Digitalis-induced augmentation of cardiopulmonary baroreflex control of forearm vascular resistance

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ABSTRACT We sought to determine whether digitalis augments cardiopulmonary baroreflex control of forearm vascular resistance in normal young men. Cardiopulmonary baroreceptor input was reduced with lower body negative pressure (LBNP) at 10 and 20 mm Hg, which decreased central venous pressure but did not alter blood pressure or heart rate. Decreases in forearm blood flow and increases in forearm vascular resistance with LBNP were greater after administration of lanatoside C (Cedilanid) than before, and the slope of the regression line relating changes in central venous pressure and those in forearm vascular resistance was steeper after lanatoside C. Vasoconstrictor responses to the cold pressor test did not differ before and after lanatoside C, which suggested that augmented responses to LBNP after the drug were not caused by a generalized change in reflex control. These results suggest that lanatoside C augments the tonic inhibitory influence of cardiopulmonary baroreceptors in normal men.


EVIDENCE from animal studies indicates that digitalis sensitizes arterial and cardiopulmonary baroreceptor reflexes in response to their natural stimuli. Administration of ouabain or acetylpronophilthadin increases the depressor response that can be obtained by stimulation of arterial baroreceptors in the isolated preparations of carotid sinus or aortic arch. Intracoronary injection of acetylpronophilthadin sensitizes vagal cardiopulmonary baroreflex and augments reflex inhibition of renal sympathetic nerve activity in response to volume expansion or coronary occlusion. More recently, it has been shown that the gain of vagal cardiopulmonary baroreflex is augmented by long-term treatment with digoxin.

Sensitization of arterial and cardiopulmonary baroreflexes by digitalis may contribute importantly to the therapeutic effects of this drug. The known vagomimetic effect of digitalis may be accounted for in part by enhancement of arterial baroreflex. Thames et al. suggested that a sensitizing effect of digitalis on cardiopulmonary baroreflex may play an important role in mediating its therapeutic effect in the treatment of heart failure: augmented inhibitory input to the vasomotor center from cardiopulmonary receptors by digitalis may result in a reduction of sympathetic outflow to the kidney, an increase in salt and water excretion, and a reduction in renin secretion in patients with heart failure.

Ferrari et al. showed that lanatoside C (Cedilanid) at a therapeutic dose augments arterial baroreflex in man. However, no study has determined whether digitalis enhances cardiopulmonary baroreflex in man. The results of previous studies suggest that reflex forearm vasoconstriction under lower body negative pressure (LBNP) at 10 to 20 mm Hg is largely mediated by cardiopulmonary baroreflex. At these pressure levels LBNP decreases central venous pressure without altering arterial pressure and heart rate, and thus lowers the inhibitory influence of cardiopulmonary receptors but not of arterial baroreceptors. Thus the purpose of this study was to determine whether digitalis augments forearm vascular response to LBNP at 10 and 20 mm Hg in man.

Methods

**Subjects and procedures.** Seventeen healthy young men (age 20.2 ± 0.3 years, mean ± SE) were studied. The study protocol was explained and informed consent was obtained. Forearm blood flow was measured with a mercury-in-silastic strain-gauge plethysmograph with a venous occlusion technique. The strain gauge was placed approximately 5 cm below
the antecubital crease. The pressure in the venous occlusion or constricting cuff was 40 mm Hg.\textsuperscript{11} Circulation to the hand was arrested by inflating a cuff around the wrist during determination of forearm blood flow. Forearm blood flow was taken as the average of four to eight flow measurements made at 15 sec intervals. The blood pressure was measured in the other arm with a sphygmomanometer. All blood pressure measurements were performed by one individual to minimize observer variation. Forearm vascular resistance was calculated by dividing the mean arterial pressure (diastolic pressure plus one-third of the pulse pressure [mm Hg]) by the forearm blood flow (ml/min/100 ml of forearm volume); these values are expressed as units throughout this article. Heart rate was calculated from an electrocardiogram. Central venous pressure was obtained from a catheter introduced into an antecubital vein and advanced into an intrathoracic vein. The pressure was measured with a pressure transducer (Tokyo Boldwin Limited; MPU 0.5), with the midaxillary line used as a reference level.

