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Left ventricular function and beta-blockade in chronic ischaemic heart failure

Double-blind, cross-over study of propranolol and penbutolol using non-invasive techniques

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SUMMARY From an original group of 32 male post-infarction patients treated with digoxin for presumed cardiac failure eight patients were recruited for the present study by means of a single-blind evaluation of the patients' clinical need for continued treatment with digoxin. Dyspnoea on effort as recorded on a standardised questionnaire was used to define failure of the left ventricle. In order to be recruited to the present study the functional class (NYHA) of the patients had to deteriorate at least one full class while on placebo instead of digoxin. During a subsequent double-blind, cross-over phase digoxin was kept constant and additional treatment with 160 mg propranolol or 40 mg penbutolol twice daily was given. Each patient received the two beta-blockers for periods of two weeks each separated by an intermediate four-week placebo period. Cardiac function was investigated using electrocardiography, apexcardiography, phonocardiography, echocardiography, and pulse curves from the carotid artery, jugular bulb, and liver before and at the end of each treatment period. The findings indicated well-preserved systolic function before beta-blockade despite the history and symptoms, and despite several indices of cardiac damage such as pronounced ischaemic electrocardiographic abnormalities, and large and hypertrophied hearts (*x*-ray and echo). Instead, many variables reflected impaired diastolic function. During beta-blockade no signs of impaired cardiac function emerged. On the contrary, enhanced diastolic filling properties were found; these also contributed to the performance of the left ventricle during systole. No differences between propranolol and penbutolol could be shown.

Beta-blockers are widely used in the treatment of patients with cardiovascular disease. At present beta-blockers are used for arrhythmias, angina pectoris, hypertension, and, recently, as prophylaxis against sudden death after myocardial infarction.[1 2] On a theoretical basis, symptoms of heart failure have been considered as contraindications to beta-blockade. In our experience, however, heart failure caused by beta-blockade is rare in patients treated with digitalis.[3]

The purpose of the present investigation was to assess any possible negative influence of beta-blockade on left ventricular function in post-infarction patients with chronic left ventricular failure clinically compensated by treatment with digoxin. The study was a double-blind, randomised cross-over study of propranolol and penbutolol using non-invasive techniques to study cardiac function.

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Patients and methods

The patients in this study had to complete an initial, single-blind run-in phase in a defined manner in order to establish the clinical indication for continuous treatment with digoxin (Fig. 1). The single-blind phase comprised three stages of six weeks each.

(1) During the first stage all patients were in functional class II because of dyspnoea on effort[4] during treatment with digoxin, 0·25 mg daily.

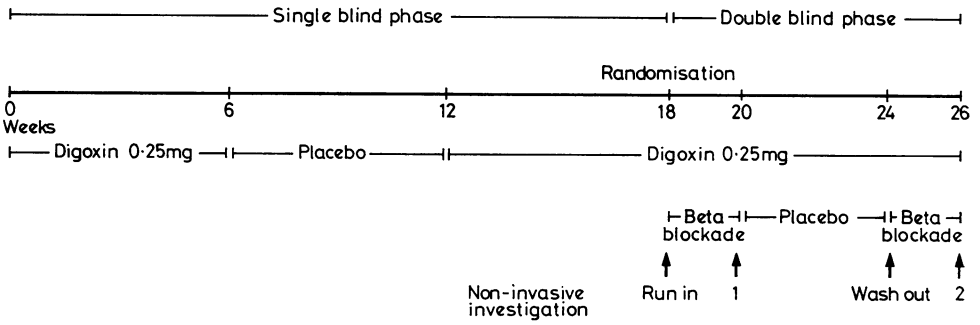

Fig. 1 *Study design. Weekly clinical check-ups took place throughout the study.*

(2) Digoxin treatment was changed to placebo and the functional class was recorded every week during the second stage.

(3) Treatment was then changed back to digoxin 0·25 mg daily for six weeks and the functional class was recorded each week.

