Correlation of Plasma Propranolol Concentration with Therapeutic Response in Patients with Angina Pectoris

By Michael Pine, M.D., Laurence Favrot, M.D., Sidney Smith, M.D., Keith McDonald, M.D., and Charles A. Chidsey, M.D.

SUMMARY

The therapeutic response to propranolol was evaluated in patients with documented coronary artery disease at doses varying from 40 to 320 mg/day. Therapeutic response was quantified by evaluating exercise performance on a treadmill and then related to plasma propranolol concentration. Plasma propranolol was defined in terms of beta-adrenergic blockade by comparison with dose (concentration) response curves in normal subjects. Individual therapeutic benefit occurred at doses which averaged 144 ± 21 mg/day and at concentrations which averaged 30 ± 7 ng/ml. There was a wide variation between both dose and concentration among the patients at maximum therapeutic response, but when the plasma propranolol was related to pharmacologic activity, the maximum therapeutic response was observed between 64 to 98% of total blockade. Despite the increased exercise performance in these patients, the double product of heart rate and systolic blood pressure was always less, suggesting either an alteration of the relation between myocardial oxygen consumption and the double product during propranolol or a reduction on oxygen delivery to the myocardium as the result of beta-adrenergic blockade of the coronary vasculature.

Although the use of propranolol is widely accepted in the treatment of patients with angina, therapeutic responses have been observed at widely differing doses.\(^1\)\(^-\)\(^4\) Optimum therapeutic dose recommendations conflict. At one extreme, dosage of the drug is recommended to be increased progressively to tolerance using a therapeutic dose which averages 417 mg/day.\(^6\) More recent studies have suggested maximum therapeutic benefit occurs at a much lower dose, 80 mg/day, with significant deterioration as the dose is increased above that level.\(^4\) The absorption of propranolol differs markedly among patients, resulting in widely variable blood levels for a given dose,\(^8\) and it is possible that this could account for the differences in oral doses required for a therapeutic response. Thus, determination of plasma propranolol concentration might be of help in arriving at the maximal beneficial dose in a given patient. However, the reported studies which have attempted to utilize plasma propranolol levels have also been conflicting.\(^1\)\(^,\)\(^4\)

The present study was designed to re-examine this problem comparing improvement in exercise tolerance with the oral dose of propranolol and its plasma level. We have used a more sensitive and specific method for the measurement of propranolol,\(^10\) which appears to be necessary to make meaningful measurement of plasma levels at lower doses of the drug in patients with angina.\(^9\) The plasma propranolol concentrations then were interpreted in terms of beta-adrenergic receptor blockade by relating them to a dose (concentration) response curve defined in normal subjects. Thus, the plasma levels could be used to assess the extent of beta blockade in the patients’ studies. Finally, the hemodynamic responses to increasing propranolol were examined in relation to the therapeutic activity of the drug.

Methods

Studies on seven normal subjects (mean age 34 years, range 28–44) were carried out to define the dose (concentration) response relationship during increasing propranolol administration. This relationship was defined in normal subjects because it was not possible to exercise the patients with angina to the level at which adrenergic stimuli were the dominant factor in heart rate control.\(^11\) Furthermore, in these patients, propranolol could not be administered to high enough doses to establish a maximum pharmacologic effect, i.e., plateau of heart rate suppression with increased propranolol concentrations. Observations during exercise were made only after initial conditioning using three practice exercise runs. Subjects were studied during a control
period and during administration of propranolol to a maximum of 640 mg/day. The drug was given four times daily and a constant oral dose was maintained for at least 48 hours prior to study. The sequence of these control and drug treatment periods was varied to avoid systematic bias in the observations.

Ten patients with coronary artery disease (mean age 61 years, range 53–71) with exercise-induced angina were studied in a similar manner until either a maximum propranolol dose of 320 mg/day or until symptoms suggestive of cardiac decompensation appeared. Each daily dose level of propranolol was given in four equal divided doses for at least 48 hours before exercise testing. All patients had coronary artery disease documented by at least one of the following criteria: 1) electrocardiographic evidence of myocardial infarction at least six months prior to study, 2) significant (greater than 70%) stenosis of at least one coronary artery at cardiac catheterization, or 3) at least one millimeter ST depression on exercise stress testing associated with angina. Informed consent was obtained from all subjects studied.

