

Cardiovascular reflexes in patients after myocardial infarction

Effect of long-term treatment with beta-adrenoceptor antagonists

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SUMMARY A double-blind study was made of men who had had a myocardial infarction at least one year previously, and who were being treated with propranolol, atenolol, or placebo. They were compared with age- and sex-matched control subjects. Under resting conditions, there were no differences between the systemic arterial blood pressures, forearm blood flows, or heart rates of the control subjects and the post-infarction patients treated with placebo. The patients, however, showed signs of reduced sympathetic effects on the cardiovascular system when their reflex responses to the Valsalva manoeuvre, lower body negative pressure, and performance of a mental task were assessed. Long-term treatment with propranolol or atenolol had little effect on resting systemic arterial blood pressure or forearm blood flow, but caused a significant reduction in resting heart rate. Differences in the reflex responses of these patients and those on placebo were attributable to the effects of the beta-adrenoceptor antagonists on resting heart rate. These results indicate that post-infarction patients do not have signs of overactivity of autonomic nervous control of the cardiovascular system. Furthermore, long-term treatment of such patients with beta-adrenoceptor antagonists does not impair cardiovascular reflexes.

Patients with an acute myocardial infarction frequently have physical signs suggestive of excessive autonomic nervous system activity. A sinus tachycardia and systemic hypertension may indicate overactivity of the sympathetic nervous system, while sinus bradycardia may indicate overactivity of the parasympathetic system.¹ It has been suggested that such autonomic "imbalance" may contribute to the high mortality of acute infarction.¹ On the other hand, it is possible that activation of the sympathetic system is a desirable reflex response that tends to improve cardiac performance, while parasympathetic-mediated bradycardia may have the useful function of reducing myocardial oxygen demand.

Reflexes mediated through the autonomic system are difficult to investigate when patients are ill, but within the first few days after infarction it has been shown that the bradycardia induced by face immersion (the "diving reflex") is increased, possibly indicating sensitisation of cardiac para-

sympathetic control.² This change is temporary,³ and little is known about other cardiovascular reflex mechanisms in patients who have suffered a myocardial infarction.^{3 4}

The value of long-term treatment with beta-adrenoceptor antagonists after a myocardial infarction is still not clear. Though they have been claimed to reduce mortality, the mechanism by which they do so is unknown. They do not appear to have much antiarrhythmic effect⁵ but one possibility is that they modify cardiovascular reflexes in a way that protects the heart from undesirable autonomic nervous influence.

We have therefore compared cardiovascular reflexes in a group of survivors of myocardial infarction (who were either untreated, or who had received beta-adrenoceptor antagonists for at least one year) with those of a matched group of healthy subjects.

Subjects and methods

Twenty-four men aged less than 60 years, who had

had a proven myocardial infarction at least 12 months previously, were studied. None suffered from angina or had symptoms or signs of heart failure; all had returned to their preinfarction level of activity. All were taking part in a trial comparing propranolol (a non-selective beta-adrenoceptor antagonist⁶), atenolol (a cardioselective beta-adrenoceptor antagonist⁶), or placebo in post-infarction patients. In that trial, the results of which will be described elsewhere (Wilcox *et al.*, in preparation), treatment began immediately after admission to a coronary care unit; thus the patients described in the present study had received either a beta-adrenoceptor antagonist or placebo for at least 12 months. No patient was receiving any other treatment.

Table 1 Details of control subjects and post-infarction patients

Group	No.	Age (y)	Months since infarct	Maximum enzyme levels	
				SHBD	AST
Control	6	47 ± 2	—	—	—
Placebo	6	52 ± 3	17 ± 1	576	108
Propranolol	6	42 ± 4	15 ± 1	584	115
Atenolol	6	48 ± 3	15 ± 1	598	101

The amounts of beta-adrenoceptor antagonists administered (propranolol 80 mg bd and atenolol 50 mg bd) were thought to be equipotent in terms of heart rate and blood pressure reduction,⁶ and were considered to be the maximum doses likely to be acceptable to the patients.

The ratios of anterior to inferior infarctions in the three treatment groups were: propranolol 5:1; atenolol 4:2; placebo 4:2.

The volunteer men who acted as age-matched controls were all members of the ambulance service. None had any known cardiovascular or other illness and none was taking any drug.

All the subjects gave their written consent to the investigation which was approved by the medical school ethical committee.

