Long-term propranolol therapy in muscular subaortic stenosis

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Twenty-one patients with muscular subaortic stenosis were treated with oral propranolol for periods of 6 to 34 months for a total of 42.5 patient years. The average follow-up was 2 years. Four patients with latent obstruction became asymptomatic on propranolol therapy. Of the 17 patients with resting obstruction, 7 improved, 2 were unchanged, 5 deteriorated, and 2 died during the period of treatment. The 7 patients with resting obstruction who are still improved on propranolol have had relatively short periods of treatment (average 15 months), and none experienced the degree of improvement that occurred in the patients with latent obstruction. This study indicates that propranolol is most effective in patients with muscular subaortic stenosis who have latent obstruction. It is of limited value in patients with resting obstruction because the benefit of propranolol therapy in the majority of these patients is eventually overtaken by progression in the disease.

It is almost 13 years since Brock (1957, 1959) introduced the concept of functional obstruction to left ventricular outflow, and though this condition has undergone extensive investigation in the intervening period, there is still not complete agreement on the most effective form of therapy. In the past eight years, surgery, which has no effect on the underlying muscle disease, has been shown to relieve the obstruction, abolish the mitral regurgitation, and produce symptomatic improvement (Morrow and Brockenbrough, 1961; Bentall, 1966; Bigelow et al., 1966; Morrow et al., 1968). However, even among surgeons there is a difference of opinion on whether the offending muscle should be divided or resected (Wigle et al., 1968). In the past five years, the beta-adrenergic blocking agents have been used as an alternate therapeutic approach with varying results. This is a report of long-term propranolol therapy in 21 patients with muscular subaortic stenosis.

Material and methods

Sixty patients have been diagnosed as having muscular subaortic stenosis in this laboratory by clinical, haemodynamic, and angiographic techniques. All pressure gradients recorded in these patients reflected true obstruction to left ventricular outflow and not catheter entrapment (Wigle, Auger, and Marquis, 1966; Ross et al., 1966; Wigle, Auger, and Marquis, 1967; Wigle et al., 1969a; Adelman et al., 1969). Of these patients, 24 were placed on propranolol therapy because of symptoms of dyspnoea, angina, presyncope, syncope, palpitations, or paroxysmal supraventricular tachycardias, or because a high pressure gradient was found at heart catheterization. All patients were started on 10 mg. propranolol four times a day, and the dose was gradually increased to a maximum of 300 mg. per day. The dose was judged to be adequate when symptoms were abolished or controlled, or when there was a reduction in the resting heart rate to between 60 and 70 a minute. In 3 patients the drug was discontinued within 2 weeks of the start of therapy because of side effects. The remaining 21 patients were made up of 11 men and 10 women with an age range of 22 to 55 years. They were treated with oral propranolol for periods of 6 to 34 months for a total period of 42.5 patient years and an average of 2 years per patient. These 21 patients were periodically reassessed both by their referring physicians and ourselves. All 21 were classified functionally according to the New York Heart Classification before and during propranolol therapy – grade 1 being asymptomatic; grade 2 symptomatic on more than ordinary exertion; grade 3 symptomatic on ordinary exertion, and grade 4 symptomatic on less than ordinary exertion or at rest. The effect of propranolol therapy on symptoms, physical findings, the electrocardio-

1 This study was supported by the Ontario Heart Foundation.
gram, the cardiothoracic ratio, and cardiac contraction, as judged fluoroscopically, were assessed and all side effects recorded. In addition, 10 patients were evaluated by a standard exercise test on and off propranolol.

On the basis of haemodynamic and ultrasound studies (Shah, Gramiak, and Kramer, 1969b; Shah et al., 1969a), these 21 patients were divided into those with resting obstruction (17 patients) and those with latent obstruction (4 patients). The 17 patients with resting obstruction had a pressure gradient across the left ventricular outflow tract at rest. Twelve of them had ultrasound recordings and all 12 showed a sharp anterior movement in systole of the anterior mitral leaflet toward the ventricular septum. The 4 patients with latent obstruction had no pressure gradient across the left ventricular outflow tract at rest, nor did they show any resting ultrasonic abnormality of the anterior mitral leaflet. They did, however, develop a pressure gradient and the ultrasonic, sharp, systolic anterior movement of the anterior mitral leaflet during pharmacological provocation.

Results
Resting obstruction (Table 1) The long-term results of oral propranolol therapy in the 17 patients with obstruction to left ventricular outflow at rest (resting obstruction) are shown in Table 1. The results are discussed in terms of the response to this drug therapy (improved, unchanged, deteriorated, or died).

