Effects of Propranolol on Reflex Vascular Responses to Orthostatic Stress in Humans

Role of Ventricular Baroreceptors

David W. Ferguson, M.D., Marc D. Thames, M.D., and Allyn L. Mark, M.D.

SUMMARY To evaluate the role of ventricular baroreceptors in humans, we studied the effects of propranolol on reflex vasoconstrictor responses to simulated orthostatic stress. We measured forearm vascular resistance in 10 normal males in the control state and during lower body negative pressure (LBNP) at -10 and -40 mm Hg before and after propranolol (0.1 mg/kg i.v.). Baseline forearm vascular resistance showed no significant change: 23.9 ± 3.4 U (± SEM) before vs 28.0 ± 0.5 U after propranolol. Reflex increases in forearm vascular resistance during LBNP at -10 and -40 mm Hg were 5.2 ± 1.2 and 21.2 ± 6.6 U before and 3.4 ± 1.2 and 10.6 ± 2.2 U, respectively, after propranolol. Thus, propranolol significantly (p < 0.05) reduced responses to LBNP at -40 mm Hg. In contrast to the effects with LBNP, propranolol did not attenuate increases in forearm vascular resistance during the cold pressor test and handgrip, thus excluding a nonspecific depression of reflexes. We also studied the effects of propranolol on carotid baroreflex-mediated vasoconstrictor responses to neck pressure at 15 and 30 mm Hg. Propranolol had no significant effect on the vasoconstrictor responses to neck pressure. In conclusion, propranolol selectively attenuates vasoconstrictor responses to LBNP. We suggest that this results from a propranolol-induced decrease in the activity of cardiac ventricular baroreceptors. The results support the view that ventricular baroreceptors play an important role in reflex adjustments to orthostatic stress in humans.

IN HUMANS, assumption of the upright posture results in pooling of blood in the lower extremities, a decrease in venous return and cardiac filling pressure and a decrease in stroke volume, but arterial pressure is usually maintained by reflex tachycardia and peripheral vasoconstriction.

These reflex adjustments have been attributed solely to the sinoaortic baroreflexes. However, recent studies in humans suggest that the cardiopulmonary baroreflexes play an important role in adjustments to orthostatic stress. Roddie, Shepherd and Whelan demonstrated that vasodilator responses to increases in venous return did not correlate with the degree of change in arterial pressure and heart rate, suggesting the presence of low-pressure baroreceptors in the intrathoracic vascular bed. Zoller et al. and Johnson et al. evaluated the responses to simulated orthostatic stress in normal males using graded lower body negative pressure (LBNP). At low levels of LBNP, forearm vasoconstriction was accompanied by decreases in central venous pressure, without significant changes in mean arterial pressure, arterial pulse pressure, arterial dP/dt or heart rate. This suggested that selective inhibition or unloading of cardiopulmonary baroreceptors triggers reflex increases in forearm vascular resistance (FVR) in humans. Higher levels of LBNP decreased arterial pulse pressure as well as central venous pressure. This presumably inhibited both arterial and cardiopulmonary baroreceptors. However, the increment in vasoconstriction from low to high levels of LBNP was small, suggesting that the cardiopulmonary rather than arterial baroreflexes play the major role in controlling forearm vascular responses to orthostatic stress.

We investigated the role of cardiopulmonary baroreceptors in reflex adjustments to orthostatic stress. We used a new experimental strategy based on recent observations of the effects of propranolol on cardiac and arterial baroreceptors in animals. The left ventricle is the site of many cardiac sensory receptors. The principal determinants of the activity of these left ventricular receptors are cardiac filling pressure and inotropic state, with a more modest contribution from left ventricular systolic pressure. Thoren observed in the cat that propranolol decreased ventricular contractility and produced a marked reduction in the sensitivity of left ventricular receptors with nonmyelinated vagal afferents (C-fibers). Thames subsequently showed that the l-isomer of propranolol produced a marked decrease in the sensitivity of ventricular C-fibers, but did not decrease the sensitivity of atrial mechanoreceptors with C-fiber vagal afferents. This differential effect was thought to result from the large influence of the inotropic state on the activity of the ventricular, but not atrial, C-fibers. The isomer d-propranolol did not have this effect. Since d-propranolol has membrane-stabilizing effects and l-propranolol does not, Thames concluded that the negative inotropic effect of the drug attenuated the discharge of left ventricular mechanoreceptors.

