Exacerbation of Vasotonic Angina Pectoris by Propranolol

ROSE MARIE ROBERTSON, M.D., ALASTAIR J. J. WOOD, M.B., CH.B., WILLIAM K. VAUGHN, PH.D., AND DAVID ROBERTSON, M.D.

SUMMARY Using a double-blind protocol, we investigated the use of propranolol in patients with coronary artery spasm as assessed by subjective and objective variables. Both low-dose (40 mg every 6 hours) and high-dose (160 mg every 6 hours) propranolol were administered. At both doses, the duration of angina attacks was significantly prolonged but the frequency was not. We conclude that propranolol at doses up to 160 mg every 6 hours as single therapy is frequently detrimental in angina pectoris due to coronary artery spasm and should not be used as the sole treatment of this disorder.

PROPRANOLOL reduces heart work for any level of physical activity and thus has become the mainstay of therapy in angina pectoris.1,2 Its effectiveness in classic angina pectoris3 and unstable angina pectoris4 is well-established. It is being investigated as a tool for salvaging the ischemic myocardium.6 However, the use of propranolol in patients with coronary artery spasm has caused reasonable concern. Theoretically, blockade of vasodilatory β-adrenergic receptors might worsen spasm by converting the effect of a sympathetic stimulus into a pure α-adrenergic vasoconstrictor response.

The clinical and morphologic spectrum of coronary artery spasm is broad.6 It may present as angina of effort or angina of rest; the anatomic substrate has ranged from atherosclerosis-free coronary arteries to severely atherosclerotic vessels. In some subjects, a single episode of clinically apparent ischemia is the only manifestation; in others, more than 30 episodes of angina may occur in a single day.

The roles of spasm and atherosclerosis in ischemic heart disease are complex. Thus, we examined the effect of β blockade on coronary artery spasm in a group of subjects with as nearly “pure” spasm as we could find. On one end of the coronary spasm spectrum are patients who have angina at rest with preserved exercise capacity and, in general, less atherosclerosis; they manifest a chronic course with periods of intense disease activity punctuated by quiescent intervals of months to years.7 We use the term “vasotonic angina” to describe this subgroup. We chose subjects with vasotonic angina to determine the effect of propranolol on coronary artery spasm.

Methods

We selected six patients who had well-characterized vasotonic angina, which was defined as chronic (at least 2 months), frequent (≥ 2 episodes daily) angina at rest with at least 2 mm of ST-segment elevation but with preservation of exercise capacity. Three subjects were male and three were female. They ranged in age from 51–72 years. Angiography revealed normal coronary arteries in one subject, mild atherosclerosis (defined as a lesion less than 50% in the affected artery) in four subjects and 70% stenosis of the affected artery in one subject. All subjects had had angina at rest for at least 10 months, and most patients had had angina for several years. No patient had ECG evidence of old myocardial infarction and there was no ECG or enzymatic evidence of recent infarction.

Each subject was admitted to the Elliot V. Newman Clinical Research Center for electrocardiographic and hemodynamic monitoring. In each patient we documented that electrocardiographic evidence of ischemia preceded any increase in heart rate or blood pressure. All patients were studied during an active phase of their disease; one patient was restudied while his disease was quiescent.

Drug trials were performed using a double-blind, placebo-controlled crossover protocol. When episodes of pain were not severe or associated with serious ventricular arrhythmias, patients were allowed to be ambulatory. Throughout the study, all patients had 0.4-mg sublingual nitroglycerin tablets at their bedside for symptomatic relief; none were on prophylactic nitrate therapy.

All study subjects had continuous Holter recording. Before the study, electrocardiographic exploration was carried out during anginal attacks to identify the lead which demonstrated the greatest ST-segment shift; thereafter, this lead was monitored in the course of the subsequent investigations. Tapes were scanned for episodes of ST-segment elevation that could not be accounted for by positional changes. Episodes lasting 30 seconds or longer and with a magnitude of 1 mm or more were enumerated and characterized. Frequency, duration, and magnitude of ST changes were tabulated for each 24-hour period. Arrhythmias with ischemic episodes were recorded. In addition, each patient was questioned daily regarding the number, length and severity of episodes of chest pain.

From the Departments of Pharmacology, Medicine, and Preventive Medicine, Division of Clinical Pharmacology, Cardiology, and Biostatistics, Vanderbilt University School of Medicine, Nashville, Tennessee.

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Dr. David Robertson is a Teaching and Research Scholar of the American College of Physicians.

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Address for correspondence: Rose Marie Robertson, M.D., Division of Cardiology, Vanderbilt Medical Center, Nashville, Tennessee 37232.

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Agents were administered in 3-day periods, with a placebo period before and after the propranolol period. Patients received either drug or placebo at 6-hour intervals. During the propranolol period, the total daily dose was 160 mg on day 1 and 640 mg on both days 2 and 3.

