Interaction of Cardiopulmonary and Somatic Reflexes in Humans

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ABSTRACT Activation of cardiopulmonary receptors with vagal afferents results predominantly in reflex inhibition of efferent sympathetic activity, whereas activation of somatic receptors reflexly increases sympathetic activity to the heart and circulation. Previous studies in experimental animals indicate that there is an important interaction between these excitatory and inhibitory reflexes in the control of the renal circulation.

The purpose of this study was to determine whether there is a similar interaction between somatic and cardiopulmonary reflexes in humans. The activity of the cardiopulmonary receptors was altered (reduced) with lower body negative pressure (−5 mm Hg), which causes a decrease in cardiac filling pressure and a small reflex increase in forearm vascular resistance without accompanying changes in arterial pressure. Activation of somatic receptors by isometric handgrip for 2 min at 10 and 20% of maximum voluntary contraction resulted in reflex vasoconstriction in the nonexercising arm. Lower body negative pressure at −5 mm Hg produced a threefold augmentation in the forearm vasoconstrictor response to isometric handgrip in the nonexercising arm. This increase in resistance was significantly greater ($P < 0.05$) than the algebraic sum of the increases in resistance resulting from lower body suction alone plus isometric handgrip alone. Furthermore, it occurred despite a greater rise in arterial pressure, which would be expected to decrease forearm vascular resistance through activation of arterial baroreceptors and through passive dilatation of forearm vessels. Thus, removal of the inhibitory influence of cardiopulmonary receptors by pooling blood in the lower extremities enhances the somatic reflex. These data suggest an interaction between cardiopulmonary and somatic reflexes in the control of forearm vascular resistance in man.

INTRODUCTION

Activation of cardiopulmonary receptors with vagal afferents reflexly inhibits sympathetic adrenergic discharge to many vascular beds in animals and humans (1–6). Conversely, activation of somatic receptors triggers excitatory reflex responses as a result of increased sympathetic adrenergic discharge (7–10). Exercise is a potent stimulus to somatic receptors and results in reflex increases in heart rate, mean arterial pressure, and systemic vascular resistance (8, 11, 12). The effects of exercise on cardiopulmonary receptors are less well-defined but the increase in ventricular contractility and stroke volume would be expected to augment the discharge of cardiopulmonary receptors with vagal afferents (13, 14) and, thus, reflexly inhibit sympathetic outflow to the resistance vessels (14). Interactions between the inhibitory cardiopulmonary reflex and the excitatory somatic reflex may, therefore, play an important role in the neural control of the circulation during exercise.

In the dog, there is an important interaction among somatic, sinoaortic, and cardiopulmonary (vagal) reflexes (15–17). The reflex renal vasoconstrictor response to stimulation of somatic afferents was markedly augmented after removal of the tonic inhibitory influence of cardiac vagal afferents on the sympathetic system (17). Conversely, the somatic reflex was inhibited after activation of the cardiopulmonary receptors by volume loading (17). The purpose of the present study was to determine whether an interaction between the somatic and cardiopulmonary reflexes

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is present in humans. The results show that the increases in forearm vascular tone, observed with isometric handgrip, are markedly potentiated by reducing the stimulus to the cardiopulmonary receptors with low levels of lower body negative pressure (LBNP).[1]

METHODS

11 healthy males, 21–33 yr, were studied. The studies were done with the subject lying supine in a warm (26°C) quiet room. The lower body was enclosed in an airtight box to the level of the iliac crests. Low levels of LBNP have been previously shown to decrease the tonic inhibitory influence from receptors in the cardiopulmonary area without changing arterial blood pressure and to result in a decrease in forearm blood flow (5, 6). Blood flow to the right forearm was measured with a Whitney mercury-in-silastic strain gauge plethysmograph (18). The strain gauge was placed around the forearm, 4–8 cm distal to the elbow. The arm was elevated and supported at the wrist so that the proximal forearm was ~10 cm above the anterior chest wall. A pneumatic cuff was placed around the upper arm and inflated intermittently above venous pressure for 6–8 s. To exclude the circulation to the hand, a second cuff applied to the wrist was inflated to suprasystolic pressures during the measurements. Forearm blood flow was calculated from the rate of increase of forearm volume during venous occlusion and expressed as milliliters per minute per 100 ml forearm volume. Arterial blood pressure was determined by sphygmomanometry from the left arm. One of us, J.L.W., performed all the blood pressure determinations to eliminate interobserver variation. Mean arterial pressure was calculated by adding one-third of the pulse pressure to the diastolic pressure. Forearm vascular resistance was calculated by dividing mean arterial pressure in millimeters of Hg by forearm blood flow.

