SYSTEMIC AND CORONARY HEMODYNAMICS OF LABETALOL IN NORMOTENSIVE PATIENTS WITH ISCHEMIC HEART DISEASE

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ciliary property of intrinsic sympathomimetic activity (carteolol), and two calcium channel antagonists (diltiazem and nicardipine) evaluated using the same study design [10, 11].

Methods and Results

Twenty-four normotensive patients with exertional angina and an ischemic electrocardiographic response to exercise stress were studied. No patients had systemic hypertension (cuff blood pressure before cardiac catheterization > 140/90 mmHg) or other forms of heart disease. All vasoactive medications were discontinued at least 48 hours prior to study. Protocols were approved by the Institutional Review Board of the University of Florida. Data from these two groups of patients have been published in two prior separate publications [1, 2].

After an overnight fast, the patients were taken to the catheterization laboratory. An antecubital cutdown was performed in the right arm and a No. 7 or 8 micromanometer-tipped catheter (Millar) or Sones catheter was placed from the brachial artery into the ascending aorta and left ventricle. A multithermistor catheter was placed into the brachial artery and advanced towards the coronary sinus. Aortic and left ventricular pressures, cardiac output, indicator, great cardiac vein and coronary sinus temperatures and three electrocardiographic leads (I, II, V₅) were measured, and arterial and coronary sinus

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SUMMARY. The systemic and coronary hemodynamic effects of combined alpha- and beta-adrenergic blockade produced by labetalol were assessed in 24 normotensive patients with angina pectoris and an ischemic electrocardiographic response to exercise stress. Both the intravenous (0.5 mg/kg) and oral (200 mg) formulations of labetalol were evaluated. At rest, labetalol produced systemic vasodilation (systemic vascular resistance -16% after intravenous and -8% after oral labetalol, both p < 0.05) without change in heart rate. Aortic pressure usually was lower and cardiac output preserved or increased. Left ventricular end-diastolic pressure was unchanged. Coronary sinus flow was usually unchanged after either route of administration. Exercise duration was prolonged in 14 of the 20 patients with severe coronary artery disease. During exercise, tachycardia was blunted (-12% after intravenous, -7% after oral labetalol, both p < 0.05) as was the increase in mean aortic pressure (-12% and -13% intravenous and oral labetalol respectively, both p < 0.05), left ventricular end-diastolic pressure [-7% and -1%, respectively, both p = not significant (NS)] was unchanged. Coronary sinus flow (-16% and -25%, respectively, both p < 0.05) was decreased as heart rate and aortic pressure were lower. Cardiac output, systemic vascular resistance, and coronary vascular resistance were similar to control exercise. The hemodynamic effects of intravenous and oral labetalol are, in general, similar. Hemodynamic responses differ from those produced by other beta-blockers and by calcium antagonists.

KEY WORDS. labetalol, beta-adrenergic blockade, alpha-adrenergic blockade, coronary artery disease, ischemia, systemic vascular resistance

Beta-adrenergic blockers and calcium antagonists are standard antianginal therapy. Labetalol is a nonselective beta blocker with the ancillary property of alpha₁-blockade; it has a unique hemodynamic profile [1-6]. Labetalol is an effective antihypertensive agent and in the experience of several investigators is useful in both hypertensive and normotensive patients with angina pectoris [7-9]. This report reviews our experiences assessing clinical and acute systemic and coronary hemodynamic effects of intravenous and oral labetalol in normotensive patients with exercise-induced angina [1, 2]. Additionally, some general comparisons are made to the effects of intravenous nonselective beta-blockade (propranolol), cardioselective beta-blockade (metoprolol), nonselective beta-blockade with the an-
blood samples were obtained for determination of oxygen saturations. Cardiac output was measured by injection of 5 mg of indocyanine green into the right atrium with sampling from either to ascending aorta or brachial artery. Repeated cardiac output determinations by this method in our laboratory are very similar (± 5%). After completing measurements at rest, supine bicycle ergometry was performed at a constant external workload. The day before catheterization this workload was predetermined by testing at one to three external workloads to determine the load that would produce typical angina symptoms after approximately 4 minutes of exercise. With occurrence of angina during supine exercise, measurements were repeated. Upon completion of exercise the patient rested at least 5 minutes until all symptoms and signs of ischemia subsided and heart rate and pressures had returned to preexercise levels (± 5%).

