Differentiation of Hemodynamic, Humoral and Metabolic Responses to $\beta_1$- and $\beta_2$-adrenergic Stimulation in Man Using Atenolol and Propranolol

ANDREW A. McLEOD, M.B., JAMES E. BROWN, M.D., CYNTHIA KUHN, Ph.D., BARBARA B. KITCHELL, Ph.D., FRANK A. SEDOR, Ph.D., R. SANDERS WILLIAMS, M.D., and DAVID G. SHAND, M.B., Ph.D.

SUMMARY The respective contributions of $\beta$-adrenoceptor subtypes to the hemodynamic, humoral and metabolic consequences of adrenergic stimulation during graded exercise in man were investigated using nonselective $\beta$-adrenoceptor blockade with propranolol and $\beta_1$-adrenoceptor blockade with atenolol. Doses of these agents that produced comparable suppression of $\beta_1$ response as measured by antagonism of cardiovascular acceleration during exercise were selected. Six healthy, nonsmoking males received these drugs in a placebo-controlled, Latin-square, randomized manner using a double-blind protocol. Both drugs produced comparable reductions of systolic blood pressure and elevation of diastolic blood pressure compared with placebo as exercise load increased. Propranolol produced higher peak epinephrine levels than atenolol or placebo (808 ± 162, 640 ± 190 and 584 ± 153 pg/ml, respectively, $p = 0.03$), but norepinephrine levels did not show significant differences. Plasma renin activity was similarly suppressed both at rest and during all grades of exercise by both drugs. Lactate levels during moderate exercise were significantly lower after propranolol than after either atenolol or placebo ($p = 0.03$), but were similar at heavy work loads. Plasma glucose values rose on placebo (from 96.5 ± 2.1 to 97.7 ± 2.7 mg/dl) and on atenolol (from 99.7 ± 2.2 to 102.1 ± 4.8 mg/dl), but fell on propranolol (from 96.4 ± 1.9 mg/dl to 87.2 ± 2.5 mg/dl, $p < 0.01$). These results indicate that blockade of vascular smooth muscle $\beta_2$ receptors does not substantially alter hemodynamics during intense short-term exercise. Stimulation of renin release and lipolysis are produced through $\beta_1$-adrenoceptor mechanisms, whereas $\beta_2$ adrenoceptors are important in the provision of carbohydrate as an energy substrate for exercising muscle.

Over the past decade, considerable advances have been made in our understanding of how catecholamines mediate their effects. In particular, it is evident that the receptors that mediate these effects are heterogeneous. Not only have these receptors been classified as $\alpha$ or $\beta$, but subtypes of each have also been proposed.1,2 These classifications of $\beta$ adrenoceptors have been helpful in explaining differences between actions of adrenergic agonists and antagonists on, for example, cardiac and bronchial tissue, but whether all $\beta$-adrenergic actions can be explained by only two classes of receptors is controversial. Ariens and Simonis3 suggested that adrenergic stimulation can be separated, depending on whether it is neurohumoral (noradrenergic, transmitter or $\beta^1$) or purely hormonal (adrenergic or $\beta^2$).

Currently classified $\beta_2$ vascular adrenoceptors are clearly important when circulating epinephrine is the stress. Marked differences in response occur when propranolol or atenolol are administered to a subject who then undergoes an epinephrine stress (e.g., hypoglycemia). When $\beta_1$ vasodilatation is blocked by propranolol, marked pressor reactions and reflex bradycardia occur.4 No such phenomenon is seen with the $\beta_2$-selective antagonists.5 Another such stress is cigarette smoking.6 In contrast, recent work has suggested that hemodynamic responses are similar for nonselective and cardioselective drugs during exercise.7,8 Exercise represents a mixed humoral and neurogenic stress, with markedly elevated levels of epinephrine occurring only at high work loads. We therefore investigated varying intensities of exercise to determine whether hemodynamic differences could be discerned between appropriate doses of propranolol (nonselective) and atenolol ($\beta_2$-selective), depending upon the exercise intensity.