The patients and the normal subjects performed graded treadmill exercise using a protocol in which estimated total oxygen consumption was increased by 3.5 ml/kg/min every three minutes. Exercise was carried to exhaustion or to 3+ pain on a scale of 0 to 4+ pain with the latter representing the most severe pain experienced by the patient during a spontaneously occurring attack of angina. Heart rate, blood pressure, and ECG were recorded every minute. These exercise periods were carried out approximately two hours after ingestion of propranolol. Hemodynamics and myocardial performance at rest were assessed by noninvasive techniques immediately prior to exercise. Left ventricular volume was calculated as the cube of the internal left ventricular diameter measured in systole and diastole using a Unidad Corporation Series 100C Echocardiograph. Care was taken to record left ventricular dimensions from the same precordial position on successive measurements in the same subject. Systolic and diastolic volumes were used to calculate ejection fraction and cardiac index. Systolic time indices were reported on an Electronics for Medicine IR-4 using PPI-20 amplifiers to obtain a phonocardiogram and carotid pulse tracing and an EDI-7 amplifier to obtain the ECG. Appropriate corrections for heart rate were made.

Blood samples were obtained for propranolol concentration and renin activity immediately before these noninvasive studies and immediately after exercise. Thus, the control renin activity represented standing values in individuals on an ad lib sodium intake. In four normal subjects, treadmill exercise and plasma propranolol determinations were repeated eight hours after ingestion of the last dose of drug to examine the relationship between blockade of exercise tachycardia and plasma propranolol at these two different time intervals. Plasma propranolol was measured by a specific and sensitive gas-liquid chromatographic assay described previously.

Data during control periods were averaged for each subject and these averages were used to calculate mean values for normal subjects and for patients. In normals, control data were compared to results obtained at the highest plasma propranolol attained by each subject using a t-test for paired samples. In patients, control data and data obtained at maximum therapeutic benefit and at maximum plasma propranolol concentrations were compared by analysis of variance using Scheffe’s method of multiple comparisons. Mean estimated total oxygen consumptions at maximum exercise in patients receiving 0, 40, 80, 160, and 240 mg/day of propranolol were also compared using Scheffé’s method of multiple comparisons. All deviations from the mean reported in this paper represent standard errors of the mean.

Results

Beta Blockade in Normal Subjects

Heart rate was suppressed in the normal subjects at rest and at all levels of exercise by propranolol. Resting heart rates averaged 59 ± 2 beats/min during control periods and were reduced to 45 ± 3 beats/min during the highest propranolol dose (P < 0.01). At maximum exercise, which represented an estimated total oxygen consumption of 36.8 ± 1.8 ml/kg/min, heart rates averaged 175 ± 3 beats/min and were reduced to 116 ± 3 beats/min during the highest propranolol dose for each subject (P < 0.01). There was a progressive decline in heart rate as propranolol dose was increased. As the concentration of propranolol in plasma was increased, tachycardia at maximum levels of exercise was reduced to a plateau value, i.e., the value at which the next increase in concentration of drug resulted in no further reduction of heart rate (fig. 1). This plateau was reached at a plasma propranolol level of 99 ± 6 ng/ml. Suppression of exercise tachycardia averaged 34% of the control value and this represented the adrenergic component of tachycardia at this level of exercise.

The effect of propranolol in producing beta blockade was shown by relating plasma concentration to inhibition of the adrenergic component of exercise tachycardia (fig. 2). Complete blockade was achieved at approximately 100 ng/ml and a 50% effective concentration (ED50) averaged 8 ± 1 ng/ml. It was notable that the dose response relationship between beta blockade and plasma propranolol was relatively flat. Thus, physiologically significant blockade was effected at a plasma concentration one-tenth of that concentration.
required for complete blockade and even plasma concentrations of 3 ng/ml had demonstrable beta blocking effects. Although most of the values were obtained shortly after ingestion of the dose (two hours), the concentration-effect relationship appeared to be independent of this time since values obtained at eight hours were indistinguishable from the other data in terms of their relationship to effect on exercise-induced tachycardia.

