Abnormal Baroreceptor-Mediated Vasodilation of the Peripheral Circulation in Congestive Heart Failure Secondary to Idiopathic Dilated Cardiomyopathy

Henrik Wroblewski, MD; Jens Kastrup, MD, PhD; Svend Aage Mortensen, MD, PhD; and Stig Haunsø, MD, PhD

Background. Peripheral edema is a major clinical problem in congestive heart failure (CHF). The function of the edema-protective baroreceptor-mediated and local nervous vasoconstrictor reflexes of the lower leg during orthostasis in moderate and severe CHF has largely been unexplored.

Methods and Results. Baroreceptor-mediated and local nervous regulation of subcutaneous blood flow of the lower leg was studied in healthy subjects and in patients with moderate and severe CHF secondary to idiopathic dilated cardiomyopathy. Blood flow was measured by the local $^{133}Xe$ washout method in the supine position and during $45^\circ$ head-up tilt. When the central baroreceptor reflex alone was activated, the changes in subcutaneous blood flow of the heart failure patients in both groups were significantly different from those of the eleven control subjects: blood flow increased $48\pm26\%$ in 10 patients with moderate CHF patients compared with the decrease in blood flow of $-36\pm15\%$ observed in 11 control subjects ($p<0.0001$ for both). A highly significant direct association was demonstrated between changes in perfusion and New York Heart Association functional class ($p=0.007$) and the left ventricular ejection fraction ($p=0.01$). Activation of the baroreceptor and local venoarteriolar axon reflexes simultaneously increased blood flow significantly ($30\pm9\%$) in 14 patients with severe CHF, compared with the increase found in 14 control subjects ($-53\pm9\%$) and in the group of 14 patients with moderate CHF ($-17\pm25\%$) ($p<0.0001$ for both).

Conclusions. Patients with CHF secondary to idiopathic dilated cardiomyopathy have an abnormal baroreceptor-mediated vasodilation in subcutaneous tissue of the lower leg during the upright position, which increases with the severity of the disease. The hemodynamic consequence is capillary hypertension and hyperemia in the leg during the upright position that may contribute to the development of edema and to the initiation of structural changes (microangiopathy) demonstrated in the microcirculation. (Circulation 1993;87:849–856)

KEY WORDS  • orthostasis  • microcirculation  • neurogenic regulation  • sympathetic vasoconstrictor reflexes

Cardiovascular and neurohumoral reflex adjustments of peripheral vascular tone and heart rate play an essential role in maintaining arterial blood pressure and cardiac output during orthostatic changes. The afferent pathway of these neurogenic central reflexes originates from receptors within the heart and lungs together with arterial baroreceptors.1 Passive upright tilt reduces stroke volume by reducing ventricular preload; thus, the cardiopulmonary and arterial baroreceptors are unloaded, which causes a decrease in the baroreflex afferent restraint on the vasomotor center. Consequently, this results in increased sympathetic efferent vasoconstrictor responses in skeletal muscle and subcutaneous tissue in the lower leg.2,3 Additionally, the local nervous venoarteriolar axon reflex contributes to the peripheral vasoconstrictor responses upon postural changes.4–6 The local venoarteriolar reflex is the response to increased venous transmural pressure. It is unaffected by spinal sympathetic blockade but is abolished by chronic sympathetic denervation or local nervous blockade, indicating that the vasoconstrictor response is due to a local axon reflex.7 Stretch receptors are believed to be situated in the small veins, whereas the “effector” side is located toward the arterioles.7 When venous transmural pressure is elevated by 25 mm Hg or more, the local reflex is elicited, and the arterioles are constricted in subcutaneous and skeletal muscle tissue.7

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Supported by grants from the Danish Heart Foundation, Danish Medical Research Council, Danish Foundation for Advancement of Medical Science, Novo Foundation, Dagny and Harry West Jørgensen Foundation, August Frederik Wedell Erichsen Foundation, Jacob and Olga Madsen Foundation, Valdemar and Thyræ Foersom Foundation, and Asta Florida Bolding Foundation, Copenhagen.

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Received June 2, 1992; final revision accepted November 24, 1992.
The arteriolar vasoconstrictor reflex plays an additional role as an edema-protective factor during large increases in venous transmural pressure as in the upright position. The reflex reduces the capillary pressure and thereby inhibits an increase in net transcapillary fluid filtration rate.6,9 A reduction in baroreflex-mediated inhibition of the vasomotor center has been reported in animal preparations of chronic congestive heart failure (CHF)10–12 and leads to an increase in neurohumoral drive.

