Assessment of Cardiac Performance With Quantitative Radionuclide Angi cardiography

Effects of Oral Propranolol on Global and Regional Left Ventricular Function in Coronary Artery Disease

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SUMMARY The effect of incremental dosages of oral propranolol (mean peak dose of 165 ± 13 mg/day) on left ventricular ejection fraction, ejection rate and regional wall motion was studied sequentially in 22 stable, resting patients with coronary artery disease using a geometry-independent first-pass radionuclide angiographic technique. All patients improved clinically, in association with a fall in heart rate and therapeutic serum propranolol levels. No significant changes were noted in ejection fraction, ejection rate or regional wall motion. No patient developed a new regional wall motion disturbance. Thus, oral propranolol administered at clinically effective antianginal dosages in patients with stable coronary artery disease does not appear to have significant deleterious effects on resting left ventricular performance.

THE PREDOMINANT CARDIAC EFFECTS of β-adrenergic blockade are inhibition of the positive inotropic and chronotropic responses to local and circulating catecholamines. When applied clinically, this may exacerbate regional ventricular dysfunction or precipitate congestive heart failure in some cases. However, a consistent negative effect upon ventricular performance after intravenous propranolol has not been demonstrated uniformly in man in the basal state. Furthermore, the relevance of acute studies to the use of propranolol for long-term patient management is unclear. Noninvasive assessment of the effects of oral therapy also have been contradictory. While one study found that propranolol decreased echocardiographic left ventricular ejection fraction and posterior wall motion, others have not reported significant changes.

Recently-developed noninvasive radionuclide techniques may offer major advantages for assessment of ventricular performance in patients with coronary artery disease. With first-pass quantitative radionuclide angiography, analysis of pump performance is based upon regional radionuclide time-activity curves. Consequently, this approach is independent of the geometric assumptions inherent in volume determinations made from cavitory outlines or single intracardiac dimensions. The present study was designed to assess the effects of chronic oral propranolol therapy upon basal left ventricular function in patients with coronary artery disease with this radionuclide technique. Left ventricular ejection fraction, mean normalized ejection rate, and regional wall motion were assessed before institution of propranolol therapy and at incremental dosages until maximal clinical improvement was achieved.

Materials and Methods

Patient Population

The study population consisted of 22 ambulatory patients with coronary artery disease (19 male and three female). Mean age was 54 years (range 27–64 years). Propranolol therapy was instituted for treatment of either angina pectoris (20 patients) or ventricular arrhythmias (two patients). No patient had sustained a myocardial infarction within the three months preceding study or had significant valvular regurgitation. The diagnosis of coronary artery disease was based upon at least one of the following criteria: 1) previous myocardial infarction defined by a documented clinical event of sustained chest pain associated with characteristic serum enzyme elevations and electrocardiographic evidence of either pathologic Q waves 0.04 sec in duration or persistent T wave inversions; 2) the clinical syndrome of angina pectoris associated with an abnormal exercise stress test manifested by at least 1 mm horizontal or downsloping ST segment depression, at least 0.08 sec in duration and in a lead with a normal resting recording, occurring in conjunction with exercise-induced ischemic chest pain; 3) angiographically demonstrable significant coronary arterial stenosis (greater than 70% decrease in luminal diameter). The diagnosis of
coronary artery disease was obvious clinically in all patients; coronary angiography was obtained in six patients. Eighteen patients had stable effort-related angina pectoris (New York Heart Association Class II or III). Two patients had Class IV angina pectoris with pain at rest before entry into the study. Two patients did not manifest significant angina, but were being treated for recurrent ventricular tachyarrhythmias. Eleven patients had previous myocardial infarction (six transmural and five nontransmural). Four patients had a history of congestive heart failure and were being treated with digitalis and/or diuretics. Although they were in a clinically compensated state at the time of study, all four had evidence of increased heart size on routine chest radiograph. On physical exam, no patient manifested a third heart sound gallop or significant pulmonary rales. Seven patients also were receiving antiarrhythmic medications. The dosages of these concomitant medications remained constant throughout the study. Patients were allowed to use sublingual nitrates as needed for relief or prophylaxis of angina, but not within the 3 hours preceding radionuclide studies. Informed consent was obtained from each patient.

