A abrupt withdrawal of \( \beta \)-blockade therapy in patients with myocardial infarction: effects on infarct size, left ventricular function, and hospital course


ABSTRACT The effects of abrupt withdrawal or continuation of \( \beta \)-blockade therapy during acute myocardial infarction were evaluated in 326 patients participating in the Multicenter Investigation of the Limitation of Infarct Size (MILIS). Thirty-nine patients previously receiving a \( \beta \)-blocker and randomly selected for withdrawal of \( \beta \)-blockers and placebo treatment during infarction (group 1) were compared with 272 patients previously untreated with \( \beta \)-blockers who were also randomly assigned to placebo therapy (group 2). There were no significant differences between the two groups in MB creatine kinase isoenzyme (15.8 ± 10.9 vs 18.2 ± 14.4 g-eq/m², respectively) estimates of infarct size, radionuclide-determined ejection fractions within 18 hr of infarction (0.44 ± 0.15 vs 0.47 ± 0.16) or 10 days later (0.42 ± 0.14 vs 0.47 ± 0.16), creatine kinase–determined incidence of infarct size (13% vs 6%), congestive heart failure (43% vs 37%), nonfatal ventricular fibrillation (5% vs 7%), or in-hospital mortality (13% vs 9%). Patients in group I had more recurrent ischemic chest pain (p = .002) within the first 24 hr after infarction, but not thereafter. However, this did not appear to be related to a rebound increase in systolic blood pressure, heart rate, or double product. In a separate analysis, 20 propranolol-eligible group I patients randomly selected for withdrawal of \( \beta \)-blockade (group 3) were compared with 15 patients randomly selected for continuation of prior \( \beta \)-blockade therapy (group 4). This comparison yielded similar results. These data indicate that the \( \beta \)-blockade withdrawal phenomenon is not a major clinical problem in patients with acute myocardial infarction. \( \beta \)-Blockade therapy can be discontinued abruptly during acute myocardial infarction if clinically indicated.

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From the Department of Internal Medicine (Cardiology Division) of the University of Texas Health Science Center, Dallas, and the MILIS Clinical Units at Barnes Hospital, St. Louis, Brigham and Women's Hospital and Massachusetts General Hospital, Boston, Medical Center Hospital of Vermont, Burlington, and Parkland Memorial Hospital, Dallas.

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There is current widespread concern that the sudden withdrawal of \( \beta \)-adrenoreceptor–blocking agents from patients with ischemic heart disease may result in a rebound adrenergic hypersensitivity manifested by an exacerbation of angina pectoris,\(^1\)–\(^5\) ventricular arrhythmias,\(^3\)–\(^6\),\(^7\) myocardial infarction,\(^2\)–\(^4\) or sudden death.\(^2\)–\(^4\) Several mechanisms have been proposed to account for these phenomena, including platelet hyperaggregability,\(^4\)–\(^5\) increased plasma renin activity,\(^4\)–\(^6\) an unfavorable leftward shift in the oxyhemoglobin dissociation curve,\(^4\)–\(^5\) an increase in triiodothyronine levels,\(^1\) a reactive increase in plasma catecholamines,\(^1\) increased numbers of \( \beta \)-adrenergic receptors, and decreased beta-adrenergic sensitivity.\(^4\)–\(^5\) A number of countermeasures have been proposed to prevent and treat the phenomenon, including the use of beta-blockers and nitrates, \( \beta \)-adrenergic receptor desensitization, platelet aggregation inhibitors, antibiotics, and inertial and volume loading.\(^3\)–\(^7\) Although these strategies may delay or moderate the rebound phenomenon, they do not prevent it completely.\(^1\)–\(^5\),\(^7\)

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receptors and/or an alteration in their affinity for β-adrenergic agonists,12 or rebound hypersensitivity to sympathetic stimulation.4, 11, 13, 14

Moreover, accurate clinical evaluation of the syndrome is confounded by an inability to distinguish between reemergence of symptoms after cessation of effective therapy and true rebound phenomena. It is reasonable, however, to postulate that rebound β-adrenergic hypersensitivity is most likely to be unmasked during acute myocardial infarction, a condition characterized by marked elevation of both plasma25-27 and local myocardial catecholamine levels.28, 29 In this situation too, urgent questions regarding the relative risks of abrupt withdrawal vs continuation of β-blockers frequently arise. This report describes the hospital course and prospectively collected measurements of infarct size, left ventricular function, and cardiac arrhythmias in clinically comparable groups of patients with acute myocardial infarction with and without abrupt withdrawal of β-blockade.