Somatic receptors were stimulated by isometric handgrip. Each subject squeezed a handgrip dynamometer (Weston dynamometer; Weston Instruments, Inc., Newark, N. J.) to the maximal force he could develop with the left hand. This measurement was taken as the subject's maximal voluntary contraction (MVC). Subjects were then asked to maintain a tension of 10 and 20% of their MVC for 2 min. Care was taken to insure that the subjects did not perform a Valsalva maneuver during the 2-min periods of handgrip exercise. In addition, the subjects were trained to avoid contracting the muscles of the nonexercising arm. The magnitude of the response to exercise was determined by the degree of vasoconstriction observed in the nonexercising right forearm.

In four subjects, central venous pressure was continuously measured with a cannula (60 cm long, 0.7 mm i.d.) inserted into an antecubital vein and advanced into an intrathoracic vein.

Heart rate was determined in all subjects by continuous electrocardiograms recorded at 2.5 mm/s.

The changes in mean arterial blood pressure, heart rate, forearm blood flow, and forearm vascular resistance, which resulted from isometric handgrip alone, were compared with those that occurred when the exercise was performed during LBNP.

Protocol. The study protocol was approved by the Human Study Committee of the University of Iowa College of Medicine, and informed written consent was obtained from all subjects.

Recordings were made during the following interventions: (*a*) LBNP at −5 mm Hg, (*b*) handgrip at 10% MVC, (*c*) handgrip at 20% MVC, (*d*) handgrip at 10% MVC plus LBNP at −5 mm Hg, and (*e*) handgrip at 20% MVC plus LBNP at −5 mm Hg. The order of these five interventions was randomized. Each study period lasted 6 min, including 2 min each of control measurements, measurements during intervention, and recovery measurements. There was a 5-min rest period between each 6-min study period. Forearm blood flow and heart rate determinations were made between 30–90 s of each 2-min interval; blood pressure was determined between 60–90 s.

Data analysis. Statistical comparisons were made with the *t* test for paired observations or by analysis of variance. Values of $P < 0.05$ were considered significant. Results are expressed in the figures and text as mean ± 1 SE.

RESULTS

Effect of LBNP (−5 mm Hg). During LBNP at −5 mm Hg, central venous pressure decreased by 1.5–2.5 mm Hg in the 4 of 11 subjects in whom it was measured. This low level of LBNP produced a small increase in the forearm resistance without significantly altering systemic arterial pressure (Table I). There was no reflex tachycardia; in fact, a slight but significant decrease in heart rate was noted.

Effect of isometric handgrip exercise. Table I and Figs. 1 and 2 show that handgrip at both 10 and 20% of MVC produced no significant change in calculated forearm vascular resistance, but there were significant increases in arterial pressure and heart rate. There was no change in central venous pressure with isometric handgrip at either 10 or 20% of MVC. The increases in heart rate and arterial pressure were greater during handgrip at 20% than during handgrip at 10% of MVC.

Effects of LBNP on responses to handgrip. Table I and Fig. 2 show that LBNP caused a greater than threefold increase in the forearm vasoconstrictor response to handgrip at 10 and 20% of MVC, an increase in the arterial pressure response at 20% of MVC, but did not alter the heart rate response. The increases in resistance and arterial pressure were greater than the algebraic sum of the increases for each intervention alone. The decrease in central venous pressure was unchanged from that observed with LBNP alone.

