The Effect of Beta-Sympathetic Blockade on Arterial Oxygen Saturation in Fallot's Tetralogy

and Jane Howard, M.S.C.T.

The right-to-left shunt in Fallot's tetralogy is the result of obstruction to ejection of blood from the right ventricle into the pulmonary circulation. There is organic stenosis of the pulmonary valve or the infundibulum, frequently associated with hypoplasia of the outflow tract and pulmonary trunk. 1 In addition, contraction of hypertrophied infundibular muscle may add a functional stenosis, during systole, which can be demonstrated by angiocardiography. Physical exertion is accompanied by sympathetic stimulation of the heart, mediated by beta receptors, 2 which not only increases heart rate, but also increases myocardial contractility. 3 This implies greater stroke power from any given end-diastolic fiber length and normally results in a decrease in heart size with more complete emptying of the heart during systole. We postulated that in Fallot's tetralogy increased outflow tract obstruction resulting from sympathetic stimulation might be one of the factors causing the fall in arterial oxygen saturation on effort, and consequently that the fall might be lessened by the administration of the beta-sympathetic blocking agent, pronethalol. 4 5 We have tested this hypothesis by observing the effect of pronethalol on the arterial oxygen saturation at rest and during exercise in patients with Fallot's tetralogy.

Patients and Methods

Observations were made on 19 patients, aged from 14 to 38 years. Nine of 17 patients with Fallot's tetralogy had functioning subclavian-pulmonary anastomoses; four had had a pulmonary valvotomy or infundibular resection or both; three had had no operation, and one had had an unsuccessful Blalock operation. There was a wide range of cyanosis and disability in the group, and in three patients (patients 1, 17, and 19), there were obvious fluctuations in the degree of cyanosis at rest, suggesting variations in infundibular tone. Two other patients who were thought to have Fallot's tetralogy were also studied: on further investigation one (patient 13) was found to have an underdeveloped right ventricle, with pulmonary stenosis, intact ventricular septum, and reversed interatrial shunt; the other (patient 18) had a single ventricle, with pulmonary stenosis and a rudimentary outflow chamber; both these patients had functioning Blalock shunts.

A fine polythene catheter (Clay Adams PE 160) was introduced percutaneously into a brachial artery, usually the right, by the Seldinger method, and advanced about six inches into the vessel; it was kept open by intermittent flushing with heparinized saline. In a few patients the introduction of the catheter was accompanied by deep pain in the arm with temporary disappearance of the radial pulse caused by arterial spasm; this always passed off in a few minutes. Because pain may be accompanied by increased sympathetic activity, 10 to 20 minutes were allowed to pass before a resting sample was taken from the arterial catheter. Each patient then walked at 1.5 m.p.h. on a level treadmill, and arterial samples were taken at 1, 3, and 5 minutes. Only two patients were unable to walk this distance. In order that exercise should continue to the point of dyspnea or tiredness, 14 patients walked for a further 1 to 5 minutes, the treadmill speed being increased to 2.25 m.p.h., usually at a slope of 3° to 7°. A final blood sample was taken at the end of this more strenuous period of exercise. In eight patients, blood pressure was recorded at rest and after 5 minutes of treadmill exercise either by connecting the arterial catheter to an electromanometer (Statham P23 Gb) or, in patients whose left subclavian artery had not been divided, by sphygmomanometry, with a cuff applied to the left arm and a stethoscope diaphragm held in place by a crepe bandage. The oxygen content

From the Department of Cardiology, St. Bartholomew's Hospital, London, England.

* Previously known as nethalide; supplied as Alderlin (I.C.I.).

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of the arterial samples, and oxygen capacity, were determined by the Van Slyke manometric method.