This report combines the results of two protocols; in both, control rest and exercise measurements were made [1, 2]. In the first, labetalol (0.5 mg/kg) was then administered intravenously over 2 to 3 minutes. Measurements at rest were repeated 15 minutes later. In the second, labetalol (200 mg) was then administered orally. Measurements at rest were repeated 45 minutes later. Exercise at the same constant external workload was repeated and measurements repeated at the same duration of exercise at which angina occurred before labetalol. If angina did not recur, exercise was continued until symptoms developed. Following completion of the study, selective coronary angiography and left ventricular angiography were done in routine fashion.

**Calculations**

Coronary sinus flow was calculated as described elsewhere [12]. Systemic and coronary vascular resistance were calculated as the ratio of mean arterial pressure and the respective blood flows. Myocardial oxygen consumption was calculated as the product of the difference in arterial and coronary sinus oxygen saturation, hemoglobin concentration, 1.34, and coronary sinus flow. Left ventricular minute work was calculated as the product of the difference of left ventricular systolic and end-diastolic pressures, cardiac output, and 0.0136. Horizontal or downsloping ST segment depression measured 0.08 seconds after the QRS complex was considered indicative of myocardial ischemia.

**Statistical Analysis**

Mean ± SD were calculated. Values at rest and during exercise and before to after either intravenous or oral labetalol were compared using a two-tailed, paired t-test. Responses after intravenous or oral labetalol were compared using an unpaired t test. P values < 0.05 were considered significant.

**Results**

**Clinical Profile**

Of the 24 patients 20 had severe (> 70% diameter narrowing), 1 moderate, and 3 no important coronary narrowing. No patient had symptomatic hypotension, bradycardia, clinically evident heart failure, or other adverse reaction. Angina was the limiting symptom during control exercise in all 24 patients. Exercise duration was not altered (± 15 seconds) in the three patients without severe coronary narrowing and in seven of those with severe narrowing. In the other 14 patients exercise duration was prolonged between 30 seconds and 3 minutes (average of 43% increase in exercise duration as compared with control exercise patients) after labetalol. Of these 14 patients exercise was terminated in 9 because of recurrent angina and in 5 because of fatigue, as neither angina or ischemic ST shifts had recurred.

Systemic and coronary hemodynamic effects at rest are summarized in Table 1 and during exercise in Table 2. Responses in the patients with and without severe coronary narrowing were in general similar and were combined. An illustrative example of the hemodynamic effects of intravenous labetalol is shown in Figure 1.

**Systemic Hemodynamics**

At rest, labetalol did not alter heart rate [−1% after intravenous labetalol and 0% after oral labetalol, both p = not significant (NS)]. Systemic vasodilation occurred as evidenced by decreases in mean aortic pressure (−8%, p < 0.05; and −7%, p < 0.10, respectively) and systemic vascular resistance (−16% and −9%, respectively, both p < 0.05). Cardiac output usually increased after intravenous labetalol (11%, p < 0.05) but did not change after oral labetalol (2%, p = NS). Left ventricular end-diastolic pressure was usually unchanged after intravenous labetalol (−6%, p = NS) and decreased slightly after oral labetalol (−17%, p = 0.05). Left ventricular minute work was usually unchanged (−1% and −7%, respectively, both p = NS).

During exercise at the same duration and load that produced ischemia during the control period, labetalol blunted exercise-induced tachycardia (−12% and −7%, respectively, both p < 0.05) and the increase in mean aortic pressure (−12% and −12%, respectively,