Controversy exists over the classification of receptor mechanisms producing renin release during exercise9 and of the mediation of the multiple metabolic responses seen. Lundborg and colleagues10 suggested that lipolysis is predominantly $\beta_1$-stimulated (but involves some $\beta_2$ receptors also), while lactate release and glucose mobilization may be predominantly $\beta_2$-mediated but also involves $\beta_2$ adrenoceptors. However, these conclusions are critically dependent on the specificity of the pharmacologic probes that have been used. While it is clear that propranolol blocks both $\beta$-receptor subtypes, the selectivity of metoprolol for the $\beta_2$ receptors is not absolute and may be lost, particularly with the higher doses studied.11 Furthermore, both propranolol and metoprolol possess membrane-stabilizing activity, which has been implicated at least in the release of lactate from exercising skeletal muscle.12 In view of this confusion, and because these metabolic
effects may be associated with fatigue (the most common side effect of \( \beta \)-adrenoceptor blockade), we compared the effects of the newer cardioselective agent atenolol (which is devoid of membrane-stabilizing activity) with those of propranolol on the metabolic responses (in addition to the hemodynamic responses) to the stress of exercise. The dosages of propranolol (40 mg) and atenolol (50 mg) were chosen to try to achieve a similar degree of suppression of exercise-induced tachycardia, with adequate effect, but also to preserve the \( \beta_1 \) selectivity of atenolol and minimize the membrane-stabilizing activity effects of propranolol. The results suggest that both drugs have similar hemodynamic effects at each intensity of exercise, and that \( \beta_1 \) receptors mediate renin and free fatty acid (FFA) release, but different responses (\( \beta_2 \)-mediated) account for effects observed on lactate and glucose levels.

**Methods**

Six healthy male subjects, ages 21–27 years, were studied using a double-blind, placebo-controlled, Latin-square design protocol. Each subject received atenolol 50 mg, propranolol 40 mg, or matching placebo as a single oral dose 2 hours before upright exercise on a bicycle ergometer (Monark-Crescent AB). Subjects were all nonsmoking, laboratory-oriented volunteers. However, to familiarize them with the staff and the experimental protocol, they also underwent the same bicycle exercise with no medications 1 week before study. During the study, they were asked to avoid alterations in their usual level of physical activity or in their diet, and to avoid alcohol for at least 24 hours and tea or coffee for at least 12 hours before each exercise session. Exercise was performed in the morning. Each session was at least 1 week apart and was preceded by a 9–12-hour fast. An i.v. cannula (Quik-Cath, Vicra, Travenol Laboratories Inc.) was placed in a forearm vein at least 30 minutes before exercise and kept patent with a teflon obturator. Heparin was not used.

Subjects rested on the bicycle for at least 10 minutes before control blood samples were drawn. They then exercised for four 4-minute periods at 300, 600, 900, and 1200 kpm/min, respectively (stages 1, 2, 3 and 4). At the end of each period, blood was taken for catecholamine, plasma renin activity (PRA), lactate, glucose and FFA determinations. Drug level estimations were also performed. Heart rate was measured from an ECG and blood pressure was measured by an exercise physiologist who was also blinded to the nature of the medication and to differences in blood pressure induced by the drugs. Diastolic pressure was recorded as phase 5 (disappearance of sounds) except in one subject who had no lower limit during exercise when the most abrupt change in Korotkoff sound was taken as the diastolic pressure.

Blood samples for drug level measurement were taken into silanized glass tubes stoppered with Teflon seals to avoid contamination.\(^\text{13}\) Samples for catecholamine assay were taken into prechilled glass tubes that contained heparin and glutathione, 1 mg/ml of blood. Samples for PRA assay were taken into tubes containing EDTA. Samples for glucose and lactate estimations were taken into glass tubes that contained sodium fluoride and oxalate. Samples for FFA estimation were taken into heparin in silanized glass tubes with a Teflon seal. At the end of the study, all samples were centrifuged and separated in the cold; those not assayed immediately were stored at \(-25^\circ\text{C}\) for later analysis.