Methods

Study population. Three hundred twenty-six patients presenting with enzymatically confirmed acute myocardial infarction were studied. These 326 patients formed part of the larger cohort of individuals enrolled in the Multicenter Investigation of the Limitation of Infarct Size (MILIS) study,30, 31 a randomized blinded trial designed to assess the efficacy of propranolol or hyaluronidase vs placebo in limiting infarct size.

Each patient fulfilled previously defined inclusion and exclusion criteria30, 32 for entry into the study. The design of the MILIS protocol30 dictated that enrolled patients were assigned to either a propranolol-eligible group (MILIS group A) with randomization to propranolol, hyaluronidase, or placebo, or a propranolol-ineligible group (MILIS group B) with randomization to either hyaluronidase or placebo. Adverse clinical criteria dictating assignment to group B included (1) a heart rate less than 55 beats/min at the time of randomization or less than 40 beats/min before randomization, (2) a systolic arterial pressure less than 100 mm Hg at randomization, one that had fallen more than 50 mm Hg from previous levels, or one that even temporarily was less than 70 mm Hg, (3) moist rales over one-third or more of the lung fields, (4) the presence of atrophicventricular block, (5) a history of asthma, (6) wheezes on physical examination, (7) pulmonary edema, or (8) administration of verapamil within the previous 6 hr.30

The 326 patients in this study were divided into four groups (figure 1). For purposes of comparing the clinical courses of patients withdrawn from β-blockade during acute myocardial infarction and those never exposed to β-blockade, we evaluated patients in two groups. Group 1 consisted of 39 patients previously taking a β-blocker regularly for at least 21 days before randomization who were randomly selected for abrupt withdrawal of β-blockade and administration of placebo. Group 2 consisted of 272 patients not previously on a β-blocker who were randomly selected to receive placebo.

To compare the relative effects of β-blockade withdrawal vs continuation during acute myocardial infarction, we also identified two other groups of patients. Because patients continued on β-blockade (group 4) had to fulfill MILIS criteria for propranolol eligibility (defined above), we required that patients withdrawn from β-blockade (group 3) also fulfill similar baseline clinical characteristics. Group 3 patients were selected as a subgroup of group 1 and comprised all 20 patients in this latter group who were eligible for propranolol but who were randomly assigned to abrupt withdrawal of β-blockade and administration of placebo. Group 4 comprised all 15 patients in the MILIS study previously taking a β-blocker regularly for at least 21 days before admission who were eligible for and randomly assigned to therapy with propranolol. All group 4 patients completed intravenous induction of propranolol (0.1 mg/kg in three divided doses over 6 min), intravenous maintenance therapy (one-quarter of the induction dose given intravenously over 30 sec), and oral maintenance therapy over a period of 9 days (individualized dosage according to the MILIS protocol).

Radionuclide ventriculography. Radionuclide ventriculograms deemed interpretable by the MILIS Core Laboratory for Radionuclide Ventriculography were obtained before randomization and within 18 hr of the onset of chest pain in 291 patients.

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

**FIGURE 1.** Representation of β-blockade therapy before and after randomization during acute myocardial infarction (MI) in each of groups 1 through 4. Patients in groups 1, 2, and 3 were randomly assigned to receive propranolol. Patients in group 4 were randomly assigned to receive placebo. Groups 3 and 4 were identified to compare the relative effects of β-blockade withdrawal (group 3) vs continuation (group 4) during acute myocardial infarction. Since group 4 patients fulfilled MILIS criteria for administration of propranolol (see text), we required that all group 3 patients fulfill similar baseline characteristics. Therefore group 3 patients were selected from all those withdrawn from β-blockade therapy (group 1) and comprised only those in this latter group who were propranolol-eligible (by MILIS criteria).
Two hundred seventy-three patients underwent repeat resting radionuclide ventriculography 10 days after myocardial infarction. Multigated equilibrium blood pool scintigrams were obtained by previously described techniques and were analyzed by blinded investigators.