With regard to the effects on arterial baroreceptors, animal studies by Angell-James and Peters and Dorwood and Korner showed that propranolol does not reduce the discharge of aortic baroreceptors and may actually increase the sensitivity of these receptors.
Because of the differential effect of propranolol on ventricular compared with atrial or arterial baroreceptors, this drug appeared to be a valuable pharmacologic tool for investigating the role of ventricular baroreceptors in reflex responses to orthostatic stress in humans. We predicted that by decreasing the inotropic state, propranolol would attenuate reflex responses to orthostatic stress mediated by cardiac ventricular baroreceptors.

We compared forearm vasoconstrictor responses to LBNP in normal males before and after the administration of propranolol. To determine the specificity of the effect of propranolol on cardiac baroreflexes, we also evaluated the effects of propranolol on vasoconstrictor responses to selective inhibition of carotid baroreceptors produced by neck pressure (NP) and on vasoconstrictor responses to the somatic pressor reflex (sustained handgrip) and cold pressor test (CPT).

Methods

Subjects

Ten healthy male volunteers, ages 23–30 years, were studied without sedation in the supine, postabsorptive state. All subjects were free of cardiovascular disease based on a medical history and physical examination and were not receiving any medication at the time of the study. Each subject gave written informed consent. The study protocol was approved by the Human Subjects Review Committee of the University of Iowa.

Procedures

Forearm blood flow was measured by venous occlusion plethysmography, using a mercury-in-Silastic Whitney strain-gauge apparatus as previously described. The strain gauge was placed approximately 5 cm below the antecubital crease of the right arm. The arm was elevated and supported so that the proximal part of the forearm was approximately 10 cm above the anterior chest wall. The pressure of the venous occlusion or congesting cuff on the right arm was 40 mm Hg. Circulation to the right hand was arrested by inflating a cuff around the wrist to 180 mm Hg during determination of forearm blood flow.

Blood pressure was measured in the left arm by sphygmomanometry, with one observer performing all measurements. Heart rate and rhythm were monitored continuously on an ECG.

FVR was calculated by dividing mean arterial pressure (diastolic pressure + 1/3 of pulse pressure in mm Hg) by forearm blood flow (ml · min⁻¹ · 100 ml⁻¹ of forearm volume); these resistance values are expressed as units (U) throughout this report.

Orthostatic stress was simulated by the technique of LBNP applied using a chamber placed over the subject’s body below the iliac crest. Measurements of forearm blood flow were recorded every 15 seconds and blood pressure was recorded every 60 seconds before and during 2 minutes of LBNP. Responses to LBNP at −10 and −40 mm Hg were determined. Values of forearm blood flow were taken as the average of the flows during the last 60 seconds of the intervention.

Carotid baroreceptors were inhibited by applying NP using the neck collar as previously described. NP was applied at 15 and 30 mm Hg for 2 minutes each to decrease transluminal carotid pressure and thereby unload the carotid baroreceptors. The somatic pressor response was evaluated through the technique of sustained (120 seconds) left handgrip using an exercise dynamometer at 30% of the subject’s maximal voluntary contraction. Responses to the CPT were evaluated by immersion of the subject’s left hand in ice water for 90 seconds. The protocol was begun after a 20-minute rest period, during which time the subjects were familiarized with the techniques.

Protocol

After baseline measurements of forearm blood flow, heart rate and blood pressure, we studied responses to LBNP at −10 and −40 mm Hg. NP at 15 and 30 mm Hg, sustained handgrip and CPT. Interventions were performed in random order. The subjects then were given propranolol, 0.1 mg/kg i.v., over 10 minutes. After a 20-minute rest period, baseline hemodynamics and response to the reflex stimuli were repeated as outlined above. In three subjects, we determined responses to LBNP before and 30 minutes after administration of vehicle.

Statistical Analysis

Baseline values before and after propranolol were compared by paired t tests, as were responses to handgrip and the CPT. Responses to the two levels of LBNP and the two levels of NP before and after propranolol were compared using analysis of variance and a least-square means procedure. Statistical significance was p < 0.05. Values are mean ± SEM.

Results

Baseline Hemodynamics

The baseline hemodynamics for the 10 subjects before and after propranolol, 0.1 mg/kg i.v., are summarized in figure 1. There was no significant change in mean arterial pressure, 83.5 ± 2.3 mm Hg before to 84.2 ± 1.8 mm Hg after propranolol. As expected, heart rate decreased significantly, from 56.6 ± 1.6 to 50.9 ± 1.0 beats/min. Forearm blood flow decreased significantly, from 4.1 ± 0.5 to 3.3 ± 0.4 ml · min⁻¹ · 100 ml⁻¹. FVR showed no significant change, 23.9 ± 3.4 U before and 28.0 ± 2.5 U after propranolol.