Adequacy of propranolol therapy was assessed by measuring trough blood levels using high-pressure liquid chromatography. To assess the differences between placebo periods and the propranolol period, the data for number of episodes and average length per episode were analyzed using a randomized complete block design. This trial method was chosen because the observations were made using the patient as his own control. The randomized block design removes the effect of differences between patients when comparisons are made between propranolol and placebo groups. One degree of freedom contrasts were used to compare the average placebo pretreatment data with the low-dose propranolol group, the high-dose propranolol group and the postpropranolol placebo group.

Results

Plasma propranolol levels were assessed during trials in four patients. On low-dose propranolol (40 mg every 6 hours), the mean plasma propranolol level was 42 ng/ml (range 28–74 ng/ml). On the high-dose regimen (160 mg every 6 hours), the mean propranolol level was 280 ng/ml (range 222–342 ng/ml). The randomized block design analysis showed no significant differences in number of episodes between initial placebo and low-dose propranolol, initial placebo and high-dose propranolol, or initial placebo and postpropranolol placebo. However, differences between the average length per episode on placebo vs propranolol were highly significant (fig. 1). The duration of ST elevation rose from a mean of 1.3 minutes (range 0.5–5.5 minutes) to 3.4 minutes (range 1.0–9.5 minutes). A comparison of prepropranolol with low-

dose propranolol values yielded an F value of 12.55°, DF = 1, 34° (p < 0.005). Also, the F value for comparing the average length of the episodes for the placebo group with that for the high-dose propranolol group was 35.6°, DF = 1, 34° (p < 0.005). There was no significant difference in the average length of ischemic episodes comparing the prepropranolol placebo to the postpropranolol placebo. In most patients, total ischemic time increased during high-dose propranolol therapy (fig. 2). However, the patient with the highest plasma propranolol level (342 ng/ml) during the high-dose propranolol trial actually had slightly less ischemic time per day than he had during the low-dose trial when his plasma propranolol level was 74 ng/ml.

One patient had ventricular arrhythmias associated with ischemic episodes. This patient had unifocal premature ventricular complexes with most episodes lasting longer than 2 minutes. These premature complexes were highly correlated with length of ischemia and were thus more numerous when the patient was taking propranolol. Bigeminy was seen only during high-dose propranolol in this patient. In the other patients, premature complexes were uncommon both before and during propranolol.

In general, ST elevations were symptomatic if they persisted for longer than 3 minutes but asymptomatic if they were shorter. Accordingly, patients with short (< 3 minutes) episodes generally had more symptomatic episodes on propranolol because the duration of their ST elevations was increased. Patients whose episodes already tended to be longer than 3 minutes were already sensing virtually all of their ischemic attacks and hence did not notice an increase in their frequency; some did note a greater severity of individual attacks.

The rate of sublingual nitroglycerin consumption is shown in table 1. Patients were permitted to take nitroglycerin any time they felt chest pain. Although there was a trend toward more nitroglycerin use during propranolol, this was not statistically significant.

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

**Figure 1.** Duration of ischemic episodes as assessed by constant electrocardiographic monitoring. Points represent the mean length of attacks for an individual subject on initial placebo, 40 mg of propranolol every 6 hours (LD-PROP), 160 mg every 6 hours (HD-PROP), and terminal placebo. For the entire group, mean episode length increased from a placebo value of 1.3 minutes to a low-dose propranolol value of 3.1 minutes (p < 0.005) and a high-dose propranolol value of 3.4 minutes (p < 0.005); finally declining during the terminal placebo to a value of 1.3 minutes.

![Figure 2](http://circ.ahajournals.org/DownloadedFrom)

**Figure 2.** Total duration of ST-segment elevation per 24 hours. Points represent the total time ischemic for an individual subject on the regimens described in figure 1. For the entire group, ischemic time per 24 hours increased from a placebo value of 37.6 minutes to a low-dose propranolol value of 38.2 minutes and a high-dose propranolol value of 61.1 minutes, finally declining during the terminal placebo to a value of 23.6 minutes. These changes were not statistically significant.
TABLE 1. Nitroglycerin Use During Placebo and Propranolol

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Patients had 0.4-mg sublingual nitroglycerin tablets at bedside to take during symptomatic attacks. Each value is the mean number of nitroglycerin tablets used per day during the trial. The total mean daily consumption suggests a trend toward increased nitroglycerin use during propranolol, but this was not significant for the group as a whole.