In human beings, CHF has also been associated with markedly depressed function of the cardiopulmonary baroreflexes.13–19 The baroreflex responsiveness may be influenced by the severity of disease.20 The vasoconstriction during upright position, induced by baroreceptor and local nervous vasoconstrictor reflexes, is an important edema-protective mechanism. Impairment of these reflexes in CHF, concurrently with increased venous pressure due to right heart failure, may participate in the preceding capillary hypertension that is likely to develop in the extremities during orthostasis with the progression of CHF. Accordingly, depression of the reflexes may be one pathophysiological mechanism in edema formation and in the development of structural changes (microangiopathy) in the microcirculation in CHF.21,22

The aim of the present study was to determine whether the central edema-protective baroreceptor-mediated sympathetic vasoconstrictor reflex in subcutaneous tissue of the lower leg was affected during the postural stimulus of head-up tilt in both moderate and severe CHF. Furthermore, the present study was aimed at evaluating whether the local venoarteriolar axon reflex was influenced at the lower leg in moderate and severe CHF.

Methods

Subjects

Baroreceptor- and local nervous–elicited vasoconstrictor reflexes of the lower leg were investigated in three groups of subjects. All subjects gave informed consent, and the investigation was approved by the local Ethical Committee.

Group 1 included 14 patients (three women and 11 men; mean age, 48 years; range, 30–64 years) with moderate CHF (New York Heart Association [NYHA] functional class II) (Table 1). All patients were receiving digoxin and diuretics, and five were also treated with angiotensin converting enzyme (ACE) inhibitors.

Group 2 included 14 patients (three women and 11 men; mean age, 44 years; range, 24–64 years) with severe CHF (NYHA functional class III or IV) (Table 1). All patients were receiving digoxin and diuretics, and seven were also treated with ACE inhibitors.

Group 3 consisted of 14 healthy control subjects (four women and 10 men; mean age, 43 years; range, 28–58 years).

All patients were stabilized and compensated on medical treatment. None of the patients received calcium antagonists, nitrates, or α- or β-blocking agents. For a minimum of 24 hours before the study, ACE inhibitors were withheld while treatment with digoxin and diuretics was maintained. All patients were in sinus rhythm and had normal plasma electrolytes and therapeutic serum levels of digoxin during the study.

The classification of heart failure based on clinical and hemodynamic findings was idiopathic dilated cardiomyopathy in all 28 patients. Coronary arteriography revealed normal coronary arteries in all patients, and endomyocardial biopsies gave no indication of inflammatory myocarditis in any of the patients. No patient had diabetes mellitus, arterial hypertension, or any symptoms or signs of peripheral or central neuropathy, peripheral atherosclerosis, or venous insufficiency of the lower limbs. The feet revealed no signs of edema or skin lesions. As an indication of the severity of ventricular dysfunction in the individual patient, the left ventricular ejection fraction was calculated by the count-based multigated frame mode radionuclide angiocardiography technique.23 Mean arterial blood pressure (MABP) was measured at the upper arm with a standard clinical sphygmomanometer at heart level; diastolic blood pressure was recorded as Korotkoff phase 5.

The course of CHF in the 28 patients from the day of investigation was as follows: 10 had died at a mean follow-up of 7 months (range, 1–16 months), six underwent cardiac transplantation at a mean follow-up of 8 months (range, 4–17 months), and 12 were alive at a mean follow-up of 26 months (range, 12–32 months) on medical therapy.

Subcutaneous Blood Flow Rate Measurement

Subcutaneous blood flow was measured 10 cm proximal to the lateral malleolus by the local isotope washout technique using 0.1–0.3 mL 133Xe dissolved in isotonic saline (10.0 mCi/mL = 370 MBq/mL) (Amersham International, Amersham, UK).24–25 The gamma emission of the isotope was registered by a sodium iodide scintillation detector with a symmetrical 20% window set around the 82-keV photopeak of 133Xe. The detector was placed at a distance of about 20 cm above the isotope depot, and the accumulated counts were registered every 20 seconds. The slope, k, of the regression line (the 133Xe

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CHF</th>
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<tr>
<td>Age (years)</td>
<td>48±10</td>
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<tr>
<td>Sex (F/M)</td>
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<tr>
<td>Duration of CHF symptoms (months)</td>
<td>17±15</td>
</tr>
<tr>
<td>NYHA III</td>
<td>14</td>
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<tr>
<td>NYHA IV</td>
<td>10</td>
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<tr>
<td>NYHA IV</td>
<td>4</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>22.2±7.6</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg) in supine position</td>
<td>88±10</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg) on tilt</td>
<td>84±9</td>
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</tbody>
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NYHA, New York Heart Association functional class; CHF, congestive heart failure. Data are expressed as mean±SD. *p<0.02 vs. control subjects.