Assessment of cardiovascular reflexes was carried

out in a temperature-controlled room set at 24°C, between 2.0 and 4.0 pm after a light lunch. All subjects rested quietly for 30 minutes before testing started and during that time chest leads were attached from which an electrocardiogram could be recorded and heart rate derived by feeding the signal into an instantaneous ratemeter (Devices Ltd.). Blood pressure was measured by sphygmomanometry in the left arm and forearm blood flow was measured in the right arm by venous occlusion plethysmography, using a mercury-in-silastic strain gauge.⁷ Forearm vascular resistance was derived by dividing mean blood pressure (diastolic pressure + one-third pulse pressure) by forearm blood flow.

Blood pressure and forearm blood flow were measured every 15 seconds during the baseline periods, which lasted at least three minutes. The coefficients of variation for blood pressure and flow during the last minute before any particular manoeuvre being carried out were invariably less than 5 per cent in any individual.

Cardiovascular reflexes were assessed using the following manoeuvres.

(1) HEART RATE VARIABILITY DURING DEEP BREATHING

Variation in RR interval during respiration (sinus arrhythmia) is dependent upon vagal efferent integrity, and is a reliable means of assessing it.⁸ The depth of respiration is not critical as long as the tidal volume is in excess of 40 per cent of the forced vital capacity, but the rate of breathing is important and was standardised at about six per minute.⁸ Heart rate variability was measured as the mean difference between maximal and minimal heart rate during this manoeuvre, with subjects supine.

(2) VALSALVA MANOEUVRE

The subjects performed a Valsalva manoeuvre by blowing into a mouthpiece and holding a column of mercury at a height of 40 mm for 15 seconds. A side-arm air leak prevented them from supporting the column by occluding the mouthpiece. Heart rate was recorded continuously throughout the

Table 2 Resting cardiovascular status and heart rate variability in groups studied

	Blood pressure (mmHg)		Heart rate (beats/min)	Variability (beats/min)
	Systolic	Diastolic		
Control subjects	122 ± 6.0	79 ± 3.0	79 ± 7.4	19.2 ± 3.2
Placebo group	125 ± 6.0	89 ± 5.0	74 ± 9.2	14.8 ± 2.5
Propranolol group	110 ± 5.0	74 ± 3.0	56 ± 1.3*	11.7 ± 2.0
Atenolol group	116 ± 6.0	78 ± 4.0	60 ± 4.4*	14.2 ± 3.5

* $p < 0.05$ for difference between treated groups and control and placebo treated subjects.

manoeuvre, while blood pressure and forearm blood flow were recorded in the 15 seconds before and within 10 seconds after the manoeuvre.

(3) LOWER BODY NEGATIVE PRESSURE

Enclosure of the body of a supine subject, distal to the level of the iliac crests, in an airtight box permits the application of negative pressure to the enclosed parts; blood pools in the veins exposed to the negative pressure, and the resulting reduction in venous return is similar to that which occurs on moving from the supine to the upright posture.⁹ The advantage of the technique is that it provides a means of assessing cardiovascular responses to a reduction in central blood volume without the subject moving and thereby interfering with the measurements. Subjects were exposed to increasing levels of lower body negative pressure ranging from 5 to 40 mmHg below atmospheric pressure for periods of one minute, with recovery periods of at least one minute between each. Heart rate was measured continuously and brachial arterial blood pressure and forearm blood flow were measured at 15 second intervals. In each individual, values obtained in the 15 seconds immediately before negative pressure were compared with those measured during the last 15 seconds of negative pressure.

Table 3 Maximum change in cardiovascular variables with lower body negative pressure at 40 mmHg

	Change in heart rate (beats/min)	Change in systolic blood pressure (mmHg)	Change in forearm vascular resistance (arbitrary units)
Controls	+18 ± 2.5	-10 ± 2.5	+33 ± 9.5
Placebo group	+6 ± 2.0	-24 ± 5.0	+10 ± 4.4
Propranolol group	+4 ± 3.0	-13 ± 4.5	+15 ± 5.8
Atenolol group	+5 ± 2.5	-13 ± 4.0	+32 ± 9.5

(4) PERFORMANCE OF A MENTAL TASK

Performance of a mental task elicits an increase in heart rate and systemic arterial blood pressure which are sympathetically mediated.¹⁰ In the present test, subjects (sitting) were shown a series of cards on which were written the names of colours in inks of different colours (for example the name green written in red ink etc.). Subjects were asked the name of the colour or the colour of ink (Bennett and Fentem, unpublished observations), and the maximum heart rates and arterial blood pressures were compared during the test which lasted about one minute.