**Left ventricular ejection fraction, end-diastolic volume index, and an average wall motion score were calculated by methods reported previously.**

**Enzymatic estimation of infarct size.** Serial blood samples from each patient were assayed for the MB creatine kinase isoenzyme by the glass-bead adsorption technique. Samples were drawn from an indwelling heparin lock on admission, hourly thereafter for 4 hr, every 2 hr for the next 4 hr, and then every 4 hr until completion of a 72 hr interval. Additional samples were drawn every 8 hr for the next 48 hr and then every 12 hr for the next 9 days. MB creatine kinase values were used to construct time-activity curves, from which infarct size could be derived. Results were expressed in gram equivalents per square meter.

**Technetium-99m pyrophosphate scintigraphic estimation of infarct size.** Technetium-99m (99m Tc) pyrophosphate scintigrams were obtained 48 to 72 hr after myocardial infarction according to methods described previously. Myocardial infarct size was determined from the 48 to 72 hr images in those patients with well-localized "3+ or 4+" uptake of 99m Tc-pyrophosphate over the anterior or anterolateral surface of the left ventricle. The largest projected image area in each of these patients was planimetered manually. Calculated infarct size was expressed in square centimeters.

**Ambulatory electrocardiography.** Twenty-four hour two-channel ambulatory electrocardiographic recordings (Del Mar Avionics Model 445), obtained on the tenth day after infarction, were interpreted by personnel blinded with respect to patient identity or clinical course.

**Patient evaluation.** Upon hospitalization, a detailed abstract of the admission workup was recorded on MILIS data forms. Thereafter a cardiologist associated with MILIS maintained an extensive daily case record until hospital discharge. Heart rates and blood pressures (by the cuff method) were monitored and recorded every 2 hr during the first 24 hr and at 4 hr intervals thereafter. Heart rates and systolic blood pressures were multiplied to derive a double product. All values obtained during each 24 hr period were reviewed and the maximum and minimum heart rates, systolic blood pressures, and double products during each period were selected for statistical analysis.

**Statistical analyses.** Continuous variables were compared by Student's t test (two-tailed). For categorical data, the chi-square test or Fisher's exact test was used. A p value < .05 was considered significant. All continuous data are presented as the mean ± SD.

### Results

**General characteristics.** The baseline general characteristics of patients in groups 1 vs 2 and groups 3 vs 4 are listed in table 1. Patients in group 1 were slightly older (p < .05) and had a greater incidence of prior systemic arterial hypertension (p < .0005). Patients in groups 3 and 4 did not differ with respect to any of these general characteristics.

**Prior β-blockade therapy.** Propranolol was the β-blocker used before infarction by 31 of 39 group 1 patients, 15 of 20 group 3 patients, and 12 of 15 group 4 patients. The mean doses of propranolol taken by patients in the 24 hr before admission were as follows: group 1, 113 ± 56 mg; group 3, 107 ± 49 mg; group 4, 93 ± 90 mg.

**Incidence of prior angina and infarction.** Table 2 details the level of patient activity producing angina 3 weeks before admission with acute myocardial infarction. Patients in group 1 had a greater incidence of angina (p < .0005) and of previous transmural myocardial infarction (p < .0005) than those in group 2. This, and the greater incidence of hypertension (table 1) in group 1 patients, presumably accounted for their prior therapy with β-blockers. There was no significant difference in the incidence of angina or of previous transmural infarction between groups 3 and 4.

**Electrocardiographic classification of acute infarction.** There was no difference between groups 1 and 2 or groups 3 and 4 in the incidence of either transmural (Q wave) or nontransmural (non–Q wave) acute myocardial infarction (table 3).