These observations were repeated after pronethalol was given intravenously in five patients and orally in 14. The intravenous dose was 1 mg./Kg. body weight injected slowly over 10 minutes; sometimes a feeling of faintness came on whereupon the injection was interrupted; atropine was held in readiness but was never required. Ten minutes were allowed to elapse to give the drug time to take effect. The oral dose used was 4 mg./Kg. body weight (150 to 300 mg.) and observations were made 1 hour later. In addition, ten of the patients were given an inert injection or tablet between the control and pronethalol tests: this was given by the same route as the pronethalol and the same observations were made. Placebo was not given after pronethalol, because of the long duration of action of the drug.

Several preliminary practice walks on the treadmill were necessary so that the patients became familiar with the apparatus and were not apprehensive during the tests.

In 14 patients the diagnosis was confirmed by routine right heart catheterization and selective angiography (with right ventricular injection), in most cases with use of a simultaneous biplane rapid film changer. Five of these patients subsequently had their cardiac lesions totally corrected, and it was possible to correlate detailed anatomic findings with the response to beta-sympathetic blockade.

Results

The resting arterial oxygen saturation was normal in only one of the patients, and low (54.5 to 92 per cent) in the remainder (table 1). In all, the saturation fell during exercise, but the drop was relatively slight (4 per cent after 5 minutes exercise) in the two patients whose resting saturation exceeded 90 per cent.

The Effect of Pronethalol

The changes in percentage saturation at rest and on exercise are given in table 2, and illustrated in figure 1A. The resting arterial oxygen saturation was not significantly changed in 13 of the 17 patients with Fallot's
**BETA-SYMPATHETIC BLOCKADE**

**Table 1 (continued)**

<table>
<thead>
<tr>
<th>Oxygen saturation (%)</th>
<th>Blood pressure (mm. Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>Pronethalol</td>
</tr>
<tr>
<td>Exercise</td>
<td>5 min. Final</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------</td>
</tr>
<tr>
<td>85</td>
<td>84</td>
</tr>
<tr>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>84</td>
<td>77.5</td>
</tr>
<tr>
<td>81.5</td>
<td>64.5</td>
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<tr>
<td>99.5</td>
<td>99.5</td>
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<tr>
<td>62.5</td>
<td>50.5</td>
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<tr>
<td>70.5</td>
<td>63.5</td>
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<tr>
<td>60.5</td>
<td>56.5</td>
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<tr>
<td>72.5</td>
<td>59</td>
</tr>
<tr>
<td>67.5</td>
<td>62.5</td>
</tr>
<tr>
<td>72.5</td>
<td>56</td>
</tr>
<tr>
<td>75</td>
<td>68</td>
</tr>
<tr>
<td>80.5</td>
<td>69.5</td>
</tr>
<tr>
<td>82.5</td>
<td>66</td>
</tr>
<tr>
<td>44.5</td>
<td>65.5</td>
</tr>
<tr>
<td>63</td>
<td>60.5</td>
</tr>
</tbody>
</table>

**Table 2**

*The Effect of Pronethalol on Arterial Oxygen Saturation (17 Patients with Fallot's Tetralogy)*

<table>
<thead>
<tr>
<th>Change in oxygen saturation</th>
<th>No significant change</th>
<th>Increase 0-5%</th>
<th>Moderate increase 5.5-10%</th>
<th>Considerable increase &gt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest</td>
<td>2</td>
<td>11</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>At end of standard exercise period*</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>At end of hard exercise period (13 patients)</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

*Five minutes at 1.5 m.p.h. on the flat, except for patients 11 and 19, who were able to walk for only 4 minutes and 3 minutes, respectively.

Patient 1 showed the most dramatic response (fig. 2). Other representative examples of the effect of pronethalol are shown in figure 3. In patient 12 (fig. 3A) the saturation at the end of exercise was similar on the two occasions, but pronethalol had the effect of delaying the fall. Patient 8 (fig. 3B) had a normal resting saturation following a very successful pulmonary valvotomy and infundibular resection, and after pronethalol it remained normal to the end of the exercise period. Patient 14 showed marked improve-
ment in her resting saturation after pronethalol, but had a steeper fall on exercise; after 5 minutes it was not significantly different from that obtained in the control study. Neither of the two patients with other forms of cyanotic congenital heart disease showed any response to pronethalol (fig. 4).

