Cardiopulmonary mechanoreceptors with C-fiber vagal afferents have been firmly established to tonically inhibit sympathetic vasomotor outflow in experimental animals, but the role played by these afferents in the integrated reflex control of the peripheral circulation in humans remains incompletely understood.

Studies in open-chest, anesthetized cats have indicated that the two main mechanical determinants of ventricular C-fiber activity are left ventricular end-diastolic pressure and contractility. Increases in left ventricular end-diastolic pressure over the physiological range produce linear increases in C-fiber activity. Decreases in ventricular contractility, induced for example by ventricular fibrillation or acute β-adrenergic blockage, greatly attenuate the increase in C-fiber activity caused by a given increase in end-diastolic pressure.

Studies in conscious humans have suggested that cardiac filling pressure and contractility, the primary determinants of ventricular mechanoreceptor discharge in experimental animals, are important determinants of sympathetic vasomotor outflow during orthostatic stress. Orthostatically induced decreases in cardiac filling pressure evoke linear increases in sympathetic nerve activity and regional vascular resistance. β-Adrenergic blockade (intravenous propranolol in normal humans) and heart transplantation (which produces ventricular deafferentation) each were found to greatly attenuate the increase in forearm vascular resistance induced by a given decrease in cardiac filling pressure.

However, recent data from intraneural recordings of muscle sympathetic nerve activity (MSNA) would appear to challenge earlier hemodynamic data suggesting the critical importance of ventricular mechanoreceptors in the reflex regulation of sympathetic vasomotor outflow in humans. Contrary to what might be expected from surgical interruption of inhibitory ventricular afferents, heart transplantation alone neither elevates baseline levels of MSNA nor attenuates the reflex increases in MSNA caused by orthostatic stress.

These findings in heart transplant recipients prompted us to reevaluate the experimental evidence suggesting that ventricular mechanoreceptor reflexes importantly regulate sympathetic outflow in normal humans. Accordingly, we have recorded muscle sympathetic nerve activity (MSNA) in healthy humans during graded orthostatic stress in a setting in which to reevaluate the role played by these afferents in the integrated reflex control of the peripheral circulation in humans.

Previous studies in humans have advanced the concept that cardiac filling pressure and contractility, the primary determinants of ventricular mechanoreceptor discharge, are important determinants of sympathetic outflow during orthostatic stress. Thus, intravenous propranolol greatly attenuated forearm vasoconstrictor response to venous pooling with lower body negative pressure (LBNP). The aim of this study was to reevaluate the experimental support for this concept by using direct measurements of sympathetic nerve activity.

Methods and Results. In 11 healthy humans, we recorded muscle sympathetic nerve activity (MSNA) with microelectrodes (peroneal nerve), as well as blood flow in the forearm and calf (venous occlusion plethysmography) at baseline and during graded LBNP. The same experiments were repeated after administration of propranolol (0.15 mg/kg i.v.), which is thought to decrease ventricular mechanoreceptor discharge. The major new findings are that propranolol neither increased baseline MSNA nor attenuated the increases in MSNA during graded orthostatic stress even though in the same subjects, propranolol simultaneously increased the baseline level of vascular resistance in both the forearm and calf and substantially attenuated the increases in regional vascular resistance during orthostatic stress.

Conclusions. Systemic β-blockade causes a marked dissociation between sympathetic outflow and vascular resistance that invalidates the use of intravenous propranolol as an experimental model to examine the reflex effects of ventricular mechanoreceptors on peripheral vascular resistance in humans. (Circulation 1992;85:1072-1076)

**KEY WORDS** • propranolol • lower body negative pressure • muscle sympathetic nerve activity
ingly, we recorded MSNA in healthy humans to determine if intravenous propranolol, which is assumed to decrease ventricular mechanoreceptor discharge, increases baseline sympathetic activity and attenuates orthostatically induced sympathetic activation.

Methods

Eleven healthy, normotensive male subjects (22–38 years of age) were studied. The protocol was approved by the institutional review board on human investigation, and all subjects gave their written informed consent.

Experiments were performed with the subjects supine and the lower body enclosed in a lower body negative pressure (LBNP) chamber; pressure in the chamber was measured with a Statham transducer. Blood flow in the forearm and calf were measured with venous occlusion plethysmography using air-filled latex cuffs. The circulation to the foot and hand was arrested during blood flow determinations that were performed every 15 seconds. Heart rate was obtained from a continuous electrocardiogram. Arterial pressure was measured every 30 seconds with an automated sphygmomanometer (Dinamap, Criticon, Tampa, Fla.). Central venous pressure, which was used as an index of the mechanical stimulus to cardiopulmonary afferents, was measured with a catheter in an intrathoracic vein. Mean arterial pressure was calculated as diastolic pressure plus one third of pulse pressure. Vascular resistance was calculated as mean arterial pressure divided by blood flow.

