Amelioration of Angina Pectoris in Idiopathic Hypertrophic Subaortic Stenosis with Beta-Adrenergic Blockade

By Lawrence S. Cohen, M.D., and Eugene Braunwald, M.D.

SUMMARY

Beta-adrenergic receptor blockade has been demonstrated to reduce obstruction of the left ventricular outflow tract in patients with idiopathic hypertrophic subaortic stenosis (IHSS) and has also proved helpful in reducing angina pectoris due to ischemic heart disease. Accordingly, the effects of oral propranolol on the level and duration of exercise required to produce angina in seven patients with IHSS were compared with a placebo. Improvement in exercise performance was observed in six patients taking propranolol orally in doses ranging from 80 mg to 480 mg daily. Clinical improvement was sustained in the four patients given propranolol since discharge from the hospital for periods up to 15 months, and in three it has been possible to obviate corrective operations. The mechanism by which propranolol is efficacious in this disease is probably related to the diminution of myocardial O2 requirements resulting from the reduction of wall tension, velocity of contraction, and heart rate induced by beta-adrenergic receptor blockade.

EXERCISE-INDUCED angina pectoris is a distressing symptom in many patients with idiopathic hypertrophic subaortic stenosis (IHSS). Exercise increases myocardial oxygen requirements by activating cardiac adrenergic receptors, and in patients with IHSS it augments the work of the left ventricle not only by increasing its output but also by increasing obstruction to left ventricular outflow.

In an earlier study it was demonstrated that pronethalol, a beta-adrenergic receptor-blocking drug, reduced the obstruction during and immediately after exercise. Subsequent clinical studies demonstrated subjective improvement in 10 of 13 patients with IHSS when propranolol, another beta-blocking agent, was administered chronically. Dyspnea was diminished in seven of nine patients, syncope disappeared in five

Additional Indexing Words:
Exercise tolerance
Congestive heart failure
Propranolol

Myocardial function

EXERCISE-INDUCED angina pectoris is a distressing symptom in many patients with idiopathic hypertrophic subaortic stenosis (IHSS). Exercise increases myocardial oxygen requirements by activating cardiac adrenergic receptors, and in patients with IHSS it augments the work of the left ventricle not only by increasing its output but also by increasing obstruction to left ventricular outflow. In an earlier study it was demonstrated that pronethalol, a beta-adrenergic receptor-blocking drug, reduced the obstruction during and immediately after exercise. Subsequent clinical studies demonstrated subjective improvement in 10 of 13 patients with IHSS when propranolol, another beta-blocking agent, was administered chronically. Dyspnea was diminished in seven of nine patients, syncope disappeared in five of six, and angina was relieved in both patients who had this symptom prior to therapy. Because beta-adrenergic receptor blockade appears to improve hemodynamics in IHSS and since recent investigations indicate that propranolol is a useful drug in the treatment of angina pectoris due to ischemic heart disease, the present study was undertaken to determine the effects of propranolol on exercise-induced angina pectoris in patients with IHSS.

Methods

Seven patients with angina pectoris in whom the diagnosis of IHSS was established by clinical, hemodynamic, and angiographic means, as described in detail previously, were studied (table 1). Their ages ranged from 29 to 46 years; six were males and one was a female. One patient (M.S.) had been operated upon previously elsewhere for relief of outflow tract obstruction, but at the time of postoperative study the residual left ventricular-aortic pressure gradient was 78 mm Hg.
Table 1

<table>
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<th>LVEF</th>
<th>BA</th>
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Abbreviations: LVEDP = left ventricular end-diastolic pressure; BA = brachial artery; HR = heart rate; and CI = cardiac index.

Exercise was performed on a motor-driven treadmill, generally at a speed of 2.2 miles per hour. The grade was increased by 2.5% every 2.5 minutes. Angina pectoris or exhaustive fatigue was the end-point signaling cessation of exercise. The dose of propranolol administered varied between 80 mg and 480 mg a day; the drug was given orally in four divided doses. The study was carried out as a single blind study with several days of propranolol being followed by several days of placebo. In each patient several crossovers between propranolol and placebo were performed. At least one full day elapsed after each crossover before treadmill exercise observations were made.
AMELIORATION OF ANGINA PECTORIS

Figure 2
R.S. (06-48-53) Relation between duration and intensity of exercise (abscissa) and heart rate (ordinate). The triangles represent the onset of angina at which point exercise had to be terminated. On the days when placebo was given this patient had to stop because of the onset of angina after an average time of 5 minutes. When propranolol was given, the patient never developed angina but had to stop because of fatigue after an average of 12.5 minutes. The exercising heart rate while the patient was receiving propranolol never reached the levels attained on those days when he received placebo.

Figure 3
D.W. (06-08-68) Angina occurred significantly later when propranolol was given than when placebo was administered, but when angina did occur with propranolol, it was at a heart rate comparable to that existing on days which placebo was given.

