Calf blood flow during prolonged tilt in idiopathic dilated cardiomyopathy and after cardiac transplantation

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Galatius, Søren, Henrik Wroblewski, Vibeke B. Sørensen, Peter Bie, Henrik Arendrup, and Jens Kastrup. Calf blood flow during prolonged tilt in idiopathic dilated cardiomyopathy and after cardiac transplantation. Am. J. Physiol. Heart Circ. Physiol. 278: H239–H248, 2000.—In severe congestive heart failure (CHF), abnormal reflex control of calf blood flow during brief head-up tilt that appears to normalize after transplantation (HTX) may be present during prolonged observation also. Therefore, we studied the effect of prolonged (30 min) 50° head-up tilt on calf skeletal muscle blood flow measured by the local 133Xe washout method in CHF and after HTX and in patients with the presence vs. absence of native right atrium (+PNA and −PNA, respectively). During brief head-up tilt, skeletal muscle blood flow increased 13 ± 42% in 9 severe CHF patients in contrast to a −28 ± 22% decrease (P < 0.01) in 11 control subjects, −24 ± 30% decrease in 15 moderate CHF patients (P < 0.05), −25 ± 14% decrease in 12 patients with recent HTX (P < 0.01), and −21 ± 24% decrease in 8 patients with distant HTX (P = 0.06). However, during sustained tilt, blood flow declined to similar levels of that in the other groups in severe CHF. HTX −PNA vs. +PNA showed blunted skeletal muscle vasomotor control (P < 0.05) and a higher systolic blood pressure (139 ± 14 vs. 125 ± 15 mmHg, P < 0.05) and heart rate (92 ± 10 vs. 83 ± 8 beats/min, P < 0.05). Thus paradox vasodilatation of calf skeletal muscle in severe CHF is present only during brief but not prolonged tilt. This may be one explanation of the rare presence of orthostatic intolerance in CHF and implies only a minor possible role for the abnormality in edema pathogenesis. Removal of all right atrium in HTX has an important hemodynamic impact that may possibly affect later clinical outcome.

heart chambers; reflex control; microcirculation; regional blood flow

DURING ORTHOSTASIS, peripheral vascular tone changes to counteract decreases in arterial blood pressure and cardiac output and to prevent edema formation. The change is initially mediated by central cardiovascular baroreceptor-mediated reflexes (25) and the local venoarteriolar reflex (13) and by adjustments of neurohormonal and local factors during prolonged orthostasis (25). In congestive heart failure (CHF), peripheral cardiopulmonary baroreceptor-mediated reflex control (15, 27) and adjustment of humoral factors are disturbed (22). After cardiac transplantation (HTX), reversal of abnormal baroreceptor-mediated peripheral reflex control may take place, although a number of both cardiac (7) and peripheral vascular abnormalities persist (27), most prominently early after HTX. However, most previous studies have been performed during brief observations and often in investigations on the forearm. In contrast, the most important hydrostatic changes during daily activities happen in the legs, particularly during prolonged upright position.

The normal response with arteriolar vasoconstriction in both upper and lower extremities (14, 21, 28) is contrasted by a paradoxical vasodilatation in subcutaneous tissue in all four extremities and in forearm skeletal muscle in patients with CHF during brief orthostasis (14, 21, 28). After HTX, the abnormal response in calf subcutaneous tissue appears to normalize (29), in contrast to continued impairment of baroreflex control of forearm blood flow (18). However, until now, reflex regulation of calf skeletal muscle blood flow during orthostasis remained unknown in CHF and after HTX.

During prolonged sitting, a sustained paradox vasodilatation in calf subcutaneous tissue has been demonstrated in CHF (26). During acute volume unloading and perhaps during prolonged sitting with less severe baroreceptor unloading, diastolic ventricular interaction with increased left ventricular dimensions despite reduction in right ventricular volume has been suggested to explain the abnormal vasodilatation in CHF (2). However, the impact of continued peripheral pooling of blood during prolonged upright position on reflex regulation of calf subcutaneous and skeletal muscle tissue blood flow may be different from brief interventions and sitting.