The detector was placed at a distance of about 20 cm above the isotope depot, and the accumulated counts were registered every 20 seconds. The slope, k, of the regression line (the 133Xe...
washout rate constant) was calculated by the least-squares method with logarithmically transformed count rates corrected for background activity. $2^{n}, 2^{p}$ Subcutaneous blood flow ($f$) is proportional to $k$ (min$^{-1}$), by the equation

$$f = (k \cdot \lambda \cdot 100 \text{ mL} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1})$$

where $\lambda$ is the tissue-to-blood partition coefficient $2^{n}, 2^{p}, 2^{m}$ ($\lambda = 10 \text{ mL} \cdot \text{g}^{-1}$ subcutaneous tissue). Relative blood flow was then calculated as $f_{\text{rel}} = f_{\text{ref}}$, where $f_{\text{ref}}$ is the washout rate constant obtained during the various hydrostatic test situations, and $k_{\text{ref}}$ is the average of the washout rate constants obtained just before and just after the test.

**Regional Vascular Resistance**

During head-up tilt, the increase in hydrostatic pressure in the vessels of the lower leg (50 cm below the level of the heart) is about 38 mm Hg, so that with a MABP of 100 mm Hg, the total pressure in the arteries of the lower leg is about 138 mm Hg. The pressure within the veins is subject to corresponding hydrostatic effects (38 mm Hg). Therefore, the pressure gradient between arteries and veins, the driving force for the flow of blood (the perfusion pressure), does not vary with height. However, hydrostatic effects cause considerable increases in transmural pressure that are reflected primarily in the state of stretch and thus of the capacity of the relatively thin-walled veins. Accordingly, when the perfusion pressure is used in calculation of local vascular resistance, the effects of gravity during head-up tilt without counterpressure and during passive leg lowering should not be taken into account.

Blood pressure relations in a vascular system can be described by the Haagen-Poiseuille equation: $F = (P_{i} - P_{f})/R$, where $F$ denotes blood flow (mL · min$^{-1}$), $P_{i} - P_{f}$ the perfusion pressure (MABP minus venous pressure, mm Hg), and $R$ the resistance (mm Hg · min · mL$^{-1}$) in the vascular system. In the present study, relative resistance, $R_{\text{rel}}$/R$^{\text{ref}}$, was calculated from obtained relative blood flow, $f_{\text{rel}}/f_{\text{ref}}$, and perfusion pressure, $P_{i} - P_{f}$.

**Procedure**

The hemodynamic studies were carried out in the morning. The subjects were lightly dressed and placed in a supine position on a tilt table. The feet were immobilized by a vacuum pillow to avoid changes in counting geometry caused by movements. Room temperature was about 23°C and was kept constant during the investigations.

To avoid the influence of the injection trauma $^{27}$ and a possible washout of $^{133}$Xe in cutis, $^{24}$ measurements were started at least 30 minutes after the injection. A single investigation consisted of seven measurements, each lasting 8–12 minutes, with the labeled area on the lower leg in the following positions: 1) supine position, leg at heart level (reference level); 2) 45° passive head-up tilt, the labeled area on the leg lowered about 50 cm below heart level (a cuff placed above the area under study was inflated to a pressure equaling that of a blood column of the same height as the vertical distance from the heart [right atrium] to the labeled area); 3) leg at reference level (cuff deflated); 4) 45° passive head-up tilt, the labeled area on the leg lowered about 50 cm below heart level, without cuff; 5) leg at reference level; 6) leg lowered 40 cm below reference level; 7) leg at reference level. All measurements were initiated 2–4 minutes after the subject was brought to the described position. The subjects were instructed not to contract their leg muscles during the procedures.