The Effect of Placebo

Placebo tablets or injections were given to 10 patients (fig. 1B). In eight, this produced no significant change in the oxygen saturation at rest compared with the control figure (between −1.5 and +2.5 per cent). The improvement at the end of 5 minutes of exercise or after hard exercise was never more than 3.5 per cent, and in at least four of the 10 patients the response to pronethalol was significantly better than after placebo. One patient (no. 17, fig. 3C) showed an 8.5-per cent increase in resting saturation after placebo injection, but there was a further 8.5 per cent increase in resting saturation after pronethalol injection; whereas there was a good response to pronethalol on exercise,
placebo was without effect. A similar pattern was observed in patient 19. Both these patients had been observed to show variations in their degree of cyanosis at rest, and in their exercise tolerance. The initial resting samples were probably taken too soon after the introduction of the arterial catheter, when the effect of anxiety and discomfort on sympathetic tone had not subsided.

Blood Pressure Changes

The blood pressure at rest and after 5 minutes of exercise was either unaffected by pronethalol or slightly reduced.

Discussion

In most of the patients, the arterial oxygen saturation during exercise fell less after beta-sympathetic blockade than it did during control experiments or after placebo. The distance and speed walked by each patient during these sets of observations remained constant. The results therefore imply a relative increase in pulmonary blood flow during exercise. In three patients there was also a marked increase in arterial saturation at rest.

The proportion of the right ventricular output which passes into the pulmonary circulation of patients with Fallot’s tetralogy depends upon the relative resistances to flow imposed by the pulmonary valve and infundibulum, and by the systemic vascular bed. Thus an increase in systemic resistance at rest, or a smaller fall than usual during exercise, would diminish the right-to-left shunt, but we do not believe that pronethalol acts in this way. In a study of normal volunteers, we found no significant change in peripheral resistance at rest or on exercise after the drug;7 and in the present series, the blood pressure was either unchanged or fell slightly. On the other hand, our results can be convincingly explained by decreased resistance to ejection of blood from the right ventricle into the pulmonary circulation. Normally during exercise increased sympathetic tone augments myocardial contractility; in other words, the external stroke work for a given end-diastolic pressure is increased, the rate of development of tension is also increased, and the ejection period is shortened. More complete systolic emptying of the right ventricle would be expected to result in greater systolic obstruction to blood flow, and consequently a larger right-to-left shunt. Beta-sympathetic blockade would prevent these changes, thereby reducing the fall in arterial oxygen saturation on effort.

Similar observations have been made by Braunwald and his colleagues on patients with hypertrophic subaortic stenosis. Isoproterenol was shown to increase the systolic left ventricular-arterial gradient by augmenting myocardial contractility, without affecting cardiac output.8 Pronethalol blocked this action, and also diminished the gradient during exercise.9

In pulmonary valve stenosis, the degree of hypertrophic outflow tract obstruction varies greatly from patient to patient and is not necessarily more severe in those with the tightest valve stenosis.10 Similarly, in Fallot’s tetralogy, in which the pathologic anatomy of the organic obstruction is very variable, it is to be expected that the extent of the secondary muscular hypertrophy will vary in the same way. It is not surprising, therefore, that in some of our patients there was no reversible dynamic component to the right

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**Figure 2**

Patient 1. Arterial oxygen saturation at rest, and during exercise. o-o control; x-x after pronethalol.
ventricular outflow tract obstruction. By contrast, the effect of pronethalol was particularly striking in three patients (nos. 1, 17, and 19) in whom variations in the degree of cyanosis at rest and on effort suggested a high degree of responsiveness to sympathetic stimulation.

