Effect of Propranolol on Myocardial Perfusion Images and Exercise Ejection Fraction in Men with Coronary Artery Disease

JOSEPH RAINWATER, M.D., PETER STEELE, M.D., DENNIS KIRCH, M.S.E.E., MICHAEL LEFREE, B.S., DOUGLAS JENSEN, M.D., AND ROBERT VOGEL, M.D.

SUMMARY Propranolol increases exercise performance in association with a decrease in exercise heart rate and blood pressure. In 30 men with coronary disease and exercise limited by angina, 15 without prior infarction and 15 with infarction, we measured left ventricular ejection fraction (LVEF) (scintillation probe) at rest and during supine bicycle exercise and myocardial blood flow distribution (MBF) (thallium-201 imaging) during treadmill exercise. Exercise was performed as control and after 1 week of treatment with propranolol (40 mg orally four times daily). Propranolol improved exercise LVEF (at the same work load) (men without infarction: control 0.37 ± 0.02, average ± SEM; propranolol 0.45 ± 0.01; n = 15, p < 0.01; and with infarction: control 0.30 ± 0.01, propranolol 0.36 ± 0.01; n = 15, p < 0.05). Propranolol also improved MBF during exercise to the same work load in men without infarction (comparison of integrated normalized count-rate differences, 607 normalized counts). In men with infarction, propranolol did not alter MBF (15 normalized counts). Placebo did not alter normalized counts by more than ± 150. Changes in exercise LVEF and MBF were related. MBF improved in 17 men with propranolol treatment and LVEF was increased in 15. Of six men who had no change in MBF, exercise LVEF increased in three and did not change in three. Propranolol was associated with a worsening of MBF in five men and all had no change in exercise LVEF. Results suggest that propranolol favorably alters MBF and LVEF in men with coronary disease, particularly in men without prior myocardial infarction.

PROPRANOLOL is an effective drug for the treatment of angina in patients with coronary disease. Increased sympathetic nervous system activity during exercise may contribute to an increase in cardiac output and heart rate. In normal dogs, propranolol decreases cardiac output, stroke volume and heart rate during dynamic exercise. Similar changes occurred during exercise in normal subjects who were given propranolol.

Studies in animals suggest that propranolol favorably alters myocardial blood flow to ischemic areas and improves performance of ischemic regions. In dogs with a chronic coronary obstruction, propranolol lessened regional performance abnormalities during exercise. That these favorable changes with propranolol were due to alteration of myocardial oxygen requirements appears to be supported by the work of Swain and associates. These investigators found that propranolol had no effect on myocardial blood flow when administered in a dose that did not alter hemodynamics.

We studied the effects of propranolol on left ventricular ejection fraction (LVEF) and myocardial blood flow during exercise in men with coronary disease. In these men, exercise was limited by angina.

Patients and Methods

Thirty men with arteriographically defined coronary artery disease were informed of the risks of the study and agreed to participate. They were selected to include men with and without prior infarction and to provide a spectrum of disease severity. Each man had

From the Division of Cardiology, Department of Medicine, Denver Veterans Administration Medical Center, University of Colorado Medical Center, Denver, Colorado.

Supported by the Veterans Administration.

Dr. Rainwater is a Research Associate and Dr. Jensen is an Associate Investigator of the Veterans Administration.

Address for correspondence: Peter Steele, M.D., Veterans Administration Medical Center, 1055 Clermont, Denver, Colorado 80220.

Received January 22, 1979; revision accepted April 24, 1981.

at least one area of at least 60% obstruction in at least one major coronary artery. Fifteen men had electrocardiographic evidence of prior transmural myocardial infarction (Q waves in three leads) and 15 had not had infarction. All men had stable angina while not being treated with antianginal medication other than nitroglycerin. All men were in normal sinus rhythm and none had valvular heart disease or systemic hypertension. In addition, all had an abnormal myocardial perfusion image after i.v. thallium-201 during maximally tolerated treadmill exercise.