Responses to LBNP

Figure 2 and table 1 summarize the vasoconstrictor responses to LBNP before and after propranolol. Results are expressed as changes in FVR. LBNP at −10 mm Hg produced an increase in FVR of 5.1 ± 1.2 U before and 3.4 ± 1.2 U after propranolol. LBNP at −40 mm Hg produced an increase in FVR of 21.2 ± 6.6 U before and 10.6 ± 2.2 U after propranolol.

Analysis of variance indicated that responses to LBNP were significantly reduced after propranolol.
TABLE 1. Reflex Responses Before and After Propranolol

<table>
<thead>
<tr>
<th></th>
<th>Lower body negative pressure (n = 10)</th>
<th>Neck pressure (n = 9)</th>
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<tbody>
<tr>
<td></td>
<td>LBPN - 10 mm Hg</td>
<td>LBPN - 40 mm Hg</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Pr</td>
</tr>
<tr>
<td>ΔHPr (beats/min)</td>
<td>-0.7 ± 1.0</td>
<td>0.0 ± 0.8</td>
</tr>
<tr>
<td>ΔSAP (mm Hg)</td>
<td>0.0 ± 1.2</td>
<td>-0.1 ± 1.0</td>
</tr>
<tr>
<td>ΔPP (mm Hg)</td>
<td>0.8 ± 1.9</td>
<td>-2.8 ± 1.3</td>
</tr>
<tr>
<td>ΔCVP (mm Hg)</td>
<td>-3.4 ± 0.3</td>
<td>-3.2 ± 0.6</td>
</tr>
<tr>
<td>ΔFBR (ml·min⁻¹·100 ml⁻¹)</td>
<td>-0.7 ± 0.1</td>
<td>-0.5 ± 0.2</td>
</tr>
<tr>
<td>ΔFVR (U)</td>
<td>5.1 ± 1.2</td>
<td>3.4 ± 1.2</td>
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</table>

Entries are mean ± SEM.
*p < 0.05, control vs propranolol.

Abbreviations: LBPN = lower body negative pressure; NP = neck pressure; C = control; Pr = after propranolol; HPr = heart rate; SAP = mean systemic arterial pressure; PP = pulse pressure; CVP = central venous pressure; FBF = forearm blood flow; FVR = forearm vascular resistance.

The least-squares mean procedure indicated that responses to LBPN - 40 mm Hg accounted for this difference (fig. 3). Before propranolol, LBPN - 40 mm Hg produced an increase in FVR of 12.5 U but after propranolol the same level of LBPN only increased FVR by 3.4 U.

Administration of vehicle did not decrease responses to LBPN. In three subjects, increases of FVR with LBPN - 40 mm Hg averaged 16.0 ± 4.7 U before and +14.1 ± 4.5 U after administration of vehicle.

Responses to NP

NP was used to selectively inhibit the carotid baroreceptors and evaluate the effects of propranolol on the carotid baroreflex. Figure 4 and table 1 summarize the findings. NP produced less vasoconstriction than did LBPN. Before propranolol, NP 15 mm Hg increased FVR 0.6 ± 0.7 U and NP 30 mm Hg increased FVR 4.5 ± 1.9 U. After propranolol, NP 15 mm Hg resulted in an increase of 1.6 ± 0.6 U and NP 30 mm Hg resulted in an increase of 3.6 ± 2.2 U. Analysis of variance and the least-squares mean procedure indicated that responses to NP did not differ before and after propranolol.

Responses to Somatic and Cold Pressor Tests

Table 1 and figure 4 summarize the responses to activation of the somatic pressor reflex by sustained handgrip and of the CPT by cold immersion. The forearm vasoconstrictor responses to handgrip and to the CPT did not differ significantly before and after propranolol. FVR increased by 11.6 ± 5.1 U during the CPT before and 15.6 ± 3.9 U after propranolol. Likewise, FVR during handgrip increased by 4.0 ± 4.6 units before and 9.6 ± 6.1 U after propranolol. These responses contrast strikingly with the attenuation of the vasoconstrictor responses to LBPN seen with propranolol.

Discussion

This study demonstrates that propranolol selectively attenuates reflex forearm vasoconstrictor responses in normal males to simulated orthostatic stress produced by graded LBPN. This effect appears to be the result of a selective decrease in the activity of ventricular baroreceptors induced by β-adrenergic blockade.