Beta Blockade and Exercise Performance in Patients with Angina

The exercise performance in the patients with angina was terminated by the development of pain of an intensity of 3+ on a scale of 1 to 4+ pain (as described in Methods). The estimated oxygen consumption associated with this level of performance averaged $12.7 \pm 0.8$ ml/kg/min during the control period (table 1). During propranolol exercise performance was greater in all patients and this response tended to increase at first as the dose was raised and then to plateau at the larger doses. The maximum increase was seen in the group as a whole at 160 mg/day with an estimated oxygen consumption of $17.2 \pm 1.1$ ml/kg/min, a value significantly greater than the control ($P < 0.01$). However, when the individual performances of these patients were examined, maximum performance was seen at doses ranging from 40 to 240 mg/day. At the individual maximum therapeutic response the mean oxygen consumption at 3+/4+ angina averaged $18.2 \pm 1.0$ ml/kg/min, or a 43% increase over control values ($P < 0.01$). The dose of drug at this level of response averaged $144 \pm 21$ mg/day.

The plasma propranolol concentration varied

![Figure 2](Image)

Figure 2

Dose (concentration) response curve relating beta-adrenergic blockade to plasma propranolol in normal subjects. Beta-adrenergic blockade was equated with suppression of the adrenergic component of exercise tachycardia.

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These data represent individual exercise studies on each patient at the various doses of propranolol. Mean $V_O_2$ was significantly increased from control values on oral doses of 40, 80, 160, and 240 mg/day ($P < 0.01$). There was no significant difference between mean $V_O_2$ over the range of dosage from 40-320 mg/day. Abbreviations: $V_O_2$ = estimated total oxygen consumption in ml/kg/min at maximum exercise tolerated by subject; $P_R$ = plasma propranolol concentration in ng/ml.
widely, both among the patients at any given dose and in individual patients as the dose was increased (table 1). For the group as a whole, plasma propranolol averaged 57 ± 21 ng/ml at 160 mg/day. However, at individual maximum therapeutic responses the average value was 39 ± 7 ng/ml, but varied as widely as did the dose of propranolol among the individual patients, extending over a sixfold range (fig. 3). Thus, propranolol concentrations as high as 90 or as low as 14 ng/ml were measured at the dose providing maximum therapeutic response.

The plasma concentrations of propranolol associated with individual maximum therapeutic benefit were related to beta blocking activity by plotting these concentrations on the dose-response curve established in normal subjects (fig. 4). Maximum exercise performance in these patients was observed at 64 to 98% of total beta blockade. Thus, despite the wide range of both dose and concentration of propranolol, therapeutic response was associated with relatively narrow range of variation of effective beta blockade. Furthermore, the therapeutic response in these patients at the highest plasma propranolol concentration observed in all patients, which averaged 134 ± 29 ng/ml, was less than at the point of maximum therapeutic benefit. Thus, oxygen consumption at maximum exercise averaged 18.2 ± 1.0 at maximum therapeutic benefit and fell to 15.8 ± 1.3 ml/kg/min at the highest plasma propranolol. This difference in exercise performance indicated that there was a plateau in the therapeutic response and perhaps even in some patients a deterioration in response as the highest propranolol concentrations were achieved. In three patients (L.G., J.L., and T.S.), clinical evidence of cardiac decompensation was observed at the highest plasma levels. From these observations it would appear that at least in some patients with angina, propranolol can be administered in excessive amounts.

Beta Blockade and Hemodynamic Changes

Heart rate and blood pressure in the patients were reduced during propranolol therapy. During maximum exercise performance in the control period, heart rate averaged 115 ± 5 beats/min, systolic blood pressure averaged 166 ± 8 mm Hg, and the product of heart rate and blood pressure (double product) averaged 192 ± 14 × 10² (fig. 5). During propranolol therapy at maximum benefit, the individual maximum therapeutic response, heart rate, blood pressure, and double product were lower and averaged respectively 103 ± 3 beats/min (NS), 148 ± 8 mm Hg (P < 0.01), and 153 ± 10 × 10² (P < 0.05), respectively. At maximal propranolol (the greatest plasma propranolol concentration achieved in a given patient), these values were further reduced, averaging 89 ± 5 beats/min (P < 0.05), 136 ± 7 mm Hg (NS), and 121 ± 9 × 10² (P < 0.05), respectively. This progressive decline in these major determinants of myocardial oxygen consumption indicated that oxygen delivery to the heart was not increased and may even have resulted in a reduction of oxygen delivery, despite the improved exercise performance.

