Effects of Oral Propranolol on Left Ventricular Size and Performance During Exercise and Acute Pressure Loading

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SUMMARY Oral propranolol (160 mg/day) was administered to 19 normal subjects for 2 weeks. Echocardiograms were performed at rest, during graded supine bicycle exercise in 10 subjects and during acute pressure loading with intravenous phenylephrine in the remaining nine subjects. Resting heart rate on propranolol decreased compared with control (52 ± 8 vs 63 ± 10 beats/min; p < 0.001), as did systolic blood pressure (99 ± 9 vs 107 ± 9 mm Hg; p < 0.01). Left ventricular end-diastolic dimension was slightly enlarged (48.3 ± 4.2 vs 47.1 ± 3.6 mm, p = 0.05), but percent dimensional shortening was unchanged (37 ± 4 vs 38 ± 5%). At each stage during supine bicycle exercise, heart rate was slower, blood pressure lower, left ventricular dimensions were larger and percent dimensional shortening was reduced on propranolol by an analysis of variance. In contrast, during acute pressure loading, while the heart rate response to increased blood pressure was blocked by atropine, there was no significant difference in left ventricular size and performance compared with control. We conclude that prolonged oral propranolol therapy has little, if any, intrinsic effect on myocardial performance in normal subjects. Its major action on the heart is competitive inhibition of β-adrenergic tone, which is most manifest during conditions associated with increased sympathetic tone, such as exercise.

THE EFFECTS of oral propranolol on left ventricular performance are controversial. Early studies using acute i.v. propranolol demonstrated decreases in left ventricular performance at rest and during exercise in animals1,2 and man.3,4 In a study of i.v. propranolol, exercise endurance decreased by 40% in normal human subjects.5 However, a study of orally administered propranolol in normal subjects did not reveal significant decreases in treadmill exercise endurance.6 Accordingly, we evaluated the effects of chronic oral propranolol on left ventricular size and performance at rest, during supine bicycle exercise and during acute pressure loading in normal subjects by echocardiography.

Methods

The study included 19 normal subjects, 10 men and nine women, ages 19–36 years. They were selected from a larger group of normal subjects because they had excellent echocardiograms in the supine position at rest. Each subject gave written informed consent on a form approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio.

All 19 subjects took propranolol, 160 mg/day, in four divided doses for 2 weeks. At the time of the study done on propranolol, which was approximately 2 hours after the last dose, serum propranolol levels were detected in all by the method of Shand,7 and ranged from 23–151 ng/ml (mean 70 ng/ml). Excellent echocardiograms were obtained in 10 subjects during supine bicycle exercise; these subjects were studied during exercise on 3 days, twice before and once during the last 4 days of propranolol therapy. The nine other subjects consented to acute pressure loading with phenylephrine and were studied with this stressful intervention before and during propranolol therapy.

Bicycle Exercise

Supine bicycle exercise was begun at 200 kpm/min and increased by 100 kpm/min every 3 minutes using a Quinton Uniwork Ergometer Model 844. Before exercise in the cycling position (feet up) and during the last minute of each 3-minute stage, blood pressure (cuff sphygmomanometer) and echocardiograms were recorded. Exercise endurance in these untrained subjects ranged from 12–30 minutes (mean 17.5 minutes). Thus, in order to use data from all the subjects, only the echocardiograms from the first 12 minutes of exercise were analyzed.

Acute Pressure Loading

An intravenous infusion of 5% dextrose and water was begun through a scalp vein needle. A baseline echocardiogram and blood pressure were then obtained. Subsequently, enough atropine was administered i.v. to raise the heart rate at least 30 beats/min or until a maximum of 1.5 mg had been given. At this point with the reflex heart rate response to increased arterial pressure blocked by atropine, enough phenylephrine (10 mg diluted in 250 ml of
0.9% NaCl) was infused over 5–10 minutes to raise the systolic arterial pressure approximately 40 mm Hg. With systolic pressure held at this level, a second echocardiogram was obtained and the infusion was terminated. The total volume of fluid used in the entire study did not exceed 50 ml.