LVEF was measured at rest and during the last 15 seconds of maximally tolerated supine bicycle exercise with a dual-crystal scintillation probe (Searle Radiographics). For these determinations, about 3 mCi of technetium-99m was injected into a venous catheter positioned in the superior vena cava and flushed with saline. The scintillation probe was positioned over the midportion of the left ventricle in the supine, anteroposterior projection and the probe simultaneously recorded a left ventricular time-activity curve and a left ventricular background curve. LVEF was calculated as the fractional fall in count rate from one end-diastolic point to the next end-systolic point divided by the end-diastolic count rate. The tails of the two curves (left ventricular and background) were matched to obtain the background-correction (correction for scattered radiation) end-diastolic count rate. LVEF was computed for three consecutive beats, beginning with the first beat after the left ventricular peak of the time-activity curve and expressed as the average of these three beats. Heart rate was determined from the ECG, and blood pressure by a cuff sphygmomanometer. All men had angina that limited supine exercise and 19 of 30 had ST-segment depression.

In 25 men with coronary disease, LVEF determined by the dual-crystal probe correlated well (r = 0.89) with contrast left cineventriculograms in the right anterior oblique projection. In 15 normal men, resting LVEF determined by the dual-crystal probe averaged 0.59 ± 0.06 (SD). Using 2 standard deviations from the mean to define the normal range, normal resting ejection fraction using this technique is 0.47-0.71.

The day after control measurement of rest and exercise ejection fraction, all patients underwent graded treadmill exercise testing (Bruce protocol). Exercise was continued to maximally tolerated work loads. During treadmill exercise, all men had angina and 21 of the 30 had at least 1 mm of ST-segment depression (eight of 15 with infarction; 13 of 15 without infarction). Sixty seconds before the termination of exercise, about 1.5 mCi of thallium-201 was injected intravenously. Within 15 minutes after the completion of exercise, a single image was obtained in 40° left anterior oblique projection with acquisition of 750,000 counts using a composite seven-pinhole collimator and a wide-field scintillation camera (Ohio Nuclear 410 or Picker 415). These images were analyzed using a computer (ADAC). The composite collimator, with six slanted pinholes and one unslanted pinhole, produces a tomographic effect. Twelve image planes of the left ventricle are created and three consecutive central planes are selected for analysis. The center of the left ventricular cavity is located and maximum counts were determined along each of 60 radial lines extending from this center and spaced at 6° intervals. This process was begun in a posterior direction and proceeded in a clockwise fashion. These maximum radial counts were normalized to a maximum count density of 100 counts per pixel and then plotted to form a circumferential profile curve of normalized counts for each of the three cross-sectional planes. Images are expressed as three curves, normalized counts plotted for circumferential distance including all myocardial segments.

After measurement of control rest and exercise LVEF (supine bicycle exercise) and recording of control exercise myocardial perfusion images (treadmill exercise), each patient was begun on propranolol, 40 mg orally four times a day. At the end of 1 week of treatment and 1–2 hours after an oral dose of 40 mg of propranolol, these studies were repeated, with exercise carried out in exactly the same fashion and to exactly the same duration as during the control studies. The first 20 men (10 with and 10 without infarction) were studied twice and unblinded. Then, 10 men (five with and five without infarction) were studied three times using a double-blind, placebo-controlled crossover design with random assignment of propranolol, 40 mg orally four times daily and placebo orally four times daily to the first and second treatment weeks. An interval of 2 weeks between treatment measurements was scheduled to allow gradual discontinuation of drug.

The tomographic scintigrams during propranolol or placebo treatment were then quantitatively analyzed as described for the control studies. Using a digital computer the three circumferential profile curves, for each study, normalized myocardial counts plotted circumferentially obtained before and during propranolol, were subtracted (propranolol minus control), allowing determination of areas of improvement or worsening in myocardial count density when the studies were compared. Integration and algebraic summing of these curves resulted in a quantitative assessment of improvement or deterioration.