**Enzymatic and pyrophosphate scintigraphic estimates of infarct size**

**Group 1 vs group 2.** The MB creatine kinase infarct size index (15.8 ± 10.9 g-eq/m²) in patients in group 1 was not significantly different from that in group 2 (18.2 ± 14.4 g-eq/m²). Similarly, myocardial infarct areas determined by planimetry of 99mTc-pyrophos-

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### TABLE 1

**General clinical characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 39)</th>
<th>Group 2 (n = 272)</th>
<th>p value</th>
<th>Group 3 (n = 20)</th>
<th>Group 4 (n = 15)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)*</td>
<td>60.3 ± 8.7</td>
<td>56.7 ± 10.7</td>
<td>&lt;.05</td>
<td>62.0 ± 6.4</td>
<td>60.7 ± 9.4</td>
<td>NS</td>
</tr>
<tr>
<td>Male (n)</td>
<td>25 (64)</td>
<td>198 (73)</td>
<td>NS</td>
<td>14 (70)</td>
<td>13 (87)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus (n)</td>
<td>11 (28)</td>
<td>45 (17)</td>
<td>NS</td>
<td>7 (35)</td>
<td>1 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>History of hypertension (n)</td>
<td>31 (80)</td>
<td>131 (48)</td>
<td>&lt;.0005</td>
<td>19 (95)</td>
<td>12 (80)</td>
<td>NS</td>
</tr>
<tr>
<td>History of CHF (n)</td>
<td>6 (15)</td>
<td>24 (9)</td>
<td>NS</td>
<td>4 (20)</td>
<td>2 (13)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data in parentheses are percentages.  
CHF = congestive heart failure.  
*Values are mean ± SD.
TABLE 2
Preceding history of angina and infarction

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 38)</th>
<th>Group 2 (n = 267)</th>
<th>p value</th>
<th>Group 3 (n = 20)</th>
<th>Group 4 (n = 15)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td></td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Three weeks before MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No angina</td>
<td>10</td>
<td>26</td>
<td></td>
<td>7</td>
<td>35</td>
<td>.61</td>
</tr>
<tr>
<td>On heavy activity</td>
<td>8</td>
<td>21</td>
<td></td>
<td>3</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>On light activity</td>
<td>8</td>
<td>21</td>
<td>&lt;.0005</td>
<td>5</td>
<td>25</td>
<td>NS</td>
</tr>
<tr>
<td>Angina at rest</td>
<td>12</td>
<td>32</td>
<td></td>
<td>5</td>
<td>25</td>
<td>NS</td>
</tr>
<tr>
<td>Angina episodes/day</td>
<td>10</td>
<td>26</td>
<td>&lt;.0005</td>
<td>3</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Change in character of angina</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>before MI</td>
<td>21</td>
<td>54</td>
<td>NS</td>
<td>8</td>
<td>40</td>
<td>NS</td>
</tr>
<tr>
<td>Previous transmural MI</td>
<td>15</td>
<td>39</td>
<td>&lt;.0005</td>
<td>7</td>
<td>35</td>
<td>3</td>
</tr>
</tbody>
</table>

MI = myocardial infarction.

*p value for group comparison of level of activity producing angina.

Phantom scintigrams (17 patients in group 1, 137 patients in group 2) were not significantly different in groups 1 (30.7 ± 11.5 cm²) and 2 (27.0 ± 16.5 cm²).

Group 3 vs group 4. The MB creatine kinase infarct size index (16.9 ± 12.0 g-eq/m²) in patients in group 3 was not significantly different from that in group 4 (10.2 ± 6.4 g-eq/m²). Infarct sizes determined by planimetry were similar in patients in groups 3 (35 ± 11.6 cm²) and 4 (27.0 ± 12.6 cm²) (p = NS).

Radionuclide ventriculography. The results of resting radionuclide ventriculography performed within 18 hr of the onset of chest pain and again 10 days after myocardial infarction in patients in groups 1 vs 2 and groups 3 vs 4 are presented in table 4.