Echocardiography

Echocardiograms were obtained on either a Picker Echoview 80-C, coupled with an Irex Continutrace 101 recorder or an Electronics for Medicine Echo IV system. Echocardiograms of the left ventricle were taken from the standard intercostal space along the left sternal border using a hand-held transducer (2.25 mHz) and were recorded on a strip-chart recorder at 100 mm/sec paper speed. The R wave of the simultaneously recorded ECG was used as the reference point, and end-diastolic dimension (Dd) of the left ventricle was measured at the level of the chordae tendineae. The end-systolic dimension (Ds) was measured as the smallest dimension between the left septal endocardium and the posterior wall endocardium during systole, even if points of maximum excursion were not exactly apposed. Simultaneous indirect carotid pulse tracings were recorded separately during the acute pressure loading studies in order to measure left ventricular ejection time (ET). Heart rate was calculated from the simultaneously recorded ECG. All echocardiograms were performed with the subject in the same position, with the hand-held transducer in the same interspace and when the same anatomic landmarks were present. The echocardiographic measurements were made during expiration and represent the average of at least three heart beats.

Figure 1 shows representative echocardiograms recorded at rest and during supine bicycle exercise. The ECG at the top of each echo indicates the increasing heart rate. Note that the anatomic landmarks are identical in each recording. Similar high-quality echocardiograms were recorded during the acute pressure loading studies.

From the echocardiographic measurements described above, the percent left ventricular dimensional shortening (%ΔD) and the normalized mean rate of left ventricular dimensional shortening (Vd) were calculated as follows:

\[
\%\Delta D = \frac{Dd - Ds}{Dd} \times 100\%
\]

\[
Vd = \frac{Dd - Ds}{Dd \times ET}
\]

Statistical Analysis

For the acute pressure loading studies, the subjects’ resting values and those obtained during acute pressure loading were compared using the paired t test, with each subject serving as his/her own control. For the exercise studies, a two-way analysis of variance for repeated measures was performed and mean differences were determined through the use of the Student Newman-Kuells mean comparison test based on the range. The latter analysis was done on a Digital Equipment Corporation System 2050 in the Office of Computing Resources at the University of

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** A) Left ventricular echogram at rest in one of the subjects showing the measurement of the end-diastolic dimension (Dd) and end-systolic dimension (Ds). B) Left ventricular echogram in the same subject during 12 minutes of supine bicycle exercise.
Texas Health Science Center at San Antonio. All values are expressed as mean ± SD.

Results

Resting Data

Data were obtained at rest in all 19 subjects (fig. 2). Resting heart rate was significantly lower on propranolol compared with the control measure (52 ± 8 vs 63 ± 10 beats/min, respectively; p < 0.001). Systolic blood pressure was also lower during propranolol therapy (99 ± 9 vs 107 ± 9 mm Hg, p < 0.01). Left ventricular Dd was larger on propranolol compared with the control measure (48.3 ± 4.2 vs 47.1 ± 3.6 mm, p = 0.05). The %ΔD was not significantly different on or off propranolol therapy (37 ± 4 vs 38 ± 5%).

Bicycle Exercise

In the 10 subjects who performed supine bicycle exercise, an analysis of variance for the exercise data showed no significant difference between any of the measures examined between the first and second control exercise studies done on different days. This analysis did demonstrate a consistent significant difference (F values) between all the measures on the propranolol study day and either of the 2 control days. However, when individual measures were examined at specific time periods during exercise by the mean comparison test, significant differences were not always found. The details of the mean comparison tests for the values on the second control period compared with those during propranolol administration are as follows:

Heart rate during exercise was significantly slower on propranolol at 6, 9 and 12 minutes of exercise (p < 0.01, fig. 3). Individual values for systolic blood pressure, although lower on propranolol, were not statistically different from control (fig. 4). Left ventricular Dd was consistently larger on propranolol, but individual values were not significantly different (fig. 5). Left ventricular Ds was significantly larger at each stage of exercise on propranolol (fig. 5). Consequently, %ΔD was significantly lower at each stage of exercise with propranolol (p < 0.05, fig. 6).