Plasma levels of propranolol were measured fluorometrically after separation by a reversed-phase HPLC method on a \( \mu \)Bondapak C18 column (Waters Assoc.). The method is a modification of that described by Nation et al.\(^\text{14}\) Free propranolol levels were measured by equilibrium dialysis. Atenolol was measured using ultraviolet detection after separation on a Zorbax CN column (Dupont Instruments) (Vergheese C, McLeod AA, Shand DG: manuscript in preparation). Plasma norepinephrine and epinephrine were measured radioenzymatically using a method based on that described by Passon and Peuler.\(^\text{15}\) Duplicate samples were assayed. PRA was measured by radioimmunoassay of angiotensin I formed after incubation for 1 hour.\(^\text{16}\) Glucose was measured using a modified glucose oxidase method. Lactate was measured by a NADH production method using Calbiochem-Bering reagents. Each sample was assayed in duplicate. Assays were validated using General Diagnostics quality control reagents. FFA estimation was performed by gas chromatography on a Supelco SP 2330 cyanosilicone column (Supelco Inc.), with n-heptadecanoate added as an internal standard. The method is an optimized modification of the technique described by Sampson and Hensley.\(^\text{17}\)

Results are mean \( \pm \) SEM. Statistical comparisons between groups were made by analysis of variance. A \( p \) value of 0.05 or less was considered significant. Each subject gave written, informed consent before participation. The study protocol was approved by the hospital committee for clinical investigation.

**Results**

**Heart Rate**

Both drugs produced a powerful suppression of the cardiac chronotropic response to exercise (table 1, fig. 1A). Peak heart rate during placebo medication was 187 \( \pm \) 4 beats/min. Atenolol decreased heart rate slightly more than propranolol for the group as a whole (atenolol peak heart rate 138 \( \pm \) 6 beats/min, propranolol 146 \( \pm \) 7 beats/min; NS). The data favor a slightly more powerful cardiac chronotropic antagonism by atenolol than propranolol in this group of subjects.

**Blood Pressure**

Both drugs reduced the systolic blood pressure at rest and at all grades of exercise. Blood pressures at rest (taken sitting erect on the bicycle) were significantly different from placebo for atenolol only. The maximal differences for drugs vs placebo were seen at intermediate exercise grades (table 1, fig. 1).
TABLE 1. Heart Rate, Blood Pressure, Catecholamine Levels, Plasma Renin Activity and Metabolic Measurements at Rest (Sitting Erect on Bicycle) and During Exercise in Six Healthy Subjects

