Adrenergic Responsiveness After Abrupt Propranolol Withdrawal in Normal Subjects and in Patients with Angina Pectoris

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SUMMARY Adrenergic responsiveness after abrupt propranolol withdrawal during exogenous and endogenous catecholamine stimulation was assessed in 10 normal subjects and 10 patients with angina pectoris. Propranolol, 160 mg/day, was administered for 2 weeks and then stopped. During an epinephrine infusion, heart rate and systolic pressure–heart rate product were significantly reduced from control in the propranolol period (p < 0.005). There were no differences from control 96 hours after the drug had been stopped in both groups or at 144 hours in the angina patients who were studied for a longer time. At 48 hours of withdrawal, heart rate and the pressure-rate product were significantly less than control level in the angina patients, but not in the normal subjects. Similar results were observed during exercise in both groups. The epinephrine-induced increase in free fatty acids was blocked by propranolol (p < 0.005), was still attenuated at 48 hours of withdrawal (p < 0.05), but returned to control levels thereafter in both groups. Resting serum triiodothyronine levels decreased with propranolol (p < 0.005) and remained low throughout the withdrawal period. Measurements of dopamine β-hydroxylase, plasma platelet factor 4, and platelet aggregation at rest and after exercise did not change significantly during or after propranolol administration. Plasma norepinephrine and epinephrine values were not changed from control during the withdrawal period at rest or after exercise. We conclude that there is no evidence of hypersensitivity to β-adrenergically mediated responses after abrupt propranolol withdrawal.

INCREASED SEVERITY of angina pectoris, ventricular arrhythmias, myocardial infarction and sudden death have been reported in patients with ischemic heart disease who are abruptly withdrawn from chronic oral propranolol therapy. Little information exists concerning the mechanism of these propranolol withdrawal phenomena, although the possibility of sympathetic hypersensitivity in the days after drug cessation has received the most interest. Other explanations include progression of underlying coronary artery disease, enhanced platelet aggregation, increased triiodothyronine levels, alterations in plasma renin activity, or continued high levels of physical activity despite withdrawal of propranolol. The purpose of this study was to assess possible mechanisms for propranolol withdrawal phenomena by serial hemodynamic, hematologic, metabolic and endocrine measurements at rest and with both exogenous and endogenous catecholamine stimulation in normal subjects and in patients with angina pectoris.

Materials and Methods

Patients

The study population consisted of 20 subjects—10 normal volunteers, ages 22–30 years, and 10 patients with angina pectoris, ages 42–66 years. The normal subjects were studied first to assess the feasibility of the protocol and to determine the magnitude of any sympathetic hypersensitivity or other reactions. The results in the normal subjects suggested that we could study selected patients with angina pectoris. Nine of the 10 patients with angina had either a previous well-documented myocardial infarction (seven patients) or angiographically proved stenosis of at least 70% of one or more coronary arteries (six patients). The remaining patient had typical angina during treadmill exercise with > 0.1 mV of horizontal ST-segment depression for > 0.08 second. All the patients had stable angina pectoris of at least 5 months duration occurring with a frequency ranging from one episode per week to three episodes per day (mean 6.5 episodes/week). Patients with severe hypertension, congestive heart failure, cerebrovascular disease, asthma or insulin-dependent diabetes mellitus were excluded. Informed consent was obtained from all subjects on a form approved by the University of Texas Health Science Center at San Antonio, Institutional Review Board.

Study Days

The same series of studies was performed on five days in the normal subjects and on six days in the angina patients. Two days, at least 48 hours apart, were used for control studies. Each subject was then given propranolol 40 mg four times per day for 12–16
days (mean 14 days) and studies were performed on one of the last 2 days of propranolol therapy, 2–3 hours after the last dose of propranolol. Propranolol was then abruptly stopped and the same studies were performed 48 and 96 hours after the first missed dose in the normal subjects, and additionally at 144 hours in the angina patients. Normal subjects were not hospitalized, but the angina patients were all hospitalized during the withdrawal phase of the study in the Special Diagnosis and Treatment Unit of the Veterans Administration Hospital.