Low-pressure cardiopulmonary mechanoreceptors are located in the atria, and autonomic reinnervation after HTX appears to depend on the operative technique used with inclusion or exclusion of the native right atrium (3). The presence or absence of native right atrium may have great impact on baroreceptor regulation of the peripheral blood flow during orthostasis after HTX.

Neuroendocrine adjustment during orthostasis is disturbed in CHF and after HTX (9, 19, 22). The plasma level of the potent vasoconstrictor endothelin (ET)-1 has been demonstrated to change in parallel with
arterial blood pressure during 30-min head-up tilt in healthy controls but not in patients with severe CHF (22). On the other hand, ET-1 receptor blockade caused vasodilator effects in CHF (6). Therefore, ET-1 may play a role in concert with other regulatory mechanisms in the control of the peripheral vasculature during prolonged orthostasis in less severe CHF and perhaps particularly after cardiac denervation in HTX.

First, we hypothesized that abnormal leg microvascular reflex control in CHF may be present in both subcutaneous and skeletal muscle tissue and may be present also during prolonged observation. Second, we hypothesized that HTX performed with a varying degree of remnant right atrium may affect baroreceptor-mediated hemodynamic responses. Third, we hypothesized that the release of the potent vasoconstrictor ET-1 during head-up tilt may play a role in the regulation of calf blood flow, perhaps particularly after cardiac denervation in HTX. Therefore, we extended previous investigations by studying the effect of prolonged head-up tilt on calf regional blood flow and on plasma ET-1 in CHF and after HTX in patients with the presence vs. absence of native right atrium (+PNA and –PNA, respectively).

METHODS
Subjects

Table 1 shows demographic data. Although ischemic heart disease is the most common cause of CHF, atheroma and many of its precursors have independent effects on microvascular function. Therefore, the study population consisted of 19 healthy controls, 24 patients with CHF due to idopathic dilated cardiomyopathy (IDCM), and 20 patients after HTX due to IDCM. The CHF patients were separated into those with moderate [New York Heart Association (NYHA) functional class II, n = 15] and those with severe symptoms (NYHA III-IV, n = 9) for descriptive and statistical purposes. The diagnosis of IDCM was based on clinical and hemodynamic findings. All patients had the absence of a history of angina or myocardial infarction and 1) an echocardiogram without regional wall motion abnormality, 2) Thirteen patients with CHF also had a normal coronary angiography, and 3) 13 patients had an endomyocardial biopsy specimen without signs of myocarditis or ischemic heart disease. In five patients, all three criteria were available, and in three patients the diagnosis was based on criteria 1 only. In HTX patients, the diagnosis was based on all three criteria in 11 patients and on only criteria 1 and 3 in 9 patients; coronary angiography had not been performed in these patients because of young age.

All heart transplant recipients were clinically stable and free from clinically or biopsy-verified rejection, infection, or other major illness. The patients were transplanted according to one of three procedures. 1) In the operative procedure described by Shumway, the right atrium is divided at the midatrial level, and the majority of the native right atrium is left in the recipient (n = 3; see Ref. 5). 2) A modified technique was used in which a greater part of the recipient right atrium is resected and the donor heart is opened between the vena cava superior and inferior and anastomozed to the recipient right atrium (n = 9; see Ref. 5). 3) A bicaval technique was used in which no native right atrium and septum are preserved and the donor heart is anastomozed cava to cava (–PNA, n = 8; see Ref. 10). In all three groups, native left atrium between the pulmonary veins is left in the recipient. The patients with native right atrial remnant (+PNA, n = 12) were grouped together for descriptive and statistical purposes. The patients were also evaluated with respect to the impact of time since HTX and were separated into the following two groups: recent HTX (<6 mo, median 2.5, range 1–6, n = 12) and distant HTX (>6 mo, median 12, range 7–39, n = 8). All patients with CHF were treated with diuretics, 22 patients were on angiotensin-converting enzyme (ACE) inhibitor treatment, 20 were on digoxin treatment, 14 were on anticoagulant treatment, and 6 were on aspirin treatment. None was treated with β-blockers. After HTX, all patients were treated with triple immunosuppression, including cyclosporine, azathioprine, and low-dose glucocorticoid, 12 patients were treated with diuretics, 1 was treated with ACE inhibitor, 14 were on aspirin, and 8 patients were treated with a calcium antagonist from the dihydropyridine class. To mirror the clinical setting and because much vasodilator therapy has long-term effects, all medication was continued until the day of study. No patient had diabetes mellitus or any signs or symptoms of peripheral or central neuropathy, atherosclerosis, or venous insufficiency of the lower limb. The calf revealed no signs of edema or skin lesions. Healthy subjects were selected among nonobese persons without a history of angina, hypertension, or diabetes. The study groups were age and sex matched. All subjects gave written informed consent, and the protocol was approved by the local ethics committee. The study conforms with the guidelines of the Declaration of Helsinki.