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
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<tr>
<td>Placebo</td>
<td>85 ± 6</td>
<td>103 ± 6</td>
<td>128 ± 9</td>
<td>160 ± 7</td>
<td>187 ± 4</td>
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<td>Propranolol</td>
<td>65 ± 4</td>
<td>83 ± 4</td>
<td>102 ± 3</td>
<td>125 ± 5</td>
<td>146 ± 7</td>
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<tr>
<td>Atenolol</td>
<td>59 ± 4</td>
<td>77 ± 4</td>
<td>97 ± 4</td>
<td>117 ± 4</td>
<td>138 ± 6</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
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<td>Placebo</td>
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<td>130 ± 7</td>
<td>152 ± 6</td>
<td>171 ± 7</td>
<td>178 ± 7</td>
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<td>Propranolol</td>
<td>107 ± 2</td>
<td>118 ± 3</td>
<td>133 ± 6</td>
<td>149 ± 5</td>
<td>170 ± 6</td>
</tr>
<tr>
<td>Atenolol</td>
<td>103 ± 3</td>
<td>110 ± 2</td>
<td>123 ± 6</td>
<td>145 ± 4</td>
<td>164 ± 6</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
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</tr>
<tr>
<td>Placebo</td>
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<td>67 ± 3</td>
<td>63 ± 3</td>
<td>65 ± 3</td>
<td>68 ± 4</td>
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<tr>
<td>Propranolol</td>
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<td>70 ± 3</td>
<td>71 ± 3</td>
<td>76 ± 4</td>
<td>77 ± 4</td>
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<tr>
<td>Atenolol</td>
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<td>70 ± 5</td>
<td>69 ± 5</td>
<td>75 ± 1</td>
<td>75 ± 4</td>
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<tr>
<td>Placebo</td>
<td>632 ± 97</td>
<td>626 ± 79</td>
<td>830 ± 87</td>
<td>1321 ± 99</td>
<td>2736 ± 179</td>
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<tr>
<td>Propranolol</td>
<td>445 ± 95</td>
<td>748 ± 85</td>
<td>1004 ± 159</td>
<td>1238 ± 101</td>
<td>2574 ± 392</td>
</tr>
<tr>
<td>Atenolol</td>
<td>633 ± 29</td>
<td>712 ± 60</td>
<td>1068 ± 91</td>
<td>1593 ± 115</td>
<td>2454 ± 323</td>
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<td>Plasma epinephrine (pg/ml)</td>
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<td></td>
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<td>Placebo</td>
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<td>144 ± 13</td>
<td>182 ± 26</td>
<td>265 ± 21</td>
<td>584 ± 153</td>
</tr>
<tr>
<td>Propranolol</td>
<td>166 ± 17</td>
<td>174 ± 12</td>
<td>216 ± 21</td>
<td>273 ± 40</td>
<td>808 ± 162</td>
</tr>
<tr>
<td>Atenolol</td>
<td>135 ± 17</td>
<td>156 ± 11</td>
<td>180 ± 15</td>
<td>261 ± 31</td>
<td>640 ± 190</td>
</tr>
<tr>
<td>PRA (ngA/ml/hr)</td>
<td></td>
<td></td>
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<tr>
<td>Placebo</td>
<td>1.5 ± 0.3</td>
<td>1.8 ± 0.3</td>
<td>2.0 ± 0.4</td>
<td>2.6 ± 0.4</td>
<td>3.9 ± 0.5</td>
</tr>
<tr>
<td>Propranolol</td>
<td>0.5 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>0.8 ± 0.2</td>
<td>1.1 ± 0.3</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td>Atenolol</td>
<td>0.8 ± 0.3</td>
<td>1.0 ± 0.3</td>
<td>1.1 ± 0.4</td>
<td>1.3 ± 0.3</td>
<td>1.5 ± 0.4</td>
</tr>
<tr>
<td>Plasma glucose (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Placebo</td>
<td>97 ± 2</td>
<td>96 ± 2</td>
<td>98 ± 1</td>
<td>98 ± 2</td>
<td>98 ± 3</td>
</tr>
<tr>
<td>Propranolol</td>
<td>96 ± 2</td>
<td>95 ± 3</td>
<td>95 ± 2</td>
<td>91 ± 3</td>
<td>87 ± 3</td>
</tr>
<tr>
<td>Atenolol</td>
<td>100 ± 2</td>
<td>102 ± 3</td>
<td>102 ± 3</td>
<td>100 ± 4</td>
<td>102 ± 5</td>
</tr>
<tr>
<td>Plasma lactate (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>10.0 ± 1.3</td>
<td>12.8 ± 1.8</td>
<td>20.3 ± 3.2</td>
<td>35.9 ± 3.5</td>
<td>71.8 ± 9.1</td>
</tr>
<tr>
<td>Propranolol</td>
<td>9.5 ± 0.9</td>
<td>11.5 ± 1.6</td>
<td>16.1 ± 3.4</td>
<td>27.7 ± 4.5</td>
<td>60.8 ± 6.8</td>
</tr>
<tr>
<td>Atenolol</td>
<td>9.7 ± 0.8</td>
<td>14.1 ± 0.7</td>
<td>19.4 ± 2.0</td>
<td>33.5 ± 3.2</td>
<td>73.3 ± 8.8</td>
</tr>
<tr>
<td>Plasma FFA (μmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>377 ± 83</td>
<td>326 ± 64</td>
<td>249 ± 48</td>
<td>202 ± 32</td>
<td>173 ± 32</td>
</tr>
<tr>
<td>Propranolol</td>
<td>208 ± 25</td>
<td>158 ± 20</td>
<td>133 ± 16</td>
<td>114 ± 17</td>
<td>92 ± 20</td>
</tr>
<tr>
<td>Atenolol</td>
<td>256 ± 74</td>
<td>216 ± 52</td>
<td>159 ± 39</td>
<td>114 ± 11</td>
<td>95 ± 11</td>
</tr>
</tbody>
</table>

Values are mean ± sem.
Abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure; PRA = plasma renin activity; FFA = free fatty acids.