Results quoted in the text are mean values ± SEM; differences between group values were compared by Student's paired or unpaired t tests as appropriate. Slopes of regressions were compared by covariance analysis.

Results

The details of the patients and control subjects are shown in Table 1. Their supine resting blood pressures, heart rates, and heart rate variability during deep breathing are shown in Table 2. The resting heart rates in the patients treated with propranolol or atenolol were significantly lower than those of the controls or placebo-treated patients, but there were no other significant differences.

COMPARISON OF CONTROL SUBJECTS WITH PLACEBO-TREATED POST-INFARCTION PATIENTS

During the Valsalva manoeuvre, the control subjects showed a significantly ($p < 0.05$) greater tachycardia than the patients, and after the manoeuvre their overshoot in systolic blood pressure and the accompanying bradycardia were more pronounced ($p < 0.05$) (Fig. 1). The bradycardia relative to the pressure overshoot was similar, however, in control subjects and patients. The Valsalva manoeuvre elicited changes in diastolic blood pressure and forearm vascular resistance which were not significantly different in the control subjects and patients (Fig. 1).

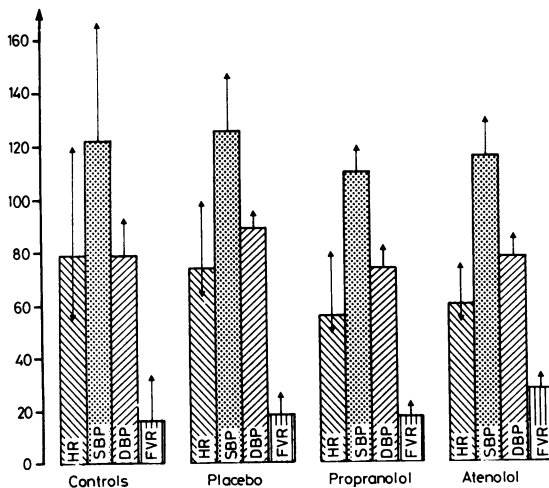


Fig. 1 Cardiovascular responses to the Valsalva manoeuvre. The blocks represent the resting values of the variables measured (HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; FVR, forearm vascular resistance), the arrows indicate the maximum (for HR, minimum also) values elicited by the manoeuvre. The common axis is for beats/min, mmHg, and arbitrary resistance units.

On exposure to lower body negative pressure the fall in systolic pressure was less and the increase in forearm vascular resistance was greater in the control subjects, but this difference did not achieve significance, probably because of the large intra-individual variation (Table 3). The post-infarction patients, however, showed a smaller rise in heart rate ($p < 0.05$, Table 3), and examination of RR interval and systolic blood pressure during lower body negative pressure showed that there was a significant ($p < 0.05$) difference between the slopes for this relation in the control subjects and the patients (Fig. 2).

The pressor response to mental stress was similar in control subjects and placebo-treated, post-infarction patients (Table 4), though the tachycardia was less ($p < 0.05$) in the latter group (Table 4).

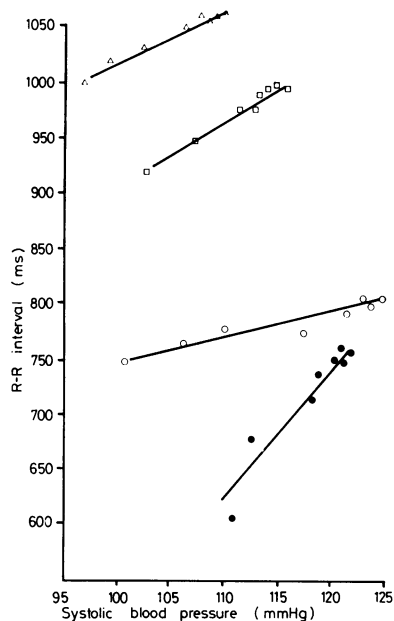


Fig. 2 Regressions of RR interval on systolic blood pressure during lower body negative pressure (LBNP). For each level of LBNP, RR interval and systolic blood pressure were measured during the last 15 seconds of a one minute exposure. In the control subjects (●) increasing levels of LBNP caused progressive falls in systolic blood pressure and shortening of RR intervals; the slope of the regression (11.5 ms/mmHg) may be taken as an index of baroreflex sensitivity.¹² The slope for the placebo-treated patients ○, 2.5 ms/mmHg is significantly ($p < 0.02$) less than that of the control subjects but not different from that of the propranolol-treated (□, 6.0 ms/mmHg) or atenolol-treated (△, 5.0 ms/mmHg) patients.