Reflex vasoconstriction in the forearm was examined under LBNP. The subject's body below the iliac crest was enclosed in a chamber that was sealed and connected to an adjustable vacuum. LBNP was applied at 10, 20, and 40 mm Hg, which produced graded decreases in central venous pressure and reflex increases in forearm vascular resistance.

To determine whether alteration in responses to LBNP was the result of a nonspecific change in neurogenic control, we assessed responses to another reflex stimulus, the cold pressor test, which was performed by placing an ice cube (2.5 × 2.5 cm) on the forehead for 60 sec. Values of forearm vascular resistance before and at the termination of cold stimulus were compared.

Protocol. The study was performed in a warm, quiet room with the subjects supine and in the postabsorptive state. After the catheter and strain-gauge plethysmograph were placed, at least 15 min was allowed for the subjects to become accustomed to the conditions before beginning the protocol.

Blood pressure, central venous pressure, and forearm blood flow were measured at rest, under LBNP at 10, 20, and 40 mm Hg, and with the cold pressor stimulus before and after administration of lanatoside C (n = 10) or saline (n = 7).

Lanatoside C (0.6 mg) was given intravenously in two divided doses; 0.3 mg was administered initially and blood pressure and electrocardiograms were monitored. Twenty minutes after the initial dose the second 0.3 mg dose of lanatoside C was given. Forty minutes after the second injection (60 min after the initial injection), the measurements were repeated as before administration of the drug.

Calculations and statistical analysis. Calculation of forearm blood flow was done independently by two of the authors from the copied records, and the average value was used for statistical analysis. Calculation was done without knowledge of whether a record was obtained before or after administration of lanatoside C. The slope of the regression line relating changes in central venous pressure and those in forearm vascular resistance was calculated by the least square method. Student’s t test for paired data and two-way analysis of variance were used for statistical analysis, and p < .05 was considered significant. All data are expressed as mean ± SE.

Results

Effects of lanatoside C on resting measurements (table 1). Lanatoside C increased resting systolic blood pressure but did not significantly alter diastolic or mean blood pressure. Resting central venous pressure and heart rate were lower after lanatoside C than before. The drug increased resting forearm blood flow but did not significantly alter resting forearm vascular resistance.

Effects of lanatoside C on responses to LBNP (table 2 and figure 1)

LBNP at 10 and 20 mm Hg. At 10 and 20 mm Hg, LBNP decreased central venous pressure and forearm blood flow and increased forearm vascular resistance before and after lanatoside C. Systolic, diastolic, and mean blood pressure and heart rate did not change significantly either before or after drug. The magnitudes of decreases in central venous pressure did not differ be-

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<td>Resting measurements before and after lanatoside C (n = 10)</td>
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<td><strong>Before</strong></td>
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<td>Central venous pressure (mm Hg)</td>
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<td>Heart rate (beats/min)</td>
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<td>Forearm blood flow (units)</td>
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<td>Forearm vascular resistance (units)</td>
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Statistical comparisons (before vs after drug): \textsuperscript{a}p < .05; \textsuperscript{b}p < .01.

<table>
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<td>Responses to LBNP before and after lanatoside C (n = 10)</td>
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<td><strong>LBNP (mm Hg)</strong></td>
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<td>ΔSystolic blood pressure (mm Hg)</td>
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<td>ΔForearm blood flow (units)</td>
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<td>ΔForearm vascular resistance (units)</td>
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Statistical comparisons: \textsuperscript{a}p < .05 (control vs LBNP); \textsuperscript{b}p < .01 (control vs LBNP); \textsuperscript{c}p < .05 (before vs after drug); \textsuperscript{d}p < .01 (before vs after drug).
fore and after lanatoside C, but decreases in forearm blood flow with LBNP at 10 and 20 mm Hg and increases in forearm vascular resistance with LBNP at 20 mm Hg were greater after lanatoside C than before. The slope of the regression line relating changes in central venous pressure and those in forearm vascular resistance with LBNP was significantly steeper after the drug than before (figure 1).