Both drugs elevated diastolic blood pressure compared with placebo by a similar amount. The elevations were significant at higher grades of exercise (stages 3 and 4) (table 1, fig. 1).

Owing to the similar degrees of suppression of systolic pressure and elevation of diastolic pressure, no great difference was found between either drug and placebo on mean blood pressure at rest or at any exercise stage.

Plasma Catecholamines

During placebo medication, norepinephrine levels rose from $632 ± 97$ pg/ml while subjects were sitting at rest on the bicycle to $2736 ± 179$ pg/ml at peak exercise. Epinephrine levels rose from $141 ± 12$ to $584 ± 153$ pg/ml (table 1, fig. 2). No significant drug effects were found except during propranolol treatment, when epinephrine levels at peak exercise were on average 38% higher than on placebo (peak epineph-
**FIGURE 1.** Effect of placebo (circles), propranolol (squares) and atenolol (triangles) on heart rate, systolic and diastolic blood pressure, and diastolic blood pressure (BP) (expanded scale) at rest and after 4 minutes of exercise at 50, 100, 150 and 200 W (stages 1–4). Bars represent SEM.

Plasma Renin Activity

Both drugs produced a similar suppression of PRA at rest and at each exercise level. Propranolol was marginally more potent than atenolol (NS) (table 1, fig. 3).

Plasma Glucose

Plasma glucose (table 1) did not differ significantly at rest between treatments but was elevated during atenolol treatment at the end of the first level of exercise (placebo 96 ± 2 mg/dl, atenolol 102 ± 3 mg/dl; \( p = 0.04 \)). Thereafter, although mean atenolol values were greater than placebo values, the difference was not significant. Glucose values during placebo therapy were slightly above resting values at the end of exercise. In contrast, propranolol glucose values began to fall at the end of stage 2, were significantly lower in all subjects by stage 3 (\( p = 0.02 \)), and lower still at the end of stage 4 (placebo 98 ± 3 mg/dl, propranolol 87 ± 3 mg/dl; \( p = 0.02 \)). At this point, glucose values in
fatty acids were almost identical for propranolol and atenolol treatments, and were much lower than placebo values.

**Drug Levels**

Atenolol levels ranged from 290 to 760 ng/ml (mean 460 ± 75 ng/ml). Propranolol levels ranged from 11 to 61 ng/ml (mean 25 ± 8 ng/ml). Free propranolol levels ranged from 0.7 to 3.4 ng/ml (mean 1.6 ± 0.4 ng/ml).

**Discussion**

This study indicates that when the physiologic stress of exercise is applied at several different intensities, a dual catecholamine response occurs, but despite markedly elevated levels of epinephrine, no hemodynamic benefit of β₁-selective adrenoceptor blockade is seen, even at high work loads. Comparable effects of atenolol and propranolol are seen on renin release and lysis, but potentially important differences exist in their effects on carbohydrate metabolism.

Other investigators have suggested that the blockade of β₂ vasodilator receptors by propranolol could produce deleterious hemodynamic effects when large amounts of epinephrine are released — for example, during insulin-induced hypoglycemia. In such situations, the use of a "cardioselective" β₁-adrenoceptor antagonist has shown benefits.

The same is true when the sympathomimetic effects of cigarette smoking have been studied. However, in 1952, Barcroft and colleagues, using indirect methods

![Graph showing catecholamines levels](image)

**Figure 2.** Effect of placebo (circles), propranolol (squares) and atenolol (triangles) on norepinephrine (filled symbols) and epinephrine levels (open symbols) at rest sitting on the bicycle and at each of the exercise grades 1-4.

Every subject were very much lower than those after atenolol (102 ± 5 mg/dl, p = 0.002) (fig. 4).

**Plasma Lactate**

Venous plasma lactate values rose during exercise from 10.0 ± 1.3 to 71.8 ± 9.1 mg/dl during placebo therapy (table 1). Mean values during atenolol therapy were almost identical, but lactate levels during propranolol were lower at the end of stage 3 (propranolol 27.7 ± 4.5 mg/dl, placebo 35.9 ± 3.5 mg/dl; p = 0.03) (fig. 5). At stage 4, however, although mean propranolol lactate levels were lower than the other two treatments, differences were not significant.