The means for the paired data were statistically compared using the t test. The Wilcoxon test was used to compare the myocardial imaging results.

**Results**

LVEF at rest was 0.53 ± 0.01 (average ± SEM) for the 15 men with coronary disease who had not had infarction and 0.40 ± 0.01 for the 15 men who had prior infarction. During control, exercise LVEF decreased in both groups (no infarction 0.37 ± 0.02; prior infarction 0.30 ± 0.01). None of these men had an increase in LVEF of 0.05 during exercise; that is, all men had an abnormal response.

Propranolol treatment did not decrease LVEF at rest in men without infarction (0.53 ± 0.01 vs 0.52 ± 0.01, NS), but was associated with a decrease in LVEF
in men with prior infarction (0.36 ± 0.01 vs 0.40 ± 0.01, p < 0.05). During exercise, LVEF improved with propranolol in both groups (men without infarction 0.45 ± 0.01 vs 0.37 ± 0.02, p < 0.01; men with infarction 0.36 ± 0.01 vs 0.30 ± 0.01, p < 0.05) (fig. 1). If a change of exercise LVEF of 0.03 or more is considered to represent a difference, then LVEF increased in 10 of the men without infarction during exercise when treated with propranolol and it did not change in five. Propranolol was less effective in men with prior infarction: Seven had an increase in exercise LVEF and eight had no change. Propranolol decreased heart rate and systolic blood pressure during exercise in both groups. It decreased resting heart rate (men without infarction 61 ± 1 beats/min vs 75 ± 2 beats/min, p < 0.01; men with infarction 71 ± 3 beats/min vs 87 ± 3 beats/min, p < 0.001) and heart rate at the end of exercise (no infarction 103 ± 4 beats/min vs 120 ± 5 beats/min, p < 0.01; with infarction 103 ± 4 beats/min vs 132 ± 4 beats/min, p < 0.01). Systolic blood pressure was not altered at rest by propranolol (men without infarction 128 ± 2 mm Hg vs 130 ± 2 mm Hg, NS; infarction 119 ± 3 mm Hg vs 122 ± 3 mm Hg, NS), but decreased modestly during exercise (men without infarction 151 ± 4 mm Hg vs 164 ± 4 mm Hg, p < 0.05; men with infarction 134 ± 4 mm Hg vs 142 ± 4 mm Hg, p < 0.05).

Ten men were studied three times with a blinded, crossover design using placebo. Placebo resulted in variation of resting and exercise LVEF of less than 0.06 in all men. The average difference was 0.02 (20 measurements: 10 at rest and 10 during exercise in 10 men). Variation in LVEF was similar in both groups of patients. During supine bicycle exercise, there was only a small difference in exercise heart rate between control exercise and exercise during placebo administration (maximal difference was 8 beats/min; average difference was 5 beats/min; one measurement in 10 patients). Systolic blood pressure during exercise varied by less than 16 mm Hg in these 10 men.

Propranolol favorably altered myocardial blood flow distribution only in men without previous infarction. These men all had a normal LVEF at rest, whereas men with prior infarction all had an abnormal LVEF at rest. Of 15 men without myocardial infarction, 12 had improved images during exercise with propranolol compared with control exercise (average improvement of 607 normalized counts). The integrated myocardial count-rate differences for the three tomographic planes, control vs propranolol, are summed and expressed as plus or minus normalized counts. An alteration in normalized counts of 150 or more represents a difference. In one man the exercise images did not change and in two men their images worsened while taking propranolol (fig. 2). In men with myocardial infarction, exercise images improved in five during propranolol treatment, did not change in five and worsened in five. The average difference for men with infarction was 15 (fig. 2). A representative pair of studies is presented in figure 3.