**Discussion**

The use of propranolol in angina pectoris is based on evidence that increased sympathetic nervous activity is pivotal in the production of anginal attacks. Beta-adrenergic blockade leads to reductions in heart rate, blood pressure and myocardial contractility, lessening myocardial oxygen demand. In addition, relaxation is impaired in hypoxic myocardial tissue during diastole; this abnormality is attenuated by beta-adrenergic blockade in vitro and may be a mechanism whereby propranolol improves exercise capacity in angina pectoris. These beneficial effects may be opposed in some patients by an increase in duration of systole and an increase in left ventricular size, factors that tend to increase oxygen demand and may reduce coronary blood flow through extravascular compressive forces.

Prinzmetal et al. described patients in whom angina pectoris occurred at rest and in whom episodes of ischemia did not bear any relationship to increased oxygen demand. Because they hypothesized that enhanced tone in a partially obstructed coronary artery gave rise to the anginal attacks in these patients, they proposed the use of nylidrin, a beta-adrenergic agonist, to elicit vasodilatation in the involved vessel. Although they found favorable results with nylidrin, the great success of beta blockade in improving classic angina pectoris together with increased awareness of the arrhythmgenic potential of beta sympathomimetics have made most investigators reluctant to use this mode of therapy. Some authors, although not advocating beta agonists, have urged caution in the use of beta antagonists on theoretical grounds.

The theoretical objections to the use of beta blockade in angina due to coronary artery spasm relate to the paucity of evidence that increased myocardial work contributes significantly to the induction or persistence of ischemia in affected patients. In the absence of this rationale for using beta blockade, the direct effect of propranolol on vascular beta receptors assumes considerable importance. Alpha-adrenergic coronary constrictor tone has been demonstrated in man and beta-adrenergic blockade might unmask alpha-adrenergic vasoconstriction in certain circumstances.

If coronary artery spasm were caused by increased sympathetic outflow, propranolol would be expected to make the vasoconstriction more intense. Some investigators have proposed that increased sympathetic nervous system activity gives rise to coronary vasospasm; however, others suggested that the primary abnormality lies in the vessel wall itself rather than in the function of the autonomic nervous system. However, even if autonomic abnormalities are not primary, powerful reflexes activated during anginal attacks can lead to hypertension and increased heart rate, which suggest sympathetic activation. Such subjects might have more intense vasoconstriction in the setting of beta blockade.

Although widely used for its beta-blocking effect, propranolol has other pharmacologic properties that could contribute to the drug's vascular effects in certain circumstances. At high doses, propranolol has recently been shown to relax potassium-induced contractures in both canine and porcine coronary arteries. Since comparable doses of atenolol do not elicit this effect and d-propranolol does, the mechanism is presumably distinct from beta blockade. Although plasma levels of propranolol during anti-anginal therapy do not reach the concentration required to demonstrate the in vitro coronary artery relaxation described, subtle vasodilatory effects might be elicited in the face of spasm.

In spite of the widespread view that beta blockade is contraindicated in patients with coronary artery spasm, the evidence for this is quite limited. Unsatisfactory results with beta blockade in vasotonic angina have been reported in several cases, but Guazzi et al. found a reduction in the number of attacks of angina after propranolol in 11 of 15 subjects with spontaneous angina pectoris associated with ST-segment elevation.

Yasue et al. reported that propranolol was detrimental in 13 subjects they studied with angina at rest associated with ST elevation. Treadmill exercise-induced anginal attacks in patients with variant angina were aggravated in 13 of 30 patients, unaffected in 11, partially suppressed in 6 and completely suppressed in none.

Our investigation differs from previous studies in that we used a double-blind protocol, we quantitated ischemia by both electrocardiographic recording and subjective measurements throughout the trial, and we considered the length and number of episodes in assessment of the efficacy of therapy. Propranolol significantly prolonged the duration of ischemia as assessed by electrocardiographic monitoring. Most of our patients did not notice worsened angina while taking propranolol. We did not observe a significant increase in the number of attacks of angina in our patients; furthermore, in one patient whose attacks had been exacerbated by propranolol during the active phase of his disease, readministration during a quiescent period did not lead to recurrence of symptomatic
or electrocardiographic evidence of ischemia.\textsuperscript{31} Nevertheless, the clinical importance of the prolongation of attacks induced by propranolol is suggested by the increased incidence of premature ventricular complexes during ischemia in one of our patients in the presence of propranolol.

Many methodologic difficulties arise in assessing therapeutic efficacy in vasotonic angina. The definition of study subjects has varied considerably in the literature. Because propranolol is effective in classic angina pectoris and in unstable angina, studies that include subjects with these conditions will be weighted toward demonstrating a favorable response to propranolol. The degree of atherosclerosis may also be important; there was a low incidence of coronary atherosclerosis in the patients worsened by propranolol in the study of Yasue et al.\textsuperscript{32,33} The degree of coronary atherosclerosis was not stated in some of the studies that reported a beneficial effect. Finally, the inherent variability of disease activity is a confounding variable which often magnifies the apparent efficacy of therapeutic agents. Vasotonic angina is characterized cyclically;\textsuperscript{31,32} because patients tend to present to physicians at peaks of disease activity, improvement is typical no matter what therapeutic approach is undertaken. Hence, studies that are not randomized or do not have multiple placebo periods must be interpreted with caution.