**Plasma FFA**

Plasma FFA levels were lower at rest after propranolol or atenolol than after placebo, but there was marked intersubject variability and differences were not statistically significant. During exercise, however, FFA levels fell (fig. 6) and both propranolol and atenolol values were similar and considerably lower than placebo values at the end of exercise (placebo 173 ± 32 μmol/l, propranolol 92 ± 20 μmol/l, atenolol 95 ± 11 μmol/l; p = 0.02 for both drugs vs placebo). This finding was true for all species of FFAs that could be individually quantitated by gas chromatography; at peak exercise, values for all of the major individual
of antagonizing the sympathetic nervous system, stated that no alteration of sympathetic outflow mediated the increase in muscle blood flow during exercise, and with the advent of $\beta$-blocking drugs, elegant studies have reached similar conclusions. Our investigations confirm this finding, but also indicate that whatever the exercise level, the blockade or sparing of $\beta_2$-vasodilator receptors produces no additional effect. Epstein and colleagues, in an early study of the effects of $\beta$-adrenergic blockade on the cardiac response to exercise, found a consistent fall in cardiac output after propranolol. Our study shows a very similar $\beta_1$ antagonism for both drugs (reduction of chronotropic response); thus, the very similar change in diastolic pressure with both atenolol and propranolol is probably due to reduction of cardiac output with compensatory vasoconstriction in nonessential vascular beds. This finding is in agreement with recently published data of Morrison et al., who found elevated diastolic pressures with both propranolol and metoprolol during dynamic exercise, but at variance with another recent report by Sklar and colleagues. These workers could detect no effect of propranolol or metoprolol on diastolic blood pressure during exercise. These investigators used metoprolol as a $\beta_1$-selective antagonist in widely varying dosages. Atenolol is probably the more selective agent in man, and studies on airway resistance after metoprolol in an oral dosage of 100 mg indicate a significant $\beta_2$-blocking effect, whereas for the comparatively low dose of 50 mg of atenolol, $\beta_2$ antagonism is not seen. Our study would thus be expected to show a clearer separation between selective and nonselective antagonists if responses do involve the $\beta_2$ adrenoceptor. Such a response is clearly seen in carbohydrate metabolism during exercise.

**Renin Release**

Both atenolol and propranolol produced marked suppression of resting PRA levels and potent antagonism of the exercise-stimulated elevation of PRA (fig. 3). The effect is apparently greater the higher the exercise level. This is consistent with the dominant role of sympathetic neuronal activation in mediating exercise-induced increases in renin release. There is no significant difference between drugs. Recent investigations using $\beta_1$- and $\beta_2$-selective antagonists in the cat are also consistent with a $\beta_1$ mechanism for renin release.

**Catecholamine Levels**

Comparable rises in catecholamines (4–9½-fold) occurred for norepinephrine and epinephrine. However, epinephrine levels were modestly, though significantly, higher during propranolol treatment at peak exercise. There are two likely mechanisms for this. First, Galbo and colleagues suggested that hypoglycemia per se is a physiologic stimulus to epinephrine

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**Figure 4.** Plasma glucose values at rest and exercise grades 1–4 during treatment with placebo (circles), propranolol (squares) or atenolol (triangles).

**Figure 5.** Plasma lactate values at rest and exercise grades 1–4 during treatment with placebo (circles), propranolol (squares) and atenolol (triangles).
release, a contention borne out by the recent studies of Felig et al.\textsuperscript{23} Second, Rizza et al.\textsuperscript{24} showed that the clearance of epinephrine after infusion appears to depend on a \(\beta\) mechanism and, thus, epinephrine levels could be increased by competition for a \(\beta\) receptor. Our results are compatible with those of other investigations, but until now, no distinction was made between the type of \(\beta\)-adrenoceptor antagonist used.

**Metabolic Responses**

Our investigations suggest a clearer separation of the adrenoceptors involved in intermediary metabolism than has previously been proposed, at least regarding the effects of acute strenuous exercise on the circulating concentrations of glucose, lactate and FFA. Thus, the data are consistent with lipolysis being mediated by the \(\beta_1\) receptors while the effects of exercise on lactate and glucose are mediated by \(\beta_2\) receptors. Of particular importance is the fact that we could find no evidence for the involvement of \(\beta_2\) receptors in lipolysis or of the \(\beta_1\) receptors in the glucose or lactate responses.

