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CLINICAL INVESTIGATION

Selective impairment of baroreflex-mediated vasoconstrictor responses in patients with ventricular dysfunction

DAVID W. FERGUSON, M.D., FRANCOIS M. ABBOUD, M.D., AND ALLYN L. MARK, M.D.

ABSTRACT Cardiac dysfunction in animals has been associated with impairment of arterial and cardiopulmonary baroreflex control of the circulation. Chronic heart failure in human beings is associated with neurohumoral excitation, which could result in part from impairment in the inhibitory influence of baroreflexes. We postulated that (1) patients with left ventricular dysfunction (LVD) have impaired baroreflex modulation of vascular resistance and (2) administration of a digitalis glycoside would immediately restore baroreflex sensitivity. Eleven patients with LVD (NYHA class, 2.8 ± 0.2, mean ± SEM; baseline left ventricular ejection fraction, 18 ± 2%; cardiac index, 2.4 ± 0.2 l/min/m^2; and pulmonary capillary wedge pressure, 26.0 ± 3.2 mm Hg) were compared with 17 normal control subjects. We measured forearm vasoconstrictor responses to simulated orthostatic stress with use of lower body negative pressure (LBNP) at −10 and −40 mm Hg to unload cardiopulmonary and arterial baroreceptors. Baseline forearm vascular resistance (FVR) was higher in patients with LVD than in normal subjects: FVR_{LVD}, 68.8 ± 15.3 U; FVR_N, 23.2 ± 2.1 U ($p < .001$). During unloading of baroreceptors with LBNP −10 mm Hg, normal subjects developed vasoconstriction (ΔVR_N at LBNP −10 mm Hg, +5.7 ± 1.6 U) but patients with LVD failed to have vasoconstriction and tended to develop vasodilation (ΔFVR_{LVD} at LBNP −10 mm Hg, −8.6 ± 8.5 U) ($p = .05$, normals vs patients with LVD at LBNP −10 mm Hg). A more marked disparity in response was seen during unloading of baroreceptors at LBNP −40 mm Hg: ΔFVR_N at LBNP −40 mm Hg, +16.6 ± 1.5 U; ΔFVR_{LVD} at LBNP −40 mm Hg, −10.3 ± 9.6 U ($p < .001$, normals vs patients with LVD). Despite high baseline values for FVR, patients with LVD developed vasoconstriction during intra-arterial infusions of norepinephrine, thereby excluding a nonspecific depression of vascular reactivity as the mechanism for abnormal responses to LBNP in patients with LVD. We also studied the short-term effects of administration of a digitalis glycoside, ouabain 0.0075 mg/kg (seven patients) or lanatoside C (Cedilanid-D) 0.02 mg/kg (three patients), on baroreflex-mediated vasoconstrictor responses to LBNP in the patients with LVD. Digitalis glycoside reduced baseline FVR from 71.8 ± 16.6 to 48.6 ± 12.0 U ($p < .02$). Responses to LBNP tended to be normalized after administration of digitalis glycoside: ΔFVR during LBNP −40 mm Hg, −11.1 ± 10.5 U before and +7.8 ± 5.6 U after the drug ($p < .05$). Thus patients with LVD show selective impairment of baroreflex-mediated vasoconstrictor responses to unloading of baroreceptors by simulated orthostatic stress. This does not appear to be caused by high baseline vascular resistance or decreased vascular responsiveness. This response is immediately normalized by administration of a digitalis glycoside, possibly because of baroreceptor sensitization.
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From the Cardiovascular and Clinical Research Centers, Department of Internal Medicine, University of Iowa College of Medicine, University of Iowa Hospitals and VA Medical Center, Iowa City.

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Address for correspondence: David W. Ferguson, M.D., Cardiovascular Division, Department of Internal Medicine, University of Iowa Hospital, Iowa City, IA 52242.

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Dr. Ferguson was the recipient of the Merck Foundation Fellowship of the American College of Cardiology (1982–83) and is a Clinician-Scientist of the American Heart Association (1983–86).

AUTONOMIC CONTROL of the heart and peripheral circulation is regulated by afferent neural mechanisms that interact with the medullary cardiovascular centers. An inhibitory influence on sympathetic efferent outflow from these centers is exerted by activation of arterial and cardiopulmonary baroreceptors in normal human beings.[1] In animals, cardiac dysfunction has been associated with impairment of both arterial and cardiopulmonary baroreflex control of the systemic circulation.[2–4] These abnormalities lead to a reduction

in baroreflex-mediated inhibition of the vasomotor centers and a consequent increase in neurohumoral drive. In human beings, heart failure has also been associated with neurohumoral excitation characterized by increased circulating levels of norepinephrine, increased plasma renin activity, and increased levels of vasopressin and angiotensin.[5–10] In addition, patients with heart failure have been demonstrated to have abnormal vascular responses to postural changes,[11, 12] but the mechanisms underlying these abnormalities remain unclear.

This study was undertaken to test the hypothesis that the presence of moderately severe ventricular dysfunction in human beings is associated with attenuation of cardiopulmonary and arterial baroreflex afferent activity resulting in an increased neurohumoral drive. This impairment would be associated with the loss of the normal forearm vasoconstrictor response to unloading of cardiopulmonary and arterial baroreceptors by lower body negative pressure (LBNP). We further hypothesized that, as seen in animal preparations,[13–17] the administration of a digitalis glycoside will sensitize the baroreceptors and augment baroreflex mechanisms.