Seven patients improved on propranolol therapy administered over periods of 6–24 months (average 15 months). Five patients, classified as grade 2 initially, improved to grade 1 on 80 mg. propranolol a day. Two patients who were grade 3 initially improved to grade 2 on 240 mg. a day, for 12 and 22 months, respectively. In the latter two patients, the degree of improvement has been borderline in that it is lessening in one, and the physical activity of the other is restricted by a leg injury.

Three patients remained in the same functional grade during the period of therapy.

One patient, who was placed on propranolol because a high pressure gradient was found at heart catheterization, was grade 1 before treatment was started. He noted an increase in energy on 160 mg. propranolol a day. Five months after propranolol was started, he developed atrial fibrillation and congestive heart failure. After treatment of congestive heart failure and conversion to sinus rhythm he has been restarted on 60 mg. propranolol a day and has remained asymptomatic. Two patients who remained in grade 2 have experienced a slight reduction in symptoms, though one has required an increased dosage over the past 12 months and the other has her activity restricted because of a leg amputation.

Five patients followed for an average of 27 months deteriorated during the second and third years of therapy on between 160 to 300 mg. propranolol a day. Many of these patients experienced an initial improvement which was not maintained despite increases in drug dosage. When propranolol was discontinued in these patients, they became even more severely incapacitated than before treatment was started, suggesting that propranolol was of benefit and that their deterioration was due to a progression in their disease. Three of these patients have subsequently undergone a successful ventriculomyotomy operation and the other two are being considered for operation.

Two patients died while on propranolol therapy: one, who had no improvement on 160 mg. propranolol a day, was being considered for operation when she died suddenly 18 months after propranolol was started; the other patient, who was also an alcoholic, gradually deteriorated, and died in hospital 2 years after propranolol was started, as a result of arrhythmias and congestive heart failure.

Latent obstruction (Table 2) The results of long-term propranolol therapy in the four

<table>
<thead>
<tr>
<th>Clinical result</th>
<th>No. of patients</th>
<th>N.Y. Heart Ass. Classification grade</th>
<th>Dosage (mg.)</th>
<th>Period of treatment (mth.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Before</td>
<td>During</td>
</tr>
<tr>
<td>Improved (7)</td>
<td>5</td>
<td>2</td>
<td>80</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>240</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td>1</td>
</tr>
<tr>
<td>Unchanged (3)</td>
<td>2</td>
<td>1</td>
<td>120</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>300</td>
<td>3</td>
</tr>
<tr>
<td>Deteriorated (5)</td>
<td>4</td>
<td>2</td>
<td>210</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>80</td>
<td>3</td>
</tr>
<tr>
<td>Died (2)</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE I Long-term oral propranolol therapy in 17 patients with resting obstruction
patients in whom there was evidence of obstruction only with provocation (latent obstruction) are shown in Table 2. All four are improved and are at present asymptomatic. Two of these patients have improved from grade 2 to grade 1 on 60 and 80 mg. propranolol a day for periods of 8 and 12 months, respectively. The two remaining patients in this group improved from grade 3 to 1 on 160 mg. propranolol a day, and have maintained this improvement for periods of 20 and 24 months, respectively. These two patients have had the most consistent and impressive clinical improvement in this series. Both had been experiencing exertional angina, presyncope, and dyspnoea, one for 5 years and the other for 15 years before the institution of propranolol therapy, and in both patients these symptoms recur if the drug is discontinued for over 48 hours.

**Symptoms** (Table 3). The effect of propranolol therapy on the symptoms in these 21 patients with muscular subaortic stenosis is shown in Table 3. The abolition of symptoms occurred in those patients with resting obstruction who improved from grade 2 to 1, and the four patients with latent obstruction; a reduction in symptoms occurred in the four patients who remained or improved to a grade 2; and with the exception of syncope and palpitations, the symptoms in the five patients who deteriorated and the two who died were unchanged or worse. Palpitations were invariably suppressed and no syncopal episodes occurred on propranolol. Presyncope was abolished only in patients with latent obstruction. Propranolol was successful in reducing the number and length of attacks of supraventricular tachycardia in only one of four patients. Congestive heart failure developed in two patients on propranolol therapy.