Resting hemodynamic changes during propranolol were comparable in the patients and the normal sub-
jects (table 2). Furthermore, similar hemodynamics were seen in the patients whether at maximum therapeutic benefit or at maximal propranolol. There was a significant decrease in heart rate ($P < 0.01$), cardiac index ($P < 0.01$), and mean blood pressure ($P < 0.05$). Stroke index tended to fall, but the changes were not significant. There was a significant increase in peripheral vascular resistance ($P < 0.05$). Ejection fraction, left ventricular ejection time, and pre-ejection period were all unchanged by the doses of propranolol administered in these patients.

In order to assess the potential relationship of renin and blood pressure in patients treated with proprano-

lol, plasma renin activity (PRA) was measured in patients and normals before and immediately after exercise (table 3). During maximal exercise in normal subjects PRA rose from $2.6 \pm 0.05$ ng/ml/hr at rest to $7.9 \pm 1.8$ ng/ml/hr ($P < 0.02$) in the control period. Propranolol administration produced a decline in both values which averaged, $1.6 \pm 0.6$ (NS) and $2.9 \pm 1.0$ ng/ml/hr ($P < 0.05$), respectively. In the patients however, PRA did not increase significantly at the exercise levels reached prior to stopping with pain. Propranolol had no significant effect on PRA in patients either before or after exercise. Thus, there was no correlation between the induction of angina during exercise and PRA or between the change in peripheral vascular resistance during propranolol therapy and PRA in the normal subjects or the patients.

Discussion

In this study, patients with angina had a large and significant increase in exercise performance on propranolol therapy (table 1). The improvement tended to be greater as the dose of propranolol was increased. Although the increase in exercise performance with doses above 40 mg/day could not be shown to be statistically significant for all ten patients, in six a large increase of at least one full grade level of exercise ($V_{O2} = 3.5$ ml/kg/min) was observed at doses above 40 mg/day. There was great individual variation in both the oral dose and the plasma propranolol concentration associated with maximum therapeutic benefit. A sixfold variation in both the dose and the plasma concentration of drug was seen in these patients when maximum benefit was obtained. There-

Table 2

<table>
<thead>
<tr>
<th>Resting Hemodynamics and Ventricular Function</th>
<th>Normal subjects</th>
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<tr>
<td>Patients with angina</td>
<td>Max Rx</td>
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<td>Oral dose</td>
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<tr>
<td>Plasma prop.</td>
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<tr>
<td>HR</td>
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<tr>
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<td>LVET</td>
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<tr>
<td>PEP</td>
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Abbreviations: Max Rx = maximum therapeutic benefit; Max Pr = maximum plasma propranolol; Oral Dose (mg/d); Plasma prop = plasma propranolol (ng/ml); HR = heart rate (beats/min); cardiac index (L/min/m²); SI = stroke index (ml/min/m²); BP = mean arterial blood pressure (mm Hg); PVR = peripheral vascular resistance (10^-5 x dyne · sec · cm⁻³ · m⁻²); EF = ejection fraction (%); LVET = left ventricular ejection time (msec); PEP = pre-ejection period (msec).

*Values differ from control ($P < 0.01$).
†Values differ from control ($P < 0.05$).

Hemodynamic values at Max Pr were not significantly different than those at Max Rx.


**Table 3**

<table>
<thead>
<tr>
<th></th>
<th>Plasma renin activity (ng/ml/hr)</th>
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<td>Rest</td>
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<tr>
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<tr>
<td>Patients</td>
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<td>±0.6</td>
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Therefore, neither one of these values appeared to provide a useful index for predicting optimal therapeutic response.