DISCUSSION

The data indicate that the reflex vasoconstrictor response to isometric handgrip is markedly augmented during LBNP. The augmentation of the response was significantly greater than the simple algebraic sum of the vasoconstriction caused by LBNP alone plus that caused by isometric exercise alone. These results are consistent with the view that LBNP reduced a tonic inhibitory influence of cardiopulmonary receptors on

[1] *Abbreviations used in this paper*: LBNP, lower body negative pressure; MCV, maximal voluntary contraction.

TABLE I

Effects of LBNP and Isometric Handgrip with and without LBN Pressure

	Heart rate	Mean arterial pressure	Forearm blood flow	Forearm vascular resistance
	beats/min	*mm Hg*	*ml/min/100 ml*	*mm Hg/ml/min/100 ml*
Effect of LBNP				
Control	63±4	88±2	5.0±0.4	19±2
LBNP (−5 mm Hg)	60±3*	86±2	4.5±0.5*	21±2*
Recovery	62±4	87±2	4.9±0.5	20±2
Effect of handgrip				
Control	60±3	86±2	4.8±0.6	21±2
10% MVC	62±3*	94±3*	4.9±0.6	22±2
Recovery	60±3	89±2	4.9±0.6	21±2
Control	62±3	88±2	4.8±0.6	21±2
20% MVC	69±4*	99±2*	5.4±0.8	22±2
Recovery	62±3	87±2	5.0±0.6	19±2
Effect of LBNP and handgrip				
Control	59±3	90±2	4.8±0.7	22±2
LBNP plus 10% MVC	60±3	94±2*	4.2±0.6*	26±3*
Recovery	60±3	88±2	4.7±0.7	21±2
Control	62±3	87±2	4.6±0.6	21±2
LBNP plus 20% MVC	68±3*	104±3*	4.5±0.6	28±4*
Recovery	63±3	87±2	4.8±0.6	20±2

Entries represent the mean value±1 SEM.

* Values that are significantly different from control ($P < 0.05$).

the vasomotor center and sympathetic efferent activity. The data further suggest that removal of the inhibitory influence augments the vasoconstrictor response to stimulation of somatic receptors. The slope of the response to handgrip at 10 and 20% MVC was not only shifted up and to the left during LBNP but it became steeper (Fig. 2). An interaction, mainly between an inhibitory cardiopulmonary reflex and excitatory somatic reflex, must take place to produce a steeper stimulus-response curve and a net response greater than the sum of the two individual reflex responses at two levels of handgrip (10 and 20% MVC).

This interpretation of the forearm vascular responses is dependent on an understanding of the effect of LBNP on the reflex influence from four groups of receptors: somatic receptors, cardiopulmonary receptors with vagal afferents, cardiopulmonary receptors with sympathetic afferents, and mesenteric receptors with spinal afferents. Naturally, this understanding is based on evidence from studies in experimental animals. The vagal afferents mediate inhibitory influences on sympathetic outflow to peripheral beds (13). These receptors are sensitive to changes in volume and, thus, LBNP would reduce the inhibitory input from these receptors and result in an increase in sympathetic vasomotor activity. Cardiopulmonary receptors with sympathetic afferents appear to mediate largely excitatory influences (19). These influences may be mediated at spinal and supraspinal levels. It should be noted that reflex effects mediated by these endings may be difficult to detect when vagal afferents and sinoaortic pathways are intact. It would be anticipated that LBNP would reduce the input from these endings. If cardiopulmonary receptors with sympathetic afferents exert a tonic excitatory influence on vasomotor outflow to the peripheral circulation, removal of such an influence would result in an inhibitory response rather than the excitatory one that we observed in the forearm during LBNP. Somatic receptors activated during exercise mediate generalized excitatory responses (20). There is little reason to suspect an important influence of LBNP on these endings. Mesenteric receptors appear to mediate excitatory influences during increases in venous pressure which, thus far, have been demonstrated to occur only at the spinal level (21). LBNP would, however, be expected to excite these endings and induce excitatory responses.