Table 1. Clinical characteristics of patients and healthy controls.

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 19)</th>
<th>CHF (n = 24)</th>
<th>HTX (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>43.6 ± 16.0</td>
<td>45.1 ± 10.7</td>
<td>45.4 ± 10.6</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>14/5</td>
<td>21/3</td>
<td>18/2</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>22 ± 8</td>
<td>3 ± 1–39</td>
<td></td>
</tr>
<tr>
<td>Duration of CHF, mo</td>
<td>17 (2–84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since HTX, mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA II/III/IV</td>
<td>15/7/2</td>
<td></td>
<td></td>
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<tr>
<td>Systolic blood pressure</td>
<td>116.7 ± 14.4*</td>
<td>115.8 ± 17.9*</td>
<td>130.5 ± 16.5*</td>
</tr>
<tr>
<td>supine, mmHg</td>
<td></td>
<td></td>
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<tr>
<td>Diastolic blood pressure</td>
<td>72.3 ± 10.7*</td>
<td>74.7 ± 13.9*</td>
<td>84.6 ± 11.1</td>
</tr>
<tr>
<td>supine, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>66.1 ± 12.6†</td>
<td>76.4 ± 20.8</td>
<td>86.9 ± 10.1</td>
</tr>
<tr>
<td>Serum creatinine, mmol/l</td>
<td>0.092 ± 0.01†</td>
<td>0.148 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>Plasma sodium, mmol/l</td>
<td>140.1 ± 2.2</td>
<td>140.8 ± 3.6</td>
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Values are means ± SD except for duration of congestive heart failure (CHF) and time since cardiac transplantation (HTX), where values are given as medians with ranges in parentheses; n, no. of subjects. NYHA, New York Heart Association functional class. *P < 0.01 and †P < 0.001 compared with HTX patients. ‡P < 0.05 compared with HTX and controls.

Hemodynamic Measurements

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 with foot support. The right leg was immobilized by a vacuum pillow to avoid changes in counting geometry caused by movements during skeletal muscle and subcutaneous blood flow measurements. Room temperature was ∼23°C and was kept constant during the investigations.

Baseline hemodynamic investigations were performed after at least 30 min of rest in the supine position. Next, 30 min
of 50° head-up tilt was performed followed by a 30-min recovery period in the supine position. Regulation of skeletal muscle and subcutaneous blood flow during orthostasis. The regulation of blood flow during head-up tilt was investigated by the local isotope washout technique in the proximal anterior tibial muscle tissue and in subcutaneous tissue just proximal of the lateral malleolus in the right leg before, during, and after 30 min of 50° head-up tilt. The two areas of investigation did not interfere with respect to detectable cross-radiation. With a 4-cm-long, 0.4-mm-diameter needle, 0.2 and 0.1 ml of $^{133}$Xe (370 MBq/ml; Amersham International, Amersham, UK; dissolved in isotonic saline in a concentration of ~100 MBq/ml; see Ref. 16) was injected slowly. Blood flow measurements were initiated a minimum of 30 min after injection.

