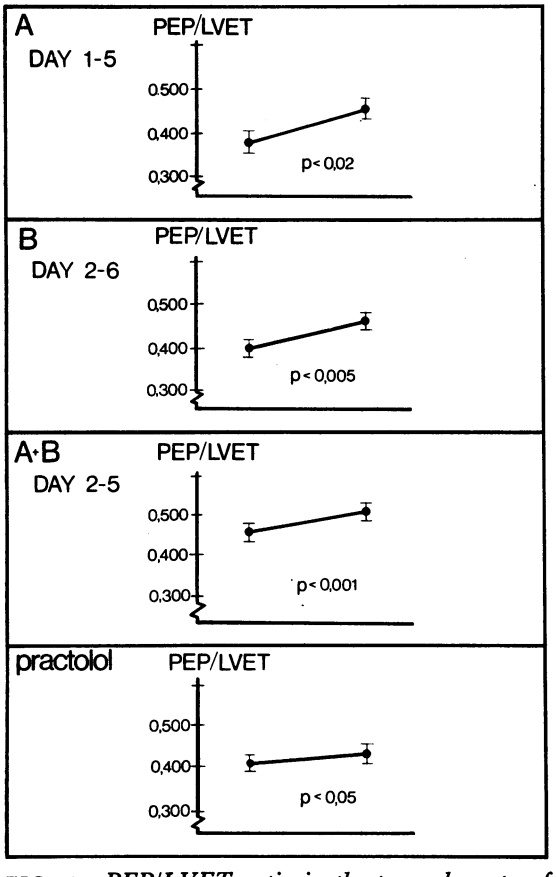


FIG. 3 *PEP/LVET ratio in the two subgroups of uncomplicated myocardial infarction on day 1 and 5 (group A) and day 2 and 6 (group B) after the onset of chest pain compared to values obtained in 10 patients with acute myocardial infarction before and 30 minutes after a dose of practolol given intravenously for chest pain on day 1 of infarction. All values are mean ± SEM.*

Heart rate, blood pressure, systolic time intervals and a/H ratio before and after i.v. injection of practolol in patients with acute myocardial infarction.

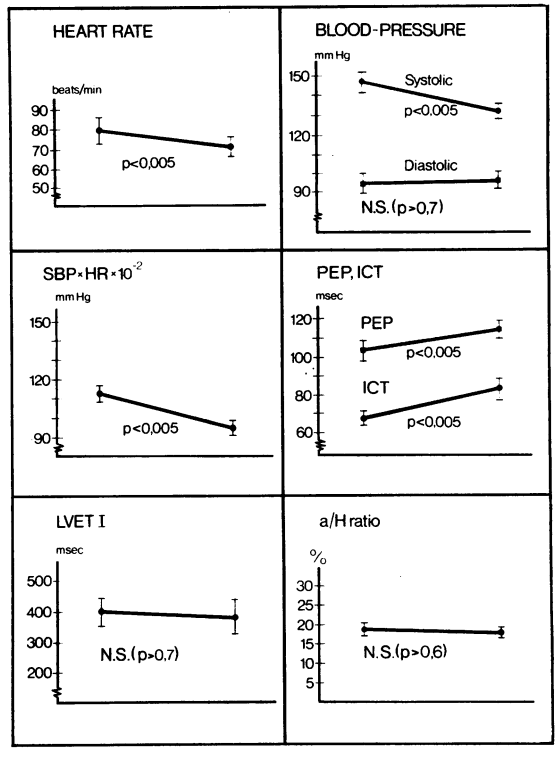


FIG. 4 *Heart rate, blood pressure, product of systolic blood pressure and heart rate, pre-ejection period (PEP), isometric contraction time (ICT), left ventricular ejection time index (LVETI), and a/H ratio in 10 patients with acute myocardial infarction before and 30 minutes after intravenous injection of practolol in an average dose of 19·5 mg. Values are mean ± SEM.*

seen from the Table. The dose of practolol needed for satisfactory relief of pain varied from 5 to 30 mg and the total dose was given in less than 8 minutes. The relief of pain was obvious within 1 to 2 minutes in all patients, but the maximal effect was seen after 10 minutes and lasted more than 30 minutes. Four patients had not been given analgesics at all for 6 hours before practolol and another 7 patients were not given analgesics for 60 minutes before the practolol. The remaining 8 patients were not given analgesics within 30 minutes before the injection of practolol as indicated in Table 5. Most patients had severe chest pain when practolol was given.