Study Protocol

All studies were performed in the fasting state, supine, in a room containing resuscitation equipment. Each study was begun by inserting a 19-gauge scalp vein needle in a forearm vein and drawing 33 ml of blood for baseline hematologic studies. The needle was then connected to an i.v. line which was periodically flushed with normal saline in an amount approximately equivalent to the amount of blood removed. The subjects were allowed to rest quietly for 30 minutes. At that time, 24 ml of blood was drawn for dopamine β-hydroxylase (DβH), baseline free fatty acids (FFA), plasma catecholamines, and propranolol levels. Then, an epinephrine infusion was begun at 0.1 μg/kg/min for 5 minutes and heart rate and blood pressure were measured every minute for 15 minutes, and at 20, 25 and 30 minutes after the beginning of the infusion. The angina patients had continuous ECG monitoring during this 30 minutes. Blood samples for FFA were obtained in the normal subjects at 8, 10, 12, 14, 16, 18, 20 and 30 minutes and in the coronary patients at 12, 14, 16, 20 and 30 minutes after the onset of the infusion. Blood for platelet factor 4 (PF4) and platelet count was taken at 15–18 minutes.

Each normal subject then underwent graded maximum supine bicycle exercise beginning at 200 kpm/min and increasing by 100 kpm/min every 3 minutes until exhaustion. On subsequent days, the subjects were instructed to exercise to the same subjective degree of exhaustion as on the first day of the study. M-mode echocardiograms of the left ventricle were recorded at rest and during the last minute of each stage of exercise by a technique previously reported. Left ventricular end-diastolic dimension, end-systolic dimension and percent dimensional shortening were measured on each of these echocardiograms. In place of supine bicycle exercise, the angina patients underwent graded treadmill testing with the Bruce protocol because of their familiarity with this type of exercise and because left ventricular M-mode echocardiography is not accurate in patients with previous myocardial infarction. Immediately after exercise, blood was drawn for PF4, platelet count, platelet aggregation, DβH and catecholamines.

Specific Assay Procedures

DβH activity was measured by the method of Nagatsu and Udenfriend. Our normal ranges have been reported. Plasma catecholamines were measured by the method of Passon and Peuler. Plasma FFAs were measured by the technique of Dole as modified by Trout. The serum propranolol levels were measured by using a modification of the fluorimetric method of Shand et al. Platelet counts were performed on EDTA anticoagulated blood using a Coulter Model C Thrombocounter (Hialeah, Florida). PF4 was measured by the radioimmunoassay method of Levine and Krentz. Platelet aggregation studies were performed by the optical density method of Born as modified by Mustard. Serum triiodothyronine levels were measured with the Kallestad Quantitopes assay kit.

Statistical Analysis

A two-way analysis of variance was used to compare pre- and postexercise values of PF4, platelet aggregation and DβH. PF4 and platelet aggregation were analyzed after conversion to natural logarithms. All remaining statistical analyses were performed using a one-way analysis of variance for repeated measures and Dunnet's test was used to identify individual differences.

Results

Heart Rate

Figure 1 represents the average heart rate at baseline, at 5 minutes of epinephrine infusion and with exercise in the normal subjects and in the angina patients for each study day. Heart rate is shown at 12 minutes of supine bicycle exercise in the normal subjects and at end-exercise in the angina patients. At rest, propranolol reduced resting heart rate in the normal subjects and in the angina patients (p < 0.005), and it remained less than control at 48 hours after withdrawal of propranolol in the angina patients (p < 0.05). Resting heart rate was unchanged during all other withdrawal periods compared with control. In both groups, the epinephrine-induced rise in heart rate was prevented by propranolol administration (p < 0.005) and remained reduced at 48 hours after withdrawal in the angina patients (p < 0.005). However, neither group showed an increase in the epinephrine-stimulated heart rate when control days were compared with the withdrawal period. During propranolol administration, the heart rate response to exercise was significantly decreased in both groups compared with control (p < 0.005), but was not different when comparing control with withdrawal values. Only three subjects had a heart rate rise 10% above control during withdrawal. Therefore, we could detect no consistent increases in heart rate at rest, with epinephrine or with exercise in any of the withdrawal periods compared with control. In fact, in the angina patients, baseline and epinephrine-stimulated heart rate remained depressed at 48 hours after propranolol withdrawal.
Systolic Blood Pressure