**Clinical findings** There were no dramatic changes in the clinical findings. The heart rate was consistently decreased by between 10 to 20 beats to 60 to 70 a minute in 17 patients. One patient had a bradycardia before propranolol was started, and was placed on atropine in addition to propranolol to maintain a heart rate of 60 a minute. Three of the patients with resting obstruction who became asymptomatic and all four patients with latent obstruction had a decrease in intensity of the apical systolic murmur. Twelve patients showed an increase in the cardiothoracic ratio of 2–4 per cent on posteroanterior chest x-rays. In three of five patients taken off propranolol for over one week, the cardiothoracic ratio reverted to its original value. In 13 patients the vigour of cardiac contraction was diminished fluoroscopically. Aside from the slower heart rate the only change in the electrocardiogram was T wave inversion in leads I, II, aVL, and the lateral precordial leads. This was seen in the three patients with resting and one patient with latent obstruction. It occurred in one patient transiently and disappeared in another patient when propranolol was discontinued (Fig. 1). Whether these T wave changes were due to the propranolol therapy or to a progression in the disease was not known.

Ten patients had a standard treadmill exercise test on and off propranolol (walking on a level at 3 miles an hour for 3 minutes). Four were not able to walk at 3 miles an hour for a full 3 minutes when off propranolol without developing symptoms, but had no trouble walking at this speed for the full 3 minutes while on the medication. Two of these four patients deteriorated on propranolol therapy despite this evidence of benefit from the drug. The other six patients experienced no difficulty walking at this speed for 3 minutes on or off propranolol, but five of these six patients had post exercise heart rates which were 20 to 40 beats a minute slower on propranolol.

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**Table 2** Long-term oral propranolol therapy in 4 patients with latent obstruction

<table>
<thead>
<tr>
<th>Clinical result</th>
<th>No. of patients</th>
<th>N.Y. Heart Ass. classification</th>
<th>Dosage (mg.)</th>
<th>Period of treatment (mth.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>2</td>
<td>1</td>
<td>60–80</td>
<td>8–12</td>
</tr>
<tr>
<td>Improved</td>
<td>2</td>
<td>3</td>
<td>160</td>
<td>20–24</td>
</tr>
</tbody>
</table>

**Table 3** Effect of long-term propranolol therapy on symptoms in 21 patients with muscular subaortic stenosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of patients</th>
<th>Abolished</th>
<th>Reduced</th>
<th>Unchanged or increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>18 (85%)</td>
<td>4</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Palpitations</td>
<td>17 (81%)</td>
<td>3</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Angina</td>
<td>15 (71%)</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (47%)</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Presyncope</td>
<td>10 (47%)</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Syncope</td>
<td>3 (14%)</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Supraventricular arrhythmias</td>
<td>4 (19%)</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2 (10%)</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
**Propranolol in muscular subaortic stenosis**

**TABLE 4  Side effects**

<table>
<thead>
<tr>
<th>Side effects</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Propranolol stopped</strong></td>
<td></td>
</tr>
<tr>
<td>Anorexia, nausea, and vomiting</td>
<td>1</td>
</tr>
<tr>
<td>Severe diarrhoea</td>
<td>1</td>
</tr>
<tr>
<td>Bradycardia and ventricular premature beats</td>
<td>1</td>
</tr>
<tr>
<td><strong>Propranolol continued</strong></td>
<td></td>
</tr>
<tr>
<td>Paraesthesiae</td>
<td>7</td>
</tr>
<tr>
<td>Headaches</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3</td>
</tr>
<tr>
<td>Visual blurring</td>
<td>2</td>
</tr>
<tr>
<td>Ankle oedema</td>
<td>2</td>
</tr>
</tbody>
</table>

![FIG. 1  Electrocardiograms taken before (left), on (centre), and off propranolol (right). The $T$ waves in leads $I$, $II$, $aVL$, and $V_4$–$6$ became inverted when the patient was placed on propranolol (centre) and reverted to their original configuration 2 weeks after propranolol was discontinued (right).](image)

**Side effects** (Table 4) Three patients given a trial of propranolol were not included in this series as the drug was discontinued within 2 weeks of the start of therapy because of side effects. One experienced anorexia, nausea, and vomiting and a second severe diarrhoea on 80 mg. propranolol a day. The third patient developed a sinus bradycardia with frequent ventricular premature beats despite the concomitant administration of atropine. A number of side effects occurred, which did not necessitate discontinuance of the medication (Table 4). The most common were paraesthesiae and headaches.

**Discussion**

In muscular subaortic stenosis, the degree of outflow tract obstruction is readily altered by physiological and pharmacological stimuli. Positive inotropism, decreased aortic pressure, decreased ventricular volume, and tachycardia are believed to produce increased obstruction. Conversely, negative inotropism, increased aortic pressure, increased ventricular volume, and bradycardia are believed to ameliorate the obstruction to outflow (Braunwald, Brockenhroug, and Frye, 1962; Braunwald and Ebert, 1962; Krasnow et al., 1963; Whalen et al., 1964; Wigle et al., 1965; Goodwin et al., 1964; Braunwald et al., 1964a, b; Wigle, 1965, 1965; Shah et al., 1965; Klein, Lane, and Golin, 1965; Mason et al., 1967).