The patients who had been consistently worse by at least one functional class during the final four weeks on placebo and reported consistent return to the previous superior functional class during the final four weeks on digoxin were selected for the second double-blind controlled phase of the study. They comprised eight out of the original 32 male patients with sinus rhythm. All had had a definite myocardial infarction from five to 64 months before the investigation. They were seen regularly at the Postmyocardial Infarction Clinic in Göteborg, Sweden, and all were treated acccording to standardised criteria.[5] All patients were free from electrocardiographic conduction defects, angina pectoris, hypertension, and chronic obstructive pulmonary disease. Patient characteristics are listed in Table 1. The patients were seen once a week during the study. The presence of cardiac symptoms was registered by means of standardised questionnaires.[6] During the present study the questionnaires were completed by trained technicians without knowledge of the treatment given. The patients were asked to abstain from alcohol throughout the entire study period and were instructed not to change their coffee, tea, and salt consumption. All patients were fully informed about all aspects of the trial and verbally agreed to participate. The procedure was approved by the local ethical review committee.

The controlled double-blind trial consisted of three parts (Fig. 1). All patients maintained their digoxin treatment unchanged throughout this part of the study. After an initial non-invasive investigation of the cardiac function the patients entered treatment period I. They were randomly allocated to treatment with either 40 mg penbutolol or 160 mg propranolol twice daily for two weeks. At the end of this period another non-invasive investigation of the cardiac function was made.

After treatment period I there was a wash-out

Table 1 *Patient characteristics at entry to double-blind phase of the study*

Case no.	*Age (y)*	*Height (cm)*	*Weight (kg)*	*Months since myocardial infarction*	*Relative cardiac vol (ml/m² BSA)**	*Electrocardiographic abnormality†*	*Echocardiographic thickness (cm)§ Post. wall*	*Septum*
1	61	180	80	16	500	+	‡	‡
2	59	180	82	64	600	+	1·4	1·6
3	52	177	78	25	540	+	1·3	1·5
4	57	178	88	8	700	+	1·5	1·3
5	58	160	70	9	500	+	1·4	1·4
6	51	176	71	6	450	+	1·2	1·3
7	58	175	79	5	500	−	‡	1·9
8	60	170	71	13	450	+	1·2	1·3

* Measured according to Jonsell[15], > 450 ml/m² BSA abnormal.
† Minnesota coded[6] Q-waves 1:1–3 and/or ST-T abnormalities 4:1–3 and/or T-wave abnormalities 5:1–3
‡ Satisfactory echo recordings not obtained.
§ Normal range < 1·2 cm.

period of four weeks. At the end of this period a non-invasive investigation of the cardiac function was made in half the patients to ascertain that the effect of beta-blockade had vanished. All patients could not be studied during this phase because of the great demand on the laboratory of non-invasive investigations from other departments. The patients originally treated with penbutolol or propranolol were then crossed over to the alternative beta-blocker during the subsequent two weeks, treatment period II. At the end of period II the final non-invasive investigation of cardiac function was made. No other concomitant drugs were permitted. All trial drugs were given to the patients in prepared boxes containing separate compartments for each morning and night. Active drugs and placebos were of the same shape, taste, and appearance.

NON-INVASIVE INVESTIGATIONS OF CARDIAC FUNCTION

The patients arrived at the laboratory in the morning after having a light breakfast and after having taken their morning dose of digoxin and the trial drug. All patients arrived at the laboratory at the same time of the week for all the non-invasive investigations during the study.

Conventional electrocardiogram, apexcardiogram, phonocardiograms, pulse curves from the carotid artery, jugular bulb, and liver, and resting blood pressures were all recorded on an ink-jet seven-channel recorder (Siemens-Elema AB, Sweden) in a sound-protected room.

Resting systolic and diastolic blood pressures (phase V) were measured after 45 minutes' rest in the supine position with an automatic device for cuff inflation and deflation, with a microphone placed over the right brachial artery and with simultaneous recording of cuff pressure, Korotkoff sounds, and electrocardiogram.

Echocardiographic recordings were made using commercially available equipment (Brüel-Kjaer, Denmark) connected to a strip chart recorder (Honeywell, USA). The standard technique[7] of examining the diameter of the left atrium and left ventricle was followed. The anteroposterior diameter of the left ventricle was measured just below the aortic root, through or close to both the anterior and posterior mitral leaflets at the end of systole and diastole. When measuring the left atrium the beam had to go through and visualise the aortic leaflets as well. The stroke volume was calculated from the end-diastolic and end-systolic volumes derived by the cube method,[8] and the ejection fraction from the stroke volume and the end-diastolic volume. The mean rate of circumferential fibre shortening was calculated.[9] The left ventricular ejection time in the formula was derived from the carotid pulse curve (corrected to the actual heart rate).