Discussion

The present study has shown shorter PEP and ICT on the first two days after uncomplicated acute myocardial infarction as compared to days 5 and 6 after acute myocardial infarction and to subjects without

Pulsecurves,ECG and PCG before (A) and 30 min after (B) i.v. injection of practolol in a patient with acute myocardial infarction.

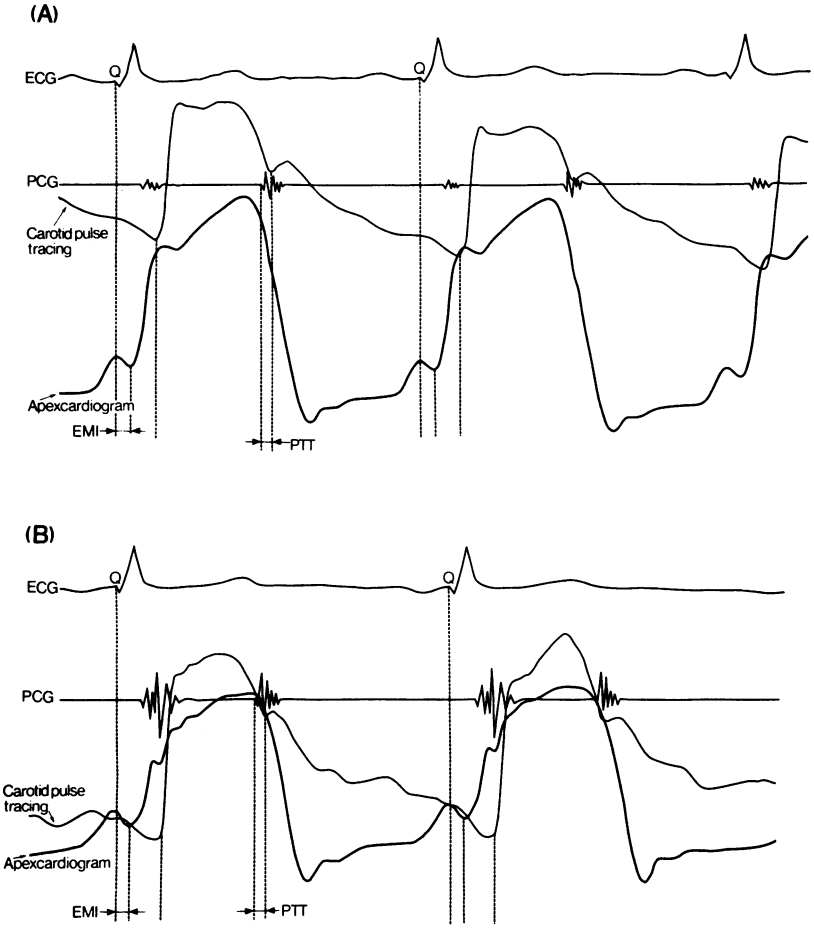


FIG. 5 *Electrocardiogram, phonocardiogram, carotid pulse tracing, and apex cardiogram before and 30 minutes after an intravenous injection of 20 mg practolol. Note that the interval Q to upstroke of carotid pulse tracing and the interval upstroke of systolic part of apex cardiogram to upstroke of carotid pulse tracing is prolonged despite unchanged pulse transmission time, indicating a prolonged pre-ejection period and isometric contraction time.*

cardiovascular disease. This is in agreement with the findings of Fabian and co-workers (Fabian *et al.*, 1972). These authors found shorter PEP and ICT on days 1 and 2 of acute myocardial infarction without left ventricular failure compared to normal controls, while these parameters on days 3, 7, and 21 were within normal limits. Jain and Lindahl (1971) also found shorter ICT on the first two days of acute myocardial infarction compared to normal controls and later stages of infarction. Samson (1970) reported normal or slightly prolonged PEP in patients with uncomplicated acute myocardial infarction. However, separate values were not given for the first two days of acute myocardial infarction. Diamant and Killip (1970) showed prolonged PEP on days 1 to 5 of acute myocardial infarction compared to normals. In contrast to our study more than 50 per cent of the patients in their study had con-

gestive heart failure, which is known to prolong PEP (Weissler, Harris, and Schoenfeld, 1968). Dowling, Sloman, and Urquhart (1971) did not find any significant changes in PEP or ICT after acute myocardial infarction, but only 4 patients were studied for more than 2 consecutive days.