Drug Protocol

After a control radionuclide angiogram, oral propranolol was instituted at 40–80 mg/day, administered in four equal doses. The dosage then was adjusted by increments of 40 or 80 mg/day every three to five days until maximal clinical improvement or drug intolerance occurred. The mean peak dosage (± SEM) was 165 ± 13 mg/day (range 80–240 mg/day). Successive radionuclide angiograms were performed after at least 48 hours at each new dosage level. Studies were obtained 2–3 hours after oral drug administration. No patient had ischemic chest pain at the time of study or during the previous 4 hours. Immediately before each nuclide study, a 10 ml blood sample was obtained for determination of serum propranolol levels. Serum was frozen and maintained at 0°C until assayed using the fluorometric method of Shand et al.14

Radionuclide Technique

Radionuclide angiograms were performed in a cardiovascular nuclear imaging laboratory. An 18 gauge 1½-inch polyethylene catheter was placed in an antecubital vein, and 5 minutes were allowed to pass to minimize any possible contributions of sympathetic activity associated with the venipuncture. Before each radionuclide study, heart rate and blood pressure were recorded. Blood pressure was measured by sphygmomanometer and mean blood pressure determined from systolic and diastolic readings in a standard manner. Patients were studied supine in the anterior position using a commercially available computerized multicrystal scintillation camera.* Reproducible techniques have been developed and validated in this laboratory for determination of left ventricular ejection fraction, mean normalized ejection rate, and regional wall motion from first-pass radionuclide angiocardiograms.8,15 Briefly, 14–20 mCi of technetium-99m pertechnetate, dissolved in less than 1 ml of normal saline, was injected rapidly into the established intravenous line and flushed with 20 ml of saline. Data were acquired in frame mode at 50 msec intervals for 20 seconds as the bolus initially passed through the central circulation. A high frequency time-activity curve was generated from a left ventricular region of interest. End-diastolic frames were used as starting points to sum together counts at 50 msec intervals over three to six cardiac cycles, forming a summed cardiac cycle. A series of sequential background frames (equal in number to the number of cardiac cycles used) was selected from the left ventricular time-activity curve just before the first discernible left ventricular beat. The sum of the background frames was subtracted from the summed cardiac cycle, forming a high count-rate, background-corrected "representative" cardiac cycle. This is analogous to a relative ventricular volume curve. Left ventricular ejection fraction was calculated directly from the "representative" cardiac cycle according to the formula:

\[
\text{Ejection fraction} = \frac{\text{Counts in end-diastole} - \text{Counts in end-systole}}{\text{Counts in end-diastole}} \times 100
\]

Normalized mean left ventricular ejection rate was determined from the same "representative" cycle. Counts during the ejection phase were fitted to a weighted least squares straight line. The slope of this line was normalized to the average counts during the ejection phase. Left ventricular ejection rate determined in this manner is equivalent to the rate of change of ventricular volume during ejection, and has been found to be sensitive to pharmacologic changes in inotropic state.9

Regional wall motion was evaluated from analog end-diastolic and end-systolic images also obtained from the "representative" cycle.8 A composite image composed of a computer-generated ring representing the end-diastolic outer perimeter superimposed upon the end-systolic image was used to evaluate wall motion. The left ventricular silhouette in the anterior position was divided into anterolateral, apical and inferior segments which were graded independently by two observers as normal, severely hypokinetic or akinetic. Their consensus was used in data analysis. Although this technique is not yet quantitative and clearly may not detect subtle changes in regional wall motion, it is sufficiently sensitive to detect regional wall motion abnormalities induced by exercise stress in patients with coronary disease.16

Left ventricular ejection fraction and ejection rate determined using these first-pass radionuclide angiographic techniques have been shown to correlate
closely with data obtained by standard contrast angiographic methods. Excellent agreement between regional wall motion analyses determined by this technique and by contrast angiography also has been demonstrated. The variability of these radionuclide parameters has been assessed in multiple sequential studies in 20 patients. The presence and location of regional wall motion abnormalities did not change from study to study. For left ventricular ejection fraction, the variability averaged 4.4 ± 3.6% (SD), and for left ventricular ejection rate, 0.56 ± 0.47 sec⁻¹. For left ventricular ejection rate, variability was greater in patients with normal function than in those with abnormal function. This was not the case for ejection fraction measurements, which demonstrated a more uniform variability over the entire clinical spectrum.

Statistical Analysis

Data are expressed as the mean ± SEM. Comparisons between radionuclide studies in individual patients were made by paired t test.

Results

Seventeen of 20 patients who were treated for angina pectoris experienced relief of chest pain (improvement of at least one New York Heart Association functional class). Of the 10 patients with class II angina before treatment, five were pain-free and five had pain only on vigorous activity after treatment. All patients were class I or II at peak propranolol dosage. Three patients developed intolerance to propranolol, manifested by excessive fatigue or dizziness associated with bradycardia. These three patients were given somewhat lower daily dosages of propranolol (80–120 mg/day) than the other patients. No patient developed congestive heart failure. The two remaining patients were treated effectively for ventricular tachyarrhythmias.