The variables studied were:

(a) Total electromechanical systole from the beginning of the QRS complex to the beginning of the aortic component of the second heart sound (QA_2).
(b) The electromechanical interval from the beginning of the QRS complex to the systolic upstroke of the apexcardiogram (EMI).
(c) The left ventricular ejection time from the beginning of the systolic upstroke of the carotid pulse tracing to the incisura (LVET) and corrected for heart rate (LVET %).[10]
(d) The pre-ejection period (PEP = QA_2 – LVET).
(e) The isovolumetric contraction time (ICT = PEP – EMI).

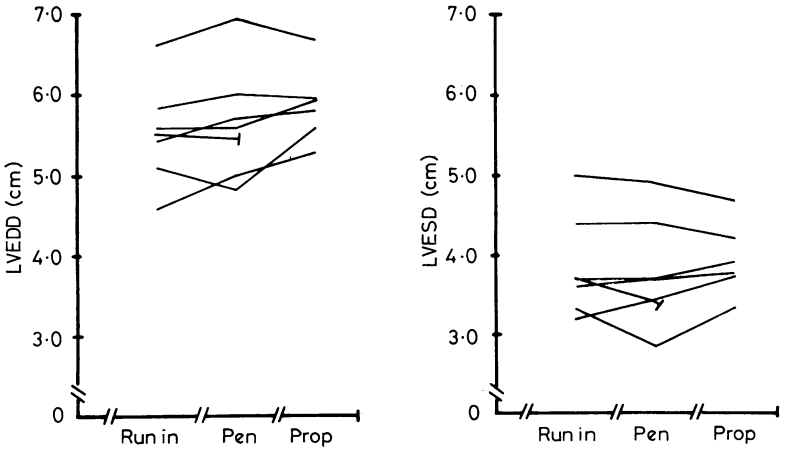

Fig. 2 *Individual measurements of LVEDD and LVESD during run-in and after penbutolol (Pen) and propranolol (Prop). Values for seven patients in one of whom complete measurements could not be obtained.*

(f) The PEP/LVET ratio.
(g) The ICT/LVET ratio.
(h) The interval between the aortic component of the second sound and the 0 point of the apexcardiogram (A_20).
(i) Pressure rise velocity during the isovolumetric contraction time, that is DBP/ICT.
(j) The total interval from the beginning of QRS to the opening of the mitral valve (QM_0).
(k) The ratio (%) of the amplitude of the "a" wave (a) and the total deflection of the apex cardiogram (H; a/H ratio).
(l) The ratio (%) of the rapid filling wave (RFW/H ratio).
(m) The amplitude of the fourth sound in the 50 Hz band relative to that of the first sound ($IV/I_{50\,Hz}$).
(n) Left ventricular end-diastolic diameter (LVEDD).
(o) Left ventricular end-systolic diameter (LVESD).
(p) Echocardiographic stroke volume (SV).
(q) Echocardiographic ejection fraction (EF).
(r) Echocardiographic mean ventricular circumferential fibre shortening (mean V_{CF}).
(s) Echocardiographic left atrial diameter (LA).

Analysis and calculation of each variable was done blindly without knowledge of the treatment or study period. All variables were derived as the mean of measurements from five consecutive beats. All methods used and the definitions of the measurement points on the electrocardiogram, phonocardiogram, carotid pulse tracing, apexcardiogram, and echocardiogram have been presented in detail elsewhere.[10–13]

Because of the small number of patients and the abnormal distributions of many variables, differences between the groups were tested by the Friedman two-way analysis of variance. Thereafter differences between two groups were tested by the Wilcoxon signed pairs rank sum test.[14]

Statistically significant differences were considered for $p < 0.05$. Findings with a $p < 0.1$ were considered biologically meaningful if consistent in other related variables and similarly observed after both beta-blockers.