Methods

Patient selection. Eleven patients with moderate-to-severe left ventricular dysfunction (defined by radionuclide ventriculography as left ventricular ejection fraction of 30% or less and typical symptoms of impaired cardiac performance) formed the study group. All patients were men, ages 22 to 57 years (37.0 ± 3.6 years, mean ± SE), and had supporting clinical, roentgenographic, and/or echocardiographic evidence of impaired ventricular function. Severity of cardiac disease ranged from class II to class IV by New York Heart Association functional classification, and the cause of the left ventricular impairment was ischemic, viral, or idiopathic cardiomyopathy. No patient was studied within 1 month of a myocardial infarction. Digitalis glycosides were withheld for a minimum of 10 days before study and this was confirmed by a negative serum assay for digitalis the day before the study began. All other medications were withheld for 24 hr under close observation. On admission, all patients underwent evaluation of blood counts and chemistries; chest x-rays, echocardiograms, and electrocardiograms were also obtained. All patients were in sinus rhythm. A resting gated radionuclide ventriculogram was obtained from all subjects within 10 days before study. All patients had normal electrolytes and blood counts. Informed written consent was obtained from all patients and the research protocol was approved by the Human Subjects Review Committee of the University of Iowa. The patients were studied in the supine postabsorptive state.

Procedures. On the morning of testing, the patients were initially taken to the cardiac catheterization laboratory for placement of hemodynamic monitoring catheters under flouroscopic visualization. A No. 7F triple-lumen thermodilution Swan-Ganz catheter was placed percutaneously with patients under local anesthesia with 1% lidocaine through a peripheral arm or subclavian vein, and a No. 5F polyethylene arterial catheter was placed percutaneously in a brachial artery. Right heart and arterial pressures were recorded on a Siemens mingograph 804 recorder, and cardiac output was determined by thermodilution (five measurements) with an Edwards 9520A thermodilution cardiac output computer. Baseline hemodynamics were recorded and included arterial pressure, right heart pressures, and cardiac index. Systemic vascular resistance (dyne-sec-cm^{-5}) was calculated as: (mean arterial pressure minus right atrial pressure)/(cardiac output) × 80. After placement of the monitoring lines, the patients were transferred to the adjacent human clinical physiology laboratory for a 30 min rest period, during which they were familiarized with the protocol.

Arterial and pulmonary arterial pressures were continuously measured with a Statham P231D pressure transducer and recorded simultaneously with heart rate and forearm blood flow on a direct-writing Gould physiologic (2800S) recorder. Cardiac output was determined in triplicate during control periods, with the average value used for calculation.

Forearm blood flow was measured by venous occlusion plethysmography with a mercury-in-silastic Whitney strain gauge as previously described.[18, 19] 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 arm was 40 mm Hg. Circulation to the hand of this arm was arrested by inflating a cuff around the wrist to 180 mm Hg during determination of forearm blood flow.

Forearm vascular resistance (FVR) was calculated by dividing mean arterial pressure (diastolic pressure plus one-third of pulse pressure [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 article.

LBNP was used to simulate orthostatic stress by placing a chamber over the patient's body below the iliac crest.[20] During study periods, measurements of forearm blood flow were recorded every 15 sec and blood pressure was determined continuously during 90 sec of baseline conditions and then during sequential LBNP at −10 and −40 mm Hg for 90 sec each. Values of forearm blood flow were taken as the average of the flows during the last 60 sec of each control or intervention period.

Responses to the cold pressor stimulus were determined in six of the patients by immersion of the patient's free hand in ice water for 90 sec while blood pressure and forearm blood flow were determined as described above. The cold pressor test was used to assess responsiveness to another reflex stimulus and thereby to determine whether abnormal responses to LBNP were specific or were a manifestation of a generalized alteration in responsiveness to reflex stimuli.

The forearm vasoconstrictor response to local intra-arterial infusion of norepinephrine was evaluated in eight patients. Forearm blood flow was measured before and during 4 min of brachial arterial infusion of norepinephrine at 37.5 ng/min in 5% dextrose in water by means of a Harvard continuous nonpulsatile pump. The total volume of infusate was less than 0.4 ml/min; no measurable changes in forearm blood flow are observed during infusion of vehicle into the brachial artery at these rates.[21]

Protocol. The study was begun after a 30 min rest period during which the patients were familiarized with the techniques. After baseline measurements of forearm blood flow, heart rate, arterial and pulmonary artery pressure, and cardiac output were performed, we studied responses to LBNP at −10 and −40 mm Hg, cold pressor test, and intra-arterial infusion of norepinephrine. Interventions were performed in random order. Ten patients were then given an intravenous, rapidly acting digitalis glycoside. Seven patients received 0.0075 mg/kg ouabain (Eli Lilly and Co.). Because of lack of continued availability of

ouabain, three patients received 0.02 mg/kg lanatoside C (Cedilanid-D; Sandoz Pharmaceuticals). The drugs were administered over 10 min. After a 20 min rest period, baseline hemodynamics and responses to LBNP were repeated.

Control subjects. Similar but less invasive studies were performed in 17 normal male volunteers, ages 24.5 ± 1.0 years (range 19 to 34). The subjects were free of cardiovascular disease on the basis of medical history, physical examination, and echocardiographic studies and were not receiving any medication at the time of the study. Arterial pressure was determined by brachial or radial arterial cannulas placed with patients under local anesthesia, and central venous pressure was determined by an 18.5 gauge polyethylene catheter inserted percutaneously in a median antecubital vein and advanced to an intrathoracic position. Forearm blood flow responses to baroreceptor unloading with LBNP were performed as described above.

Statistical analysis. Comparisons between normal control subjects and patients with LVD were performed by the Wilcoxon rank-sum test. Intragroup comparisons were performed by the Wilcoxon signed-rank test. Values in the text, figures, and tables are expressed as mean ± SEM. Statistical significance was taken as $p < .05$.

