Assessment of relative actions of beta-adrenergic blocking drugs on heart rate and left ventricular ejection using a non-invasive method in patients with aortic Starr-Edwards prostheses

Marion R. Crouchman
From the Department of Cardiology, St. Bartholomew's Hospital, London

The relative effects on heart rate and left ventricular ejection at rest and during exercise of M & B 17,803a, propranolol, and practolol were studied in the same 6 patients with Starr-Edwards aortic valve replacement. Changes in left ventricular ejection were measured phonocardiographically, an increase in ejection being associated with a reduction in the time between the R wave of the electrocardiogram and the opening sound of the prosthesis (A1).

At the three selected equivalent dose levels there was no significant difference in the reduction of heart rate produced by intravenous administration of the three drugs, either at rest or on exercise.

All three drugs prolonged the RA1 interval at rest and on exercise, but at the highest dose (30 mg) M & B 17,803a and practolol increased left ventricular ejection at rest, possibly due to their intrinsic sympathomimetic activity.

On exercise, M & B 17,803a and practolol were not statistically distinguishable, and both produced significantly less reduction in left ventricular ejection than the equivalent doses of propranolol.

It is concluded that intravenous administration of M & B 17,803a in the same doses as practolol produces a similar effect on heart rate and left ventricular ejection.

It is also concluded that there is no fixed relation between changes in heart rate and left ventricular ejection, at rest or during exercise, after the administration of beta-adrenergic receptor blocking agents.

Drugs possessing beta-adrenergic receptor blocking properties may depress left ventricular ejection by antagonizing the effects of sympathetic stimulation or circulating catecholamines. This may be clinically unimportant, or even desirable, as in the treatment of angina pectoris, but in the presence of myocardial disease may precipitate or aggravate heart failure (Stephen, 1966). In this study, the relative effects of three beta-adrenergic blocking agents - propranolol, practolol, and M & B 17,803a (Fig. 1) - on heart rate and left ventricular ejection, at rest and during submaximal exercise, have been compared.

Patients and methods
All three drugs were investigated in the same 6 patients (Table 1). These were men aged from 40 to 60 years, who had had Starr-Edwards aortic valve prostheses inserted at St. Bartholomew's Hospital in the previous eight years, for isolated aortic valve disease. All were in sinus rhythm, with normal PR interval, and no evidence of cardiac failure. Treatment with diuretics and anti-coagulants was not interrupted, the nature of the investigation was explained, and verbal consent was obtained.

The patients were exercised upright on an Elema-Schoenander bicycle ergometer. The electrocardiogram was obtained from precordial electrodes placed over the sternum, the thoracic spine, and in the left axilla below the inferior border of pectoralis major, thus avoiding skeletal muscle artefacts. The phonocardiogram was obtained from a suction microphone placed in the second intercostal space at the right sternal edge. Phonocardiogram and electrocardiogram were recorded simultaneously on a S.E. Laboratories ultraviolet recorder with Sanborn channels, at a paper speed of 100 mm/sec. Each investigation was completed within a 2-hour period from the initial warm-up, and the heart rate was...
allowed to return to resting levels between exercise periods.

A warm-up period of 10 minutes was followed by a 10-minute rest. The patient was then exercised continuously for 2 minutes at each of three preselected work loads (150, 450, and 600 kpm/min). Electrocardiogram and phonocardiogram were recorded during the rest period, and after 2 minutes at each work load. In most patients, blood pressure was also estimated, using a sphygmomanometer cuff, before, and immediately after, exercise. Care was taken to prevent the patient from gripping the bicycle handlebars, thus avoiding a possible rise in blood pressure due to the hand-grip phenomenon. The patient was rested for 10 minutes after completion of the highest exercise load, before the first dose of the beta-blocker to be investigated was administered intravenously. Recordings were taken at rest 2 to 3 minutes after injection, and the patient then exercised again at the same three work loads, with recordings as in the control run. Two further exercise runs were similarly executed, after intravenous injection of the same beta-blocker, at increasing doses.

The whole procedure was repeated twice, at intervals of at least 48 hours, using the three beta-blockers in random order. The doses employed were as follows.

Propranolol 2 mg + 4 mg + 6 mg (accumulative dose 12 mg)
Practolol 5 mg + 10 mg + 15 mg (accumulative dose 30 mg)
M & B 17,803a 5 mg + 10 mg + 15 mg (accumulative dose 30 mg).

There were no side-effects to the investigation.

**Measurements**

Heart rate was measured by the RR interval of the electrocardiogram. Changes in left ventricular ejection were measured by the RA1 interval. This was taken as the time, in msec, from the peak of the QRS complex on the electrocardiogram to the first high frequency component of the opening sound of the aortic prosthesis (A1) (Fig. 2). Ten consecutive beats were measured at rest and at each exercise level. The values obtained after administration of the three drugs were compared with the control values, and with each other, at rest and on exercise, using Student’s ’t’ test and analysis of variance. For purposes of comparison the data obtained at the three exercise loads were combined.