Skeletal muscle and subcutaneous blood flow rate calculations. The gamma emission of the isotopes was registered by a sodium iodide scintillation detector with a symmetric 20% window set around the 82-keV photopeak of $^{133}$Xe. The detectors were placed at a distance of ~20 cm above the isotope depot, and the accumulated counts were registered every 5 s. The slope k of the regression line (the $^{133}$Xe washout rate constant) was calculated by the least-squares method with logarithmically transformed count rates corrected for background activity (16, 28). Blood flow (f) is proportional to k (min$^{-1}$) as follows: $f = k \times 100 \times 100 \text{ml} \times 10^{-3} \times 10^{-1} \times 10^{-6} \text{g}^{-1}$, where $k$ is the tissue-to-background partition coefficient ($k = 0.7 \text{ml/g in skeletal muscle tissue}$ and $k = 10 \text{ml/g in subcutaneous tissue using } ^{133}\text{Xe}$). In skeletal muscle, calculated blood flow rates from the later part (i.e., > 20 min after injection) of the washout curve are underestimated by ~50% due to counter-current venoarterial diffusion (23). Accordingly, all calculated absolute skeletal muscle blood flow values obtained from the formula given above were multiplied by a factor of two.

The head-up tilt investigations consisted of a triad of blood flow measurements: 1) supine position, legs at heart level (reference flow); 2) 50° passive head-up tilt, the labeled areas on the legs lowered ~65 cm below the heart level for 30 min; 3) return to pretilt level for 30 min. The entire registration lasted for ~70 min. Blood flow rates are given as absolute values. The blood flow rates immediately after head-up tilt are expressed as relative values to the reference flow and are calculated as $f_{\text{ref}} = k_{\text{ref}}/k_{\text{ref}}$, where $k_{\text{ref}}$ indicates the reference rate. Analyses of $k_{\text{ref}}$ were started when the washout curves were stable, i.e., 3–4 min after head-up tilt and 3–4 min after return to the supine position. Thus five k values of 5-min intervals during head-up tilt and five k values in the supine position after head-up tilt could be obtained. $k_{\text{ref}}$ is the washout rate constant obtained immediately before the tilt procedure, after a minimum of 30 min supine rest after injection.

The blood pressure relationship in a vascular system can be described by the Haagen-Poiseuille equation: $F = (P_a - P_v)/R$. $F$ denotes blood flow (ml/min), $P_a$ and $P_v$ denote mean arterial and venous pressure (mmHg), respectively, and $R$ is resistance (mmHg·min·ml$^{-1}$) in the vascular system. The perfusion pressure does not vary because of alterations in hydrostatic pressure caused by a change in position, because an identical increase in hydrostatic pressure is added on the arterial and venous side of the vascular bed. Accordingly, when perfusion pressure is used in the calculation of local vascular resistance, the effects of gravity during head-up tilt should not be taken into consideration. Arterial blood pressure was measured at the upper arm with a standard clinical sphygmomanometer at the heart level; diastolic blood pressure was recorded as Krotkoff phase 5. A rough estimate of the absolute vascular resistance was made by taking mean arterial blood pressure as perfusion pressure. The relative blood flow resistance, $R_{\text{ref}}/R_{\text{ref}}$, was then calculated from the obtained relative blood flow, $f_{\text{rel}}/f_{\text{rel}}$, and the perfusion pressure.

Blood Sampling Procedures and Hormonal Assays

Blood samples for ET-1 analysis were taken immediately before head-up tilt after a minimum of 30 min at rest in the horizontal position, with 5-min intervals during head-up tilt and at 5 and 30 min after return to the supine position. Blood samples (10 ml) were obtained from an indwelling catheter in the antecubital vein into precooled polyethylene tubes containing EDTA (5 mmol/ml blood) and aprotinin (540 KIU/ml blood). The analysis was performed as previously described (12). The antibody used in this study primarily recognizes ET-1. There is a 17% cross-reactivity with human big ET-1 and 7% cross-reactivity with ET-2 and ET-3. Thus the term ET-1 is used for the immunoreactivity measured as described above in relation to the applied commercially available antibody. All ET-1 values were expressed as picograms per milliliter. Recovery of unlabeled ET-1 was 95 ± 3% when 6 pg/ml were added. Results were not corrected for incomplete recovery. The interassay coefficient of variation was 9% and the intra-assay coefficient of variation was 11% at the level of 2.4 pg/tube.

Statistics

Comparison was performed by one-way ANOVA between groups and one-way ANOVA for repeated measurements within groups. When significant values were found, Student’s t-tests for unpaired/paired data or the corresponding nonparametric test were used when appropriate. A P value < 0.05 was considered significant. Values are presented as means ± SD in the text and means ± SE or mean/median and scatterplot of individual values in Figs. 1–6 if not otherwise indicated.