Results

Characteristics of patients with LVD. The clinical characteristics and resting hemodynamics for the 11 patients with LVD are shown in tables 1 and 2. The cause of the LVD was ischemic cardiomyopathy in six patients, viral cardiomyopathy in two, and idiopathic congestive cardiomyopathy in three. All patients had had classic symptoms of impaired ventricular performance (dyspnea, fatigue, orthopnea, or paroxysmal nocturnal dyspnea) for at least 1 month (mean 3.3 months) before the study. All patients had cardiomegaly by roentgenographic or echocardiographic criteria. Moderate-to-marked impairment of resting left ventricular systolic function was demonstrated by echocardiography (minor axis dimension change, 0.13 ± 0.03; normal, 0.28 to 0.41) and radionuclide ventriculography (left ventricular ejection fraction, 17.8 ± 1.7%; normal >50%).

Hemodynamic measurements confirmed moderate-to-severe impairment in resting cardiac performance (heart rate, 102.8 ± 5.4 beats/min; cardiac index, 2.4 ± 0.2 l/min/m^2; right ventricular end-diastolic pressure, 10.8 ± 2.1 mm Hg; mean pulmonary artery pressure, 33.6 ± 3.6 mm Hg; mean pulmonary capillary wedge pressure, 26.0 ± 3.2 mm Hg; and systemic vascular resistance, 1420 ± 116 dyne-sec-cm^{-5}.

Responses to baroreceptor unloading with LBNP: comparison of patients with LVD to normal subjects. Figure 1 and table 3 summarize the peripheral vascular responses to unloading of baroreceptors with LBNP and compare the responses of normal subjects with those of patients with LVD. In normal subjects, LBNP −10 mm Hg produced an increase in FVR from a control value of 23.2 ± 2.1 U to 29.0 ± 3.2 U ($p < .01$), and LBNP −40 mm Hg produced a further vasoconstrictive response with FVR increasing to 39.8 ± 2.7 U (p

TABLE 1
Clinical characteristics of patients with LVD

Demographic data						Noninvasive diagnostic data				
							Echocardiogram			
Patient No.	Sex	Age (yr)	Clinical diagnosis	Duration of symptoms (mo)	NYHA class	CXR (CT ratio)	LVEDD (cm)	ΔD	EPSS (cm)	RNV-LVEF (%)
1	M	52	IHD:AMI,IMI	1.0	3	0.51	7.3	0.11	1.5	30
2	M	35	IHD:AMI	2.0	3	0.43	7.0	0.17	2.3	23
3	M	38	IHD:AMI,LatMI	1.5	3	0.53	—	—	2.2	17
4	M	52	IHD:AMI	1.3	2	0.51	6.2	0.23	1.0	22
5	M	30	Prob. VCM	4.0	4	0.63	5.4	0.07	2.0	12
6	M	22	CCM	1.5	2	0.54	6.8	0.03	2.3	15
7	M	23	VCM	14.0	4	0.63	8.0	—	2.4	22
8	M	35	IHD:AMI	2.5	3	0.54	6.3	0.24	0.8	15
9	M	29	CCM	1.0	2	0.52	5.9	0.12	2.6	16
10	M	57	IHD:AMI	1.0	3	0.56	—	—	—	13
11	M	34	CCM	6.0	2	0.63	8.0	0.06	3.5	11
Mean		37.0		3.3	2.8	0.55	6.8	0.13	2.1	17.8
±SEM		±3.6		±1.2	±0.2	±0.02	±0.3	±0.03	±0.3	±1.7

LVD = left ventricular dysfunction; CXR = chest x-ray; RNV = radionuclide ventriculogram; NYHA = New York Heart Association; CT = cardiothoracic; LVEDD = left ventricular end-diastolic dimension (normal 3.5 to 5.7 cm); ΔD = minor axis dimension change (normal 0.28 to 0.41); EPSS = E-point septal separation (normal < 0.5 cm); LVEF = left ventricular ejection fraction; IHD = ischemic heart disease; AMI = anterior wall myocardial infarction; IMI = inferior wall myocardial infarction; LatMI = lateral wall myocardial infarction; VCM = viral cardiomyopathy; CCM = congestive cardiomyopathy of unclear etiology.

TABLE 2
Resting hemodynamic characteristics of patients with LVD

Patient No.	HR (bpm)	MAP (mm Hg)	CI (l/min/m^2)	SVI (ml/m^2)	$\overline{RAP}$ (mm Hg)	RVEDP (mm Hg)	$\overline{PAP}$ (mm Hg)	$\overline{PCWP}$ (mm Hg)	SVR (dyne-sec-cm^{-5})
1	81	80	2.8	34	9	10	27	22	1033
2	90	86	3.5	39	0	2	12	5	983
3	112	77	2.0	18	7	11	42	33	1333
4	65	88	2.3	35	1	2	13	8	1785
5	126	97	1.5	12	22	22	38	30	2143
6	109	82	1.8	16	8	11	31	25	1741
7	122	91	2.2	18	24	19	44	39	1218
8	100	98	3.2	32	4	4	37	26	1253
9	103	86	3.0	29	8	10	38	31	1200
10	112	91	2.8	25	10	9	44	33	1117
11	111	90	1.6	14	15	19	44	34	1818
Mean	102.8	87.8	2.4	24.7	9.8	10.8	33.6	26.0	1420
±SEM	±5.4	±2.0	±0.2	±2.9	±2.3	±2.1	±3.6	±3.2	±116

LVD = left ventricular dysfunction; HR = heart rate; MAP = mean arterial pressure; CI = cardiac index; SVI = stroke volume index; $\overline{RAP}$ = mean right atrial pressure; RVEDP = right ventricular end-diastolic pressure; $\overline{PAP}$ = mean pulmonary artery pressure; $\overline{PCWP}$ = mean pulmonary capillary wedge pressure; SVR = systemic vascular resistance.