Figure 2 shows average systolic blood pressure at baseline, with epinephrine stimulation and with exercise. At rest, systolic blood pressure did not change significantly during these three phases at any time period. With epinephrine infusion systolic blood pressure rose consistently on propranolol in both groups (p < 0.005), but there was no difference between the control and withdrawal measurements. Propranolol significantly blunted the systolic blood pressure rise with exercise in both groups (p < 0.005), but control and withdrawal values were not different from each other. In only two instances was there more than a 10% increase in withdrawal values as compared to control. Thus, consistently exaggerated systolic blood pressure responses after abrupt propranolol withdrawal did not occur at rest, with epinephrine infusion, or with exercise.

Systolic Blood Pressure—Heart Rate Product

Figure 3 illustrates the average systolic blood pressure—heart rate product. Propranolol reduced systolic blood pressure—heart rate product at baseline, during epinephrine and exercise in both groups, but withdrawal values again showed no differences from control except at 48 hours, when the products at baseline and during epinephrine were still depressed in the angina patients.

Free Fatty Acids

Figure 4 demonstrates the baseline and the peak FFA response to epinephrine infusion in both the normal subjects and in the angina patients. In all normal subjects and angina patients, the peak FFA response occurred 12–16 minutes after the onset of the epinephrine infusion. Propranolol did not change baseline FFA levels in either group and there were no differences in baseline control and withdrawal values. In response to the epinephrine infusion, propranolol blocked the rise in FFAs in both the normal and the angina patients (p < 0.005). However, FFA did not rise higher during the withdrawal period than during the control period in either group. In fact, the FFA rise in response to epinephrine was decreased at 48 hours of withdrawal compared with control (p < 0.05) in both groups. Thus, the epinephrine-stimulated FFA rise, although effectively blocked by propranolol, was not exaggerated after abrupt propranolol withdrawal.

Left Ventricular Performance and End-diastolic Dimension

Figure 5 demonstrates the average percent change in left ventricular dimensional shortening (%ΔD) as

![Figure 1. Average heart rate on the ordinate is displayed at baseline, with epinephrine infusion and with exercise in normals (left) and in angina patients (right). C1 = control day one; C2 = control day 2; P = during propranolol; 48, 96, 144 = 48, 96 and 144 hours after abrupt propranolol withdrawal.](http://circ.ahajournals.org/lookup/fig/1407573284)

![Figure 2. Average systolic blood pressure, at baseline, with epinephrine and with exercise.](http://circ.ahajournals.org/lookup/fig/1407573284)
measured by M-mode echocardiography in nine of the 10 normals. All measurements were made at 12 minutes of supine bicycle exercise because this was the minimal level achieved by all subjects. The echocardiogram of the tenth patient could not be adequately measured at 12 minutes. At rest, %ΔD was unchanged with propranolol or during withdrawal. With exercise, %ΔD was significantly decreased on propranolol (p < 0.005) but was not different from control during the withdrawal period. End-diastolic dimension at rest was not significantly changed during the study (table 1). However, during exercise, end-diastolic dimension was significantly increased on propranolol compared with control (p < 0.005) and remained increased at 48 hours after withdrawal (p < 0.05). Withdrawal values for end-diastolic dimension at 96 hours were unchanged from baseline values both at rest and with exercise.

Propranolol Levels

Serum propranolol levels after 12–16 days (mean 14 days) of oral propranolol drawn 2-3 hours after the last dose averaged 71.3 ± 10 (± sd) ng/ml in the normals (range 23–155 ng/ml) and 55.9 ± 19.9 ng/ml in the angina patients (range 27–102 ng/ml) (NS). Propranolol levels drawn at 48, 96 and 144 hours after withdrawal were unmeasurable in all cases.

Catecholamines

In the angina patients, average control values for norepinephrine were 156 ± 69 pg/ml at rest and 1123 ± 494 pg/ml after exercise. Control epinephrine values at rest were 18 ± 16 pg/ml at rest and 59 ± 33

<table>
<thead>
<tr>
<th>TABLE 1. Average (= sd) Left Ventricular End-diastolic Dimension (mm) in Nine of the Normal Subjects</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>C1</td>
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<td>C2</td>
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<tr>
<td>P</td>
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<tr>
<td>48</td>
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<tr>
<td>96</td>
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</tbody>
</table>

* p < 0.005; † p < 0.05, compared with C1 and C2.