Before accepting this hypothesis, one must compare the present metabolic data with those that suggested a mixed receptor response, particularly with regard to the dosages and pharmacologic properties of the \(\beta\) blockers used. The doses of atenolol and propranolol used here were clearly equipotent regarding their ability to block exercise-induced tachycardia, which is considered the optimal test of \(\beta_1\)-receptor blockade in man.\textsuperscript{25} The fact that the effects of both drugs on FFA levels were indistinguishable supports the hypothesis that lipolysis is mediated by the \(\beta_1\) receptors.

Previous studies of propranolol\textsuperscript{12, 19, 26} have indicated that this drug attenuates exercise-induced increases in plasma lactate concentration. The present study supports this conclusion at intermediate exercise grades. Even during strenuous exercise, lactate concentrations were reduced on propranolol, although the changes just failed to reach statistical significance. In contrast, the effect of atenolol was clearly indistinguishable from placebo. Thus, the effects of propranolol on lactate production or release must reside in its ability to block the \(\beta_1\) receptors or its membrane stabilizing activity, neither property was evident at these doses of atenolol. Which of these properties of propranolol is critical is unclear. Detailed studies on this question have been performed on alpenolol\textsuperscript{12} (nonselective) and metoprolol\textsuperscript{10} (\(\beta_1\)-selective), both of which possess membrane-stabilizing activity. Lundborg et al.\textsuperscript{10} showed differences between metoprolol and propranolol, although significant effects on lactate levels were only shown for the postexercise recovery period. Based on their experience using muscle biopsies after alpenolol and atenolol, Frisk-Holmberg et al.\textsuperscript{11} suggested that the reduced plasma lactate rise may be due to the failure of lactate to cross the muscle membrane because it accumulated within skeletal muscle. They suggested that this might be due to the non-\(\beta\)-blocking actions of alpenolol. However, Kaiser and Tesch reported another study with crossover placebo control that indicated no difference of intramuscular lactate concentration between propranolol (80 mg) and control treatment.\textsuperscript{27} In our study, atenolol clearly did not affect the lactate response, and we believe this rules out involvement of the \(\beta_1\) receptor, although this does not agree with findings made during forearm exercise by Hartling et al.\textsuperscript{28} The results are most consistent with a \(\beta_1\)-mediated antagonism by propranolol of lactate production by glycolysis or glycogenolysis.

The effects of atenolol and propranolol on the response of plasma glucose to acute exercise were clearly different. Compared with placebo and atenolol, propranolol produced a clear-cut reduction in plasma glucose during exercise. Again, atenolol could not be distinguished from placebo, ruling out involvement of the \(\beta_1\) receptor. Several mechanisms may be involved in the reduction of glucose produced by propranolol, including enhanced utilization or clearance of glucose,\textsuperscript{29} impaired hepatic glycogenolysis,\textsuperscript{29} and reduced gluconeogenesis (either directly or by reduction in the precursors lactate and glycerol).\textsuperscript{30} In addition, effects might be produced indirectly through alteration of pancreatic insulin and glucagon release.\textsuperscript{30, 31} It is unlikely that the restriction of FFA and glycerol produced by propranolol accounts for the decrease in glucose. Our results indicate that atenolol suppressed lipolysis to an equal degree, and yet did not result in decreased glucose levels. Concerning lactate availability, the fall in

![Figure 6](http://circ.ahajournals.org/)

**Figure 6.** Plasma free fatty acid (FFA) values at rest and exercise grades 1–4 during treatment with placebo (circles), propranolol (squares) and atenolol (triangles).
lactate with propranolol was most marked with submaximal exercise and was much less evident at the highest exercise grade. This could be related to the increase in epinephrine levels seen at the highest exercise grade partially overcoming antagonism and pointing to a $\beta_2$-mediated stimulation of skeletal muscle glycogenolysis. These changes would seem too small to affect gluconeogenesis, however. If skeletal muscle glycogenolysis were affected selectively by propranolol, an increased uptake of circulating glucose could certainly occur in the face of diminished FFA availability. However, biopsy studies suggest an equal availability.

