Effects of Digitalis on Cardiopulmonary Baroreflex in Man

AKIRA TAKESHITA, M.D. AND TAKUROH IMAMURA, M.D.*

We examined 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 mmHg which decreased central venous pressure (CVP) but did not alter blood pressure (BP) or heart rate (HR). Decreases in forearm blood flow and increases in forearm vascular resistance with LBNP were greater after 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 cedilanid. Vasoconstrictor responses to a cold pressor test did not differ before and after cedilanid, which suggested that augmented responses to LBNP after cedilanid were not due to a generalized change in reflex control. These results suggest that cedilanid 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.^{1,2} Sensitization of arterial and cardiopulmonary baroreflexes by digitalis may be an important contribution to the therapeutic effects of this drug. Thames et al.^{1,2} suggested that 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 reduction of sympathetic outflow to the kidney, increase in salt and water excretion and reduction in renin secretion in heart failure.

Ferrari et al.³ showed that cedilanid at a therapeutic dose augments arterial baroreflex in man. However, no studies have examined whether digitalis enhances cardiopulmonary baroreflex in man. Previous studies suggest that reflex forearm vasoconstriction during lower body negative pressure (LBNP) at 10 to

20 mmHg is largely mediated by cardiopulmonary baroreflex.⁴ The purpose of this study was to examine whether digitalis augments forearm vascular response to LBNP at 10 and 20 mmHg in man.

METHODS

Seventeen healthy young men (average age 20.2 ± 0.3 years, mean $\pm$ SE) were studied. The study protocol was explained and informed consent was obtained. Forearm blood flow was measured using a mercury-in-silastic strain gauge plethysmograph with a venous occlusion technique as described in detail previously.⁵ Blood pressure was measured in the other arm with a sphygmomanometer. Forearm vascular resistance was calculated by dividing mean arterial pressure (diastolic pressure plus one-third of the pulse pressure in mmHg) by forearm blood flow (ml/min/100 ml of forearm volume); these values are expressed as units throughout this report. Heart rate was calculated from an electrocardiogram. Central venous pressure was obtained from a catheter introduced into an antecubital vein and advanced into an intraathoracic vein. Pressure was measured with a pressure transducer (Toyo Baldwin Limited, MPU 0.5) using the mid-

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*Research Institute of Angiocardiology and Cardiovascular Clinic, Faculty of Medicine, Kyushu University, and
The First Department of Internal Medicine, Miyazaki Medical College, Japan

TABLE I RESPONSES TO LBNP BEFORE AND AFTER CEDILANID (n = 10)

Lower body negative pressure (mmHg)	Before cedilanid			After cedilanid		
	10	20	40	10	20	40
Systolic blood pressure (mmHg)	0.6 ± 0.6	-0.5 ± 0.7	-7.5 ± 1.9**	0.9 ± 0.7	-0.6 ± 1.1	-10.4 ± 3.2*
Diastolic blood pressure (mmHg)	-0.3 ± 1.0	-0.2 ± 0.7	0.7 ± 1.9	1.1 ± 1.1	0.9 ± 1.5	3.1 ± 1.9
Mean blood pressure (mmHg)	-0.7 ± 0.6	-0.5 ± 0.5	-2.3 ± 1.3	1.0 ± 0.8	0.5 ± 1.0	-1.3 ± 1.7
Central venous pressure (mmHg)	-1.3 ± 0.2*	-4.2 ± 0.4**	-7.3 ± 0.7**	-1.4 ± 0.2**	-3.5 ± 0.4**	-6.1 ± 0.6***
Heart rate (beats per minute)	-2.0 ± 1.4	-0.7 ± 1.4	6.6 ± 3.1	0.8 ± 0.9	2.1 ± 1.1*	7.8 ± 2.8*
Forearm blood flow (units)	-0.8 ± 0.2*	-1.6 ± 0.3**	-2.5 ± 0.4**	-1.9 ± 0.6**	-2.9 ± 0.6**	-4.1 ± 0.7**
Forearm vascular resistance (units)	4.8 ± 1.4*	13.1 ± 2.8**	24.4 ± 4.2**	9.2 ± 2.6*	23.6 ± 5.4**	45.2 ± 12.6**

* = $p < 0.05$ (control vs during LBNP); ** = $p < 0.01$ (control vs during LBNP)
 * = $p < 0.05$ (before vs after cedilanid); ** = $p < 0.01$ (before vs after cedilanid)

axillar line as a reference level.

Reflex vasoconstriction in the forearm was examined during lower body negative pressure (LBNP) as described previously.⁶ LBNP was applied at 10, 20 and 40 mmHg which produced graded decreases in central venous pressure and reflex increases in forearm vascular resistance. Blood pressure, central venous pressure and forearm blood flow were measured at rest, during LBNP at 10, 20 and 40 mmHg and with cold pressor stimulus before and after administration of cedilanid, 0.6 mg, (n = 10) or saline (n = 7).

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

The slope of regression line relating changes in central venous pressure and those in forearm vascular resistance was calculated using the least square method. Paired Student's t test and two way analysis of variance were used for statistical analysis, and $p < 0.05$ was considered significant. All data are expressed as mean ± standard error (SE).