**Results**

**Chronotropic effects**

All three drugs produced slowing of the heart rate both at rest and on exercise when compared to control values, and there was no significant difference between the degree of negative chronotropic effect exerted by the drugs at the selected equivalent dose levels. At rest, the average reduction in heart rate

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**FIG. 1 The chemical structure of the three beta-adrenergic blockers.**

Propranolol

```
O-\text{CH}_2\text{CH}_2\text{NH}_2\text{CH}_3
\text{CH}_3
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Practolol

```
O-\text{CH}_2\text{CH}_2\text{NH}_2\text{CH}_3
\text{OH}
```

M&B 17803a

```
O-\text{CH}_2\text{CH}_2\text{NH}_2\text{CH}_3
\text{COCH}_3
\text{CH}_3\text{CH}_2\text{CONNH}
```

**FIG. 2 The RA1 interval.**
TABLE 1  Clinical details of patients studied

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)</th>
<th>Preop. status</th>
<th>Interval after operation</th>
<th>Postop. status</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>Congenital aortic stenosis and insuff.; symptomatic for 2 yr; severe LV hypertrophy</td>
<td>2 mth</td>
<td>Heart size decreased; clinically normal LV</td>
<td>Frusemide 40 mg o.d.; warfarin; Slow K 2 b.d.</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>Congenital aortic stenosis with aortic insuff. after subacute bact. endocard.; 20 pints beer and 120 cigarettes a day</td>
<td>20 mth</td>
<td>Heart size slightly decreased; high alcohol intake; probable myocardial disease</td>
<td>Warfarin</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>Starr-Edwards aortic valve replacement Oct. 1964; ball variance; ball replaced Jan. 1970</td>
<td>7 yr, 2 mth</td>
<td>Heart size increased; early diastolic murmur present</td>
<td>Frusemide 40 mg o.d.; warfarin; Slow K 2 b.d.</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>Rheumatic aortic stenosis, severely symptomatic (chest pain); severe LV hypertrophy</td>
<td>2 yr, 6 mth</td>
<td>Heart size decreased; asymptomatic</td>
<td>Warfarin</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>Severe aortic stenosis; symptomatic for 6 mth with angina</td>
<td>8 mth</td>
<td>Heart size decreased; clinically normal LV</td>
<td>Frusemide 40 mg o.d.; Slow K 2 b.d.</td>
</tr>
<tr>
<td>6</td>
<td>43</td>
<td>Rheumatic aortic stenosis with aortic incompliance after subacute bact. endocard.; large heart, small dissecting aneurysm of ascending aorta</td>
<td>3 mth</td>
<td>Heart size decreased</td>
<td>Frusemide 40 mg o.d.; Slow K 2 b.d.; warfarin</td>
</tr>
</tbody>
</table>

TABLE 2  Changes in RA1 interval from control levels

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise 1</th>
<th>Exercise 2</th>
<th>Exercise 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
<td>SE</td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg</td>
<td>3.7</td>
<td>2.9</td>
<td>6.2</td>
<td>1.6</td>
</tr>
<tr>
<td>6 mg</td>
<td>5.4</td>
<td>4.7</td>
<td>11.2</td>
<td>3.3</td>
</tr>
<tr>
<td>12 mg</td>
<td>8.3</td>
<td>4.7</td>
<td>10.8</td>
<td>4.2</td>
</tr>
<tr>
<td>Practolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mg</td>
<td>4.2</td>
<td>2.5</td>
<td>5.8</td>
<td>1.6</td>
</tr>
<tr>
<td>15 mg</td>
<td>5.9</td>
<td>4.5</td>
<td>7.2</td>
<td>2.9</td>
</tr>
<tr>
<td>30 mg</td>
<td>5.9</td>
<td>3.4</td>
<td>9.0</td>
<td>2.9</td>
</tr>
<tr>
<td>M &gt; B 17,803a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mg</td>
<td>3.1</td>
<td>4.2</td>
<td>4.4</td>
<td>1.6</td>
</tr>
<tr>
<td>15 mg</td>
<td>3.4</td>
<td>3.4</td>
<td>5.5</td>
<td>2.1</td>
</tr>
<tr>
<td>30 mg</td>
<td>-1.4</td>
<td>4.4</td>
<td>5.4</td>
<td>2.1</td>
</tr>
</tbody>
</table>

SE = standard error of the mean.

was 12 beats/min (practolol 30 mg), 13 beats/min (M & B 17,803a 30 mg), and 13 beats/min (propranolol 12 mg); at the highest work load, the average reduction in heart rate was 25 beats/min (practolol 30 mg), 24 beats/min (M & B 17,803a 30 mg), and 26 beats/min (propranolol 12 mg) (Fig. 3). These negative chronotrophic effects, both at rest (P < 0.01) and on exercise (P < 0.001), were significant in respect to control values, as was the inhibition of exercise tachycardia compared with slowing of the heart rate at rest (P < 0.001).

Effects on RA1 interval
At rest (Fig. 4), all drugs produced prolongation of the RA1 interval. In the case of propranolol, this effect was maximal at the highest cumulative dose level (12 mg), and averaged 8.4 msec from control values. The maximal prolongation produced by practolol occurred at 15 mg, and averaged 6.4 msec. At the highest dose of practolol, the RA1 interval was less affected, with average prolongation 4.2 msec. A similar effect was observed with M & B 17,803a, which produced maximal prolongation of
the resting RA₁ interval at 5 mg, with an average increase of 3.8 msec, which was not significantly different from the effects of the lower doses of the other two beta-adrenergic blockers (3.4 msec for propranolol, and 5.3 msec for practolol). At the 15 mg accumulative dose level of M & B 17,803a, the average prolongation fell slightly to 3.2 msec, and at the highest dose the drug decreased the RA₁ interval by an average of 1.4 msec from control levels, and by an average of 4.6 msec from the preceding dose.