Ten men underwent imaging a third time while taking placebo with an average difference in normalized counts of 22 (fig. 2). The range of count-rate difference was 143 to −132. A change of ±150 is considered to represent an alteration in myocardial blood flow distribution.

Propranolol decreased heart rate during treadmill exercise in both groups (no infarction 103 ± 4 beats/min vs 138 ± 5 beats/min, p < 0.001; prior infarction 112 ± 3 beats/min vs 135 ± 5 beats/min, p < 0.001). There were no differences in either exercise systolic blood pressure or blood pressure at rest.

Changes in exercise myocardial blood flow distribution and changes in exercise LVEF during treatment with propranolol appear to be related. Myocardial images during treadmill exercise improved in 17 men, 12 without prior infarction and five with infarction. LVEF during supine bicycle exercise improved in 14 of these 17 men, 10 without and four with infarction. Exercise LVEF did not change with propranolol in three men. In six men the images did not change and in three men with infarction it improved. It was not altered in one man without infarction and in two men with infarction. Propranolol resulted in worsening of the blood flow images in five men, all in the group with infarction. These five had no change in exercise LVEF.

**Discussion**

The results of this study suggest that propranolol improves global left ventricular performance and myocardial blood flow during exercise in men with coronary disease, and these two phenomena appear to be associated. The beneficial effect of propranolol on ejection fraction during exercise was more apparent in men without myocardial infarction. These men had normal ejection fraction at rest, whereas in men with prior infarction and depressed resting ejection fraction, only seven of 15 had an improvement in ejection fraction during exercise.
A similar relationship between improved myocardial blood flow images and depressed resting ejection fraction was observed. Five men with left ventricular dysfunction at rest actually had worsening of their blood flow image during propranolol treatment. Worsening of the images occurred primarily in infarcted segments.

Exercise testing during treatment with propranolol was matched to the control exercise in respect to work load and duration. Heart rate changed substantially during propranolol treatment, which may explain the favorable results. Propranolol may improve ventricular performance and blood flow distribution by decreasing myocardial oxygen requirements. In some patients with infarction, propranolol may produce enough left ventricular dilation to increase the myocardial oxygen requirement because of increased myocardial wall tension.

Uncertainty about this last point highlights the principal problem with this study: Left ventricular end-diastolic and end-systolic volumes were not measured. The scintillation probe is nicely adapted for measurement of ejection fraction, where ventricular count-rates can be divided to obtain a volume ratio. End-diastolic and end-systolic volumes can be calculated using this method, but this calculation requires determination of cardiac output and blood volume, which we did not do. Regional ischemia decreases augmented ventricular performance during exercise in dogs. Propranolol improves performance as lengthening of myocardial segments, which produces ventricular dilation. Propranolol decreases the extent of the abnormal lengthening during exercise in dogs with a coronary stenosis. Presumably, ventricular dilation occurs in our patients during exercise; propranolol may improve this in some segments, but may not be able to improve performance in infarcted segments. Whether this occurs is uncertain, as neither left ventricular volume nor regional performance was measured. The relationship between regional performance and flow distribution in patients receiving propranolol would be of interest.

Battler and associates gave propranolol to 10 patients with coronary disease. Although six had prior myocardial infarction, none of the 10 had a resting ejection fraction of 0.45. Ejection fraction was measured at rest and during supine bicycle exercise during treatment with propranolol and control using an equilibrium blood pool imaging system. Control exercise resulted in a decrease in ejection fraction in most patients. With propranolol, exercise ejection fraction was improved.
Acknowledgment
The authors acknowledge the expert technical assistance of Michael Adams, Hanni Cohen and Carol Vandello.

References
Effect of propranolol on myocardial perfusion images and exercise ejection fraction in men with coronary artery disease.
J Rainwater, P Steele, D Kirch, M LeFree, D Jensen and R Vogel

Circulation. 1982;65:77-81
doi: 10.1161/01.CIR.65.1.77

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
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/65/1/77.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/