Abbreviations: C1 = control day 1; C2 = control day 2; P = during propranolol; 48, 96 = 48 and 96 hours after abrupt propranolol withdrawal.
pg/ml after exercise. There were no significant changes in any of the withdrawal periods as compared to control in norepinephrine or epinephrine either at rest or after exercise.

Dopamine $\beta$-Hydroxylase

In the angina patients, resting mean D$\beta$H levels were unchanged throughout the study and all D$\beta$H levels drawn after exercise were slightly but significantly increased over resting values ($p < 0.05$). This increase in D$\beta$H with exercise was identical in all phases of the study (table 2).

**Platelet Factor 4**

Table 3 demonstrates the geometric means and 95% confidence limits for plasma PF$_4$ concentrations at baseline, after epinephrine infusion and after exercise in both groups of patients. All epinephrine and exercise values are significantly increased over control ($p < 0.001$), but are not further modified by either propranolol administration or withdrawal.

**Platelet Aggregation**

Mean baseline threshold to aggregation with adenosine diphosphate was 0.30 ± 0.10 µM in normals and 0.47 ± 0.3 µM in angina patients, and these values did not change during exercise. In both groups mean aggregation data did not change on propranolol or during the withdrawal period compared with control at rest and after exercise.

**Triiodothyronine Levels**

Baseline total serum triiodothyronine was measured in each phase of this study (table 4). Control values in normal subjects and in angina patients were equivalent. In both groups, propranolol significantly reduced total serum triiodothyronine ($p < 0.05$), and this reduction persisted throughout the entire withdrawal period.

**Patient Responses**

Most of the angina patients noted symptomatic improvement during propranolol therapy and their mean

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**Table 3. Platelet Factor 4 (mg/ml) Expressed As Geometric Mean (± SD)**

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<thead>
<tr>
<th></th>
<th>Normal subjects</th>
<th>Angina patients</th>
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<tbody>
<tr>
<td></td>
<td>Base</td>
<td>Epi</td>
</tr>
<tr>
<td>C$_2$</td>
<td>5.8</td>
<td>24</td>
</tr>
<tr>
<td>P</td>
<td>7.5</td>
<td>23</td>
</tr>
<tr>
<td>48</td>
<td>6.1</td>
<td>19</td>
</tr>
<tr>
<td>96</td>
<td>6.8</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>(4.7–7.2)</td>
<td>(21–52)</td>
</tr>
<tr>
<td>144</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>(7.8–15.5)</td>
<td>(19–52)</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% confidence limits.

Abbreviations: Base = baseline; Epi = epinephrine; Ex = exercise. See table 1 for other abbreviations.
exercise duration on the treadmill increased from 422 ± 111 seconds to 454 ± 128 seconds (p < 0.005). No patient experienced increased angina during the withdrawal period compared with the control period and mean exercise duration returned to control values. Routine monitoring during the study periods revealed no new arrhythmias at rest, with epinephrine or with exercise.

**Discussion**

Shand and Wood suggested that hypersensitivity to sympathetic stimulation may cause adverse clinical reactions temporally related to abrupt propranolol withdrawal.6 Data from animal research offer some support for a hypersensitivity mechanism. Increased sensitivity to exogenous catecholamines has been noted after surgical cardiac denervation in dogs.23 Such hypersensitivity could be caused by an increased number of β-adrenergic receptors, by increased binding affinity of β-adrenergic receptors for catecholamines, by increased rates of cyclic adenosine monophosphate formation unrelated to receptor number or by increased myocardial or circulating catecholamines. Recently, Sporn et al.24 observed increased binding of a radioligand to β-adrenergic receptors in the cerebral cortex of rats that had undergone chemical sympathectomy with 6-hydroxydopamine. Of special interest is a report by Glaubiger and Lefkowitz25 showing that the number of cardiac β-adrenergic receptors increased in rats treated with propranolol for 2 weeks. However, even if this increase in cardiac β-adrenergic receptors reported in propranolol-treated rats reflects the response in patients with coronary artery disease, this need not imply an augmented physiologic response. Therefore, we measured multiple physiologic responses to β-adrenergic stimulation before, during and after a course of propranolol.