Acute Pressure Loading (table 1)

In the nine subjects who underwent acute pharmacologic pressure loading, there was no significant difference between the average values on propranolol compared with control for heart rate, systolic blood pressure, and the echocardiographic measures of left ventricular size and performance.

Discussion

Our data indicate that oral propranolol decreases heart rate and blood pressure at rest in normal subjects and slightly increases end-diastolic size, but does not significantly alter left ventricular performance.
During supine bicycle exercise, an analysis of variance showed that there was a consistent significant difference between control and drug for all measures studied. Heart rate was slower, blood pressure lower, left ventricular size larger and \( \% \Delta D \) lower during exercise on propranolol therapy. In contrast, during the stress of acute pressure loading, neither heart rate, blood pressure, left ventricular size or performance were significantly different on propranolol compared with control.

Previous studies of oral \( \beta \)-adrenergic blocking agents in normal subjects and patients with coronary artery disease have shown results similar to ours in the resting state. Chamberlain\(^9\) studied normal subjects after oral pronethalol by cinefluoroscopy in the upright position. Eight of his 10 subjects showed an increase in overall heart size in systole and diastole. Our data showed a barely significant increase in left ventricular end-diastolic dimension in the supine position. Presumably, Chamberlain's results are a combination of an enlargement of the left ventricle, right ventricle and right atrium, all of which make up the cardiac silhouette in the anteroposterior view. Pine and co-workers\(^9\) evaluated oral propranolol in normal subjects and patients with coronary artery disease by echocardiography. They demonstrated no significant change in ejection fraction at rest in either group at doses of propranolol that maximally blocked the heart rate response to treadmill exercise. Similarly, two recent studies using radionuclide angiography did not reveal any change in ejection fraction at rest in patients with coronary artery disease on oral propranolol in doses that resulted in maximal clinical benefit.\(^{14,15}\) These results are similar to those found by Sonnenblick and associates,\(^{16}\) who studied patients with radiopaque epicardial left ventricular markers placed during corrective cardiovascular surgery. These investigators used i.v. propranolol and found insignificant changes in left ventricular diastolic size and the velocity of shortening of the distance between the clips. Therefore, oral propranolol at rest may slightly increase left ventricular size coincident with a significant decrease in heart rate, but indices of left ventricular performance are unaffected.

Our results during exercise are also similar to those of other studies. Chamberlain found that the increase
in end-diastolic and end-systolic heart size detected by cinefluoroscopy after oral pronethalol persisted during upright bicycle exercise compared with a control exercise study. Sonnenblick and associates evaluated supine bicycle exercise after i.v. propranolol and found that the distance between surgically placed epicardial clips in their patients remained larger during exercise compared with control and that the velocity of shortening of the distance between the clips at the isochronal point was less. These data are also consistent with a study in previously instrumented running dogs by Horwitz and co-workers using i.v. propranolol. They found that the end-diastolic and end-systolic dimensions of the left ventricle determined by small endocardial ultrasonic crystal implants were larger during exercise after propranolol and stroke volume was significantly less. Therefore, during exercise, β-adrenergic blockade causes a significant increase in heart size and a decrease in left ventricular performance that persists throughout exercise. In contrast to the results during exercise, acute pressure loading of the left ventricle in our study showed no significant effects on heart rate, blood pressure, left ventricular size and left ventricular performance after oral propranolol. This experimental situation seemed to be one with relatively little sympathetic or parasympathetic activity. Parasympathetic action on the heart was blocked by i.v. atropine, such that heart rate was faster than at rest during acute pressure loading. The usual vagally mediated decrease in heart rate produced by an increase in blood pressure was blocked. Also, the increase in blood pressure produced by the phenylephrine undoubtedly resulted in baroreceptor inhibition of centrally mediated sympathetic tone, since the same dose of propranolol that significantly reduced the heart rate–blood pressure response to bicycle exercise did not affect the heart rate during acute pressure loading after atropine. Therefore, during acute pressure loading, preload (left ventricular Dd), afterload (systolic blood pressure) and heart rate were the same before and after propranolol and the parasympathetic and sympathetic nervous systems had little, if any, influence on the heart. If propranolol had any intrinsic depressant properties besides competitively inhibiting β-adrenergic effects, one might expect that when the ventricle was under increased afterload stress it would demonstrate them. However, no significant difference in ventricular performance was observed before and during propranolol therapy. Thus, oral propranolol appears to have little direct effect on myocardial performance in normal human subjects.