RESULTS

Orthostasis and Skeletal Muscle Blood Flow

The course of absolute skeletal muscle blood flow and vascular resistance as a result of prolonged head-up tilt is shown in Fig. 1A. The relative change in the first minutes after head-up tilt is presented in Fig. 1B. In patients with severe CHF, head-up tilt resulted in a 13 ± 42% increase in skeletal muscle blood flow, in contrast to a reduction in patients with moderate CHF (-24 ± 30%, P < 0.05), in patients with recent HTX (-25 ± 14%, P < 0.01), in controls (-28 ± 22%, P < 0.01), and in patients with distant HTX (-21 ± 24%, P = 0.06) who did not differ from each other (Fig. 1B). Correspondingly, skeletal muscle vascular resistance was unchanged in patients with severe CHF (1 ± 29%) during baroreceptor unloading in contrast to a 60 ± 77% increase in patients with moderate CHF (P < 0.05), in patients with recent HTX (36 ± 26%, P < 0.01), in patients with distant HTX (35 ± 49%, P = 0.1), and in controls (61 ± 67%, P < 0.05) who did not differ from each other (Fig. 1B). However, the initial increase in skeletal muscle blood flow at head-up tilt in patients with severe CHF was followed by a gradual decrease and a corresponding increase in vascular resistance in the second half of the 30-min tilt period to levels similar to the other groups (Fig. 1A).
Orthostasis and Subcutaneous Blood Flow

The course of absolute subcutaneous blood flow and vascular resistance in the supine position and during baroreceptor unloading is shown in Fig. 2A. The relative change in the first minutes after head-up tilt is presented in Fig. 2B. During the first minutes of head-up-tilt, subcutaneous blood flow was reduced by only 13\% (range = 5 to 32\%) in patients with severe CHF, by 14\% (range = 4 to 52\%) in patients with distant HTX, and by 37\% (range = 1 to 132\%) in patients with recent HTX compared with a 62\% (range = 4 to 114\%) reduction in controls (P < 0.01 compared with severe CHF and distant HTX; P < 0.05 compared with recent HTX). Controls and moderate CHF did not differ from each other, and recent HTX differed only significantly from controls (Fig. 2B). In patients with severe CHF, an initial insignificant reflex reduction in blood flow and increase in vascular resistance at head-up tilt (at 7 min) was followed by a further decrease/increase during the tilt period to values significantly different from pretilt values (P < 0.01 at 22 min). In contrast, the immediate reflex response in HTX patients appeared to weaken during the tilt period (Fig. 2A).

Mode of HTX, Arterial Blood Pressure, Heart Rate, and Skeletal Muscle Blood Flow

Cardiac transplant recipients without preserved right native atrium (−PNA) had significantly higher resting systolic blood pressure than those with preserved right native atrium (+PNA; 139 ± 14 vs. 125 ± 15 mmHg, P < 0.05, Fig. 3A), a trend toward a higher diastolic blood pressure (89 ± 11 vs. 81 ± 10, not significant; P = 0.1), and a higher heart rate (92 ± 10 vs. 83 ± 8, P <
During 30-min head-up tilt, cardiac transplant recipients – PNA had a gradual decrease in systolic and diastolic blood pressures toward values identical to those of patients + PNA (Fig. 3A). The higher heart rate in cardiac transplant recipients – PNA showed an abrupt slowing at the end of the tilt period to values almost identical to those of patients + PNA (Fig. 3A). In patients – PNA, skeletal muscle blood flow tended to be higher and vascular resistance lower before head-up tilt but became significantly different from HTX patients + PNA only during the tilt (minutes 10–30, P < 0.05) and recovery periods (minutes 50–60, P < 0.01, Fig. 3B), indicating attenuated baroreceptor control of skeletal muscle blood flow. In contrast, subcutaneous blood flow and vascular resistance did not differ significantly between patients with different modes of HTX.