Group 1 vs group 2. There was no significant difference between patients in groups 1 and 2 in left ventricular ejection fractions or left ventricular average wall motion scores either within 18 hr of the onset of chest pain or 10 days later. Left ventricular end-diastolic volume index was similar in the two groups early but was greater in patients in group 1 than in group 2, 10 days later (p < .05). The mean change in ejection fraction from before randomization to day 10 in group 1 patients (−0.01 ± 0.13) was not significantly different from that in group 2 (0.01 ± 0.11) (p = .61).

Group 3 vs group 4. There was no significant difference between groups 3 and 4 in left ventricular ejection fractions, end-diastolic volume indexes, or average wall motion scores, either before randomization or 10 days after infarction. The mean change in ejection fraction from before randomization to day 10 was similar in patients in groups 3 (−0.01 ± 0.08) and 4 (0.07 ± 0.11) (p = 16).

Ambulatory electrocardiographic recordings 10 days after infarction. There was no significant difference in the frequency of premature ventricular depolarizations, multif orm or R-on-T premature ventricular depolarizations, paroxysmal ventricular depolarizations, atrial flutter, or atrial fibrillation between patients in different groups.

Hospital course

Group 1 vs group 2. The mean highest and lowest heart rates, systolic blood pressures, and double products (heart rates × systolic blood pressures) recorded during each of the first 11 days after myocardial infarction are illustrated in figure 2. There was no significant difference between the two patient groups in the maximum double product recorded during either the first 24 hr (13260 ± 3710 vs 13770 ± 3790, p = .44) or during each of the ensuing 10 days. The minimum double products recorded during the first and second 24 hr periods after randomization were lower in those

TABLE 3
Electrocardiographic classification of acute myocardial infarction

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 38)</th>
<th>Group 2 (n = 265)</th>
<th>p value</th>
<th>Group 3 (n = 19)</th>
<th>Group 4 (n = 15)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td></td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Transmural</td>
<td>23</td>
<td>61</td>
<td></td>
<td>166</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Nontransmural</td>
<td>11</td>
<td>29</td>
<td>NS</td>
<td>6</td>
<td>32</td>
<td>NS</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>10</td>
<td></td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

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TABLE 4
Results of radionuclide ventriculography performed before randomization and within 18 hr after myocardial infarction and 10 days later

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
<th>Group 3</th>
<th>Group 4</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.44±0.15</td>
<td>0.46±0.16</td>
<td>NS</td>
<td>0.47±0.17</td>
<td>0.46±0.14</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDVI (ml/m²)</td>
<td>97.7±30.1</td>
<td>88.3±26.8</td>
<td>NS</td>
<td>86.3±33.0</td>
<td>78.8±22.1</td>
<td>NS</td>
</tr>
<tr>
<td>LV average wall motion score</td>
<td>2.3±0.8</td>
<td>2.2±0.7</td>
<td>NS</td>
<td>2.2±0.7</td>
<td>2.3±0.8</td>
<td>NS</td>
</tr>
<tr>
<td>10 days after MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.42±0.14</td>
<td>0.47±0.16</td>
<td>NS</td>
<td>0.43±0.13</td>
<td>0.53±0.18</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDVI (ml/m²)</td>
<td>104.5±35.9</td>
<td>87.7±26.7</td>
<td>&lt;.05</td>
<td>97.7±49.2</td>
<td>80.7±22.7</td>
<td>NS</td>
</tr>
<tr>
<td>LV average wall motion score</td>
<td>2.3±0.6</td>
<td>2.0±0.8</td>
<td>NS</td>
<td>2.4±0.5</td>
<td>2.0±0.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

EDVI = end-diastolic volume index; EF = ejection fraction; LV = left ventricular; MI = myocardial infarction.

*Left ventricular average wall motion score is computed by summing segmental wall motion scores (on a scale from 3 to −1), and dividing by the number evaluated.

withdrawn from β-blocker therapy (group 1) (6600 ± 1870 and 7150 ± 1650, respectively) than in those never exposed to a β-blocker (group 2) (7670 ± 2330 and 7900 ± 1870) (p < .05). Thereafter, the minimum double products recorded on each of the following 9 days were similar.