The discussion focuses on the following questions: (1) Could the attenuation of vasoconstrictor responses to LBPN be explained by a nonspecific influence of an increase in baseline resistance after propranolol or by a

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

**Figure 1.** Effects of propranolol (Pr) on baseline hemodynamics in 10 subjects. Mean arterial pressure did not change significantly after propranolol. Heart rate slowed significantly. There was a significant decrease in baseline forearm blood flow, but changes in forearm vascular resistance were not significant. Although not shown in the figure, control values (C) for central venous pressure did not differ before and after propranolol (4.8 ± 0.8 mm Hg). Values are mean ± SEM.
generalized nonspecific depression of reflex responses induced by β-adrenergic blockade? (2) Can the high-pressure arterial baroreceptors be implicated in the effects of propranolol rather than the effect being due solely to an effect on the low-pressure cardiac baroreceptors? (3) Could propranolol exert a central nervous system effect that could explain the responses? (4) Could the attenuation of vasoconstrictor responses to LBNP be explained by an effect of propranolol on the subjects’ renin-angiotensin-aldosterone system?

There was no significant increase in baseline FVR in these subjects after propranolol. There was no attenuation of reflex vasoconstrictor responses to the CPT or sustained handgrip after propranolol. In fact, these responses tended to be augmented, presumably reflecting peripheral β2-adrenergic blockade with unopposed peripheral α-adrenergic vasoconstriction. Thus, attenuation of reflex responses to LBNP cannot be explained by a tendency for baseline resistance to be increased. If this were the mechanism, one might have expected attenuation of the other reflex responses as well. The same consideration applies to the possibility of a nonspecific depression of reflexes by propranolol.

We considered the possibility that the high-pressure arterial baroreceptors might be involved in the effect of propranolol. While LBNP, -10 mm Hg is believed to inhibit exclusively the cardiopulmonary baroreceptors, high levels, such as LBNP, -40 mm Hg, inhibit the arterial baroreceptors since LBNP, -40 mm Hg causes a fall in arterial pressure and narrowing of the pulse pressure. One might argue that since the greatest attenuation of reflex vasoconstriction by propranolol was seen at LBNP, -40 mm Hg, the attenuation could be due to an effect of the drug on the arterial baroreceptors. This seems unlikely; a previous study from our laboratory suggests that carotid baroreceptors do not contribute importantly to reflex forearm vasoconstrictor responses to LBNP, even at -40 mm Hg. Nevertheless, to evaluate the influence of propranolol on carotid baroreflex control of FVR, we studied the effects of selective unloading of the carotid baroreceptors through the use of NP. This decreases the transmural carotid pressure, thereby reducing the tonic inhibitory influence of the carotid baroreceptors on the vasomotor centers and on sympathetic vasoconstrictor tone. Propranolol did not attenuate forearm vasoconstrictor responses to NP. This strongly suggests that the carotid baroreceptors play little role in the attenuation of forearm vasoconstriction to LBNP after propranolol.

We could not examine the aortic arch baroreceptors in humans. Data from animal studies suggest that these baroreceptors are less important in initiating reflex vasoconstrictor responses to hypotensive stimuli than are the carotid baroreceptors. More important, studies in animals have shown that propranolol has no direct effect on aortic baroreceptors or may even increase the sensitivity of these baroreceptors. Based on the responses to NP in this study and on studies in animals, it seems unlikely that arterial baroreceptors (aortic or carotid) played a significant role in the influence of propranolol on responses to LBNP observed in this study.

We also considered the possibility that central nervous system effects of propranolol could account for its effect on responses to LBNP. However, if one were to postulate a central nervous system effect resulting in attenuation of reflex vasoconstrictor mechanisms, we would have expected that there would be an attenuation of all of the reflexes studied. Such was not the case.

Although propranolol does inhibit renin secretion, it is unlikely that this mechanism would explain the observations in this study. These subjects were normal males in a sodium-repleted state, and therefore probably had low basal renin levels. Thus, propranolol

### Table 1. (Continued)

<table>
<thead>
<tr>
<th>Cold pressor test (n = 6)</th>
<th>Sustained handgrip (n = 6)</th>
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<tr>
<td></td>
<td>C</td>
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<td></td>
<td>7.3 ± 3.6</td>
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<td>20.3 ± 4.0</td>
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<td>-6.3 ± 3.1</td>
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<td></td>
<td>-0.5 ± 0.3</td>
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<tr>
<td></td>
<td>11.6 ± 5.1</td>
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</table>

### Figure 2. Effects of propranolol on responses to lower body negative pressure (LBNP). Propranolol significantly attenuated the vasoconstrictor response to graded LBNP at -10 and -40 mm Hg. p < 0.05, analysis of variance with least-squares mean procedure.
would not have been expected to produce much further decrease in plasma renin. Moreover, the reflex stimuli were short (90–120 seconds) and the rapid time course of the responses mitigates against a role of the renin-angiotensin system.