We have tried to correlate the degree of response to pronethalol with the surgical findings in the five patients later submitted to total correction (table 3). In three patients whose arterial oxygen saturation during exercise was increased considerably by pronethalol, there was much muscular hypertrophy in the right ventricular outflow tract proximal to the main organic stenosis which was either valvular or high infundibular. On the other hand, another patient, in whom muscular hypertrophy was a prominent feature, failed to respond. Fourteen patients had angiocardio-grams, but only in one did the films convincingly show a contractile infundibular narrowing (patient 17, fig. 5); he responded well to beta-sympathetic blockade. In other patients, the films showed a valve stenosis or a fixed infundibular stenosis, without demonstrating much variation in the diameter of the outflow portion of right ventricle during the

Figure 3

course of the cardiac cycle; however, opacification was often poor as a result of the right-to-left shunt and consequent reduction in pulmonary blood flow. Neither of the two patients with diagnoses other than Fallot's tetralogy responded to pronethalol. One had pulmonary stenosis associated with an underdeveloped right ventricle, and the other a

![Graph showing arterial oxygen saturation at rest and during exercise](image1)

**Figure 4**

Arterial oxygen saturation at rest, and during exercise. ○ ○ control; • • after placebo; x---x after pronethalol. A, left. Patient 13. Pulmonary stenosis with underdeveloped right ventricle, intact ventricular septum, and reversed interatrial shunt. B, right. Patient 18. Single ventricle with pulmonary stenosis. In both these patients, oxygen saturation during exercise is slightly lower after pronethalol.

![X-ray images of the heart](image2)

**Figure 5**

### Table 3

**Anatomic Details in Five Patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Previous closed operations</th>
<th>Anatomic findings at open operation (total correction)</th>
<th>Angiocardiogram</th>
<th>Response to pronethalol during exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Blalock</td>
<td>No valve stenosis. Annular infundibular stenosis, 1 cm. below valve; long muscular stenosis. Ventricular septal defect 2.5 cm. diameter; no crista supraventricularis discernible</td>
<td>Immediately subvalvular stenosis</td>
<td>Considerable</td>
</tr>
<tr>
<td>9</td>
<td>Failed L. Blalock</td>
<td>No valve stenosis. Immediately subvalvular fibromuscular stenosis. Considerable muscular hypertrophy proximal to stenosis</td>
<td>Severe infundibular stenosis (poor filling). Left pulmonary artery occluded</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>Blalock</td>
<td>No valve stenosis. Low fibromuscular infundibular stenosis, with long infundibular chamber. Large ventricular septal defect of A-V communis type</td>
<td>Infundibular stenosis, 1 cm. long, 2 cm. below valve</td>
<td>None (5 min.) Moderate (hard exercise)</td>
</tr>
<tr>
<td>17</td>
<td>Pulmonary valvotomy and infundibular resection</td>
<td>Stenosis of bicuspid pulmonary valve (orifice 1.25 cm. diameter). Hypertrophy of crista supraventricularis and infundibular muscle right up to valve ring</td>
<td>Long infundibular stenosis, with increased narrowing in systole and early diastole (5 mm.), and relaxation in late diastole (12 mm.) (fig. 5)</td>
<td>Considerable</td>
</tr>
<tr>
<td>19</td>
<td>Pulmonary valvotomy; later infundibular resection</td>
<td>No valve stenosis. Fibrous high infundibular stenosis, with proximal muscle hypertrophy</td>
<td>Fixed infundibular stenosis (8 mm. diameter)</td>
<td>Considerable</td>
</tr>
</tbody>
</table>
single ventricle with rudimentary outflow chamber; there was no angiocardiographic evidence of muscular hypertrophy, and the obstruction to pulmonary blood flow in these patients is likely to be the result of fixed organic stenosis.

We had suspected that a patient with a large Blalock shunt would be less dependent on blood flow through the right ventricular outflow tract and would therefore show less fall in oxygen saturation on exercise, and less response to pronethalol, than a comparable patient with a good result from a pulmonary valvotomy or infundibular resection. Our results, however, showed no obvious difference in the pattern of response between those patients who had had previous direct operations and those who had had anastomotic operations, but there were too few in each group to draw any firm conclusions.