Recently good correlations have been demonstrated between systolic time intervals, haemodynamic parameters, and intraventricular indices of contractility (Weissler, Harris, and White, 1963; Ahmed *et al.*, 1972; Diamond *et al.*, 1972; Mirsky, Pasternac, and Ellison, 1972; Willems *et al.*, 1971). In view of recent data the shorter PEP and ICT on the first two days of acute myocardial infarction in the present study could be caused by a higher left ventricular contractility. These findings suggest that sympathetic activity is raised during the first days in the coronary care unit. The shorter ICT on the first two days of acute myocardial infarction observed by Jain and Lindahl (1971) were thought to be caused by an increase in circulating catecholamines (Gazes, Richardson, and Woods, 1959; Valori, Thomas, and Shillingford, 1967; Wallace, 1968). In the present study the values of PEP and ICT returned to normal by days 5 and 6 after infarction suggesting that the increase in sympathetic activity at the early stage of acute myocardial infarction was abolished. Jain and Lindahl (1971) repeated their noninvasive recordings two to three weeks after admission to hospital and found that the systolic time intervals had almost returned to normal. A successive reduction of adrenergic activity in patients during the initial phase of myocardial infarction is indicated by a stepwise decrease in urinary catecholamine excretion during the first 10 days in hospital (Wallace, 1968). An increase in left ventricular end-diastolic pressure (LVEDP) results in a shortening of PEP (Talley *et al.*, 1971). The increase in PEP during the first 5 to 6 days of acute myocardial infarction in this study could be due to a reduction of LVEDP. However, this is not very likely and was not indicated from the analyses of the a/H ratio.

In animals with experimental myocardial infarction and patients with acute myocardial infarction, left ventricular catheterizations have almost always shown signs of impaired left ventricular performance with increased LVEDP even when no other signs of heart failure appeared (Fluck *et al.*, 1967; Enright, Hannah, and Reis, 1970; Gunnar *et al.*, 1970; Kumar *et al.*, 1970; Russell *et al.*, 1970). A significantly higher a/H ratio of the apex cardiogram at the early stage of infarction was found in this study in agreement with others (Jain and Lindahl, 1971). Good correlation has been found between LVEDP and a/H ratio in patients who have had myocardial infarction or power failure for other reasons (Rios and Massumi, 1965; Epstein *et al.*, 1968; Voigt and Friesinger, 1970; Kahn *et al.*, 1972). The a/H ratio of $8 \pm 0{\cdot}5$ per cent in the normal control subjects does not differ from that of other investigators (Diamond and Benchimol, 1963; Rios and Massumi, 1965; Epstein *et al.*, 1968; Jain and Lindahl, 1971). An increase in preload or LVEDP shortens the PEP while a rise of afterload prolongs the PEP (Talley *et al.*, 1971). During the first 5 days after acute myocardial infarction no significant changes were found in the initially raised a/H ratio, which makes it reasonable to assume that the preload is unchanged at a high level. The prolongation of PEP during these 5 days after acute myocardial infarction is thus most likely caused by reduced contractility of the left ventricle.

Both for patients with acute myocardial infarction and those with chest pain without acute myocardial infarction a decrease was seen in the LVET corrected for heart rates (rel. LVET and LVETI) compared to the control group without known cardiovascular disease. Good correlation has been found between the LVET and the left ventricular stroke volume (Braunwald, Sarnoff, and Stainsby, 1958; Weissler, Peeler, and Roehll, 1961; Wallace *et al.*, 1963; Harris *et al.*, 1966; Fabian *et al.*, 1972). The decrease in LVET was most pronounced in the patients with acute myocardial infarction and might be caused by myocardial damage as well as immobilization in bed. In the patients with no acute myocardial infarction the reduction of LVET could be just the result of immobilization. The ratio between the uncorrected PEP and LVET has been found to correlate well with the contractility index and the ejection fraction of the left ventricle (Ahmed *et al.*, 1972; Garrard *et al.*, 1970). The PEP/LVET ratio was significantly increased both for the patients with acute myocardial infarction and those with chest pain without myocardial infarction, indicating a reduction in left ventricular performance.