The exacerbation of vasotonic angina by propranolol demonstrated in this study must be interpreted with caution. Even the highly selected group of patients in our study may be heterogeneous in their response to propranolol. One patient in our study did not experience a worsening of angina during either high- or low-dose propranolol and some patients have recalled improvement during previous outpatient propranolol treatment. Among the mechanisms by which propranolol has been proposed to benefit classic angina pectoris, improvements in ventricular relaxation would presumably be advantageous in vasotonic angina as well. Reduction in heart work by reduced heart rate, blood pressure and ventricular contractility may also be somewhat beneficial in vasotonic angina. Finally, patients in our study were not on chronic vasodilator therapy with either nitrates or calcium-channel blockers, although they had access to sublingual nitroglycerin for symptomatic anginal attacks. Concomitant vasodilator therapy might have negated the detrimental effects of propranolol observed in this study. Even higher propranolol doses might have yielded a more favorable clinical response. Nevertheless, these data strongly suggest that propranolol in doses up to 640 mg daily should be avoided as the sole treatment of vasotonic angina pectoris.

References

Adrenergic Responsiveness in Prehypertensive Subjects

THEODORE A. KOTCHEN, M.D., GORDON P. GUTHRIE, JR., M.D., HARLEY MCKEAN, PH.D., AND JANE M. KOTCHEN, M.D., M.P.H.

SUMMARY To determine if alterations in adrenergic activity precede hypertension, we evaluated the pressor effect of an α agonist (phenylephrine) and the chronotropic effect of a β agonist (isoproterenol) in prehypertensive young men. The subjects were selected from a 5-year follow-up of individuals in the upper ("high") and lower ("low") deciles of the blood pressure distribution in a high school population. At follow-up, the blood pressure differences between groups were maintained. The baroreflex slopes of the high (n = 13) and low (n = 10) blood pressure groups did not differ. The dose of phenylephrine required to increase systolic blood pressure by 20 mm Hg (PD20) was greater in the high blood pressure group than in the low blood pressure group (250 ± 38 μg vs 167 ± 35 μg, p < 0.05). The dose of isoproterenol required to increase the heart rate by 25 beats/min (CD20) was also greater in the high than in the low blood pressure group (1.9 ± 0.5 μg vs 0.9 ± 0.2 μg, p < 0.05). The increase in plasma renin activity in response to treadmill exercise was less in the high than in the low pressure group (1.8 ± 0.6 ng/ml/hr vs 3.4 ± 0.7 ng/ml/hr, p < 0.03). Overall, systolic blood pressure correlated with PD20 (r = 0.52, p < 0.01) and CD20 (r = 0.62, p < 0.001). Plasma norepinephrine correlated with systolic blood pressure (r = 0.44, p < 0.04) and with PD20 (r = 0.63, p < 0.001). We conclude that baroreflex sensitivity is not altered in young men with relatively high blood pressure. Insensitivity to α and β agonists may be related to the positive correlation of systolic blood pressure with plasma norepinephrine concentration.

IN 1973, we obtained standardized measurements of blood pressure in all high school seniors residing in Bourbon County, Kentucky, which has a predominantly white, rural population with a high prevalence of hypertension. Five years later, follow-up measurements were taken in persons in the upper and lower deciles of the original blood pressure distribution, by sex. Follow-up blood pressure measurements were highly correlated with blood pressure measurements recorded 5 years earlier, and blood pressure differences between groups were maintained. Other investigators have demonstrated an association between blood pressure measurements repeated over time in adolescents and young adults. Because of this "tracking" phenomenon and because blood pressure tends to increase with age, these young adults with relatively higher blood pressures are at increased risk for developing hypertension. The association between borderline hypertension and the development of established hypertension is well documented. Identification of adolescents and young adults who maintain relatively high blood pressures over time provides the opportunity to evaluate mechanisms of blood pressure control in the "prehypertensive" state.

Alterations in sympathetic nervous system activity have been described in patients with essential hypertension. These alterations include decreased sensitivity of arterial baroreceptors, increased vasoconstrictor responses to infusion of norepinephrine, and decreased endogenous β-receptor sensitivity. Whether these alterations precede the onset of hypertension or are secondary to elevated arterial pressure

From the Department of Medicine, University of Kentucky College of Medicine, Lexington, Kentucky.
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Address for correspondence: Theodore A. Kotchen, M.D., Division of Endocrinology, Department of Medicine, University of Kentucky College of Medicine, Lexington, Kentucky 40536.
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R M Robertson, A J Wood, W K Vaughn and D Robertson

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