Our results demonstrate that the abrupt withdrawal of propranolol after chronic oral administration in both normal subjects and patients with angina pectoris does not result in an exaggerated response of various hemodynamic, metabolic, hematologic and endocrine measures at rest or with high levels of stimulation by exogenous or endogenous catecholamines. The withdrawal study days encompass the time period in which most cases of propranolol withdrawal phenomena have been reported. Even when coronary events occurred 2 weeks or more after abrupt propranolol withdrawal, most were preceded by increasing angina beginning in the first 48 hours after withdrawal.3,5 In reports that contain detailed information,1,2,4,5,22 of 23 patients had either increasing symptoms or an acute event in the first 6 days after withdrawal of propranolol.

Two studies with different conclusions from ours purport to have demonstrated hypersensitivity to isoproterenol infusions within the first 6 days after withdrawal.26,27 In the study of Boudoulas et al. of normal subjects,26 increases in pulse pressure and heart rate over baseline were observed at 24–48 hours. We have shown that at 48 hours after stopping propranolol there is still substantial β-adrenergic blockade of receptors modulating cardiac and metabolic activity. Other investigators have also found that blockade by propranolol lasts 48 hours or more after the last dose of the drug.27–29 The 2-day course of propranolol in the study by Boudoulas and co-workers may have been too short to produce this effect. The study by Nattel et al.27 dealt with hypertensive patients without symptomatic coronary artery disease. The possibility that altered baroreceptor responses or other pathophysiologic alterations unique to the hypertensive state may have been responsible for their findings must be considered. Our study of patients with angina and coronary artery disease using 2 weeks of propranolol therapy is likely to be more relevant to the usual situation in which propranolol withdrawal phenomena occur than are the studies of Boudoulas et al.26 and Nattel et al.27

In evaluating the possibility of hypersensitivity after propranolol withdrawal, we chose a wide range of physiologic measurements known to be under sympathetic control. The epinephrine-stimulated rise in FFAs is a well-known β-receptor-mediated response that has been studied by various investigators.30–32 Although β-adrenergic blockade with propranolol was clearly demonstrated, we found no increase in FFA mobilization in the withdrawal period to suggest β-receptor hypersensitivity. Similar results were obtained in a recent study in dogs.34 With the combined α and β stimulation of epinephrine, we saw no exaggerated heart rate response in either our normal subjects or angina patients. Although the dose of epinephrine was purposely low to avoid precipitation of angina pectoris, it was enough to cause reproducible and significant hemodynamic effects. The reflex response to the α-vasoconstrictor properties of epinephrine could mask some of the expected heart rate increase; however, even heart rate–systolic blood pressure products showed no exaggerated changes in the withdrawal period compared with control. In addition, exercise to a symptom-limited maximum failed to provoke any rebound increase in heart rate or systolic blood pressure. Furthermore, in a previous study in dogs, we found no evidence of increased sensitivity to isoproterenol after propranolol withdrawal.34

We considered the possibility that circulating catecholamine levels increased after propranolol

<p>| TABLE 4. Total Serum Triiodothyronine (ng/dl) (± sd) |</p>
<table>
<thead>
<tr>
<th>Normal subjects</th>
<th>Angina patients</th>
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<tbody>
<tr>
<td>C₂</td>
<td>157 ± 24</td>
</tr>
<tr>
<td>P</td>
<td>139 ± 25†</td>
</tr>
<tr>
<td>48</td>
<td>135 ± 24†</td>
</tr>
<tr>
<td>96</td>
<td>141 ± 29‡</td>
</tr>
<tr>
<td>144</td>
<td>—</td>
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</table>

*p < 0.005; †p < 0.1; ‡p < 0.05 compared with C₂. Abbreviations: see Table 1.
withdrawal. This was not the case either at rest or during exercise in the coronary disease patients in whom we measured plasma norepinephrine and epinephrine at 48, 96 and 144 hours after propranolol withdrawal. In addition, serum $D\beta H$, which has been proposed by some investigators as an index of chronic sympathetic tone, was not altered after propranolol withdrawal at rest or with exercise.