< .001 compared with control). In contrast, the patients with LVD had a higher control FVR value of 68.8 ± 15.3 U ($p < .001$ compared with control level in normal subjects) and showed no vasoconstriction during LBNP −10 mm Hg. Indeed, FVR tended to decrease during LBNP −10 mm Hg (60.2 ± 8.9 U) and during LBNP −40 mm Hg (58.5 ± 8.5 U). Comparison of the responses to LBNP −10 mm Hg showed a difference between normal subjects and patients with LVD: ΔFVR at LBNP −10 mm Hg, +5.7 ± 1.6 U for normal subjects; −8.6 ± 8.5 U for patients with LVD ($p = .05$). These differences were more pronounced during LBNP −40 mm Hg: ΔFVR at LBNP −40 mm Hg, +16.6 ± 1.5 U for normal subjects; −10.3 ± 9.6 U for patients with LVD ($p < .001$). This absence of vasoconstriction in patients with LVD was observed despite a fall in left ventricular filling pressure (pulmonary artery diastolic pressure) from a control value of 28.7 ± 2.5 to 24.2 ± 2.9 mm Hg during LBNP −10 mm Hg ($p < .01$) and 17.0 ± 3.8 mm Hg during LBNP −40 mm Hg ($p < .01$ compared with control). Mean arterial pressure did not decrease during LBNP −10 mm Hg (89.3 ± 1.6 mm Hg at control to 88.3 ± 2.1 mm Hg during LBNP −10 mm Hg) but decreased significantly to 83.5 ± 1.7 mm Hg during LBNP −40 mm Hg ($p < .01$ compared with control).

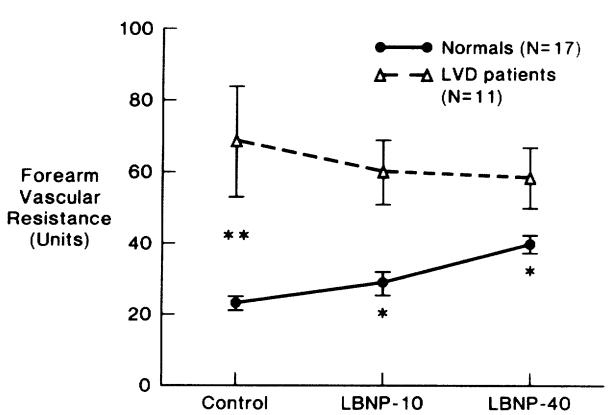

FIGURE 1. Responses of normal subjects and patients with LVD to LBNP at −10 and −40 mm Hg. Control FVR was significantly higher in patients with LVD compared with normal subjects. Normal subjects had significant vasoconstriction at LBNP −10 and −40 mm Hg. In contrast, patients with LVD had no vasoconstriction and tended to experience vasodilation during LBNP. Values are mean ± SEM. * $p <$ .01 vs control; ** $p < .01$ normal vs LVD.

Although vasoconstriction was not observed in the patients with LVD during LBNP, some of the patients actually showed a paradoxic vasodilator response to the simulated orthostatic stress produced by LBNP. As seen in table 3, three of the patients (Nos. 3, 7, and 11) showed vasodilatation during one or both levels of LBNP, defined as a 20% fall in FVR over control values. Two other patients (Nos. 2 and 6) demonstrated a withdrawal of forearm vasomotor tone during LBNP, defined as no change in FVR despite a drop in mean arterial pressure. Thus five of the 11 patients with LVD demonstrated a paradoxic forearm vascular response (vasodilation or withdrawal of vasomotor tone) during unloading of baroreceptors with LBNP.

Responses to cold pressor stimulus and intraarterial infusion of norepinephrine. Six of the patients with LVD underwent cold pressor stimulation and eight underwent intra-arterial infusion of norepinephrine. These responses are summarized in figure 2. Intra-arterial infusion of norepinephrine at 37.5 ng/min for 4 min

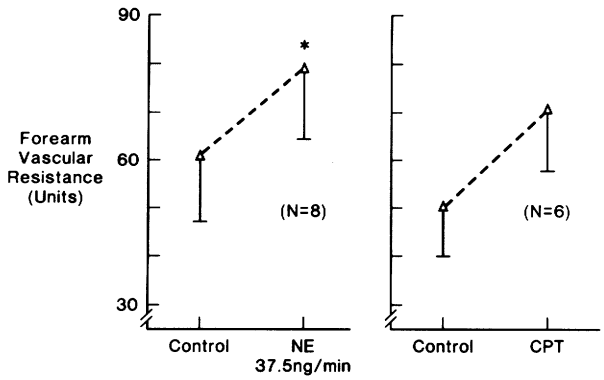

FIGURE 2. Responses of patients with LVD to intra-arterial infusion of norepinephrine (NE) and cold pressor test (CPT). Patients with LVD had significant vasoconstriction during NE infusion and tended to have vasoconstriction during CPT, but the results were not significant ($p = .14$). Values are mean ± SEM. * $p < .05$ NE vs control.

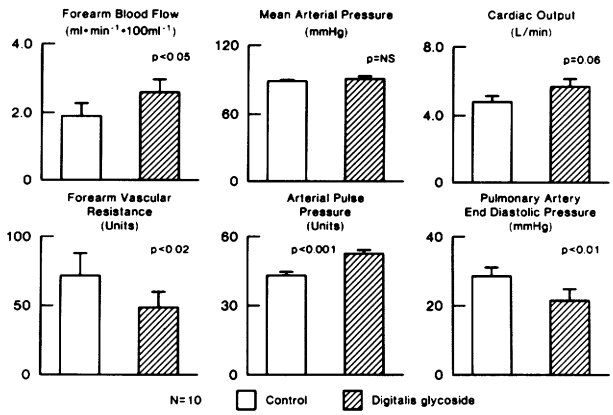

FIGURE 3. Effects of digitalis glycoside on baseline hemodynamics in 10 patients with LVD. Forearm blood flow significantly increased and FVR significantly fell after digitalis. Arterial pulse pressure significantly increased and there was a tendency for an increase in cardiac output after digitalis. There was no change in mean arterial pressure, and although not shown in the figure, there was no change in heart rate after administration of digitalis (97.8 ± 6.3 beats/min before vs 93.9 ± 6.5 beats/min after digitalis). Values are mean ± SEM.

resulted in a significant increase in FVR from a control value of 61.1 ± 13.8 U to 79.3 ± 14.6 U ($p < .03$). There was no evidence of a systemic pressor effect at this dose of norepinephrine. The cold pressor stimulus tended to result in forearm vasoconstriction, with an increase in FVR from a control value of 50.5 ± 10.1 U to 71.0 ± 13.0 U during immersion of the hand in ice water. Although these results did not achieve statistical significance ($p = .14$), four of the six patients had an increase in FVR of 47% or greater.