Thus, LBNP could augment the response to handgrip either by withdrawing an inhibitory cardiopulmonary reflex or by augmenting an excitatory mesenteric reflex. The role of the mesenteric reflex may be minor for the following reasons. It has been shown by Clement et al. (22), that in the rabbit with sinoaortic

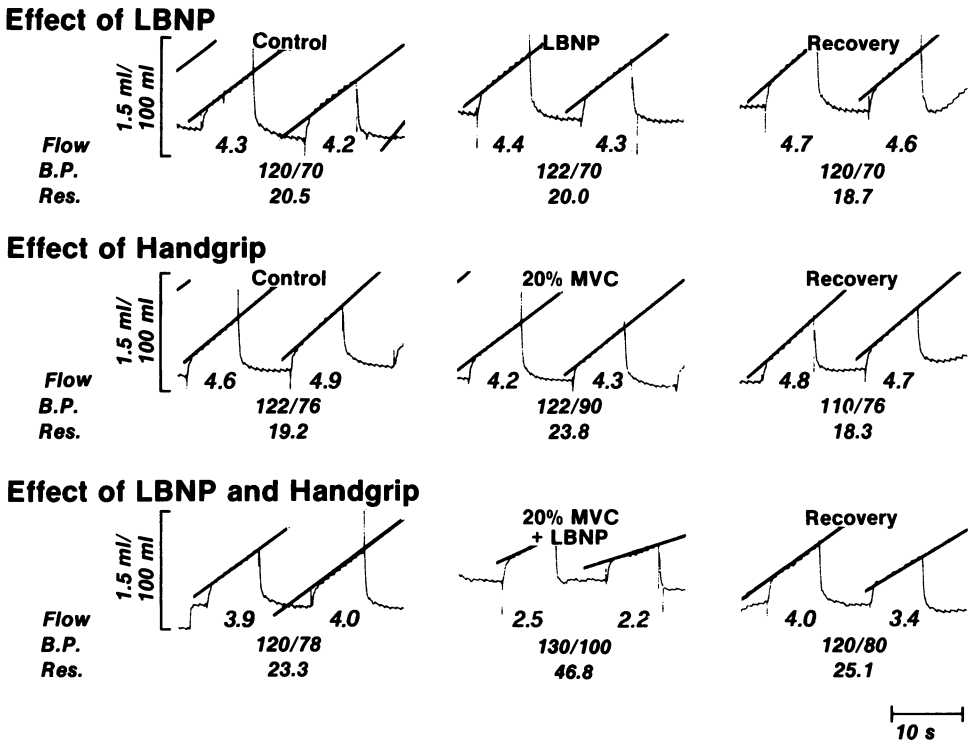

FIGURE 1 Plethysmographic tracings obtained in one subject before, during, and after three interventions: (*a*) LBNP at −5 mm Hg, (*b*) handgrip at 20% of MVC, and (*c*) LBNP and handgrip. Calculated value of forearm blood flow in milliliters per minute per 100 ml of forearm volume are shown beneath each tracing. Corresponding values of arterial pressure (B.P., millimeters of Hg) and calculated forearm vascular resistance (Res.) are also shown. This figure shows responses of a subject in whom the reflex effects were particularly striking.

baroreceptor denervation, expansion of the blood volume reduces renal nerve activity. After section of the vagal nerves, no change in renal nerve activity was observed during volume expansion, even though the discharge of mesenteric receptors would most likely have been augmented during increases in venous pressure that normally accompany volume expansion. We have observed similar results in the dog (23). In addition, it should be noted that the suction box used in our studies applies negative pressure at and below the level of the iliac crests. Venous pressure in most mesenteric and other intraabdominal veins would be expected to decrease during LBNP so that the discharge of tonically active excitatory receptors in this area would be reduced. On this basis, it is most likely that the augmentation of the excitatory somatic reflex in the forearm by LBNP is mainly the result of a withdrawal of an inhibitory cardiopulmonary reflex, but we cannot completely exclude the possibility that mesenteric veins in the pelvis are distended during LBNP and contribute to the excitatory reflex.

In the present study, as well as in previous studies in man (5, 6), LBNP at low levels of suction was sufficient to cause reflex forearm vasoconstriction in the absence of tachycardia and significant decreases in arterial pressure. Because this level of LBNP does not significantly change arterial pressure (5, 6), it seems reasonable to suggest that low level LBNP, like nonhypotensive hemorrhage in animals, decreases the tonic inhibitory influence of cardiopulmonary receptors on efferent sympathetic activity without importantly altering the stimulus to the arterial baroreceptors (24, 25).