Table 4 Maximum change in systemic arterial blood pressure and heart rate during performance of mental task

	Change in systolic blood pressure (mmHg)	Change in diastolic blood pressure (mmHg)	Change in heart rate (beats/min)
Controls	+30 ±1.5	+17 ±2.1	+22 ±2.7
Placebo group	+24 ±2.0	+17 ±1.9	+11 ±1.5
Propranolol group	+17 ±2.5	+16 ±1.5	+14 ±2.0
Atenolol group	+22 ±2.7	+21 ±2.1	+12 ±1.4

COMPARISON OF PLACEBO-TREATED AND BETA-ADRENOCEPTOR ANTAGONIST-TREATED POST-INFARCTION PATIENTS

During the Valsalva manoeuvre the maximum heart rates seen in the propranolol-treated or atenolol-treated patients were significantly ($p < 0.05$) lower than in the placebo-treated patients, but this was entirely attributable to the differences in the resting state (Fig. 1), as were the differences in maximum systolic pressures seen after the manoeuvre. While the bradycardia after the manoeuvre was less ($p < 0.05$) in the propranolol- or atenolol-treated patients, the bradycardia relative to the pressure overshoot was similar in all groups of patients. The changes in diastolic blood pressure and forearm vascular resistance elicited by the Valsalva manoeuvre were not different in the three groups of patients (Fig. 1).

The patterns of cardiovascular response to lower body negative pressure were similar in all three groups of patients (Table 3), and the slopes for the regressions of RR interval on systolic blood pressure during lower body negative pressure showed no significant differences between the placebo-treated and beta-adrenoceptor antagonist-treated patients (Fig. 2).

The cardiovascular responses to mental stress were similar in all three groups of patients (Table 4).

Discussion

We studied asymptomatic patients who had sustained myocardial infarction more than a year previously. It is possible that patients with heart failure or other complications of the infarction would have shown different responses to our tests of autonomic nervous function.

Under resting conditions the patients treated with placebo had similar heart rates and blood pressures to the healthy subjects. The tests of cardiac parasympathetic effects (heart rate variability⁸ and cardiac slowing relative to the pressure overshoot after the Valsalva manoeuvre¹¹), showed no differences between these groups. Some tests of cardiovascular sympathetic effects, however, indi-

cated a relative reduction of activity in the post-infarction patients compared with healthy subjects. The patients showed less tachycardia during the Valsalva manoeuvre,¹¹ during lower body negative pressure,¹² and during performance of a mental task.¹³ In the patients there was also a smaller overshoot of blood pressure after the Valsalva manoeuvre, and there was a relatively greater fall in blood pressure and a smaller increase in peripheral vascular resistance in response to lower body negative pressure. All these changes are consistent with reduced sympathetic efferent effects, but as the pressor response to mental stress was intact, some sympathetic efferent pathways must have been normal in these patients. It is possible that the post-infarction patients had some abnormality on the afferent side of the reflex arc, but it is difficult to envisage a single abnormality that would account for the responses seen. It is, of course, by no means certain that the differences in sympathetic responses that we detected between the control subjects and the post-infarction patients were the results of the previous infarction. For example, it is quite possible that they were the result of different levels of habitual activity in the two groups.

Long-term treatment with either a cardio-selective or a nonselective beta-adrenoceptor antagonist had remarkably little effect on the results of our tests of autonomic function. Patients treated with propranolol or atenolol had significantly lower resting heart rates than patients treated with a placebo, a finding consistent with the known effects of these drugs. The reduction in the overshoot of systolic arterial pressure after the Valsalva manoeuvre in these patients could be attributed to the effect of the drugs on cardiac output, as has been seen in subjects treated acutely.¹⁴ Performance of a mental task, however, elicited changes in heart rate and systolic arterial pressure which, as percentages of the resting values, were similar to those seen in the placebo-treated patients. This may indicate that long-term treatment with beta-adrenoceptor antagonists does not attenuate the cardiovascular effects of cortical activation.

Our findings show that several months after a myocardial infarction the parasympathetic innervation of the heart functions normally, though the sympathetic innervation of the cardiovascular system has, for some reason, lesser effects than in normal subjects. There is nothing to suggest that patients who have had an infarction have overactive autonomic nervous systems that might prejudice their response to an infarction. The "autonomic imbalance" seen in acute myocardial infarction is therefore likely to be a result and not a cause of infarction.

It seems that long-term treatment with beta-adrenoceptor antagonists does not have a distinct effect on cardiovascular reflexes in post-infarction patients.

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