Orthostasis and Plasma ET-1

Plasma ET-1 at baseline was lower in controls (4.2 ± 0.9 pg/ml) than in patients with CHF (7.5 ± 4.8, P < 0.005) and after HTX (6.3 ± 2.4, P < 0.001), with the two patient groups not differing from each other. During 30-min 50° head-up tilt, plasma ET-1 increased significantly only in recent HTX (18 ± 14%, P < 0.01) and in moderate CHF (13 ± 12%, P < 0.05; Fig. 4), and the increase in plasma ET-1 was directly associated with the fall in skeletal muscle blood flow in recent HTX (r = −0.81, P < 0.005, Fig. 5). Plasma ET-1 changes did not relate to any hemodynamic parameter in the other study groups.

Orthostasis, Arterial Blood Pressure, and Heart Rate

Heart rate and systolic and diastolic blood pressures in the supine position before head-up tilt were significantly higher in patients after HTX compared with controls and patients with CHF (Table 1 and Fig. 6). Patients with CHF had a higher heart rate but similar systolic and diastolic blood pressures compared with controls. Systolic blood pressure was unchanged during the entire investigation in controls and showed a fall during the last 10 min of the tilt period in CHF (P < 0.01) and a sustained fall during the tilt period in HTX (P < 0.01). In controls, diastolic blood pressure showed...
a sustained increase during the tilt period ($P < 0.001$); in CHF and HTX, diastolic blood pressure was unchanged during the entire investigation. Heart rate showed a sustained increase during the tilt period in controls ($P < 0.001$), was unchanged during the tilt in CHF, and showed a gradual increase during the first 20 min of tilt ($P < 0.01$) followed by a gradual slowing in the remaining tilt period. All three groups had a rebound decrease to below pretilt values in the supine position after tilt. There was no difference in these parameters between patients with moderate and severe CHF and no difference between patients with HTX < 6 mo and > 6 mo before the investigation.

**DISCUSSION**

The major new findings in the present study are that 1) the attenuated baroreceptor-mediated reflex control in severe CHF of the calf microcirculation during brief upright posture is not a lasting phenomenon during prolonged orthostasis, 2) removal of all native right atrium in HTX was associated with an impaired calf skeletal muscle blood flow reflex control and resulted in a higher resting arterial blood pressure and heart rate and in orthostatic intolerance, and finally 3) changes in skeletal muscle blood flow during upright posture in recent HTX were inversely associated with changes of the vasoconstrictor ET-1 in plasma.

In healthy subjects, the passive upright tilt procedure induces both instantaneous and gradually arising alterations in several neurohormonal reflex mechanisms (19). The net peripheral vascular effect of the activation of these reflex mechanisms in healthy subjects is peripheral vasoconstriction; this is appropriate because it serves to maintain arterial blood pressure and to prevent edema formation (20).

**Orthostasis and Calf Skeletal Muscle Blood Flow**

Patients with CHF exhibit vasodilatation in skeletal muscle of the forearm during brief periods of head-up tilt, resulting in increased blood flow and decreased
vascular resistance (15). However, results are conflicting as to whether upper and lower extremities are equally controlled from cardiopulmonary baroreceptors (24). The present study demonstrated paradox vasodilatation also in calf skeletal muscle during head-up tilt in patients with severe CHF. A number of mechanisms for the paradox vasodilatation have been suggested. 1) The vasodilator response appears to be mediated by a central nervous system β-adrenergic vasodilator reflex, because local β-receptor blockade and proximal nerve blockade has been shown to reverse the abnormal vasodilatation (15). 2) It has also been suggested that resetting of baroreceptors in CHF results in reduced tonic activity with increased sympathetic drive. During head-up tilt, the reduction in filling pressures improves left ventricular contractility and decreases atrial and ventricular volume, leading to activation of atrial and ventricular baroreceptors (1, 3) However, an intriguing hypothesis has recently come up, suggesting that diastolic ventricular interaction in CHF results in increased inhibitory baroreceptor activity with reduced sympathetic outflow (2). The mechanism of diastolic ventricular interaction is increased left ventricular end-diastolic dimensions during volume unloading despite reductions in right ventricular volume and right atrial pressure (2).

We found that this abnormal reflex control of calf skeletal muscle vasodilatation was normalized early after HTX and remained normal. The early normalization does not imply a significant role of gradual cardiac reinnervation (4).