We have found the oral dose of pronethalol used in the study (approximately 4 mg./Kg.) effective in blocking the tachycardia produced in normal volunteers by inhaled isoproterenol. This effect, however, is rarely fully developed as soon as 1 hour after administering the drug; in retrospect the 14 patients who received oral pronethalol were exercised too soon after taking it. We are therefore unlikely to have observed the maximum possible effect of the drug in this group.

Therapeutic Implications

Patients with Fallot’s tetralogy may have attacks of extreme cyanosis and syncope that are usually provoked by effort or emotion. The attacks may even cause death. Wood and Braudo and Zion produced evidence to show that during these episodes the infundibulum contracts more completely than usual. They offer no explanation of the mechanism of this infundibular shut-down, but Johnson suggested that norepinephrine might be responsible. Although our observations have been confined to exercise studies, it is probable that cyanotic attacks occurring under other circumstances are also due to increased sympathetic activity, with resulting increase in myocardial contractility and increased systolic obstruction of the right ven-

tricular outflow tract. Our evidence suggests that a beta-sympathetic blocking agent such as pronethalol might be effective in relieving or preventing these attacks. We have not yet had the opportunity to confirm this.

Our results do, however, show clearly that beta-sympathetic blockade has a beneficial effect on the response to exercise of many patients with Fallot’s tetralogy. Subjective exercise tolerance would not necessarily be improved, but clearly a clinical trial of a suitable beta-sympathetic blocking agent is indicated in those patients who have not yet had a total corrective operation. Unfortunately, pronethalol has disadvantages that make it unsuitable for long-term treatment. Many patients are nauseated, or complain of an unpleasant sensation of faintness or unreality; furthermore the drug has been found to increase the incidence of thymic tumors and lymphosarcomas in mice. These actions are almost certainly not inherent in beta-sympathetic blockade, and long-term administration must await the availability of a beta-sympathetic blocking drug without important side effects.

Summary

In many patients with Fallot’s tetralogy, the fall in arterial oxygen saturation that occurs during exercise can be reduced by prior administration of the beta-sympathetic blocking drug, pronethalol. In a few patients there is also a rise in arterial oxygen saturation at rest.

During exercise, increased stimulation of beta-sympathetic receptors in the heart enhances myocardial contractility; this leads to more complete systolic emptying of the right ventricle, and increased systolic obstruction to ejection of blood into the pulmonary circulation by hypertrophied infundibular muscle. It is this dynamic component of the right ventricular outflow tract obstruction that is abolished or reduced by beta-sympathetic blockade. The phenomenon occurs most readily when valve or high infundibular stenosis is associated with infundibular muscle hypertrophy proximal to the organic ob-
struction, and can sometimes be demonstrated by angiocardiography.

Beta-sympathetic blocking drugs may have a place in the treatment of cyanotic attacks in Fallot's tetralogy, and possibly in the long-term management of the patients in whom total correction has not yet been undertaken.

Acknowledgment

We wish to thank Dr. G. W. Hayward, Dr. D. Weitzman, Mr. O. S. Tubbs, and Mr. I. M. Hill for permission to study patients under their care. This work was done while one of us (D. A. C.) was in receipt of an Aylwen Bursary. Pronethalol ("Aldrin") was supplied by the Pharmaceutical Division of Imperial Chemical Industries, Ltd.

References


“Brights Disease”

By Richard Bright—1827

There has not yet, perhaps, been sufficient time, since this disease of the kidneys first attracted attention, to say to what extent life may be prolonged while the body is under its influence; but I believe, with care, its fatal effects may be kept at bay, and a hazardous life may be protracted for many years. Should that care be neglected, the chance of life will be greatly diminished.—Original Papers of Richard Bright on Renal Disease. Edited by A. Arnold Osman. London, Oxford University Press, 1937, pp. 98-99.
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MICHAEL HONEY, DOUGLAS A. CHAMBERLAIN and JANE HOWARD

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