Results

There were no significant differences between the run-in and wash-out measurements. Therefore, the wash-out results have been omitted. The results are presented in Table 2.

CARDIAC FUNCTION BEFORE BETA-BLOCKADE

The patients had several signs of myocardial damage with electrocardiographic abnormalities, enlarged hearts, and myocardial hypertrophy (Table 1). Six out of eight patients had abnormally prolonged EMI but otherwise the indices of systolic function showed signs of little or no impairment as indicated by findings of normal LVET per cent, PEP/LVET, and high DBP/ICT. A clearly reduced EF and mean V_{CF} was found in only two patients. However, the diastolic function

Table 2 *Results of non-invasive cardiac function studies before (run-in) and after two weeks of penbutolol or propranolol in eight patients with chronic congestive failure after myocardial infarction treated with digoxin.*

Variable	*Run-in*	*Penbutolol*	*Propranolol*	*Probability*	*Normal range*
SBP (mmHg)	127 (116–163)	123 (97–164)	120 (107–150)	NS	—
DBP (mmHg)	85 (70–95)	76 (66–97)	75 (71–92)	NS	—
HR/min	58 (48–92)	54 (40–59)	53 (42–66)	< 0·05	—
QA_2 (ms)	395 (356–425)	421 (391–458)	414 (382–434)	< 0·05	—
EMI (ms)	45 (34–72)	42 (28–69)	45 (25–74)	NS	< 40
LVET (ms)	300 (247–321)	314 (283–342)	315 (257–327)	< 0·05	—
LVET (%)	98 (94–105)	98 (95–112)	97 (90–111)	NS	> 90
PEP (ms)	98 (81–117)	109 (79–131)	102 (81–125)	NS	< 130
PEP/LVET	0·32 (0·26–0·44)	0·34 (0·26–0·45)	0·34 (0·23–0·49)	NS	< 0·45
ICT (ms)	49 (31–83)	67 (40–74)	57 (37–76)	NS	< 100
ICT/LVET	0·16 (0·11–0·20)	0·22 (0·13–0·24)	0·19 (0·11–0·34)	NS	< 0·35
A_2O (ms)	176 (149–198)	178 (150–190)	177 (158–189)	NS	< 150
QM_0 (ms)	476 (385–499)	473 (391–520)	472 (407–535)	NS	Not defined
DBP/ICT (mmHg/s)	1600 (1145–2452)	1210 (1029–1650)	1422 (1211–1919)	NS	775–1200
a/H (%)	7·0 (3·5–26·0)	10·5 (4·6–26·5)	7·5 (2·4–24·3)	NS	< 15
RFW/H (%)	3·6 (1·2–20·9)	3·7 (1·1–12·2)	4·2 (2·7–8·1)	NS	< 5
IV/I50Hz (%)	10·9 (4·0–24·3)	6·3 (2·9–18·4)	8·0 (3·4–10·2)	< 0·02	< 20
LA (cm)	4·2 (3·8–6·0)	4·4 (3·9–6·0)	4·3 (3·8–6·1)	NS	< 4·0
LVEDD (cm)	5·5 (4·6–6·6)	5·7 (4·8–6·9)	5·9 (5·3–6·7)	< 0·06	< 5·6
LVESD (cm)	3·7 (3·2–5·0)	3·6 (2·8–4·9)	3·9 (3·3–4·4)	NS	—
SV (ml)	100 (64–110)	128 (86–211)	138 (98–197)	< 0·1	—
CO (l/min)	6·5 (3·3–10·5)	6·7 (3·7–12·4)	7·7 (4·6–9·5)	< 0·1	—
EF (%)	0·67 (0·56–0·73)	0·70 (0·61–0·80)	0·68 (0·64–0·80)	< 0·1	> 0·60
Mean V_{CF} (circ/s)	1·01 (0·83–1·23)	1·10 (0·86–1·16)	1 06 (0·96–1·26)	NS	> 1·0

Median values and observed range within parentheses. Normal ranges according to Wikstrand,[10 11] and Swedberg.[13]

was more compromised in a number of patients as indicated by findings of abnormal prolongation of A_20 in seven, abnormally large LA in six, and abnormally high a/H ratio or IV/I_{50Hz} in four of the patients.