Group 1 patients had a greater number of episodes of ischemic chest pain during the first 24 hr after randomization (2.4 ± 2.4 vs 1.2 ± 2.0; p < .005) and a marginally greater number of episodes during the second 24 hr period (0.9 ± 1.6 vs 0.5 ± 1.0; p = .08) than did group 2 patients. During each of the ensuing 9 days, there was no statistically significant difference between the two groups in the frequency of anginal pain. No differences were detected between the two groups with respect to the incidence of orthopnea, rales extending over more than one-third of the lung fields, or the presence of a third heart sound or murmur of mitral regurgitation during any 24 hr period within the first 11 days after randomization.

The incidence of various hospital complications is presented in table 5. Patients who had their β-blockers withdrawn abruptly during acute infarction (group 1) and patients never exposed to β-blockers (group 2) had similar incidences of all except two complications analysed, including creatine kinase–determined infarct extensions31 (p = .17) and hospital death (p = .37). Impulse conduction defects (first- or second-degree atrioventricular block, complete heart block, or atrioventricular dissociation) occurred more frequently in group 1 patients (p < .05), and cardiogenic shock occurred marginally more frequently in group 1 patients (p = .05).

Group 3 vs group 4. The mean highest and lowest heart rates, systolic blood pressures, and double products recorded during each of the first 11 days after myocardial infarction are illustrated in figure 3. The minimum and maximum double products were higher in those in whom prior β-blockade therapy was stopped after randomization (group 3) than in those in whom β-blockade therapy was continued after randomization (group 4) during most of the study period. This was due to the effects of continued β-blockade in the latter group.
TABLE 5
Complications during hospital admission

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 39)</th>
<th>Group 2 (n = 272)</th>
<th>Group 3 (n = 20)</th>
<th>Group 4 (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus tachycardia (&gt;100/bpm) during hospitalization</td>
<td>9/39 (23%)</td>
<td>49/272 (18%)</td>
<td>NS</td>
<td>5/20 (25%)</td>
</tr>
<tr>
<td>Ventricular tachycardia (≥3 consecutive PVDs)</td>
<td>16/39 (41%)</td>
<td>109/272 (40%)</td>
<td>NS</td>
<td>6/20 (30%)</td>
</tr>
<tr>
<td>Nonfatal ventricular fibrillation</td>
<td>2/39 (5%)</td>
<td>21/272 (7%)</td>
<td>NS</td>
<td>0/20 (0%)</td>
</tr>
<tr>
<td>Discharged on antiarrhythmics</td>
<td>10/39 (26%)</td>
<td>50/272 (18%)</td>
<td>NS</td>
<td>2/20 (10%)</td>
</tr>
<tr>
<td>Intraventricular conduction defects*</td>
<td>7/39 (18%)</td>
<td>54/272 (20%)</td>
<td>NS</td>
<td>3/20 (15%)</td>
</tr>
<tr>
<td>Impulse conduction defects*</td>
<td>11/39 (28%)</td>
<td>45/272 (17%)</td>
<td>NS</td>
<td>6/20 (30%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>16/39 (43%)</td>
<td>100/272 (37%)</td>
<td>NS</td>
<td>8/20 (42%)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>6/39 (16%)</td>
<td>17/272 (6%)</td>
<td>&lt;.05</td>
<td>3/20 (16%)</td>
</tr>
<tr>
<td>Ventricular septal rupture</td>
<td>0/39 (0%)</td>
<td>3/272 (1%)</td>
<td>NS</td>
<td>0/20 (0%)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>9/39 (23%)</td>
<td>34/272 (13%)</td>
<td>NS</td>
<td>3/20 (15%)</td>
</tr>
<tr>
<td>CK-determined infarct extension</td>
<td>5/39 (13%)</td>
<td>17/272 (6%)</td>
<td>NS</td>
<td>2/20 (10%)</td>
</tr>
<tr>
<td>Died during hospitalization</td>
<td>5/39 (13%)</td>
<td>23/272 (9%)</td>
<td>NS</td>
<td>2/20 (10%)</td>
</tr>
</tbody>
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*Intraventricular conduction defects are defined as left anterior hemiblock, left posterior hemiblock, left bundle branch block, right bundle branch block, or any combination thereof.