It has recently been suggested that patients with severe CHF have increased capillary pressure in the lower extremities during daily activities in the upright position because of the finding of continued paradox vasodilatation in subcutaneous tissue during prolonged sitting (26). This hypothesis is challenged by the findings in the present study in which an initial paradox vasodilatation in calf skeletal muscle in patients with severe CHF is followed by a normal vasoconstriction after 15 min of passive head-up tilt. Prolonged orthostasis results in continued peripheral pooling of blood and extravasation of body fluids. Therefore, a likely explanation for this finding is that the above-discussed diastolic ventricular interaction showing an initial increase in left ventricular dimension and decreased sympathetic outflow during orthostasis in patients with severe CHF (2) does not persist during prolonged orthostasis. The present finding of a normal vasocon-

![Graph of correlation between relative changes in skeletal muscle blood flow at head-up tilt and relative changes in plasma ET at head-up tilt in patients with HTX](http://ajpheart.physiology.org/)

![Graph of correlation between relative changes in skeletal muscle blood flow at head-up tilt and relative changes in plasma ET at head-up tilt in patients with HTX](http://ajpheart.physiology.org/)

Fig. 4. A: course of plasma endothelin (ET) levels in supine position, in upright position during 30-min 50° head-up tilt (between vertical dotted lines), and during 30-min recovery in supine position. Values are means ± SE. For the sake of clarity and because SE did not differ significantly within groups, SE is not being presented elsewhere. See RESULTS for details. B: individual relative changes in plasma ET at head-up tilt (at 5 min). NYHA, New York Heart Association. *Recent HTX and moderate CHF had a significant increase in plasma ET (P < 0.01 and P < 0.05, respectively) that was higher than in healthy controls (P = 0.01 and P = 0.1, respectively).
striction after some time in the upright position may explain why patients with CHF rarely suffer from orthostatic intolerance despite an initial paradox peripheral vasodilatation.

Orthostasis and Subcutaneous Tissue Blood Flow

Central reflex control of subcutaneous tissue blood flow may depend more on low-pressure cardiopulmonary mechanoreceptors in contrast to skeletal muscle blood flow, which appears to be controlled from both cardiopulmonary and sinoaortic high-pressure baroreceptors (14). Thus the combined activation of both high and low pressure and local reflexes during head-up tilt may result in different responses in subcutaneous tissue and skeletal muscle. Paradox vasodilatation has been demonstrated in previous studies both in forearm and calf subcutaneous tissue during brief unloading of baroreceptors in patients with severe CHF and in calf subcutaneous tissue during prolonged sitting (15, 26, 28). In contrast, we found that patients with severe CHF had no average paradox vasodilatation but an absence of changes in subcutaneous tissue blood flow and vascular resistance at head-up tilt. In the present study, 22 of the patients were treated with ACE inhibitors not withheld before the study. Acute ACE inhibitor treatment has been found to improve arterial and cardiopulmonary baroreceptor function and increase vascular resistance during baroreceptor unloading (8). In previous studies from our laboratory, in contrast, only ~50% of the patients were treated with ACE inhibitors, and the treatment was withheld 24 h before the investigation (26, 28). Supporting an ACE inhibitor effect is the finding in the previous studies of higher resting subcutaneous vascular resistance in severe CHF compared with controls, in contrast to similar values in the present study.

In contrast to the finding of a normal skeletal muscle vasoconstriction during tilt in cardiac transplant recipients, these patients and particularly distant HTX had an attenuated reflex control of subcutaneous tissue blood flow. These findings support the hypothesis that reflex control of subcutaneous tissue is mediated from cardiopulmonary baroreceptors (14) and do not support any significant impact of reinnervation of the denervated heart. However, although very indicative of differences in regional baroreflex control, the present data add to an unclear mosaic of results from previous studies. Normalized arterial baroreceptor function has been suggested after HTX (11), but Mohanty et al. (18) found a markedly attenuated total forearm vasoconstrictor response to graded lower body negative pressure, indicating disturbed cardiopulmonary baroreceptor function. Wroblewski et al. (29), in contrast, found that the vasoconstrictor response in calf subcutaneous tissue during 45° tilt appeared to be normalized early after HTX.