RESULTS

Effects of Cedilanid on Resting Measurements

Cedilanid increased ($p < 0.01$) resting systolic blood pressure (118 ± 2 mmHg before vs 128 ± 2 mmHg after) but did not significantly alter diastolic or mean blood pressure. Resting central venous pressure (CVP) and heart rate (HR) were lower ($p < 0.01$) after cedilanid than before (CVP 3.2 ± 1.4 vs 1.7 ± 1.1 mmHg and HR 58.7 ± 3.4 vs 55.0 ± 2.8 beats/min). Cedilanid increased ($p < 0.05$) resting forearm blood flow (4.2 ± 0.4 vs 5.5 ± 0.8 ml/min/100 gm) but did not significantly alter resting forearm vascular resistance.

Effects of Cedilanid on Responses to LBNP (Table I)

LBNP at 10 and 20 mmHg

At 10 and 20 mmHg levels, LBNP decreased central venous pressure and forearm blood flow and increased forearm vascular resistance both before and after cedilanid. Systolic, diastolic

and mean blood pressure and heart rate did not change significantly either before or after cedilanid. The magnitude of decreases in central venous pressure did not differ before and after cedilanid but decreases in forearm blood flow with LBNP at 10 and 20 mmHg and increases in forearm vascular resistance with LBNP at 20 mmHg were greater after cedilanid 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 ($p < 0.05$) after cedilanid ($y = -0.8 - 7.4x$, $r = 0.998$) than before ($y = 0.1 - 3.3x$, $r = 0.998$).

LBNP at 40 mmHg (Table I)

In contrast to LBNP at 10 and 20 mmHg, LBNP at this level decreased systolic blood pressure as well as central venous pressure and increased heart rate both before and after cedilanid. Decreases in systolic blood pressure were not different but decreases in central venous pressure were less after cedilanid than before. Decreases in forearm blood flow were greater and increases in forearm vascular resistance tended to be greater after cedilanid than before.

Responses to Cold Pressor Test

Changes in mean blood pressure (5.2 ± 1.0 vs 3.8 ± 1.1 mmHg), forearm blood flow (-0.8 ± 0.3 vs -1.5 ± 0.5 ml/min/100 gm) and forearm vascular resistance (9.6 ± 2.9 vs 9.6 ± 3.8 unit) during cold pressor test did not differ significantly before and after cedilanid.

Effects of Saline on Resting Measurements and Responses to LBNP

Mean blood pressure, forearm blood flow and forearm vascular resistance at rest and during LBNP at 10, 20 and 40 mmHg were not different before and after saline injection. The slope of the regression line relating changes in central venous pressure and those in forearm vascular resistance with LBNP was not different before ($y = -6.5 - 5.4x$, $r = 0.993$) and after ($y = -2.7 - 4.6x$, $r = 0.944$) saline injection.

DISCUSSION

The principal finding of this study was that cedilanid at a therapeutic dose augmented reflex forearm vasoconstriction in response to LBNP at 10 and 20 mmHg in normal men. In other words, vasoconstricting responses to reduction of

the inhibitory influence of cardiopulmonary receptors with LBNP were augmented after cedilanid. The slope of the regression line relating changes in central venous pressure and those in forearm vascular resistance was steeper after cedilanid. These results suggest that cedilanid augments the gain of the inhibitory influence of cardiopulmonary receptors in normal men.

There are several questions which should be addressed in interpreting the results. First, we should consider the possibility that augmented reflex forearm vasoconstriction during LBNP at 10 and 20 mmHg after cedilanid was caused by nonspecific mechanisms such as a greater reflex stimulus or a difference in baseline central venous pressure or forearm vascular resistance. The magnitude of decreases in central venous pressure with LBNP at 10 and 20 mmHg did not differ before and after cedilanid (Table I), which suggests that levels of reflex stimulus were not different. Baseline central venous pressure was lower after cedilanid than before. However, in a previous study in our laboratory, decrease in baseline central venous pressure by nitroglycerin did not alter the slope or reflex forearm vasoconstriction with LBNP.⁶ Baseline forearm vascular resistance may significantly influence vascular responses to reflex sympathetic activation.⁷ However, baseline forearm vascular resistance did not significantly differ before and after cedilanid. Furthermore, reflex vasoconstrictor and pressor responses to cold pressor stimulus did not differ before and after cedilanid. It appears that augmented reflex forearm vasoconstriction with LBNP at 10 and 20 mmHg after cedilanid was not accounted for by nonspecific mechanisms.

Second, we should consider the possibility that forearm vasoconstriction with LBNP at 10 and 20 mmHg might be mediated by reflex mechanisms other than cardiopulmonary baroreflex. In particular, we should consider possible contribution of arterial baroreflex since it is shown that digitalis at a therapeutic dose augments arterial baroreflex in man.³ However, two lines of evidence suggest that arterial baroreflex is unlikely to be involved in the exaggerated response to LBNP at 10 and 20 mmHg after cedilanid. First, LBNP at 10 and 20 mmHg does not decrease mean blood pressure or pulse pressure or increase heart rate.⁴ 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.³

We also considered the possibility that observed findings with cedilanid might be related to a placebo effect. However, saline did not alter the forearm vascular responses to LBNP or the slope of the regression line relating changes in central venous pressure and those in forearm vascular resistance.

Based on these considerations we interpret the results to suggest that cedilanid augments the cardiopulmonary baroreflex in man. As was suggested previously,^{1,2} this sensitizing effect of digitalis on cardiopulmonary baroreflex may play an important role in mediating its therapeutic effect in the treatment of heart failure.

Obviously, we can not determine the mechanisms of digitalis-induced augmentation of cardiopulmonary baroreflex in man from these studies. It is demonstrated in animal experiments that digitalis sensitizes cardiac receptors.^{1,2} In addition, increase in ventricular contractility⁸ is known to augment 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.

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