*Impulse conduction defects are defined as Mobitz type I or II second-degree atrioventricular block, complete heart block, or atrioventricular dissociation.

CK = creatine kinase; PVDs = premature ventricular depolarizations.

There did not appear to be a transient rebound increase in double product in group 3 patients (figure 3).

Group 3 patients had a greater frequency of chest pain than group 4 patients during the first 24 hr after randomization (2.8 ± 2.7 vs 0.8 ± 0.8; p < .005) but not during any of the ensuing 10 days. The two groups did not differ significantly in the incidence of orthopnea, rales extending over more than one-third of the lung fields, or the presence of an S₃ or murmur of mitral regurgitation during any 24 hr period up to the eleventh day after randomization.

Hospital complications occurring in patients in groups 3 and 4 are listed in table 5. There was no significant difference in the occurrence of any in-hospital complication analyzed. However, patients withdrawn from β-blocker therapy exhibited a trend toward a higher incidence of sinus tachycardia (p = .06), impulse conduction defects (p = .28), congestive heart failure (p = .13), and cardiogenic shock (p = .24). Two patients (10%) who were withdrawn from β-blocker therapy (group 3) and one patient (7%) who continued on propranolol (group 4) had enzyme-determined infarct extension. Two group 3 (10%) and two group 4 (13%) patients died while in the hospital.

Discussion

The β-blockade withdrawal syndrome was first described in a series of case reports. However, its pathophysiology, its frequency, and its timing after withdrawal of β-blockade are controversial. Moreover, there is disagreement regarding its very existence. The controversy regarding the existence of this syndrome stems partly from basic differences between patient populations* and divergent objective criteria* and the condition during which urgent decisions regarding abrupt withdrawal of β-blockers are most frequently required.

The data presented here indicate that withdrawal of β-blockade in patients with acute myocardial infarction did not result in a greater initial infarct size, worse left ventricular function 10 days after infarction, or a higher in-hospital mortality than were seen in a comparable group of patients never exposed to β-blockade. Furthermore, abrupt withdrawal of β-blockade did not result in either a greater incidence of creatine kinase–determined infarct extension or in-hospital congestive heart failure or arrhythmias, including nonfatal ventricular fibrillation. Similar results were obtained in a

*References 8, 10, 11, 13, 15, 16, 18–23, 36, 38, 39–41.
comparison of patients previously taking β-blockers and eligible for randomization to β-blockers after infarction, who received either placebo (group 3) or propranolol (group 4). Also noteworthy is the fact that there was no evidence of a rebound increase in systolic blood pressure, heart rate, or double product, frequently used indexes of myocardial oxygen consumption,43, 44 in the group 1 patients. Although the plot of daily maximum heart rate for group 3 patients (figure 3) suggests a rebound increase in heart rate after withdrawal of β-blockade, there was no apparent rise in maximum double product in the ensuing 4 days.

Although the data presented here suggest that β-blockers may, when clinically indicated, be discontinued abruptly at the onset of acute myocardial infarction with an acceptable risk, it should be emphasized that they are derived from a post-hoc analysis of the MILIS study, the original design of which did not include a hypothesis regarding the question of a β-blockade withdrawal syndrome.

In both sets of comparisons (groups 1 vs 2 and groups 3 vs 4), patients in whom β-blockade was abruptly withdrawn (group 1 and group 3) had a higher incidence of ischemic chest pain during the first 24 hr after infarction. However, this did not appear to be related to an exaggregated increase in heart rate, systolic blood pressure, or double product in group 1 patients. Group 3 patients displayed a higher maximum double product during day 1 but also during most of the ensuing 10 days, when there was no difference in the frequency of ischemic pain. We cannot exclude the possibility that the observed early increased incidence of recurrent ischemic chest pain may have been caused by “rebound” increases in left ventricular size or contractility, two additional determinants of myocardial oxygen consumption.45 However, others46 have failed to demonstrate echocardiographic evidence of increases in these determinants after withdrawal of propranolol and exercise provocation in normal subjects and patients with angina. The prolonged (24 hr) and possibly even as long as 72 hr47 cardiac and hemodynamic actions of propranolol, the predominant β-blocker used before infarction in our patients, also argues against a major withdrawal effect within the first 24 hr.