LBNP at 40 mm Hg (table 2). In contrast to LBNP at 10 and 20 mm Hg, LBNP at 40 mm Hg decreased systolic blood pressure as well as central venous pressure and increased heart rate before and after lanatoside C. Decreases in systolic blood pressure were not different, but decreases in central venous pressure were smaller after the drug than before. Decreases in forearm blood flow were greater and increases in forearm vascular resistance tended to be greater after drug than before.

Responses to cold pressor test (table 3). Changes in systolic and mean blood pressure, forearm blood flow, and forearm vascular resistance during the cold pressor test did not differ significantly before and after lanatoside C.

Effects of saline on resting measurements and responses to LBNP (table 4 and figure 2). Mean blood pressure, forearm blood flow, and forearm vascular resistance at rest and under LBNP at 10, 20, and 40 mm Hg were not different before and after injection of saline. The slope of the regression line relating changes in central venous pressure and those in forearm vascular resistance with LBNP was not different before and after saline (figure 2).

Discussion
The principal finding of this study was that lanatoside C at a therapeutic dose augmented reflex forearm vasoconstriction in response to LBNP at 10 and 20 mm Hg in normal men. In other words, vasoconstrictive responses to reduction in the inhibitory influence of cardiopulmonary receptors with LBNP was augmented after lanatoside C. The slope of the regression line relating changes in central venous pressure and those in forearm vascular resistance was steeper after the drug. These results suggest that lanatoside C augments the gain of the inhibitory influence of the cardiopulmonary receptors in normal men.

There are several questions that should be addressed in interpreting the results. First, we should consider the possibility that augmented reflex forearm vasoconstriction during LBNP at 10 and 20 mm Hg after lanatoside C was caused by nonspecific mechanisms such as a greater reflex stimulus or a difference in baseline central venous pressure or forearm vascular resistance. The magnitudes of decreases in central venous pressure with LBNP at 10 and 20 mm Hg did not differ before and after the drug (table 2), which suggests that levels of reflex stimulus were not different. Baseline central venous pressure was lower after the drug than before (table 1). However, in a previous study in our laboratory the decrease in baseline central venous pressure caused by nitroglycerin did not alter the slope or reflex forearm vasoconstriction with LBNP. Baseline

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<td>Responses to cold pressor stimulus before and after lanatoside C (n = 10)</td>
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<td>Before</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
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<td>Forearm blood flow (ml/min/100 ml)</td>
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<td>Forearm vascular resistance (units)</td>
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Statistical comparisons (control vs cold pressor test): $^a p < .05; ^b p < .01$.
Changes in systolic and mean blood pressure, forearm blood flow, and forearm vascular resistance were not different before and after drug.
forearm vascular resistance may significantly influence vascular responses to reflex sympathetic activation. However, baseline forearm vascular resistance did not differ significantly before and after lanatoside C. Furthermore, reflex vasoconstrictor and pressor responses to cold pressor stimulus did not differ before and after lanatoside C (table 3). Thus it appears that augmented reflex forearm vasoconstriction with LBNP at 10 and 20 mm Hg after lanatoside C was not accounted for by nonspecific mechanisms.

Second, we should consider the possibility that forearm vasoconstriction with LBNP at 10 and 20 mm Hg might be mediated by reflex mechanisms other than cardiopulmonary baroreflex. In particular, we should consider the possible contribution of arterial baroreflex, since it has been shown that digitalis at a therapeutic dose augments arterial baroreflex in man. However, two lines of evidence suggest that arterial baroreflex was unlikely to be involved in the exaggerated response to LBNP at 10 and 20 mm Hg after lanatoside C. First, LBNP at 10 and 20 mm Hg does not increase mean blood pressure or pulse pressure or increase heart rate. Thus these levels of LBNP presumably do not inhibit arterial baroreceptors. Second, available evidence suggests that digitalis augments the vasodilator response to arterial baroreceptor stimulation but not the vasoconstrictor response to arterial baroreceptor deactivation in man.