Effects of digitalis glycoside on responses to baroreceptor unloading in patients with LVD. Ten of the patients with LVD received a rapidly acting intravenous digitalis glycoside (ouabain or lanatoside C), and their control hemodynamic values and reflex responses to LBNP were compared before and after the drug. These results are summarized in figures 3 and 4.

After digitalis glycoside there was no significant change in control mean arterial pressure or heart rate; however, there was a significant fall in control FVR from 71.8 ± 16.6 to 48.6 ± 12.0 U ($p < .02$) associated with an increase in forearm blood flow from 1.9 ± 0.4 to 2.6 ± 0.4 ml·min^{-1}·100 ml^{-1} ($p < .05$). In addition, pulmonary arterial end-diastolic pressure fell from a control value of 28.6 ± 2.8 mm Hg to 21.5 ± 3.6 mm Hg after digitalis glycoside ($p < .01$) and there was an increase in arterial pulse pressure from 43.2 ± 1.9 to 52.6 ± 2.0 mm Hg ($p < .001$). In addition, there was a tendency for an increase in resting cardiac output from 4.8 ± 0.4 l/min before to 5.7 ± 0.5 l/min after digitalis ($p = .06$) (figure 3).

Reflex vascular responses to baroreceptor unloading with LBNP −10 mm Hg tended to be altered by digitalis glycoside (ΔFVR at LBNP −10 mm Hg, −9.2 ± 9.4 U before vs +3.0 ± 6.8 U after), but this difference was not statistically significant. There was, however, a significant reversal in responses to LBNP −40 mm Hg: ΔFVR at LBNP −40 mm Hg, −11.1 ± 10.5 U before digitalis vs + 7.8 ± 5.6 U after ($p < .05$) (figure 4).

Discussion

This study demonstrates that patients with LVD have abnormalities in control of the peripheral circulation during simulated orthostatic stress. This abnormality appears to be caused by selective impairment of cardiopulmonary and/or arterial baroreflexes and is immediately reversed by the administration of a digitalis glycoside.

Although previous studies have noted abnormal pe-

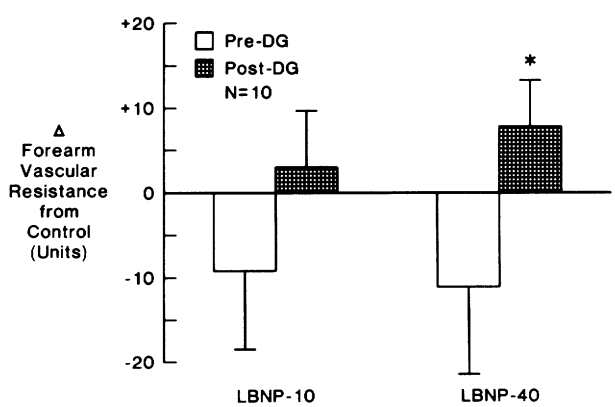

FIGURE 4. Effects of digitalis glycoside (DG) on reflex forearm vascular responses to LBNP at −10 and −40 mm Hg in patients with LVD. Digitalis tended to reverse the vasodilator response to LBNP −10 mm Hg ($p = .05$) and significantly reversed the vasodilation response to LBNP −40 mm Hg, resulting in forearm vasoconstriction. Values are mean ± SEM. * $p < .05$.