The analyses of apex cardiograms and systolic time intervals showed shorter PEP, ICT, and LVET and higher a/H ratio at an early stage of acute myocardial infarction compared to normal controls. Furthermore, the patients with acute myocardial infarction had higher heart rates and systolic blood pressures. These data indicate a depressed ventricular function during the initial stage of acute myocardial infarction, which is compensated for by a higher ventricular filling pressure and increased sympathetic activity. Sympathetic activity and the stroke volumes were reduced and the left ventricular filling pressure remained at a high level during the first 5 to 6 days in the patients with uncomplicated myocardial infarction.

An intravenous injection of the selective beta$_1$-adrenergic blocking agent practolol on the first day of infarction made all parameters normal with the exception of the high a/H ratio, which was unchanged. The injection of practolol thus abolished the increased sympathetic activity resulting in reduction of heart rate, systolic blood pressure, and PEP or ICT to normal levels. The reduction of heart work by practolol was also demonstrated by a pronounced diminution of the degree of chest pain in the acute phase of myocardial infarction. This supports the hypothesis that beta-adrenergic blockade in acute myocardial infarction might diminish the severity and extent of myocardial ischaemia and possibly limit the area of infarction (Maroko *et al.*, 1971; Kahn *et al.*, 1972; Libby *et al.*, 1973). The LVETI and rel. LVET were not changed by practolol, indicating that the stroke volumes were not reduced. This is in agreement with the studies by Jewitt, Burgess, and Shillingford (1970). The beta-blocking agent propranolol, which is not cardioselective and may increase peripheral resistance under some conditions, has been reported to reduce LVETI and thus stroke volume in man (Harris *et al.*, 1966). Practolol did not aggravate congestive heart failure in the patients with uncomplicated infarction, as was demonstrated by an unchanged high a/H ratio at the early stage of infarction. This is in agreement with clinical experience with this beta-adrenergic blocker (Jewitt, Mercer, and Shillingford, 1969; Jewitt *et al.*, 1970; Jewitt and Croxson, 1971). No clinical signs of manifest left ventricular failure appeared in the present study after a single injection of practolol.

Carotid pulse tracings, phonocardiograms, and electrocardiographic measurements that give indirect measures of left ventricular function can be obtained by using a noninvasive technique and analysing the apex cardiogram. It is an advantage that repeated measurements can be performed during several days. Recordings made during 5 days in patients with uncomplicated acute myocardial infarction demonstrated a prolongation of PEP and ICT, an increasing PEP/LVET ratio, a decreasing LVET, and a constant, raised a/H ratio. This indicated a reduction in left ventricular contractility, ejection fraction, and stroke volume, with an increased left ventricular filling pressure. The intravenous injection of practolol during the first day of acute myocardial infarction with chest pain caused prolongation of PEP and ICT, indicating impairment of left ventricular contractility. However, practolol did not change LVET and the PEP/LVET ratio as much as the measurements altered during 5 days in the untreated patients with acute myocardial infarction. It is suggested that practolol abolished an excessive sympathetic activity that occurs during the first day of acute myocardial infarction. The reduction of heart work without clinical signs of deterioration of left ventricular function in these patients with uncomplicated acute myocardial infarction resulted in pronounced relief of pain.

It seems likely that cardioselective beta-adrenergic blockade in patients with acute myocardial infarction might reduce the severity and extent of myocardial ischaemia and thus limit the area of infarction, as has been shown in animal experiments (Maroko *et al.*, 1971; Kahn *et al.*, 1972; Libby *et al.*, 1973). Beta-blocking agents should not be given to patients who need their increased sympathetic activity to maintain cardiac output at an adequate level. In such patients beta-blockade might precipitate manifest heart failure. Noninvasive techniques are valuable for evaluating the pain-relieving effect of practolol in patients with acute myocardial infarction. For ethical reasons a placebo was not given in the present study to the patients with severe chest pain; the pain-relieving effect of practolol was obvious within a few minutes.

A study of continuous beta-blockade during the first 24 hours of myocardial infarction has been started. Blockade prolonged for such a period is likely to be necessary to limit the area of myocardial infarction or to prevent this process occurring from prolonged ischaemia

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