Multiunit recordings of postganglionic sympathetic nerve activity were obtained with unipolar tungsten microelectrodes inserted into a muscle nerve fascicle of the peroneal nerve posterior to the fibular head by using the technique of Valbo et al. Briefly, the neural signals were amplified, filtered (700–2,000 Hz bandwidth), rectified, and integrated to obtain a mean voltage display of MSNA. A recording of MSNA was considered acceptable when the neurogram revealed spontaneous pulse synchronous bursts that increased during the Valsalva maneuver but not during arousal stimuli (loud noise, skin pinch). Sympathetic bursts were detected by inspection of the filtered and mean voltage neurograms; the interobserver and intraobserver variability in identifying bursts is <10% and <5%, respectively. Nerve traffic was expressed both as bursts per minute, an index of the frequency of activity, and as bursts per minute times mean burst amplitude, an index of integrated (total) nerve activity.

Experimental Protocol

In our initial experiments, we compared the effects of propranolol on MSNA and forearm vascular responses to graded LBNP. After 30 minutes of rest, we measured MSNA, forearm blood flow, heart rate, arterial pressure, and central venous pressure during LBNP at −5, −10, −20, and −40 mm Hg for 3 minutes at each consecutive level. The same experiments were repeated 20 minutes after administration of propranolol (0.15 mg/kg i.v.). This dosing regimen has been shown to produce near-maximal β-adrenergic blockade of several hours’ duration. In four of these subjects, we also examined MSNA responses during rapid 10-minute intravenous infusion of 500 and 1,000 ml of normal saline before and after propranolol. To test the effects of propranolol on vascular responses in the calf, in five of the subjects we also performed LBNP (−5, −10, and −20 mm Hg) on only the right leg and pelvis while measuring reflex changes in calf blood flow in the left leg, which was excluded from the LBNP chamber by the method of Vissing et al.

Data Analysis

Responses during graded LBNP before and after propranolol were compared by using repeated measures analysis of variance with Scheffé’s post hoc test. Baseline values before and after propranolol were compared by paired t test. A value of p<0.05 was considered statistically significant. Results are presented as mean ± SEM.

Results

Before propranolol, graded LBNP, as expected, increased MSNA and forearm resistance in proportion to the progressive decrease in central venous pressure evoked by this maneuver (Table 1 and Figures 1 and 2). Propranolol had no effect on baseline values of arterial pressure or MSNA but significantly decreased baseline heart rate, increased baseline forearm resistance, and increased the absolute level of central venous pressure at each level of LBNP. Most importantly, propranolol had no effect on the graded increases in MSNA during LBNP. In the same subjects, however, propranolol greatly attenuated the increases in forearm vascular resistance during LBNP at −5, −10, and −20 mm Hg but did not attenuate the increase in forearm resistance during LBNP at −40 mm Hg (Table 1 and Figure 1). Propranolol also greatly attenuated LBNP-induced increases in vascular resistance in the calf (Table 2). Figure 2 shows that propranolol did not alter the slope of the relation between central venous pressure and MSNA during either increases (saline infusion) or decreases (LBNP) in central venous pressure.

Discussion

The major new findings from this study are that intravenous propranolol neither increased baseline MSNA nor attenuated the increases in MSNA during graded orthostatic stress, even though in the same subjects, propranolol simultaneously increased baseline vascular resistance in both the forearm and calf and markedly attenuated the orthostatically induced increases in regional vascular resistance. Thus, our peripheral vascular data confirm and extend previously reported observations regarding effects of propranolol on forearm vascular responses to LBNP, but our neurophysiological data demonstrate that propranolol-induced attenuation in vasoconstrictor responses during orthostatic stress should not be interpreted as providing experimental support for the importance of ventricular mechanoreceptors in humans.