**Statistical Methods**

Comparisons between groups were carried out using a one-way ANOVA and a Student's $t$ test for unpaired data.

To detect the independent variables that were significantly associated with relative change in subcutaneous blood flow during head-up tilt, multiple least-squares regression analyses with stepwise elimination of the least nonsignificant independent variable parameter were carried out. $^{29}$ The analyses included only patients with CHF. As independent variables for relative change in subcutaneous blood flow during tilt, the following parameters were chosen: 1) NYHA functional class, 2) left ventricular ejection fraction, 3) duration of CHF, 4) age of the subject, and 5) MABP. Items 2–5 were selected as independent variables in the multiple regression analysis for the determinants of NYHA functional class.

**Results**

**Baroreceptor Nervous Reflex (45° Head-Up Tilt With a 40 mm Hg Local Counterpressure)**

Application during tilt of a local counterpressure of the same magnitude as the increase in vascular transmural pressure abolishes activation of the local vasoconstrictor reflex. $^{30}$ However, vasoconstriction induced by baroreceptor-mediated reflex mechanisms and perfusion pressure is unaffected.

Activation of the baroreceptor reflex alone during head-up tilt increased the relative subcutaneous blood flow significantly in both 10 severe (mean, 48%) and nine moderate (3%) CHF patients compared with the decrease in blood flow (−36%) observed in 11 healthy control subjects ($p < 0.0001$ for both) (Table 2; Figure 1, left panel). Decreases in the corresponding subcutaneous vascular resistance in the group of severe (−28%) and in the group of moderate (−1%) CHF patients were found, compared with the increase in the control subjects (65%) (Figure 1, right panel) ($p < 0.0001$ for both). An identical abnormal increase in the subcutaneous blood flow was seen in the group of patients on (25%, $n=10$) and off (29%, $n=9$) ACE inhibitors compared with the decrease registered in control subjects (−36%) (Table 2) ($p < 0.0001$ and $p < 0.001$, respectively).

In all patients with CHF, multiple regression analysis revealed a significant direct association between the change in subcutaneous blood flow during activation of the baroreceptor reflex alone and the severity of heart failure characterized by NYHA functional class ($p = 0.007$) and the left ventricular ejection fraction (LVEF) ($p = 0.010$). The linear equation was: change in blood flow = 1.11 + 0.23(NYHA) − 0.02(LVEF).

**Combined Baroreceptor and Local Nervous Reflex (45° Head-Up Tilt)**

When the central and local vasoconstrictor axon reflexes were activated simultaneously, blood flow in-
creased significantly (30%) in 14 patients with severe CHF compared with the decrease in blood flow (−53%) in 14 control subjects and in 14 patients with moderate CHF (−17%; p < 0.0001 for both) (Table 2; Figure 2, left panel); a decrease in the corresponding vascular resistance in the group of severe CHF (−26%) was seen, in contrast to an increase in the patients with moderate CHF (12%) and an increase in the control subjects (105%) (Figure 2, right panel) (p < 0.0001 for both). An identical abnormal increase in the subcutaneous blood flow was seen in both patients on (16%, n = 12) and off (2%, n = 16) ACE inhibitors compared with the decrease (−53%) found in control subjects (Table 2) (p < 0.0001 for both).

In all patients with CHF, multiple regression analysis revealed a significant direct association between the change in subcutaneous blood flow during tilt and the severity of heart failure characterized by NYHA functional class (p < 0.0001, r = 0.70).

Local Venoarteriolar Axon Reflex

Lowering of the lower leg 40 cm beneath the reference level corresponding to an increase in local venous transmural pressure of about 30 mm Hg caused a decrease in the relative subcutaneous blood flow to identical levels in the three groups: 11 patients with moderate CHF (−37%), nine with severe CHF (−39%), and 12 control subjects (−45%) (Table 2; Figure 3, left panel). The corresponding relative increases in vascular resistance were also identical (63%, 76%, and 95%, respectively) (Figure 3, right panel). An identical decrease in the subcutaneous blood flow was seen in the group of patients on (−36%, n = 7) and off (−40%, n = 13) ACE inhibitors compared with the decrease registered in control subjects (−36%) (Table 2).

Absolute Subcutaneous Blood Flow Rate and Subcutaneous Vascular Resistance

The baseline absolute subcutaneous blood flow in the supine position in patients with severe CHF was approximately 50% of the value in control subjects and moderate CHF patients (Figure 4, left panel). The corresponding subcutaneous vascular resistance was approximately 35% higher in patients with severe CHF than in control subjects and moderate CHF patients (Figure 4, right panel).