The variability of plasma levels after oral dosing has been shown before and demonstrated to be largely the result of variation in effective absorption of propranolol among patients. There are several metabolites of propranolol which have pharmacologic activity, but only 4-hydroxy propranolol has been found to have beta blocking activity. This metabolite has a much shorter half-life than propranolol and, if it were present in significant quantities, would have influenced the dose (concentration) response relationship differently at 2 and 8 hours after a dose of propranolol. Since such a difference in this relationship was not present (fig. 2), it seems unlikely that 4-hydroxy propranolol is present in significant quantities. Furthermore, all of our studies were performed only after 48 or more hours of dosing and this metabolite has been inferred to be absent after this length of time. Therefore, it seems reasonable to relate pharmacologic activity and/or therapeutic response to plasma propranolol despite the fact that at present one cannot rule out the possibility that metabolization of the drug may differ between the normal subjects and the patients.

The plasma propranolol concentrations in these patients measured at maximum therapeutic response ranged from 14 to 90 ng/ml and many were below levels accurately measurable by the standard fluorimetric technique, but easily quantified by the gas-liquid chromatographic assay used in this study. In order to interpret the pharmacologic effect of plasma propranolol levels in the patients, these values were related to a dose-response curve obtained in normal subjects wherein blockade of the adrenergic component of exercise tachycardia was compared to plasma propranolol. This dose response curve was defined at maximal exercise so that the adrenergic component of the exercise tachycardia would be large (34%) in order to minimize errors of estimating blockade at increasing propranolol concentration. Consequently, a well-defined relationship between concentration and blockade was established with total blockade at 100 ng/ml and an ED_{50} at 8 ng/ml. It was notable that very low concentrations of circulating drug produced significant pharmacologic effect. Using this relationship between blockade and concentrations it was possible to interpret the plasma propranolol values in patients at the maximum therapeutic response in terms of percent adrenergic blockade. Maximum therapeutic response occurred at 64 to 98% of total blockade. Considering the effect of propranolol in terms of one of its actual pharmacologic functions, i.e., blockade of the chronotropic beta-adrenergic receptors in the heart, it is apparent that there is a smaller variability in the therapeutic response among patients than when one looks at either the absolute dose or plasma level.

Beta blockade is competitive and surmountable by increasing amounts of norepinephrine released from the nerve or secreted from the adrenal, a release that might be expected during increasing exercise. Therefore, it is unlikely that a dose-response curve relating propranolol concentration to inhibition of exercise tachycardia is the same for all levels of exercise. It might seem inappropriate to relate a curve derived from normals at maximal exercise to patients at lesser exercise levels. However, the dose-response curves in normals differ only slightly at mild, moderate, and maximal exercise with ED_{50} of 3, 5, and 8 ng/ml, respectively. Furthermore, the precision of estimating the average dose-response curve is less at lower levels of exercise, with correlation coefficients of 0.72, 0.86, and 0.90, at mild, moderate, and maximal exercise, respectively. Finally, an estimate of the dose-response curve made in patients did not differ from the curve obtained in normal subjects at a comparable exercise level, although it was substantially less precise (correlation coefficient = 0.61). Thus, relating plasma propranolol to inhibition of heart rate at maximal exercise in normal subjects should provide a reasonable indication of beta blockade in patients with angina.

In this study, noninvasive measures of supine resting myocardial performance were not useful in assessing the relative extent of beta-adrenergic blockade in normals or in predicting the therapeutic benefit in patients. Furthermore, although resting heart rate fell significantly with propranolol therapy, the relation between changes in resting heart rate and plasma propranolol was far less consistent than that between suppression of tachycardia during maximal exercise in the normal subjects and plasma propranolol. This observation is not surprising in view of the relative importance of nonadrenergic, parasympathetic influences in regulating resting heart rate in contrast to the almost exclusive dependence of the heart rate on adrenergic control during strenuous exercise. A significant fall in resting cardiac index was also
observed and this was due almost entirely to the reduction in heart rate with an insignificant decline in stroke index. These findings are consistent with hemodynamic studies after acute intravenous propranolol administration in normal subjects and patients with coronary artery disease.20-28 By contrast, there was no significant change at rest in the ejection fraction, pre-injection period, or left ventricular ejection time during propranolol therapy in either normals or patients. Previous measurements of left ventricular ejection time in resting subjects given intravenous propranolol are in agreement with the present data when correction is made for changes in heart rate.27-29 Thus, plasma propranolol appears to be superior to standard methods of assessing cardiac function in indicating the degree of beta blockade present in a patient on propranolol therapy.