CARDIAC FUNCTION AFTER BETA BLOCKADE

Blood pressure and heart rate

Penbutolol and propranolol did not reduce the systolic or diastolic blood pressures. The heart rate was reduced equally by penbutolol and propranolol.

Systolic and diastolic time intervals

QA_2 was equally prolonged by both penbutolol and propranolol because of a prolongation of LVET. This prolongation was caused by the decrease in heart rate since LVET per cent was not influenced.

Phono- and apexcardiographic measurements

The IV/I_{50Hz} was lowered by beta blockade. The four patients with a/H ratios above 15 per cent at run-in returned to normal during beta-blockade. The reduction was most pronounced when the comparison was made between run-in values and propranolol. No patient had a pathological third heart sound.

Echocardiographic measurements

Left atrial diameter was not affected by beta-blockade. LVEDD was increased by both beta-blockers, the difference being most pronounced between run-in values and propranolol. LVESD was not affected by beta blockade but tended to be reduced by penbutolol compared with propranolol.

Stroke volume was increased by beta-blockade. This difference was more pronounced for propranolol. The effect on stroke volume was sufficient to cause an increased cardiac output despite the lowered heart rate. Ejection fraction was improved by both beta-blockers. Mean V_{CF} was not changed by beta-blockade.

Comparison between penbutolol and propranolol

No consistent differences between the two beta blockers were observed.

Clinical observations and side effects

The body weight of the patients was not changed. Four patients spontaneously reported less dyspnoea on exertion while on beta-blockers in contrast to placebo; this improvement was reflected in statements of an increased level of physical performance. No patient reported an increase of dyspnoea on effort during beta blockade.

Discussion

The eight patients of the present study all had a clinically verified indication for digoxin. This was checked because of the conflicting opinions on the role of digoxin for heart failure in patients with sinus rhythm. The design of the study and the doses of the beta blockers used were such that any serious negative effects of these agents would most probably have been disclosed.

In the diagnosis of left ventricular dysfunction the systolic time intervals alone do not provide enough information.[10] More complete information is required on the size of the left ventricle and left atrium, the filling pattern of the left ventricle, contractility, and valvular function. This can be obtained by combining echocardiography, phonocardiography, apexcardiography, and recording of systolic and diastolic time intervals. Pathological systolic time intervals appear at a late stage in left ventricular dysfunction since the altered filling pattern during diastole and ventricular hypertrophy may compensate for the impaired systolic left ventricular function.[10 16 17] Therefore, diastolic function must also be studied when impairment of the left ventricular function is considered.

Invasive assessment of left ventricular function may have yielded interesting data for correlation with the present non-invasive findings. Catheterisation and angiocardiography were, however, not performed as it was not considered ethically justifiable to perform repeated invasive investigations in our patients. Regardless of whether invasive or non-invasive methods have been used, there is

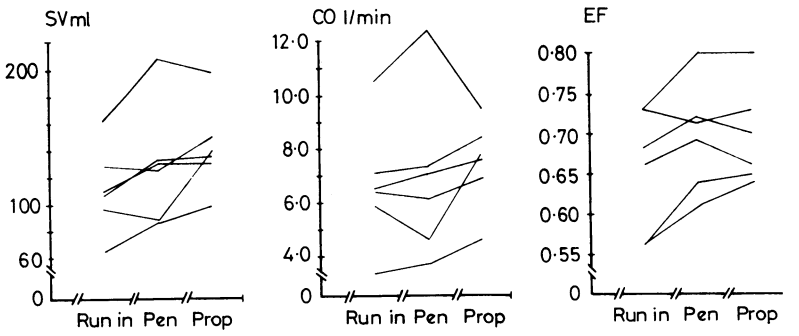

Fig. 3 *Individual measurements of stroke volume (SV), cardiac output (CO), and ejection fraction (EF) during run-in and after penbutolol (Pen) and propranolol (Prop). Values for six patients with complete sets of measurements.*

a lack of agreement on universally accepted indices of the function of the left ventricle during the various intervals of the cardiac cycle.