The marked augmentation of the reflex response to isometric exercise when the cardiopulmonary receptors were inhibited by LBNP suggests an interaction between the two reflexes rather than a summation of the responses. Several studies have reaffirmed the concept of interaction of reflexes in the control of circulation. We have shown such interactions between arterial baroreceptors and chemoreceptor reflexes (26), between cardiopulmonary receptor and arterial baroreceptor as well as chemoreceptor reflexes (27, 28), and between somatic and arterial as well as cardiopulmonary reflexes in animals (16, 17). This is the first demonstration that an excitatory reflex in man is augmented by removing the tonic inhibitory influence of the cardiopulmonary receptors.

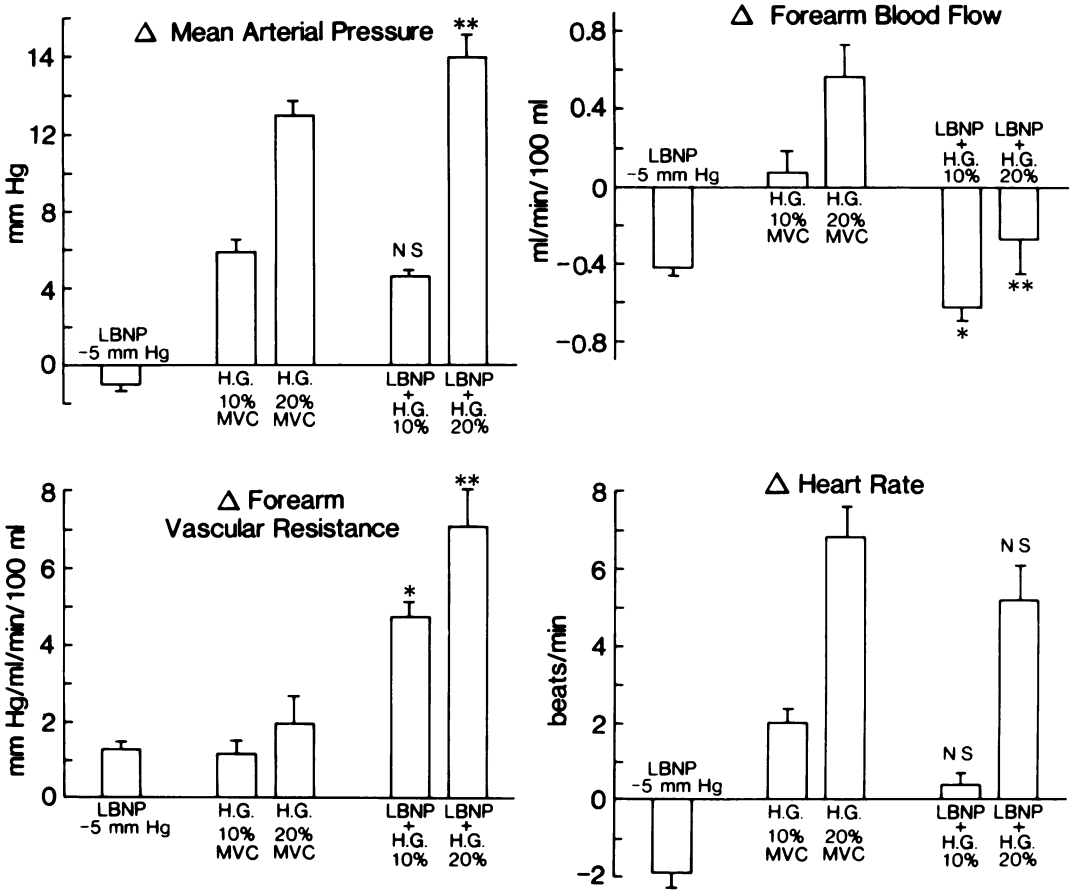

FIGURE 2 Changes in mean arterial pressure, forearm blood flow, forearm vascular resistance, and heart rate that resulted from LBNP at −5 mm Hg, from isometric handgrip (H.G.) at 10 and 20% of MVC, and during concomitant LBNP and H.G. at 10 and 20% of MVC. The changes in each subject were calculated by subtracting the value obtained during the intervention from the control value. Asterisk (*) indicates that response to LBNP plus H.G. at 10% MVC is significantly greater ($P < 0.05$) than the algebraic sum of LBNP alone plus H.G. at 10% MVC alone. Double asterisk (**) indicates that response to LBNP plus H.G. at 20% MVC is significantly greater than the algebraic sum of LBNP alone plus H.G. at 20% MVC alone. Changes that are not significantly different are so indicated. Data presented as mean±SE.

The absence of a significant increase in calculated forearm vascular resistance during handgrip alone does not mean that there was no increase in vasomotor tone of forearm resistance vessels. The rise in arterial pressure during exercise was significant, and vasomotor tone had to increase for vascular caliber to be maintained and for calculated resistance not to decrease passively. Thus, there was a vasoconstrictor response that was not apparent from the calculated resistance changes. The association of an increase in resistance in the face of a significant augmentation of the arterial pressure response, as was seen during concomitant exercise and LBNP, indicates that a major potentiation of this increase in vasomotor tone had taken place.

Despite an increase in arterial pressure, which would be expected to inhibit sympathetic activity by activating arterial baroreceptors, the activation of somatic receptors by exercise causes reflex increases in heart rate and in vasomotor tone. The most likely explanation for the sustained excitatory response is the reported inhibition of the arterial baroreceptor reflex during exercise (11, 29). Although the arterial baroreflex is suppressed during exercise, the input from the baroreceptors can modulate the somatic reflex. Work by Kumada et al. (15), as well as previous work from our laboratory (16, 17), has shown that, in the dog, the reflex vasoconstriction produced by electrical stimulation of the central end of the cut sciatic nerve is augmented by lowering carotid sinus pressure and reduced when carotid sinus pressure is elevated. The increase in arterial pressure during exercise could thus be expected to buffer the excitatory somatic reflex but not prevent it. The marked potentiation of the vaso-