On exercise, all three drugs produced prolongation of the RA₁ interval in respect to control values, and this was progressive with increasing accumulative dose levels (Fig. 5). However, practolol and M & B 17,803a were statistically indistinguishable from each other at all dose levels, and resulted in significantly less prolongation of the RA₁ interval than did the equivalent dose of propranolol (P < 0.01). The average prolongation produced by propranolol at 12 mg was 10.6 msec, compared with 9.1 msec at 30 mg of M & B 17,803a, and 9.4 msec at 30 mg of practolol.

The slight changes observed in diastolic blood pressure were not consistently related to the alterations in the RA₁ interval.

**Discussion**

Measurement of the interval from the onset of ventricular activation to the opening sound of the aortic valve prosthesis (QA₁) has proved a sensitive and accurate noninvasive method of assessing changes in left ventricular ejection (Gibson, Broder, and Sownton, 1970). This interval represents left ventricular activation time, isovolumetric contraction time, and the time taken by the ball of the prosthesis to travel from one end of the cage to the other – a quantity which reflects the initial acceleration of blood into the ascending aorta. In the present study, we have simplified this measurement by excluding the QR interval of the electrocardiogram.

During exercise at increasing levels, there is progressive shortening of the RA₁ interval as the heart rate increases, due to the effects of sympathetic stimulation and circulating catecholamines. The negligible effect on the RA₁ interval produced by atropine or ventricular pacing (Gibson et al., 1970)
indicates that the response seen in exercise is not simply a function of heart rate or of vagal withdrawal. The relation between the PR interval and the RA
interval therefore defines the increase in ventricular ejection produced by exercise.

The method used allowed measurements to be made on a beat-to-beat basis, thus eliminating the need to achieve a steady state at each exercise level. Systematic differences between hemodynamic variables may occur between two consecutive exercise runs in the same patient (Burkart, Barold, and Sowton, 1967), but these were minimized by a preliminary warm-up period.

The RA
interval will be shortened by a fall in diastolic blood pressure as the isometric contraction time is shortened, but the changes in RA
interval observed in the present study were not consistently related to the small changes in diastolic blood pressure observed.

As all the patients studied had had severe aortic valve disease before valve replacement we must assume that left ventricular function remained impaired, and any tendency for beta-blocking drugs to interfere with myocardial contraction might be particularly evident.

The three beta-adrenergic blocking drugs studied here differ in several ways. Propranolol and M & B 17,803a have membrane stabilizing (quinidine-like) actions, not possessed by practolol. It seems unlikely that this effect plays a part in producing the present results as the concentration of propranolol needed to produce an effect on the membrane potential in vitro is about one hundredfold greater than the plasma levels associated with beta-adrenergic blockade with doses similar to those used in the present study (Coltart and Shand, 1970).

Unlike propranolol, practolol and M & B 17,803a have intrinsic sympathomimetic properties, and the decrease in RA
interval found at rest with the higher doses of these two drugs may be an indication of this effect. The fall in heart rate was less noticeably affected, indicating that the RA
interval is probably a more sensitive index of sympathetic activity than heart rate alone. These findings provide evidence for the first time of intrinsic sympathomimetic activity of beta-adrenergic blocking drugs in man. The intrinsic sympathomimetic activity of these drugs is evident only when natural sympathetic tone is low, and would not be expected to produce noticeable effects in the presence of the considerable sympathetic stimulus of exercise.

The differences found on exercise are not clearly related to the known pharmacological properties of the drugs. Practolol and M & B 17,803a produced less change in RA
interval for a given change in heart rate than did propranolol. M & B 17,803a resembles practolol in being cardioselective in action, with relatively little effect on the bronchi (Leary and Coleman, 1971). It has been suggested that the relatively small effect of practolol on cardiac output, compared to propranolol, is due to the cardioselectivity of practolol and an absence of action on the peripheral circulation (Gibson and Hamer, 1971). However, Briant and his colleagues (1971) found little difference in peripheral vascular effects between propranolol and M & B 17,803a, so it is difficult to assess the part played by such a mechanism in producing the present findings. An alternative possibility is a differential effect on the beta-adrenergic receptors concerned with heart rate and myocardial performance.

References

Requests for reprints to Dr. Marion R. Crouchman, Department of Cardiology, St. Bartholomew's Hospital, London E.C.1.
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M R Crouchman

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