Left Ventricular Ejection Fraction and Ejection Rate

The overall group of 22 patients showed no significant change in either left ventricular ejection fraction or ejection rate as propranolol therapy was instituted (figs. 1 and 2). During the control period, ejection fraction averaged 63 ± 3%; at the intermediate dosage (defined as one dosage level below the peak), 63 ± 3%; and at the peak propranolol dosage, 64 ± 3% (P > 0.05 for all comparisons). Although individual variations were encountered, no significant trend in ejection fraction measurement was noted. Mean values for left ventricular ejection rate for these studies were 3.28 ± 0.24 sec⁻¹, 2.89 ± 0.22 sec⁻¹, and 3.01 ± 0.18 sec⁻¹, respectively (P > 0.05 for all comparisons). No significant change in left ventricular ejection fraction or ejection rate occurred as propranolol was increased in the 11 patients with previous myocardial infarction, the three with abnormal (< 50%) or two with borderline (50–55%) control ejection fraction, or the four with a history of congestive heart failure. Changes in either ejection fraction or ejection rate within individual patients were comparable to those seen in the previously reported study on the variability of these radionuclide techniques.

However, the majority of patients in this study had normal control ventricular performance. This may result in a greater intrinsic variability in ejection rate measurements, which in turn might mask small differences. Nevertheless, no trends were noted, even in the patients with abnormal performance. For the propranolol group, interstudy variability for ejection fraction and ejection rate averaged 4.5% ± 3.3% and 0.52 ± 0.47 sec⁻¹ (SD), respectively.

Regional Wall Motion

Six patients demonstrated abnormalities in regional wall motion in 15 myocardial segments during the control period. All six patients had sustained a previous transmural myocardial infarction. There was no observable change in the presence or location of these regional wall motion abnormalities as propranolol dosages were increased (fig. 3). No patient developed new abnormalities in wall motion, and all 16 patients with normal initial regional per-
There was significant variation in the serum levels associated with any given oral propranolol dosage. A clinical response, defined either by a decrease in resting heart rate of at least 20 beats/min or relief of angina, occurred at both high and low serum propranolol levels.

**Blood Pressure and Heart Rate**

Heart rate decreased in all patients as the propranolol dosages were increased (fig. 4). Mean values for heart rate at control, intermediate, and peak dosages were 80 ± 3 beats/min, 66 ± 2 beats/min, and 59 ± 1 beats/min, respectively. Compared to the control study, intermediate and peak propranolol dosages significantly reduced heart rate ($P < 0.01$ and $P < 0.001$, respectively). Mean arterial blood pressure during the three study periods averaged 97 ± 3 mm Hg, 92 ± 2 mm Hg, 90 ± 3 mm Hg, respectively. There was a small but statistically significant difference between mean blood pressure in the control period and at the peak propranolol dosage ($P < 0.05$).

**Discussion**

This study demonstrates that oral propranolol has minimal effects upon basal global and regional left ventricular pump performance as measured by radionuclide angiocardiography. The propranolol treatment schedule resulted in substantial improvement in angina pectoris and reduction in resting heart rate. Mean peak propranolol dosage and corresponding serum concentrations were at levels that previously have been demonstrated to produce clinically effective $\beta$ blockade.

The radionuclide technique used in this study agrees closely with contrast angiography, and has been demonstrated to be sufficiently sensitive to detect enhanced myocardial function induced by isoproterenol, aminophylline, and supine exercise and depressed function induced by adriamycin therapy and stress-induced ischemia. Sequential data also have been obtained with low variability,
indicating the suitability of the method for this type of study.\textsuperscript{15}

The results of this study are similar to those of Reduto et al., who studied the effects of decreasing oral dosages of propranolol in patients with documented coronary artery disease in whom the drug was being tapered before elective coronary artery bypass surgery.\textsuperscript{21} Using comparable radionuclide methods for measuring ejection fraction, ejection rate and regional wall motion, propranolol did not affect basal left ventricular performance during drug withdrawal. Furthermore, epidemiologic study of propranolol usage in a hospitalized population has indicated that drug-induced heart failure is a relatively uncommon phenomenon. In addition, adverse reactions are not dose-dependent and frequently occur at low dosages.\textsuperscript{22}

Previous studies of the effects of propranolol on left ventricular function have not shown uniform results. Many of these investigations report acute administration of intravenous propranolol.\textsuperscript{1-5, 23, 24} The predominant finding has been a negative inotropic effect manifested by reduction in cardiac index, stroke index, rate of change in systolic ventricular pressure, and systolic ejection rate, or development of new or worsening areas of asynergy. However, some investigations have failed to demonstrate any impairment in left ventricular function.\textsuperscript{1} It is unclear whether the effects of chronic oral propranolol therapy would be the same as those of the drug when administered by the intravenous route.