This study supports the concept that ventricular baroreceptors play a significant role in reflex vascular responses to orthostatic stress in humans. These cardiac baroreceptors exert a tonic inhibitory influence on the brainstem vasomotor centers. This inhibitory influence attenuates sympathetic outflow from these centers. Deactivation of these baroreceptors by reducing cardiac filling pressure, as with LBNP, reduces their tonic inhibitory influence, with a resultant increase in peripheral sympathetic tone and vasoconstriction.

Propranolol, a β-adrenoceptor antagonist, reduces cardiac contractility. This negative inotropic effect is known to reduce the activity of left ventricular, but not left atrial, C-fibers in cats. With the administration of this negative inotropic agent and reduced ventricular baroreceptor activity, one would expect less baseline inhibitory input to the central nervous system. Thus, removal of this lessened inhibitory tone by deactivating the ventricular baroreceptors with LBNP would reduce the magnitude of reflex vasoconstriction after propranolol.

Acknowledgment

The authors gratefully acknowledge the research assistance of Jinx Tracy and the secretarial assistance of Linda Mohr and Jan Ellsworth in the preparation of the manuscript.

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Controlled Trial of Captopril in Chronic Heart Failure: A Rest and Exercise Hemodynamic Study

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SUMMARY Although many studies have shown acute hemodynamic improvement in patients with congestive heart failure treated with vasodilating drugs, long-term controlled studies with both hemodynamic and exercise capacity measurements are not available. We studied the converting-enzyme inhibitor captopril in 16 ambulatory patients in New York Heart Association functional class II–IV heart failure who were clinically stable on digoxin and diuretics. The acute response to open-label captopril was quantified by blood pool scintigraphy, right-heart catheterization at rest and during exercise, and measurements of exercise capacity. The patients were then randomized to maintenance therapy with captopril or matching placebo and were restudied after 3 months. The two groups were similar in their clinical characteristics and pretreatment rest and exercise hemodynamic measurements. Both displayed similar acute beneficial responses to captopril at rest, with a mean reduction in left ventricular filling pressure from 24 ± 9 to 14 ± 6 mm Hg (p < 0.001) and increases in cardiac index, from 2.1 ± 0.5 to 2.5 ± 0.61/min/m² (p < 0.01), and stroke index, from 25 ± 8 to 34 ± 8 ml/m² (p < 0.001). Directionally similar hemodynamic improvement was noted during exercise.

After 3 months, these beneficial hemodynamic changes were sustained only in the patients randomized to captopril. Concomitantly, the captopril patients increased their exercise capacity as measured by the duration of bicycle exercise (9.0 ± 2.2 vs 11.7 ± 1.4 min, p < 0.01), maximal work load (360 ± 80 vs 460 ± 50 kpm/min, p < 0.005) and oxygen consumption (12.9 ± 2.3 vs 15 ± 1.8 ml/kg/min). The placebo group showed either no change or a worsening over the 3 months compared to their pretreatment measurements. These findings demonstrate that captopril is an effective adjunctive agent for the treatment of chronic heart failure and that it produces long-term hemodynamic improvement together with an increase in exercise capacity.

VASODILATORS are commonly used to treat patients with severe congestive heart failure. The premise for this therapy has been the assumption that the acute hemodynamic improvement demonstrated with a variety of vasoactive drugs would be sustained with long-term treatment and accompanied by clinical improvement.1,2 Only a few uncontrolled studies have reported sustained hemodynamic benefit during chronic vasodilator therapy,3–9 although there is more evidence for functional improvement.10 Unfortunately, few adequately controlled trials have been performed, and these have not included both initial and follow-up invasive hemodynamic measurements.

The present study was designed to evaluate comprehensively the long-term therapeutic response to captopril, an angiotensin converting-enzyme inhibitor, in patients with chronic heart failure. Acute hemodynamic improvement after captopril administration has been well demonstrated,9,11-15 but the degree of long-term benefit is less clear. Our study was designed as a prospective, controlled, 3-month trial to answer the questions: Are the acute beneficial effects of captopril on cardiac function sustained? Do patients improve, as judged by objective measurements of exercise capacity, if their cardiac performance improves?
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Circulation. 1983;67:802-807
doi: 10.1161/01.CIR.67.4.802
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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