The various measurements recorded in the present study have been analysed with particular attention to consistent changes in related measurements, and special importance has been attached to changes observed during treatment with both of the two beta-blockers. In addition, special attention was paid to detecting adverse effects of beta-blockade on cardiac function. This type of pattern-recognition analysis has previously been used in our laboratory.[10 11 13 18]

Propranolol lacks intrinsic stimulating activity and penbutolol is a more recent non-selective beta-blocker with an intrinsic stimulating activity of approximately 15 per cent.[19] The doses were considered equipotent in the reduction of exercise tachycardia.[20]

The finding of predominant impairment of diastolic cardiac function in our patients is in agreement with an earlier study. The results regarding pressure rise velocity (DBP/ICT) may be interpreted as showing that the contraction may have been more powerful in several postinfarction patients compared with reference subjects. This observation could not be explained by treatment with digitalis, nor could it be explained by differences in the end-diastolic pressure as judged from the a/H ratio from the apexcardiogram.[10] Patients with a much higher diastolic pressure may, however, have a normal "a" wave in the apexcardiogram.[21]

In the present study the non-invasive signs of improved pump function after beta-blockade as reflected by increased stroke volume, cardiac output, and ejection fraction were the result of an increased LVEDD but an essentially unchanged LVESD. End-systolic dimensions have been shown to discriminate patients with different degrees of impaired left ventricular function.[22] These findings may support the interpretation of our data that the working point of the left ventricle was shifted to a more favourable position on the Starling curve. Thus there were no signs of impaired systolic function during beta-blockade in our patients. Some patients may have had asymmetric ventricular contractions caused by local dyskinesia. Because the patients constituted their own controls the changes observed should be valid, though absolute individual levels may be false. In particular, the calculations of stroke volume and cardiac output must be interpreted with caution but ejection fraction is more reliable since similar errors are introduced in both the numerator and the denominator.

The ratio PEP/LVET has been found to be closely correlated with the contractility index of the left ventricle.[23 24] This ratio was not significantly influenced by beta-blockade nor was ICT nor DBP/ICT. A measure of the duration of the relaxation between closure of the aortic and opening of the mitral valves can be constructed as the difference $QM_0 - QA_2$. The interval tended to be shorter during beta-blockade, demonstrating a faster rate of relaxation despite the lowering of the heart rate; this indicates a more favourable situation regarding the time for left ventricular filling. Improved filling of the left ventricle during the rapid and slow-filling phase may explain the signs of a less vigorous atrial contraction after beta-blockade as indicated by the constant a/H ratio and lowered $IV/I_{50\,Hz}$. 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.[25 26] The contraction phase and the relaxation phase can be influenced partly independently of one another.[27–29] The findings in our study might indicate a direct influence of the beta-blockers on cellular function during relaxation.

In severe congestive cardiomyopathy some patients have improved dramatically when they were treated with beta-blockade. The individual response, however, is variable.[13 18] The mechanism of action of beta-blockers in this condition is probably somewhat different from that in our patients.

Dyspnoea on effort is the symptom defining the clinical entity of cardiac failure in the present study. In patients without pulmonary disease dyspnoea on effort may be caused by increased pulmonary capillary pressure reflecting an increased filling pressure of the left ventricle. The increased filling pressure may in turn be a result of left ventricular systolic dysfunction or diastolic dysfunction (left ventricular distensibility) or a combination thereof. In patients with decreased left ventricular distensibility, an increased filling time may compensate for the difficulty in filling the ventricle. The situation is analogous to that in mitral stenosis where stroke volume decreases with increasing heart rate because the degree of filling of the left ventricle is more time-dependent than under normal conditions. The major functional impairment after not too extensive infarction may not be in emptying the ventricle but rather in a decreased filling capacity caused by hypertrophy, fibrosis, or scarring. Well-preserved systolic contractile function in intact parts of the myocardium may compensate for dyskinetic areas. This hypothesis is supported by the present findings together with those in a previous study.[10] It may contribute to the explanation as to why precipitation of failure

is rarely seen after beta-blockade. The lowering of the heart rate after beta-blockade may, therefore, improve the cardiac function and symptoms in many post-myocardial infarction patients. There may also be a direct effect of beta-blockers on left ventricular distensibility.

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