In a study by LeWinter and associates, conscious, chronically instrumented dogs were given oral propranolol until the heart rate increase to i.v. bolus injections of isoproterenol was less than 10%. They found modest (9–12%) but statistically significant decreases in both isovolumic and ejection phase indices of left ventricular performance on propranolol compared with control during acute simultaneous pressure and volume loading at matched heart rates and end-diastolic pressures. They suggested that the volume loading prevented the ventricle from increasing preload during acute pressure loading to maintain stroke volume. In our nine subjects during propranolol therapy, Dd increased from an average of 44.7 ± 3.4 mm after atropine to 48.2 ± 2.8 mm during the subsequent phenylephrine infusion, when blood pressure was augmented but heart rate was unchanged (p < 0.005). Therefore, our normal human subjects were allowed to use preload increase to help compensate for the increase in afterload, and consequently, were less severely stressed than the dogs described above. This difference in loading conditions probably explains why we were unable to detect any difference in performance during acute pressure loading on oral propranolol therapy.

Our study is unique in that we used M-mode echocardiography to assess left ventricular size and performance at rest, during exercise and during acute pressure loading in human subjects on prolonged oral propranolol therapy. We have shown that echocardiography is a sensitive and reproducible technique for detecting changes in left ventricular size and performance during manipulations in heart rate and blood pressure, prolonged oral digoxin therapy, oral quinidine therapy, and during handgrip and bicycle exercise. Furthermore, in this study there was no significant difference between measurements made during control exercise on day 1 vs day 2 by an analysis of variance. Therefore, we believe that M-mode echocardiography is a sensitive and reproducible method for evaluating left ventricular size and performance under a variety of conditions in subjects with symmetrically contracting left ventricles, such as normal subjects. This technique would not be expected to be accurate in patients with segmental wall motion abnormalities.

Based on our data and those of others, propranolol

| Table 1. Comparison of Control Values to Those on Propranolol During Acute Pressure Loading in Nine Subjects |
|---------------------------------|----------|----------|----------|----------|
| HR (beats/min) | SBP (mm Hg) | Dd (mm) | %ΔD | Vd (sec⁻¹) |
| C 88 ± 12 | 157 ± 10 | 46.9 ± 2.5 | 34 ± 6 | 1.11 ± 0.17 |
| P 85 ± 16 | 154 ± 11 | 48.2 ± 2.8 | 35 ± 3 | 1.16 ± 0.11 |

Values are mean ± SD.

Abbreviations: C = control; P = during propranolol therapy; HR = heart rate; SBP = systolic blood pressure; Dd = end-diastolic dimension; %ΔD = percent dimensional shortening; Vd = normalized mean rate of left ventricular dimension shortening.
apparently has little, if any, intrinsic depressant effects on the myocardium. Its major action on the heart seems to be competitive, \(\beta\) -adrenergic blockade, which is most manifest during periods of intense sympathetic stimulation, such as exercise. These conclusions are consistent with those of others who studied the effects of i.v. propranolol using different techniques in both animals and man.\(^2\)\(^,\)\(^6\) However, patients with a history of overt congestive heart failure who are dependent on sympathetic tone for the maintenance of resting ventricular performance would be expected to be adversely affected by oral propranolol. Other patients with more subtle degrees of left ventricular dysfunction may be variably affected, depending on their need for increased sympathetic tone. Some evidence suggests that these patients may benefit from concomitant digoxin therapy.\(^{23}\) Future studies should be directed at this mild left ventricular dysfunction group, using techniques applicable to studying patients with segmental wall motion abnormalities during exercise.

References

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