Propranolol is known to suppress total serum $T_3$ levels in normal and hyperthyroid subjects. Increases in free $T_3$ over control have been reported to occur after withdrawal of propranolol in a few patients with hypertension. Total $T_4$ did not increase after propranolol withdrawal in our normal subjects and angina patients, but we cannot exclude the possibility that free $T_3$ increased. However, in one previous study, free and total $T_3$ were closely related and changed in a parallel fashion. Accordingly, we believe that thyroid activity is not increased during the period when propranolol withdrawal phenomena occur and that the effect of $\beta$-adrenergic blockade on thyroid function is considerably more sustained than the effect on the other parameters we measured.

Finally, there has been considerable interest in the role of platelets in atherosclerotic cardiovascular disease. Platelet aggregation may be enhanced in some patients with coronary artery disease. In one study, this enhanced platelet aggregation returned toward normal with propranolol therapy but showed a rebound increase after the sudden withdrawal of propranolol. Platelet aggregation was not significantly enhanced in our angina patients compared with the normal subjects. We found no decrease in aggregation thresholds in response to ADP with propranolol. This was true for both normal subjects and angina patients when assessed both at rest and after exercise. Platelet counts were unchanged in all phases of the study. Furthermore, $PF_4$ showed no change when comparing control, propranolol, and withdrawal phases, again at baseline, after epinephrine infusion and after exercise. Since $PF_4$ is an in vivo technique for assessing platelet secretion, these data complement the in vitro lack of changes seen in platelet aggregation. Therefore, we found no evidence to implicate abnormalities in platelet aggregation or secretion in the propranolol withdrawal phenomena.

Presumably, any of the phenomena described in angina patients after abrupt propranolol withdrawal ultimately, regardless of the mechanism, reflect an alteration in the myocardial oxygen supply-demand ratio. Major determinants of myocardial oxygen demand include heart rate, systolic blood pressure, contractility and left ventricular size. We have measured heart rate, systolic blood pressure, left ventricular size and percent left ventricular shortening in normal subjects and heart rate and systolic blood pressure in angina patients and have shown no increases over control after propranolol withdrawal. Therefore, it is unlikely that there was increased myocardial oxygen demand during withdrawal in our subjects at rest or with exercise. Furthermore, if the catecholamine-stimulated rise in FFAs is an important influence on myocardial energetics, as suggested recently, it does not appear to be an important mechanism for increasing myocardial oxygen consumption after abrupt propranolol withdrawal.

Recent evidence suggests that the propranolol withdrawal phenomena do not occur often. If one examines the early reports of these phenomena, one was a single institutional report within a larger randomized trial. Over the whole trial, propranolol withdrawal phenomena were not reported with increased frequency over control. Another of these reports involved 14 patients. In nine of these patients, increasing angina was noted even before abrupt propranolol withdrawal. Patients with angina pectoris may be unstable and the natural history, with or without $\beta$-adrenergic blockade, often leads to myocardial infarction or sudden death. Patients scheduled for catheterization or surgery may be at particularly high risk regardless of the state of $\beta$ blockade.

Our patients had mild-to-moderate angina pectoris. Most patients demonstrating propranolol withdrawal phenomena have moderate or severe angina. In this sense, our patients may not have been the ideal group to study. However, we did not wish to provoke the propranolol withdrawal phenomena, but rather tried to demonstrate a potential mechanism for these phenomena. We could not do so in the first 6 days after withdrawal, a time which encompasses most reported cases.

We cannot exclude the possibility that an occasional patient may have an idiosyncratic reaction to sudden propranolol withdrawal. None of our normal subjects or angina patients had evidence of this type of response. We have shown that there is no generalized sympathetic hypersensitivity in either normal subjects or patients with angina pectoris to explain propranolol withdrawal phenomena. It is important to remember that we have not investigated every possible mechanism that has been suggested. However, it would appear that most propranolol withdrawal phenomena reflect the natural history of an unstable high-risk disease.

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