TABLE 3
Responses of normal subjects and patients with LVD to LBNP

	Forearm blood flow (ml·min^{-1}·100 ml^{-1})			FVR (U)			Arterial pulse pressure (mm Hg)			Mean arterial pressure (mm Hg)		
	C	−10	−40	C	−10	−40	C	−10	−40	C	−10	−40
Normal subject No.												
1	5.0	4.9	3.2	18.4	18.8	27.2	50	50	35	92	92	87
2	3.5	2.9	1.9	22.9	25.5	43.2	42	42	30	80	74	82
3	3.1	2.4	1.5	24.8	32.5	48.7	65	55	55	77	78	73
4	4.4	3.3	1.7	20.5	27.3	42.9	60	55	25	90	90	73
5	1.7	1.2	1.2	51.2	72.5	73.3	64	65	55	87	87	88
6	3.7	3.2	2.0	23.5	26.9	42.5	59	56	32	87	86	85
7	3.1	2.3	2.2	29.7	40.0	39.5	65	65	52	92	92	87
8	4.3	2.4	1.7	22.3	39.6	51.8	56	50	44	96	95	88
9	3.2	2.6	2.5	28.8	35.8	36.8	65	63	55	92	93	92
10	9.2	5.0	3.3	11.1	21.0	32.7	52	45	38	102	105	108
11	3.9	4.4	2.2	21.5	19.3	35.5	42	44	40	84	85	78
12	3.8	4.5	2.3	27.4	23.6	42.2	92	92	65	104	106	97
13	5.0	4.2	2.7	16.4	19.5	30.4	65	65	50	82	82	82
14	4.6	4.1	3.2	17.0	19.0	23.8	53	53	47	78	78	76
15	2.6	2.4	1.7	23.8	25.8	36.5	53	54	45	62	62	62
16	4.7	4.1	2.9	21.1	24.9	35.5	57	52	40	99	102	103
17	7.0	5.0	2.9	14.6	20.4	34.5	80	80	75	102	102	100
Mean	4.3	3.5[B]	2.3[B]	23.2	29.0[B]	39.8[B]	60.0	58.0[A]	46.1[B]	88.6	88.8	85.9
±SEM	±0.4	±0.3	±0.2	±2.1	±3.2	±2.7	±3.0	±3.1	±3.1	±2.6	±2.9	±2.9
LVD patient No.												
1	2.9	2.7	2.5	28.6	31.1	31.6	40	43	41	83	84	79
2	3.2	3.1	3.0	31.9	31.9	30.3	50	51	43	102	99	91
3	1.7	2.0	1.7	51.8	41.0	47.1	53	52	45	88	82	80
4	1.6	1.6	1.5	55.6	56.3	58.7	47	45	41	89	90	88
5	1.0	1.1	0.9	93.0	89.1	97.8	38	33	40	93	98	88
6	1.4	1.1	1.3	59.3	70.0	56.2	38	35	40	83	77	73
7	0.5	0.9	1.1	174.0	92.2	76.4	35	40	47	87	83	84
8	3.8	2.9	2.6	22.6	29.3	33.5	39	37	35	86	85	87
9	1.8	1.3	1.3	48.3	69.2	60.0	46	45	40	87	90	78
10	2.4	2.5	2.3	38.3	36.0	35.2	50	49	43	92	90	81
11	0.6	0.8	0.8	153.3	116.3	116.3	46	44	45	92	93	90
Mean	1.9	1.8	1.7	68.8	60.2	58.5	43.8	43.1	41.8	89.3	88.3	83.5[B]
±SEM	±0.3	±0.3	±0.2	±15.3	±8.9	±8.5	±1.8	±1.9	±1.0	±1.6	±2.1	±1.7

PAEDP = pulmonary artery end-diastolic pressure; CVP = central venous pressure; C = control; −10 = LBNP at −10 mm Hg; −40 = LBNP at −40 mm Hg.

Statistical comparisons: [A]$p < .05$; [B]$p < .01$ for LBNP vs control.

ripheral vascular responses to upright posture in patients with heart failure,[11, 12] the mechanisms responsible for these findings have remained unclear. This study is unique in that we have attempted to determine the mechanisms responsible for these impaired reflex vascular responses to orthostatic stress by studying responses of these same patients to intra-arterial infusions of norepinephrine and to the cold pressor stimulus. In addition, we have also examined patients with LVD who are not receiving digitalis glycosides. This appears to be important, since studies in animals have suggested that digitalis alters arterial and cardiopulmonary baroreceptor function (see below). Finally, although previous investigators have reported the effects of a digitalis glycoside on resting hemodynamics in patients with heart failure,[22] we have examined the

TABLE 3
(Continued)

PAEDP (LVD) or CVP (normal) (mm Hg)			Heart rate (bpm)		
C	−10	−40	C	−10	−40
5.0	3.0	−1.0	60	59	75
—	—	—	51	50	70
5.0	2.0	−4.5	47	48	64
3.0	0.0	−9.0	59	56	88
—	—	—	67	66	81
6.3	4.5	−0.5	53	48	76
—	—	—	75	72	81
7.3	4.5	1.3	89	90	101
5.5	2.5	0.0	38	41	44
—	—	—	72	68	68
4.2	2.0	−0.2	71	72	75
—	—	—	50	50	67
4.4	3.9	0.5	58	59	77
4.4	1.5	−3.2	60	58	70
7.0	4.0	0.0	60	62	86
6.0	3.0	0.0	72	74	100
9.4	6.2	2.0	60	62	60
5.6	3.1[B]	−1.2[B]	61.3	60.9	75.5[B]
±0.5	±0.5	±0.9	±3.0	±2.9	±3.4
24	17	10	73	74	76
21	15	5	89	85	87
30	23	10	112	110	111
14	11	5	64	64	69
38	34	31	118	120	117
28	24	15	94	104	96
40	39	37	129	129	130
31	22	15	94	89	95
21	16	7	97	95	98
30	26	13	110	110	108
39	39	39	108	112	110
28.7	24.2[B]	17.0[B]	98.9	99.3	99.7
±2.5	±2.9	±3.8	±5.8	±6.0	±5.4

effects of digitalis glycosides on reflex vascular responses as well.

The discussion will focus on the following points: (1) possible mechanisms for the impairment of vasoconstrictor responses to LBNP, (2) relative contribution of cardiopulmonary and arterial baroreflexes in this abnormal response, (3) possible mechanisms for the paradoxic vasodilator response seen in five of the 11 patients with LVD, (4) possible explanations of the short-term reversal and normalization of vasoconstrictor responses to LBNP after administration of a digitalis glycoside, and (5) potential pathophysiologic implications of this study.

Mechanisms of impaired forearm vasoconstrictor responses to LBNP. Compared with the normal control subjects, the patients with LVD failed to develop vasoconstriction during graded levels of LBNP. Previous studies by Brigden and Sharpey-Schafer[11] and Goldsmith et al.[12] have shown that patients with heart failure have abnormal vascular responses to postural change, but the mechanism(s) underlying these abnormalities have remained unclear. We evaluated several possible mechanisms in this study, including the following: (1) the influence of high baseline FVR resulting in an inability to further vasoconstrict despite intact reflexes, (2) a nonspecific depression of reflex responsiveness in these patients, (3) the failure of LBNP to produce an adequate stimulus for reflex-mediated vasoconstriction in the patients with LVD, or (4) impairment in arterial and/or cardiopulmonary baroreflexes, as is seen in certain animal preparations of heart failure.[2–4]

The 11 patients in this study had baseline FVR that was significantly higher than normal (table 3). However, despite this high baseline resistance, the eight patients who underwent intra-arterial infusions of norepinephrine showed significant forearm vasoconstrictor responses that were similar in magnitude to those previously reported in normal subjects.[21] This argues against a depression of vascular responsiveness due to high baseline resistance as the mechanism for the failure of forearm vasoconstriction during LBNP.