During perturbations in central venous pressure over the physiological range, changes in regional vascular resistance normally are closely correlated with changes in MSNA. Thus, the salient feature of our study is that administration of propranolol causes a striking dissociation between MSNA and regional vascular resistance. This dissociation might possibly be related to comparison of blood flow measurements in the arm with sympathetic nerve recordings in the leg. However, our
TABLE 1. Effects of Propranolol on Neurocirculatory Responses During Lower Body Negative Pressure

<table>
<thead>
<tr>
<th></th>
<th>Control Lower body negative pressure (mm Hg)</th>
<th>Propranolol Lower body negative pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline -5 -10 -20 -40 Baseline -5 -10 -20 -40</td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>58±2 57±2 57±2 61±2 65±2* 52±2†</td>
<td>53±2† 53±2† 53±1† 56±2†</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>81±2 80±2 79±2 78±2 74±2* 83±3</td>
<td>82±3 80±3 79±3 74±2*</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>58±3 58±4 60±4 58±3 56±3 52±3</td>
<td>53±3 53±4 52±3 50±4</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>4.1±1.7 2.5±1.2* 1.5±1.0* -0.6±1.0* -2.6±1.9* 4.7±1.4</td>
<td>3.6±1.2* 2.6±1.1* 0.1±1.5* -1.7±1.6†</td>
</tr>
<tr>
<td>Forearm blood flow (ml/min · 100 g)</td>
<td>3.5±0.4 2.9±0.3* 2.7±0.3* 2.2±0.2* 1.8±0.2* 2.5±0.2†</td>
<td>2.5±0.2† 2.3±0.2† 2.2±0.2† 1.9±0.2†</td>
</tr>
<tr>
<td>Forearm vascular resistance (units)</td>
<td>26.1±3.7 30.6±4.0* 31.1±4.3* 38.7±5.6* 46.2±8.6* 36.5±3.9† 37.5±3.9† 35.2±4.6† 37.7±5.8† 48.8±8.1†</td>
<td></td>
</tr>
<tr>
<td>Muscle sympathetic nerve activity (bursts per minute)</td>
<td>11±6 14±6* 17±6* 20±8* 28±9* 12±5</td>
<td>16±6* 21±6* 25±5* 33±8*</td>
</tr>
<tr>
<td>Total activity</td>
<td>248±35 353±41* 453±44* 606±77* 875±104* 292±45</td>
<td>392±39* 537±75* 706±74* 1,026±103*</td>
</tr>
</tbody>
</table>

bpm, Beats per minute.
Values are mean±SEM for 11 subjects.
*p<0.05 vs. baseline; †p<0.05 propranolol vs. control.

additional experiments in which we measured blood flow in the calf eliminated this possibility.

The use of propranolol to study the reflex effects of ventricular afferents in humans previously was based on the assumption that acute β-adrenergic blockade rather selectively attenuates the stimulation of ventricular mechanoreceptors, presumably by decreasing ventricular contractility, but does not produce a nonspecific, generalized reduction in sympathetic vasomotor responsiveness.4 This assumption was indirectly supported by the finding that propranolol had no effect on forearm vasoconstrictor responses to several other reflex sympathetic stimuli including the cold pressor test, handgrip, and carotid sinus hypotension. In contrast, in our study the propranolol-induced dissociation between sympathetic activity and vascular resistance provides direct evidence that attenuation in central sympathetic outflow cannot explain the robust effect of intravenous propranolol on vasoconstrictor responses to LBNP.

Although our study was not designed to define the underlying mechanisms causing this dissociation, at least two possibilities should be considered. First, intravenous propranolol increased baseline vascular resistance, presumably because of blockade of postjunctional vascular β-receptors resulting in unopposed α-adrenergic vasoconstrictor drive. This increased baseline vascular resistance possibly might have caused a nonspecific suppression of vascular reactivity to superimposed reflex sympathetic stimuli16,17 such as LBNP. This possibility, however, is unlikely because our

FIGURE 1. Graphs of summary data showing central venous pressure, muscle sympathetic nerve activity, and forearm vascular resistance at baseline and during graded lower body negative pressure (LBNP) under control conditions (solid lines) and after intravenous administration of propranolol (broken lines). Values are mean±SEM for 11 subjects. Propranolol greatly attenuated the progressive increases in forearm resistance during LBNP (−5 through −20 mm Hg) but had no effect on the corresponding increases in muscle sympathetic nerve activity. *p<0.05 from baseline.
FIGURE 2. Graphs of data showing that propranolol has no effect on the relation between changes in central venous pressure and in muscle sympathetic nerve activity (MSNA) during decreases in central venous pressure with lower body negative pressure (LBNP) or during increases in central venous pressure with intravenous infusion of saline. Left panel: Summary data (mean±SEM) for seven subjects during LBNP and four subjects during saline infusion. Right panel: Segments of original recording of MSNA from one subject during LBNP at –40 mm Hg at baseline, and after infusion of 1,000 ml of normal saline, both under control conditions and after administration of propranolol.

study the propranolol-induced increase in baseline forearm resistance was modest and far from maximal. Furthermore, previous studies have demonstrated that there is no correlation between baseline forearm resistance and the subsequent increase in forearm resistance during LBNP and that intravenous propranolol does not attenuate increases in forearm resistance during reflex vasoconstrictor stimuli other than LBNP.