constrictor response to exercise during LBNP which we observed might have been greater if the simultaneous rise in arterial pressure had been prevented.

The complexity of the neural control of the circulation is evident from the fact that we observed a small but significant bradycardia at a time when there was forearm vasoconstriction. This finding may be best explained by a withdrawal of an excitatory reflex during LBNP. In this regard, it is known that activation of atrial receptors with vagal afferents by volume loading or by distention of pulmonary vein left-atrial junctions can result in tachycardia at a time when vasomotor outflow to the periphery is decreasing (30). This is thought to be the basis for the Bainbridge reflex (30). More recent evidence suggests that cardiac receptors with sympathetic afferents could also contribute to this reflex (24). It can be suggested that reduced input from atrial receptors with vagal afferents or from cardiac receptors with sympathetic afferents during LBNP was responsible for the small bradycardia that we observed.

On the basis of our results, a mechanism for the significant increase in sympathoadrenal response to exercise noted in humans and animals with heart failure (31, 32) can be suggested. There is evidence in animals that the sensitivity of atrial receptors with vagal afferents (33, 34) is reduced in congestive heart failure. Kivowitz et al. (12) has demonstrated a 5–10% increase in systemic vascular resistance with 15% handgrip in patients with coronary artery disease or mild heart failure (class I and II). In patients with class III heart failure, the increase in systemic vascular resistance with the same level of handgrip was >30%. Several investigators have shown that the sympathoadrenal response to exercise is increased in patients with heart failure (35–37). We speculate that the altered sensitivity and, thus, reduced inhibitory influence of cardiopulmonary receptors in heart failure may contribute to this increased sympathoadrenal response to exercise in patients with heart failure. The observation that reducing the influence of cardiopulmonary receptors in man leads to an augmentation of the vasoconstrictor response to isometric exercise is consistent with this view. Studies investigating cardiopulmonary receptor function in patients with heart failure should advance our understanding of the importance of these receptors and their interactions with other reflexes in the heart failure syndrome.

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