We should also consider the contribution of somatic receptor reflexes, which are activated by exercise and trigger excitatory reflexes. It has been shown in man that excitatory reflexes mediated by somatic receptor activation is augmented when central venous pressure is lowered. Thus lower central venous pressure after lanatoside C might have caused exaggerated excitatory somatic receptor reflexes. However, subjects were relaxed while under LBNP and did not exercise. Thus it is unlikely that somatic reflexes had a major role in the exaggerated response to LBNP after lanatoside C. It is also unlikely that reflexes originating from the abdominal visceral receptors contributed to the exaggerated response to LBNP after the drug, since the supraspinal influence of these reflexes has been suggested to be inhibitory. It is our view that the reflex forearm vasoconstriction under LBNP at 10 and 20 mm Hg resulted largely from reduction in the tonic inhibitory influence of cardiopulmonary receptors on the vasomotor centers.

![FIGURE 2. Relationship between changes in central venous pressure (ΔCVP) and those in forearm vascular resistance (ΔFoVR) under LBNP at 10, 20, and 40 mm Hg before (open circles) and after (closed circles) saline. The slope of the regression line was not different before (y = -1.6 - 5.4 x, r = .993) and after saline (y = -2.7 - 4.6 x, r = .944) (n = 7).](http://circ.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.109.886732)
We also considered the possibility that the findings observed with lanatoside C might be related to a placebo effect. However, saline did not alter the forearm vascular responses to LBNP or produce a change in the slope of the regression line relating changes in central venous pressure and those in forearm vascular resistance.

On the basis of these considerations we interpret the results to suggest that lanatoside C augments the cardiopulmonary baroreflex in man. As was suggested previously,3, 4 this sensitizing effect of digitalis on cardiopulmonary baroreflex may play an important role in mediating its therapeutic effects in the treatment of patients with heart failure.

Obviously we cannot determine the mechanisms of the digitalis-induced augmentation of cardiopulmonary baroreflex in man from these studies. It has been demonstrated in animal experiments that digitalis sensitizes cardiac receptors.3, 4, 21-23 In addition, the increase in ventricular contractility24, 25 is known to augment the firing of the left ventricular receptors. It is conceivable that, as in animals, these mechanisms have contributed to the digitalis-induced augmentation of cardiopulmonary baroreflex in man.

We should also consider the effect of digitalis on resting vascular resistance and central venous pressure. In our subjects, who were healthy volunteers, we found that lanatoside C increased forearm blood flow and did not significantly alter forearm vascular resistance within 40 min after the administration of the drug. Several studies have shown that digitalis increases systemic as well as forearm vascular resistance in normal men.26, 27 Digitalis has a direct vasoconstrictor effect on arteries and veins,28 and the increase in vascular resistance by digitalis in normal men was considered to be caused by such direct vasoconstrictor effect of the drug.27 However, other studies in men or animals with healthy hearts have demonstrated little or no increase in vascular resistance after digitalis29, 30 or a return of vascular resistance to the control level after initial elevation within 30 to 60 min after administration of digitalis.31-33 The variation in these results may be accounted for by the fact that digitalis sensitizes arterial and cardiopulmonary baroreceptors, which cause sympathetic withdrawal and thus may offset the direct vasoconstrictor action of the drug.32, 33 It has been shown that digitalis exerts the vasodilator effect in patients with heart failure,25 but our subjects had no evidence of cardiac disease or heart failure. We also found that lanatoside C decreased central venous pressure. It has been shown in animals that digitalis tends to reduce venous return by hepatic venoconstriction, which leads to pooling of blood in the portal venous system.34 An increased hepatic venous wedge pressure after digitalis has been observed in patients without heart failure.35

In summary, our results indicate that lanatoside C at a therapeutic dose augments reflex forearm vasoconstriction in response to LBNP at 10 and 20 mm Hg, suggesting that this drug augments the tonic inhibitory influence of cardiopulmonary baroreceptors in normal men.

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