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Figure 4
G.S. (06-31-23) Ability to exercise increased as the dose of propranolol was raised. While 200 mg of propranolol a day was administered, the patient walked an average of 16 minutes and achieved a grade of 15% in contrast to the days on which placebo was given when he walked for an average of 11 minutes and achieved a grade of 10%. When he received 400 mg of propranolol daily, exercise was discontinued because of fatigue and angina pectoris did not occur.

Results
Four of the seven patients exhibited significantly improved exercise tolerance on the days on which they received propranolol in comparison to the days on which placebo was administered (figs. 1 to 4). These four patients were able to walk for an average of 6.9 minutes and to achieve an average grade of 5% before being stopped by angina pectoris while they received placebo. When they received propranolol, they walked for an average of 12.5 minutes and achieved an average grade of 10%. In two of these four patients the treadmill was stopped because of angina, but the other two patients did not develop this symptom while they were receiving propranolol and were forced to stop only because of fatigue.

Two of the seven patients demonstrated modest increases in both duration and grade of treadmill exercise when propranolol was given, while one patient was not improved by propranolol therapy. In all seven patients propranolol slowed heart rate both at rest and at any level of exercise. The degree of improvement of exercise tolerance was not dependent upon the extent of slowing which occurred. In some instances (fig. 3), angina...
occurred at the same heart rate when the patient was receiving propranolol as when he was receiving the placebo, while in others angina developed at slower heart rates during beta-blockade (fig. 4).

In patient G. S., an analysis of two doses of propranolol demonstrated a greater therapeutic effect from 400 mg than from 200 mg of propranolol daily. An analysis of paired differences between drug and placebo studies for the entire group of seven patients showed a statistically significant increase in exercise tolerance when propranolol was administered ($P < 0.05$).

Discussion

Angina pectoris is a common symptom in patients with IHSS and at times is a major factor limiting their ability to exert themselves. The effects of beta-adrenergic receptor blockade on the myocardial oxygen requirements of patients with IHSS are complex. Since beta-adrenergic receptor blockade has been demonstrated to diminish obstruction to the left ventricular outflow tract and to decrease the left ventricular-aortic gradient, it is likely that it also tends to reduce left ventricular wall tension. In addition, the velocity of ventricular contraction and heart rate are also diminished by beta-blockade. Wall tension, velocity of contraction, and heart rate have all been demonstrated to be important determinants of the myocardium's oxygen requirements. A diminution in all three of these by beta-adrenergic receptor blockade, therefore, would be expected to lower myocardial oxygen needs. On the other hand the negative chronotropic effect and diminution of sympathethic stimulation of the heart induced by beta-adrenergic receptor blockade would tend to increase ventricular end-diastolic volume and by Laplace's law to increase wall tension at any left ventricular systolic pressure. In spite of these opposing actions it appears that the net effect of beta-blockade is to diminish myocardial oxygen requirements in patients with IHSS and thereby to reduce the frequency of angina pectoris.

In the four patients in this study in whom propranolol had the most striking results, the drug has been administered since discharge from the hospital, and some beneficial effects have been sustained in each of them for periods up to 15 months. In three of these patients symptoms were severe enough to warrant serious consideration of operative correction prior to the administration of propranolol, but they are now capable of full-time work. In these individuals beta-adrenergic receptor blockade has clearly been of benefit in obviating operation.

It should be emphasized that certain patients with heart disease may require heightened sympathetic drive to maintain adequate cardiac function. Previous studies have indicated that beta-adrenergic blockade may result in progressive sodium retention leading to increasing fluid accumulation and edema. Indeed, in one of our patients who was treated chronically with propranolol, fluid retention and pulmonary edema occurred. These manifestations of congestive heart failure were controlled with more adequate diuretic therapy and treatment with propranolol did not have to be discontinued. The dangers of congestive heart failure in patients undergoing beta-adrenergic receptor blockade must be realized, however, when this course of therapy is instituted and the drug is probably contraindicated in patients with IHSS in whom symptoms of heart failure rather than myocardial ischemia are most prominent.

References


Embryology of the Heart—Harvey, 1628

In a Hen's egg I shewed the first beginning of the Chick, like a little cloud, by putting an egg off which the shell was taken, into warm water and clear, in the midst of which cloud there was a point of blood which did beat, so little, that when it was contracted it disappeared, and vanish'd out of our sight, and in its dilatation, shew'd it self again red and small, as the point of a needle; insomuch as betwixt being and not being seen, as it were betwixt being and not being, it did represent a beating, and the beginning of life.—The Anatomical Exercises of Dr. William Harvey: De Motu Cordis 1628; De Circulatione Sanguinis 1649 (first English text). Edited by Geoffrey Keynes. London, The Nonesuch Press, 1653, p. 34.
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Circulation. 1967;35:847-851
doi: 10.1161/01.CIR.35.5.847

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/35/5/847

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