During head-up tilt procedure, absolute blood flow increased and was approximately 70% higher in severe CHF patients than in control subjects, in whom a decrease was demonstrated (Figure 4, left panel). How-

![Figure 1](http://circ.ahajournals.org/doi/10.1161/01.CIR.87.3.852)
ever, the blood flow level in severe CHF during tilt did not increase to the level seen in control subjects in the supine position. The absolute subcutaneous vascular resistance during tilt decreased and was approximately 45% lower in severe CHF patients than in control subjects, in whom an increase in vascular resistance was seen (Figure 4, right panel).

Patients with moderate CHF had a slight decrease in absolute blood flow during head-up tilt. However, the blood flow value was approximately twice as high as in control subjects (Figure 4, left panel). The absolute subcutaneous vascular resistance during tilt was almost unchanged from the supine to the tilted position in patients with moderate CHF (Figure 4, right panel).

**Mean Arterial Blood Pressure**

The baseline MABP was reduced (88 mm Hg) and control subjects. On passive upright tilt, the fall in MABP was not significant in any of the three groups (Table 1).

**Discussion**

This study demonstrates that patients with CHF due to idiopathic dilated cardiomyopathy have an abnormal baroreceptor-mediated vasodilation in subcutaneous adipose tissue of the lower leg during the upright position, in contrast to the normally expected vasocostrictor response. This paradoxical vasodilation tended to increase with the clinical progression of the disease. The local vasoarteriolar sympathetic axon reflex was intact in both severe and moderate CHF and elicited identical decrease in relative subcutaneous blood flow and increase in vascular resistance. However, when the baroreceptor and local nervous reflexes were activated simultaneously, the unaffected local nervous vasoarterial reflex was unable to prevent the paradoxical vasodilation in CHF.

**FIGURE 2.** Plots of combined baroreceptor and local nervous reflexes (the relative change in subcutaneous blood flow [left panel] and vascular resistance [right panel] during 45° head-up tilt). The values were calculated as blood flow (or vascular resistance) during head-up tilt divided by the mean value of blood flow (or resistance) in the horizontal position before and after head-up tilt. p<0.0001 for both congestive heart failure (CHF) groups vs. control subjects. Healthy subjects (circles) and patients with CHF New York Heart Association (NYHA) functional classes II (triangles) and III or IV (squares).

**FIGURE 3.** Plots of local nervous reflex (the relative change in subcutaneous blood flow [left panel] and vascular resistance [right panel] during lowering of the lower leg 40 cm below heart level). The values were calculated as blood flow (or vascular resistance) during lowering divided by the mean value of blood flow (or resistance) in the horizontal position before and after lowering. p=NS for both congestive heart failure (CHF) groups vs. control subjects. Healthy subjects (circles) and patients with CHF New York Heart Association (NYHA) functional classes II (triangles) and III or IV (squares).
CHF in animals and in humans is characterized by increased neurohumoral activity with elevated levels of circulating catecholamines, plasma renin, angiotensin, and vasopressin.31-36 In addition, patients with severe CHF have demonstrated blunted baroreceptor control with unchanged or decreased vascular resistance in subcutaneous and skeletal muscle tissue of the forearm during orthostatic stress.13,15,17,19,37 The decrease of forearm vascular resistance in the upright position demonstrated in severe CHF can be abolished or normalized by proximal nerve blockade and local β-receptor blockade (propranolol), respectively. This indicates a central nervous–mediated β-adrenergic vasodilator reflex.38,39 Another mechanism behind the abnormal vasodilatation has been suggested by Abboud et al.40 During head-up tilt, cardiac size is reduced in CHF patients, which is proposed to restore cardiac wall motion to the same extent toward normal and thereby induce vasodilation.