A cold pressor stimulus was used in six patients to determine whether the absence of vasoconstriction with LBNP might reflect a nonspecific or generalized depression of reflex responsiveness as opposed to a selective impairment of baroreceptor mechanisms. In two of the six patients, FVR fell 11% to 14% during the cold pressor test, but in four patients FVR increased by more than 47%. Thus, although a generalized depression in reflex responsiveness may be involved in some subjects, our results indicate that patients with LVD frequently fail to experience vasoconstriction during orthostatic stress despite intact reflex responsiveness and vascular reactivity.

We considered the possibility that LBNP did not produce an adequate stimulus for unloading of baroreceptors in these patients. It is known that the veins of patients with heart failure are less distensible than normal,[23, 24] and thus comparable levels of LBNP in normal subjects and in patients with LVD might not result in sufficient levels of peripheral venous pooling to decrease cardiac filling pressures. However, as seen in

table 3, LBNP −10 mm Hg produced a significant fall in pulmonary arterial end-diastolic pressure and LBNP −40 mm Hg produced a further fall in cardiac filling pressure as well as a significant fall in mean arterial pressure, although without a narrowing of pulse pressure. Thus the abnormal reflex vascular responses cannot be explained by a lack of decrease in cardiac filling pressures during LBNP. In particular, it would seem difficult to explain the paradoxic reflex vasodilation observed in five of the 11 patients on the basis of an inadequate venous pooling during LBNP.

We propose that the abnormal vascular response to LBNP in the patients with LVD results from disorders of baroreceptor-mediated control of the systemic circulation, as has been shown in animal preparations of heart failure. Higgins et al.[2] demonstrated marked attenuation of systemic and regional circulatory responses to arterial baroreceptor hypotension and hypertension in dogs with heart failure induced by tricuspid avulsion and progressive pulmonary artery stenosis. In a similar preparation of canine heart failure, Greenberg et al.[3] demonstrated decreased sensitivity of atrial type B receptors to volume loading. Zucker et al.[4] showed that dogs with heart failure induced by aortocaval fistula had marked attenuation of the sensitivity of medulated left atrial type B receptors to any given change in left atrial pressure. The mechanism for this depressed sensitivity was thought to be due to a decreased left atrial compliance and structural alterations in the neural receptor endings with loss of their normally distinct end-arborizations.

Attenuation of arterial and cardiopulmonary baroreflexes would result in a decreased afferent inhibitory influence on the brainstem vasomotor centers, resulting in an increase in efferent sympathetic outflow and neurohumoral excitation. Studies in patients with heart failure have demonstrated this neurohumoral excitation with increased circulating levels of norepinephrine, plasma renin, and angiotensin.[5–10] We did not measure plasma norepinephrine or renin activity in our patients, but a state of neurocirculatory excitation was suggested by resting tachycardia and elevated baseline total systemic vascular resistance and FVR in nine of the 11 patients (tables 2 and 3).

Relative impairment of arterial and cardiopulmonary baroreflexes. On the basis of data from these experiments and from previous studies, we suggest that cardiopulmonary baroreflexes are predominantly involved in our findings, but we cannot exclude an associated abnormality in arterial baroreflexes. The reasons for implicating cardiopulmonary baroreflexes are twofold. First, previous evidence from human studies suggests that cardiopulmonary baroreflexes play the predominant role and arterial baroreflexes a minor role in control of FVR during LBNP.[19, 20, 25, 26] Thus a major abnormality in baroreflex control of FVR as we found in our patients would seem most likely to relate to cardiopulmonary baroreflexes. Second, the abnormality in reflex vascular control was evident with LBNP −10 mm Hg, which altered the determinant of cardiopulmonary baroreceptor activity (cardiac filling pressure) without altering determinants of arterial baroreceptor activity such as arterial pulse pressure, mean pressure, or heart rate (table 3). Higher levels of LBNP at −40 mm Hg produced a continued significant fall in cardiac filling pressure, with a small but significant decline in mean arterial pressure but no change in arterial pulse pressure. Although we cannot directly measure the relative influence of LBNP on sinoaortic vs cardiopulmonary baroreceptors in these patients, these two lines of reasoning suggest that the abnormal reflex vascular responses involve predominantly the cardiopulmonary baroreflexes, but we cannot exclude some associated impairment of arterial baroreflexes.

Paradoxic vasodilatory response to LBNP in patients with LVD: a proposed mechanism. As noted in the results, five of the 11 patients with LVD demonstrated forearm vasodilation (withdrawal of vasomotor tone) during LBNP. Brigden and Sharpey-Schafer[12] similarly demonstrated that upright tilt in patients with heart failure was associated with forearm vasodilatation. The mechanism(s) responsible for reflex vasodilation during orthostatic stress in patients with LVD remain unclear, but we speculate that it might result from paradoxic stimulation of ventricular baroreceptors during LBNP. In this regard, it is important to recognize that there are several determinants of cardiac sensory receptor activity, particularly ventricular baroreceptor activity. Although their activity is strongly influenced by cardiac diastolic pressure, it is also modulated by systolic events, including contractile force.[27, 28] Thus, although the activity and inhibitory influence of ventricular afferents usually decrease as cardiac filling pressure decreases, Oberg and Thoren[29] have reported paradoxic increases in cardiac vagal efferent activity during decreases in cardiac volume produced by hemorrhage, presumably because of increased contractile force.