A second and more likely possibility is that the propranolol-induced dissociation between sympathetic activity and vascular resistance is caused in part by blockade of prejunctional β-receptors, in which stimulation is thought to facilitate release of norepinephrine from peripheral sympathetic nerve terminals. In ex vivo experimental preparations, blockade of prejunctional β-receptors attenuates the increases in both norepinephrine release and vascular resistance evoked by a given level of sympathetic nerve stimulation, with this attenuation being most evident at low rather than high levels of sympathetic stimulation. Thus, in our human subjects, blockade of prejunctional β-receptors provides a potential explanation for the observations that propranolol attenuated the increase in forearm resistance elicited by a given increase in sympathetic activity during graded LBNP and that this attenuation was most evident at low rather than at high levels of reflex sympathetic activation.

We considered several possible explanations for the finding that propranolol affected neither baseline sympathetic activity nor the sympathetic responses to LBNP. First, this dose of propranolol may not have caused a sufficiently large decrease in ventricular contractility to significantly reduce ventricular mechanoreceptor discharge. However, this possibility is unlikely because only slightly larger doses of propranolol decrease ventricular afferent discharge in cats, and this same dose of propranolol decreases ventricular contractility in humans. Second, directionally opposite effects of propranolol on contractility and on central venous pressure might possibly account for the failure of intravenous propranolol to alter baseline levels of sympathetic activity. However, such effects cannot explain the failure of

| TABLE 2. Effect of Propranolol on Calf Vascular Resistance During Lower Body Negative Pressure |
|-----------------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|
| Control | Propranolol |
| Lower body negative pressure (mm Hg) | Baseline | −5 | −10 | −20 | Baseline | −5 | −10 | −20 |
| Mean arterial pressure (mm Hg) | 73±2 | 74±3 | 73±2 | 72±2 | 75±3 | 76±3 | 75±3 | 74±3 |
| Calf blood flow (ml/min · 100 g) | 2.0±0.2 | 1.6±0.2* | 1.5±0.2* | 1.2±0.2* | 1.4±0.1† | 1.5±0.2 | 1.4±0.1 | 1.3±0.2 |
| Calf vascular resistance (units) | 39.3±3.3 | 52.2±8.1* | 52.3±7.2* | 68.0±12.0* | 56.4±6.0† | 54.2±6.1 | 55.2±6.1 | 62.8±7.5 |

Values are mean±SEM for five subjects.
*p<0.5 vs. baseline; †p<0.5 propranolol vs. control.
propranolol to alter reflex increases and decreases in sympathetic activity in the experiments in which we systematically altered central venous pressure over the physiological range. A third possibility, suggested by experiments in cats, is that propranolol causes a downward shift and a decrease in the slope of the relation between cardiac filling pressure and ventricular afferent discharge.2-3 Thus, in our studies, an effect of propranolol on ventricular afferent reflexes might be more evident during increases than during decreases in cardiac filling pressure. However, our additional experiments with volume loading demonstrate that propranolol had no effect on efferent sympathetic activity during increases or decreases in central venous pressure.

A final consideration, supported by recent observations in heart transplant recipients,6,7 is that in humans, reflex mechanisms other than ventricular mechanoreflexes are capable of increasing MSNA during orthostatic stress. If these various afferent inputs converge on some of the same central vasomotor circuits producing neural occlusion,23 removal of any one of these reflex inputs, such as reduced ventricular afferent discharge with propranolol, may not be sufficient to cause a detectable attenuation in the integrated reflex response. Thus, our study should not be interpreted to suggest that ventricular mechanoreceptors play no role either in the tonic restraint of sympathetic outflow during recumbency or in the reflex activation of sympathetic outflow during orthostatic stress. However, our data demonstrate that systemic β-blockade dissociates vascular resistance from sympathetic nerve activity and thus invalidates the use of intravenous propranolol as an experimental approach to study the reflex effects of ventricular mechanoreceptors on peripheral vascular resistance in humans.

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