Some studies indicate that these autonomic changes reported in CHF may be reversible. Reversal of experimental heart failure in the dog is associated with normalization of baroreceptor function,41 and improvement in baroreceptor function with medical treatment has been found in human heart failure.14,17,42,43 Cody et al44 examined the response to postural tilt in patients with heart failure before and after acute and chronic ACE inhibition. Before administration of captopril, neither vascular resistance nor plasma norepinephrine increased with tilt. After acute captopril, tilt was accompanied by systemic but not peripheral vasoconstriction and an increase in plasma norepinephrine. Baroreceptor function may have improved because captopril decreases cardiac filling pressures. However, chronic ACE inhibition was characterized by the absence of an increase of systemic or peripheral vascular resistance on tilt. In contrast, Kassiss and Amtorp42 demonstrated that 3 weeks on felodipine therapy could normalize the baroreceptor control of systemic vascular resistance and forearm subcutaneous vascular resistance in CHF. Ferguson et al17 found that intravenous administration of digitalis glycoside immediately restores baroreflex-mediated forearm vasoconstrictor response to lower-body negative pressure in patients with heart failure. This reversal of the baroreflex seen by digitalis and felodipine therapy is possibly because of baroreceptor sensitization.

We decided to study the conditions of the lower leg in heart failure because the arteriolar vasoconstrictor reflexes play a significant role as an edema-protective factor by reducing the capillary pressure and thereby the increase in net transcapillary fluid filtration rate during large increases in venous transmural pressure as in the upright position. Impairment of the reflexes may result in capillary hypertension preceding the formation of edema and the development of structural changes in the microcirculation in CHF.21,22

With the progression of CHF, there appears to be an increase in the supine baseline peripheral vascular resistance and a decrease in the peripheral blood flow.44,45 Most investigators have described reduced blood flow responses in the arm and in the leg during exercise and postischemic hyperemia in patients with CHF.46-49 However, a completely normal vasodilator capacity and vascular resistance have also been demonstrated in CHF.50,51 This discrepancy could be due in part to differences in the duration or severity of CHF in the patients studied. In comparison, the present study showed that baseline vascular resistance in the supine position was significantly increased in severe CHF and that the peripheral blood flow was decreased; in moderate CHF, however, baseline vascular resistance was identical to the normal subjects. Furthermore, the present study demonstrated that during activation of the combined central and local reflex of the lower leg (unloading of baroreceptors with 45° passive upright tilt), control subjects developed vasoconstriction, but patients with both moderate and severe CHF failed to produce vasoconstriction; patients with severe CHF even tended to develop vasodilation. A more marked disparity in response was seen during activation of the baroreceptor reflex alone (tilt with application of a local counterpressure of the same magnitude as the increase in local vascular transmural pressure40,52), which in both
Paradoxical Vasodilation During Orthostasis in CHF

CHF groups resulted in an additional increase in blood flow and a corresponding further decrease in subcutaneous vascular resistance. Multiple regression analysis revealed a direct association between this paradoxical vasodilation during activation of the baroreceptor reflex alone and the severity of heart failure characterized by NYHA functional class and left ventricular ejection fraction.

The paradoxical vasodilation during tilt was influenced by ACE inhibitor treatment (Table 2) that was withheld for a minimum of 24 hours before the study. An identical abnormal increase in the subcutaneous blood flow during tilt was seen in patients on and off ACE inhibitor treatment. This agrees with previous findings that acute and chronic ACE inhibition are characterized by the absence of a reflex increase of the peripheral vascular resistance on tilt.14

We have recently demonstrated structural microangiopathy (increased hyalinosis of the basement membranes) in the terminal arterioles in skin biopsies. This arteriolar hyalinosis contributed to an increased minimal vascular resistance of the lower leg in idiopathic dilated cardiomyopathy.21 The larger arterioles and arteries are richly innervated with adrenergic sympathetic nerve fibers,53 but the terminal arterioles (diameter, 50–100 μm) are absent in the nerve supply.24 Therefore, the abnormal vasodilation during orthostasis seems to be operating in the arteries and larger arterioles and not in the hyalinized terminal arterioles. The capillary hypertension from the paradoxical vasodilation in the upright position in the small arteries may induce the structural alterations demonstrated in the terminal arterioles.21

The paradoxical vasodilation during orthostasis demonstrated in the present study, concurrently with the increased venous pressure due to right heart failure, may participate in an elevated microvascular stress (capillary hypertension) with increased capillary filtration rate that results in the formation of edema and in development of microangiopathy in the arterioles in CHF.

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Abnormal baroreceptor-mediated vasodilation of the peripheral circulation in congestive heart failure secondary to idiopathic dilated cardiomyopathy.
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Circulation. 1993;87:849-856
doi: 10.1161/01.CIR.87.3.849

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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