An alternative explanation for the increased frequency of recurrent chest pain within the first 24 hr after withdrawal of β-blockers is based on a postulated temporal dissociation of the effects of these agents on myocardial oxygen supply and demand during the period of withdrawal. β-Blockers not only decrease myocardial oxygen demand46, 47 through their negative inotropic, chronotropic, antihypertensive, and anti-lipolytic effects, but they may also decrease myocardial oxygen supply46, 48 through their effect on diastolic blood pressure46 and enhancement of coronary vasoconstriction.48 An imbalance between these relative effects during the withdrawal period, with persistent limitation of coronary flow when myocardial oxygen demand is rising, might also contribute to the observed transiently increased frequency of angina. Indeed, the effects of propranolol appear to be temporally dissociated,17 with a shorter duration of its negative inotropic than chronotropic effect.13, 17, 41

Patients in whom β-blockers were discontinued (group 1) had a higher incidence of impulse conduction defects (p = .05) and cardiogenic shock (p = .05) than patients never exposed to such therapy (group 2). This was confirmed in a separate analysis of patients with similar baseline characteristics (group 3 vs group

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**FIGURE 3.** Comparison of maximum and minimum heart rates, blood pressures, and double products (heart rate × systolic blood pressure) in each 24 hr period during the first 11 days after acute myocardial infarction in patients in groups 3 and 4. Asterisks directly above values indicate a significant difference in that value between patients in groups 3 and 4 on that day (*p < .05, **p < .0002).
These data suggest that the higher incidence of cardiogenic shock in group 1 patients was related to the higher incidence of prior myocardial infarction (p < .0005) and hypertension (p < .0005) in this group.

Although the comparison of clinically matched, propranolol-eligible patients in groups 3 and 4 did not identify any significant adverse affects resulting from discontinuation of propranolol, those withdrawn from propranolol (group 3) exhibited a tendency toward a higher incidence of sinus tachycardia (p = .06), impulse conduction defects (p = .28), congestive heart failure (p = .13), and cardiogenic shock (p = .24). Moreover, they displayed a nonsignificant trend toward a greater impairment of left ventricular ejection fraction 10 days after infarction (p = .13). Failure to demonstrate a significant difference in these variables may well represent a type II error due to small sample sizes. However, this comparison considers only the effect of β-blocker withdrawal, but compares these effects to continued β-blocker therapy, a management strategy considered by some to reduce mortality and morbidity independently in patients with acute myocardial infarction.30, 51 Although withdrawal of β-blockers may not have an independent, clinically significant detrimental effect during acute myocardial infarction, we cannot exclude an increased incidence of complications resulting from this strategy when compared with continued use of β-blockers.

The data from the present study are at variance with evidence from several other studies identifying a rebound effect.2-8, 10, 11, 13-16, 36 Many of these studies have identified reactive changes to withdrawal of β-blockade at a biochemical8, 10, 11, 13, 14, 36 or cellular5 level, often unaccompanied by objective clinical evidence of rebound.5, 8, 36 These laboratory-determined observations should therefore not be construed as implying a clinically relevant withdrawal syndrome. A number of clinical studies in patients with both angina pectoris4, 5 and hypertension10, 11, 13 and in normal individuals15, 16 have provided evidence for a rebound syndrome after withdrawal of β-blockade. Since withdrawal reactions were most prominent among patients with angina deriving the greatest antianginal benefit from the drug,4 these phenomena may simply be related to the removal of a therapeutic agent initially instituted for, and effectively suppressing, anginal episodes rather than to a "rebound effect."18 In confirmatory studies in patients with hypertension,10, 11, 13 the possibility that altered baroreceptor responses or other pathophysiologic alterations unique to the hypertensive state may have contributed to the observed results must also be considered. Moreover, our study of patients with acute myo-

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Abrupt withdrawal of beta-blockade therapy in patients with myocardial infarction: effects on infarct size, left ventricular function, and hospital course.

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