It was of interest to note the effects of propranolol on renin secretion because of the recent speculation regarding the potential vasotoxic effects of renin.30 Although a rather marked increase in PRA occurred after exercise consistent with previous observations in normal subjects,31 there was no change in PRA in the patients with angina induced by exercise. This may reflect the fact that the exercise stimulus was less intense in the patients. However, it would seem clear that renin has little role in the hemodynamic changes associated with angina. Furthermore, with propranolol administration, PRA at rest was not significantly changed despite the notable increase in peripheral vascular resistance in both the normals and the patients. Thus, it seems unlikely that the renin angiotensin system is involved in the hemodynamic response to propranolol in this setting.

When myocardial oxygen consumption was estimated from the double product of heart rate and systolic arterial pressure, the exercise ceiling in patients on propranolol at 3+4/4 angina was found to occur at a lower calculated myocardial oxygen requirement. This was true despite the increase during propranolol in over-all exercise tolerance. A reduction in the double product associated with the termination of exercise in patients with angina on propranolol has been reported in other studies.33,35 It is possible that increases in ventricular volume and in the ratio of ventricular wall tension to systolic arterial pressure renders the double product a poor index of myocardial oxygen consumption in patients. However, the work of Jørgensen et al.35 in normals suggests that this may not be true. From their studies it seems more probable that coronary blood flow to potentially ischemic areas is actually reduced relative to myocardial oxygen demands when patients are treated with propranolol.

In both normals and patients with coronary artery disease, total coronary blood flow falls and total coronary vascular resistance rises in response to acute intravenous propranolol administration.36,38 These changes in coronary hemodynamics can be explained by the decrease in myocardial oxygen requirements of the heart secondary to the changes in heart rate, blood pressure, and myocardial contractility resulting from the beta blocking effects of propranolol.34 However, propranolol blocks beta-adrenergic receptors in the coronary circulation35,38 and it is equally possible that this effect is directly responsible for some of the reduction of coronary blood flow. Furthermore, in experiments in dogs intravenous propranolol was associated with a redistribution of myocardial blood flow from the epicardial to the endocardial region in both normal dogs and animals with acute coronary occlusion.37-39 Additional animal experiments have indicated that propranolol therapy may have different effects on coronary flow to ischemic and nonischemic areas.40 Thus, there is evidence that propranolol can influence regional myocardial flow independent of its effect on heart rate, arterial pressure, and myocardial contractility.

If propranolol were to reduce blood flow to potentially ischemic areas relatively more than it reduces myocardial oxygen consumption in man, then maximum therapeutic benefit would occur with plasma propranolol levels which minimize this imbalance of supply and demand. Further increasing adrenergic blockade would result in greater reduction of myocardial oxygen demand, but such change might produce a relatively greater decrease in myocardial oxygen delivery thus causing a deterioration in exercise capacity. This balance between reduced oxygen demand and reduced oxygen delivery secondary to propranolol therapy could explain in part why maximum exercise performance occurred at less than complete beta blockade in these patients, ranging from 64 to 98%, and why a plateau or even deterioration of the therapeutic response was seen at higher propranolol levels. However, it is also possible that this plateau or deterioration of exercise performance with increasing propranolol beyond the dose at which the patient achieves the maximum therapeutic benefit can be caused by decreased ventricular function in these patients. The observation that maximum therapeutic benefit occurred at less than complete blockade may be in accord with this possibility. Thus, patients with impaired cardiac function are dependent upon adrenergic stimulation. Complete withdrawal of this support may lead to deterioration of cardiac performance and contribute to the development of angina as a result of ventricular dilation and increase of wall tension. More critical examination of this important problem is required to determine which of these factors is of greater importance in controlling the extent.

Circulation, Volume 52, November 1975
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of therapeutic response to beta blockade at increasing propranolol levels in patients with angina.

Acknowledgement

We wish to recognize the expert clinical assistance of Arlene Niccoli in conducting these studies and the technical assistance of Dorothy Walker in the drug analyses.

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Circulation. 1975;52:886-893
doi: 10.1161/01.CIR.52.5.886

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:
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