The beta-adrenergic blocking agents have been advocated in the treatment of this condition because they slow the heart rate, thereby increasing ventricular volume, and decrease myocardial contractility. They also prevent arrhythmias and may decrease myocardial oxygen consumption (Epstein and Braunwald, 1966, 1967). The beta-blocking agents have been shown to ameliorate the intensification of the outflow tract obstruction which follows exercise and the administration of isoprenaline. However, the intensification of the obstruction produced by premature ventricular contractions, the Valsalva manoeuvre, and amyl nitrite may or may not be prevented, and in most acute experiments the beta-blocking agents have had little effect on the degree of obstruction at rest (Goodwin et al., 1964; Harrison et al., 1964; Cherian et al., 1966; Flamm, Harrison, and Hancock, 1968).
Some investigators have reported favourable clinical results of long-term propranolol therapy in patients with muscular subaortic stenosis. Scheu, Bollinger, and Wirz (1966), Cherian et al. (1966), Rosenblum et al. (1967), and Parker et al. (1969) reported subjective improvement in a total of 21 out of 27 patients. Cohen and Braunwald (1967, 1968) showed amelioration of angina and increased exercise tolerance in five of eight patients on oral propranolol therapy. Of these five patients maintained enough of a beneficial effect to obviate the need for operation for periods of up to three years. The other two eventually required an operation. Sloman (1967) and Bliss, Moffat, and Gantt (1967) noted that, though most patients had some initial improvement, this improvement was not usually maintained.

Recently, Flamm et al. (1968) and Stenson et al. (1969) reported that propranolol reduced the resting gradients and might prevent gradients from developing in patients with labile and latent outflow tract obstruction. Patients with labile obstruction had resting gradients which varied spontaneously from absent or very small to as high as 80 mm. Hg. They suggested that propranolol was of no benefit in patients who had persistently high gradients at heart catheterization, but was effective in patients with labile and latent obstruction.

In the present study, the patients were divided into those with resting and those with latent obstruction on the basis of haemodynamic and ultrasound studies. Of the 17 patients with resting obstruction, eight had labile obstruction during heart catheterization, but the results of long-term propranolol in these patients were no different than in the other nine in whom the degree of left ventricular outflow tract obstruction remained relatively constant. All four patients with latent obstruction had complete relief of their symptoms, including two patients who were grade 3. Not one patient with resting obstruction had this degree of improvement. In fact, of the eight patients with resting obstruction in grade 3 before therapy, only two maintained even minimal improvement into the second and third years of therapy, while four deteriorated and two died. In contrast, of the eight patients in grade 2 before therapy, five improved, two were unchanged, and only one deteriorated. It is important to note, however, that the patients with resting obstruction who improved have only been treated for an average of 15 months compared to an average treatment period of 27 months for those who deteriorated. Long-term propranolol therapy

**FIG. 2** Simultaneous left ventricular and aortic pressure tracings taken from a patient with latent obstruction during amyl nitrite (A) and isoprenaline (B) provocation, before (top) and after (bottom) 3 mg. propranolol was administered intravenously.

A: Top: This patient had no pressure gradient across the left ventricular outflow tract at rest but a gradient readily developed after the inhalation of amyl nitrite (↑). Bottom: After 3 mg. propranolol was administered intravenously the inhalation of amyl nitrite (↑) did not provoke a gradient despite a comparable drop in aortic pressure. (A)

B: Top: Similarly, in this same patient a pressure gradient readily developed after the administration of 1.5 μg. isoprenaline intravenously (↑). Bottom: However, after the administration of 3 mg. propranolol intravenously, 1.5 μg. isoprenaline (↑) failed to provoke a gradient. (B)
was therefore of greatest benefit to patients with latent obstruction and patients with resting obstruction in grade 2, but these patients have had relatively short periods of treatment (6 months to 2 years).

These results correlate with haemodynamic evidence that beta-adrenergic blockade prevents pharmacological provocation of a gradient in patients with latent obstruction (Fig. 2) but only ameliorates the intensification of the gradient in patients with resting obstruction (Fig. 3) (Harrison et al., 1964; Flamm et al., 1968). The results also correlate with ultrasound recordings carried out by Shah et al. (1969a) who studied the effects of treatment on the abnormal systolic movement of the anterior mitral leaflet found in muscular subaortic stenosis. These studies, which included 16 of the 21 patients in this series, showed that propranolol had no effect on the sharp systolic anterior movement of the anterior mitral leaflet, though this movement was abolished by a successful ventriculomyotomy. Popp and Harrison (1969), however, reported that this ultrasonic abnormality was abolished in one patient on long-term oral propranolol therapy and in two patients during the acute administration of propranolol.