We speculate that in some patients with LVD, reduced cardiac size caused by venous pooling during LBNP allows for a greater degree of cardiac fiber shortening and hence a paradoxic mechanical activation of cardiac baroreceptors with resultant decreased

inhibitory influence on the brainstem vasomotor centers and consequent peripheral vasodilation. Why would this occur in patients with LVD but not in normal subjects? The diastolic compliance curve of the left ventricle in patients with heart failure and cardiac enlargement is abnormal. An orthostatic stress may shift the heart to a flatter portion of the compliance curve, resulting in greater compliance as suggested by Abboud et al.[30] This could result in greater shortening of cardiac fibers for the same contractile state and hence greater activation of cardiac sensory nerve endings.

Mechanism of effects of digitalis glycosides on response of patients with LVD to LBNP. After the intravenous administration of a digitalis glycoside, the patients with LVD showed a decrease in baseline FVR and a reversal of their abnormal forearm vascular responses to LBNP (figure 4). In the control state, LBNP −40 mm Hg produced forearm vasodilatation, but after the digitalis glycoside the same level of LBNP resulted in forearm vasoconstriction. The possible mechanisms that could account for these effects include (1) direct effects of digitalis on the forearm vasculature, (2) direct sensitizing effect of digitalis on the impaired cardiopulmonary and/or arterial baroreceptors, (3) an indirect short-term inotropic effect of digitalis on cardiopulmonary baroreceptors, or (4) a combination of the above.

We considered possible direct effects of digitalis on the forearm vasculature. Digitalis is known to have a direct vasoconstrictive effect on isolated vascular smooth muscle.[31] In addition, peripheral vasoconstricting effects of digitalis were observed in normal subjects by Mason and Braunwald,[22] but these investigators observed that patients with heart failure had a vasodilator response to digitalis administration, presumably by an indirect mechanism. We also observed a decrease in baseline forearm resistance after digitalis in patients with LVD (figure 3). Thus it would be difficult to explain the effects of digitalis solely on the basis of a direct vasoconstrictor effect of the drug.

Studies in animals have suggested that the digitalis glycosides can directly sensitize arterial and cardiopulmonary baroreceptors. Quest and Gillis[14] demonstrated in the isolated feline carotid sinus preparation that direct application of ouabain or acetylstrophanthidin increased spontaneous firing of the carotid sinus nerve and augmented the depressor response of the carotid sinus to elevation of arterial pressure. Direct application of 25 to 100 μg of acetylstrophanthidin to the left ventricular epicardium of anesthetized dogs by Sleight et al.[13] caused hypotension and bradycardia associated with increased firing of left ventricular receptors with nonmyelinated vagal afferents (C-fibers). Thames[15] demonstrated that intracoronary injection or epicardial application of acetylstrophanthidin in anesthetized dogs produced significant decreases in renal sympathetic nerve activity accompanied by a modest fall in heart rate and arterial pressure. Vagotomy and epicardial application of lidocaine prevented these reflex responses after acetylstrophanthidin. These findings suggested that the effect of acetylstrophanthidin was due to an augmentation of the inhibitory influence of cardiac receptors with vagal afferent fibers. Zucker et al.[17] further demonstrated an augmented sensitivity of left atrial stretch receptors to volume loading in anesthetized dogs after intravenous injection of ouabain (20 μg/kg). The depressant effects of volume expansion or coronary occlusion on renal sympathetic nerve activity in dogs was also found to be augmented by the administration of intracoronary acetylstrophthandin by Thames et al.[16] Similar effects were seen during long-term administration of digitalis in dogs with therapeutic blood levels of digitalis.[32]

Recent studies in normal human beings by Ferrari et al.[33] showed that the intravenous administration of lanatoside C (0.8 mg) increased significantly the bradycardic and hypotensive effect of carotid baroreceptor stimulation produced by neck suction but did not significantly affect the tachycardic and hypertensive responses in the neck elicited by pressure-induced carotid sinus deactivation. Thus one possible explanation for our observations is a direct sensitizing effect of digitalis on cardiopulmonary and/or arterial baroreceptors.

Another possible mechanism is an indirect effect of digitalis on ventricular baroreceptors mediated through the inotropic action of the drug. For example, it is known that isoproterenol can augment and propranolol can attenuate the influence of ventricular baroreceptors.[19] We observed an increase in cardiac output and a decrease in cardiac filling pressure after digitalis in the patients with LVD, indicative of an inotropic effect. Thus one other explanation for our findings is an effect of digitalis on ventricular baroreceptors resulting from a positive inotropism. Further studies with other inotropic agents will be needed to evaluate this possibility.

Increased activity of cardiac and/or arterial baroreceptors after digitalis could explain a decrease in baseline FVR and a restoration of reflex vasoconstrictor responses to LBNP. By increasing resting inhibitory afferent influence on the vasomotor centers, the resting sympathetic outflow from these centers would be di-

minished and vascular resistance decreased. In addition, because the resting activity of cardiac and/or arterial baroreceptors is increased after digitalis, the unloading of these baroreceptors by lowering cardiac filling pressures with LBNP would be expected to decrease the firing of these inhibitory afferents resulting in reflex vasoconstriction.

Pathophysiologic implications. In summary, this study demonstrates that patients with LVD have abnormal forearm vascular responses (impaired vasoconstriction and paradoxic vasodilation) to peripheral venous pooling produced by LBNP. This abnormality cannot be explained by high baseline forearm resistance, decreased vascular reactivity, or a generalized depression of reflex responsiveness. It appears to relate instead to a selective abnormality in cardiopulmonary and perhaps arterial baroreflexes. This impaired afferent limb of the baroreflex arc would contribute to the disinhibition of brainstem vasomotor centers and result in the neurohumoral excitation characteristic of heart failure. Administration of digitalis glycoside immediately restores baroreflex-mediated vasoconstrictor responses to LBNP in these patients presumably through a direct sensitizing or indirect mechanical (inotropic) effect on cardiac baroreceptors. These findings provide new insight into the pathogenesis of heart failure in human beings as well as into the mechanism of action of digitalis in patients with LVD.

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