Three studies have used noninvasive parameters to assess the functional effects of oral propranolol therapy. LeWinter et al. showed no change in left ventricular cardiac dimensions in normal subjects.\textsuperscript{17} Pine et al. and Frishman et al. both studied patients with coronary artery disease.\textsuperscript{6, 7} The former study demonstrated no drug effect upon echocardiographic indices of performance, while the latter demonstrated a significant fall in echocardiographic ejection fraction, from 68% to 59%. However, the inadequacies of conventional echocardiographic parameters for assessment of ventricular function in patients with coronary artery disease and regional left ventricular dysfunction are well recognized.\textsuperscript{25} This technical aspect, as well as patient selection, may explain the inconsistencies of these studies. The first-pass radionuclide techniques employed in the present study appear more appropriate for the study of this patient population. The contrasting efficacy of these two techniques in the evaluation of coronary artery disease has been reported by Henning et al., who showed a poor correlation between echocardiographic and radionuclide assessment of ejection fraction in patients with regional ventricular abnormalities. Echocardiographic analysis frequently yielded disparate results.\textsuperscript{26}

During experimental myocardial ischemia, $\beta$ blockade has been shown to improve regional function in ischemic myocardial zones, presumably by decreasing oxygen consumption.\textsuperscript{27-29} In addition, propranolol has been shown to reduce myocardial ischemia and damage and improve myocardial oxygenation during the acute phase of myocardial infarction.\textsuperscript{30, 31} In the present study, no patient was studied during demonstrable myocardial ischemia. No patient complained of angina at the time of radionuclide study or during the preceding hours. None experienced a myocardial infarction during the preceding three months, although 11 patients had documented prior myocardial infarction. Thus, these data which were obtained in patients with stable coronary artery disease cannot be extrapolated to patients with ongoing ischemia due to unstable angina or acute infarction. Both these clinical situations would be associated with severe resting myocardial oxygen supply-demand imbalances which may be altered significantly by propranolol in association with concomitant changes in ventricular performance.

The effects of propranolol upon basal performance in patients with profound myocardial dysfunction and left ventricular failure may differ from those in the present study. Coltart et al. only noted adverse reac-
tions to intravenous propranolol in patients with preexisting severe ventricular dysfunction.2

Although subtle changes in wall motion induced by beta blockade may not be detected by the imaging techniques used, the most likely explanation for the results of this study are that the degree of β-adrenergic support to left ventricular function is probably of small magnitude in the basal state. In contrast, the autonomic nervous system plays an increasingly important role in circulatory adjustments to stress. Sonnenblick et al. showed that propranolol did not affect resting cardiac function, but prevented both increases in contractility and decreases in left ventricular dimensions normally associated with exercise.35 In addition, studies of muscle taken from experimentally denervated hearts demonstrated completely normal myocardial contractility, and denervated conscious dogs exhibited normal myocardial performance in the basal state.33,34 Finally, the relatively modest slowing of the resting heart rate in man during β-adrenergic blockade stands in direct contrast to the pronounced increases in heart rate associated with adrenergic stimulation, thereby suggesting a low level of adrenergic support at rest. Thus, in the basal state β-adrenergic blockade would be expected to result in minimal negative inotropic action.

Although ejection fraction is a commonly used clinical parameter of global left ventricular performance, it depends on variables other than intrinsic myocardial contractility. Changes in heart rate, preload and afterload affect left ventricular ejection fraction.36 In the present study, the significant reduction in heart rate (possibly resulting in increased end-diastolic volume) and small decrease in arterial blood pressure (possibly reflecting reduced afterload) may have masked negative effects of propranolol upon myocardial contractility. However, since left ventricular volumes and peripheral vascular resistance were not measured in this study, the relative importance of simultaneous changes in these parameters cannot be assessed. It should be noted that Tarazi and Dusant described a decrement in peripheral vascular resistance after chronic oral propranolol in a group of hypertensive patients.38 These changes were different from those observed after acute intravenous administration of the drug.

In summary, except for effects upon heart rate, oral propranolol administered at clinically effective antianginal dosages to patients with coronary artery disease does not appear to have significant effects upon radionuclide measures of left ventricular performance at rest. These data suggest that the development of congestive heart failure associated with propranolol administration in stable patients, particularly those with normal resting function, is relatively unusual and is not related to decreased basal ventricular performance.

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References

20. Alexander J, Dainiak N, Duffy T, Schwartz P, Gottschalk A, Zaret BL: Prospective non-invasive assessment of adriamycin-
34. Donald DE: Myocardial performance after excision of the intrinsic cardiac nerves in the dog. Circ Res 34: 417, 1974
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