There is at present only limited information available on the natural history of muscular subaortic stenosis. This lack of knowledge makes it difficult to assess the efficacy of various forms of therapy in this condition. In a recent excellent review of 98 patients, followed for an average of 3 years, Frank and Braunwald (1968) found that only 14 patients deteriorated and 10 died. Of the remaining 74 patients, 54 remained stable, 14 fluctuated, and six patients in grade 3-4 actually improved. Parker (1969) had no deaths and only one patient deteriorated in a series of 18 patients followed for an average of 4-2 years.

**Fig. 3** Simultaneous left ventricular and aortic pressure tracings from a patient with resting obstruction taken under control conditions (Panel 1); after the inhalation of amyl nitrite (Panel 2); after the intravenous administration of 2 µg. (Panel 3), and 3 µg. isoprenaline (Panel 4, bottom) before (top) and after (bottom) the intravenous administration of 3 mg. propranolol. At rest, there was a gradient of 15 mm. Hg across the left ventricular outflow tract both before (Panel 1, top) and after (Panel 1, bottom) propranolol was given. Propranolol did not ameliorate the intensification of the gradient that occurred after the inhalation of amyl nitrite (Panel 2), but did ameliorate the intensification of the gradient that occurred after 2 µg. isoprenaline was administered (Panel 3). However, after the propranolol was given, 3 µg. isoprenaline (Panel 4, bottom) provoked a gradient that was comparable to the gradient provoked by 2 µg. isoprenaline before propranolol was administered.
A retrospective and prospective analysis of the clinical course in 60 haemodynamically proven cases seen in this laboratory (Wigle et al., 1969b) revealed that muscular subaortic stenosis in our experience was a disease of gradual progression with an average of 10 years elapsing between the discovery of the murmur and the onset of symptoms (grade 2). Of these 60 patients, 40 (66%) developed more severe symptoms (grade 3-4) an average of 5 years later. This experience contrasts with that of Frank and Braunwald (1968) and of Parker (1969) who only had a 22 percent incidence of grade 3 and 4 symptomatology.

Taking into consideration the progressive nature of this condition in our experience, the failure of propranolol to abolish the gradient in patients with resting obstruction and the ability of propranolol to prevent provocation of a gradient in patients with latent obstruction, our results of long-term propranolol therapy in patients with muscular subaortic stenosis may be interpreted as follows. (1) Patients with latent obstruction benefit from propranolol therapy because in these patients the drug prevents obstruction from developing with exercise or other provocative stimuli. (2) Patients with resting obstruction in grade 2 may have maintained improvement at the completion of this study because of the mildness of their symptoms and because they have only been followed for an average of 15 months. As our natural history study indicates that grade 2 symptomatology lasts an average of 10 years, this is too short a period of treatment to determine whether this improvement will be maintained. (3) Patients with resting obstruction in grade 3-4 experienced only limited benefit from the drug because progression of the disease eventually overcame the propranolol benefit. Deterioration in these patients was probably appreciated because of the longer period of follow-up on propranolol therapy (average 27 months) and because the rate of deterioration appears to accelerate in more severely symptomatic patients.

Though this interpretation suggests that patients with resting obstruction at present classified as improved on propranolol therapy may deteriorate with a longer period of follow-up, it is still our present policy to administer the drug to all symptomatic patients with muscular subaortic stenosis and to those with severe degrees of obstruction to outflow. If these patients develop evidence of deterioration, the ventriculomyotomy operation is recommended.

We wish to express our gratitude to Drs. N. Ranganathan, G. D. Webb, Y. Marquis, and P. Auger for their assistance in studying these patients; to Dr. R. O. Davies of Ayerst Laboratories for his helpful advice and for supplying the propranolol for this study; to Miss Jean McMeehan, Miss Rose Marie Csepló, Mrs. Ruth Kuerzi, Mrs. Pamela Casson, and Mrs. Ann Oppryszko for excellent technical assistance; and to the Department of Art as Applied to Medicine, University of Toronto, and to the Department of Medical Photography, Toronto General Hospital (Mr. Robert Paget, Director), for help in preparing the figures.

References


Addendum

Since this study was submitted for publication two additional patients with latent muscular subaortic stenosis have been treated with propranolol. Both have had complete relief of their symptoms.