The most likely explanation for the observed differences is probably the effect of propranolol on an intrahepatic $\beta_2$ mechanism. Still and Mayer suggested that $\alpha$-receptor-mediated glycogenolysis was dominant, but recent investigations indicate that much of this response might be secondarily mediated through pancreatic glucagon release. Recent studies using radioligand binding techniques suggest that the receptor subtype is indeed $\beta_2$ and lead us to propose that the disparity between propranolol and atenolol in our study is best explained by propranolol antagonism of a physiologically important $\beta_2$-glycogenolytic mechanism.

In conclusion, after acute oral administration, the postulated hemodynamic benefits of a $\beta_2$-selective adrenoceptor antagonist (atenolol) cannot be demonstrated when dynamic exercise is the physiologic stress, but a marked separation exists between the effects of this drug and propranolol on carbohydrate metabolism. Antagonism of glucose production by propranolol is likely to have significant effects in an active subject, is likely to reduce effort tolerance, and could be implicated in the development of fatigue on exertion, which is a common side effect in young patients. Further investigations of the metabolic effects of these drugs when given chronically are indicated.

References

The Effect of Nifedipine on Arterial Pressure and Reflex Cardiac Control

RUFUS A.B. McLEAY, M.B., TERENCE J. STALLARD, A.I.M.L.T., ROBERT D.S. WATSON, M.D., AND WILLIAM A. LITTLER, M.D.

SUMMARY Nine patients with untreated essential hypertension (mean casual blood pressure 173/109 ± 14/7 mm Hg) (± SD) were studied in the control state and after 16 weeks of treatment with nifedipine, 10 mg orally every 8 hours. Direct arterial blood pressure monitored continuously over 24 hours showed that nifedipine significantly reduced systolic and diastolic blood pressure throughout the day and the night. The variability of blood pressure was not altered by nifedipine therapy. There was no significant change in heart rate after nifedipine therapy.

Chronic nifedipine therapy increased forearm blood flow and decreased forearm vascular resistance, consistent with its action as a vasodilator. The absolute blood pressure responses to tilt, handgrip and cold were reduced, but the percent increase in pressure was not altered by therapy. Plasma renin activity was not altered by chronic nifedipine therapy.

At each study, the sensitivity and setting of the baroreflex response to i.v. phenylephrine was measured. After chronic nifedipine therapy there was resetting of the sinoaortic baroreflex and an increase in its sensitivity. Successful control of blood pressure with nifedipine led to a significant reduction in the left ventricular mass index.

NIFEDIPINE is one of a group of drugs known as calcium antagonists.1 These drugs are vasodilators and are useful in the short-term treatment of both moderate and severe hypertension.2-5 However, the evidence for the hypotensive activity of nifedipine is limited and the mechanism and mode of action of blood pressure reduction remains uncertain.

We measured the effect of nifedipine on direct arterial pressure and its variability in hypertensive patients and studied the effect of nifedipine on forearm blood flow and resistance, sinoaortic baroreflex activity, the responses to tilt, isometric exercise and cold, and the renin-angiotensin system.

Patients and Methods

Ten patients with moderate essential hypertension entered the study, but one declined to complete the protocol and has been excluded. Complete studies were performed in nine patients, seven males and two females, whose average casual blood pressure was greater than 160/95 mm Hg on at least three separate occasions over a period of 1 month or more. The mean casual blood pressure for the group was 173 ± 14/109 ± 7 mm Hg (± SD). The mean age was 40 years (range 33–53 years). No patient had evidence of target organ damage, defined as clinical evidence of ischemic heart disease or cerebrovascular disease, left ventricular (LV) hypertrophy, renal impairment or accelerated hypertension. An underlying cause for hypertension was excluded after clinical examination and measurement of plasma electrolytes and creatinine, catecholamine excretion and i.v. pyelography. None of the nine patients had received hypotensive therapy and none was receiving any medication at the time of study. All patients gave informed consent to
Differentiation of hemodynamic, humoral and metabolic responses to beta 1- and beta 2-adrenergic stimulation in man using atenolol and propranolol.

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