Role of Preserved Native Right Atria in Cardiac Transplant Recipients

This study demonstrates for the first time that differences in cardiac transplant operational technique with preservation or removal of native right atrium have an impact on peripheral hemodynamic parameters. The development and recommendation of the cava-cava technique with removal of the native atrium in contrast to the classic technique with preserved right atrium is based on reports of a higher likelihood of obtaining sinus rhythm and less incidence of tricuspid regurgitation (10). Bernardi et al. (3) suggested that...
patients without preserved right atrium and complete vagal denervation had both parasympathetic and sympathetic reinnervation in contrast to patients with preserved right atria in which only sympathetic reinnervation was demonstrated. However, we found that patients without preserved native right atrium had higher arterial blood pressure and heart rate and were more orthostatic intolerant, perhaps finally resulting in the abrupt slowing of the heart rate at the end of the tilt period. In dogs with progressive removal of cardiopulmonary baroreceptors, increasing arterial blood pressure was demonstrated with decreasing response to vagal blockade (17). Thus our data do not suggest any significant functional role of cardiac reinnervation. In addition, the patients without native right atrium appeared to have attenuated reflex control of skeletal muscle blood flow, whereas the groups did not differ with respect to impaired control of subcutaneous tissue blood flow. This suggests ventricular control of calf subcutaneous tissue blood flow and to some extent atrial control of skeletal muscle blood flow. The present data suggest that clinical outcome may possibly differ in HTX, depending on the degree of remnant native right atrium.

Orthostasis and ET-1

ET-1 is an extremely potent vasoconstrictor that has been demonstrated to rise in plasma during 60° head-up tilt in healthy controls in association with a parallel increase in arterial blood pressure (22). In the present study, during a 50° head-up tilt, healthy controls had no significant increase in plasma ET-1. In contrast, cardiac transplant recipients with recently denervated right atrium had the highest increase in plasma ET-1 at head-up tilt, an increase with a highly significant correlation to the parallel decrease in skeletal muscle blood flow. This is the first direct evidence of endogenous circulating ET-1 having a role in the immediate regulation of the peripheral microcirculation and indicates that this potent vasoconstrictor may have a role as a "rescue" hormone during certain phases of the cardiovascular response to orthostasis.

Orthostasis, Blood Pressure, and Heart Rate

The increase in diastolic pressure in healthy controls during head-up tilt may mirror storage of blood in conduit arteries at unchanged systolic blood pressure (6), and the subsequent transient rebound fall in diastolic blood pressure in the supine position may be caused by a decline in the stored blood in relatively distended conduit arteries. The directionally opposite changes in heart rate and pulse pressure (systolic-diastolic blood pressure) during and after head-up tilt agree well with the general view that heart rate is controlled via arterial baroreceptors (19). The decrease in systolic blood pressure and absence of a parallel immediate increase in heart rate at head-up tilt in HTX indicates the absence of any significant effector sympathetic inotropic and chronotropic innervation and supports other findings in the present study of lack of any significant cardiac reinnervation. The delayed gradual increase in heart rate during head-up tilt probably mirrors the positive chronotropic effect of circulating norepinephrine after increased catecholamine spillover in HTX (9).

In summary, patients with severe CHF secondary to IDCM had abnormal vascular responses in calf skeletal muscle and subcutaneous tissue only during brief, but not prolonged, upright tilt. The finding may explain why patients with CHF rarely suffer from orthostatic intolerance despite an initial paradox peripheral vasodilatation and implies only a minor role of this abnormality in the edema pathogenesis. After HTX, a normal reflex response is found in skeletal muscle but not in subcutaneous tissue. However, the subgroup of patients with complete removal of all native right atrium also appeared to have attenuated skeletal muscle reflex response. These patients also had a higher arterial blood pressure, orthostatic intolerance, and a higher heart rate. The findings in HTX indicate different regional reflex control of subcutaneous tissue and skeletal muscle blood flow and suggest that transplantation with varying degree of remnant right atrium may have important hemodynamic impact. Finally, in the early period after HTX, reflex control of skeletal muscle blood flow during orthostasis appeared to be dependent on release of the potent vasoconstrictor ET-1, indicating a so far unknown instant hemodynamic role of circulating ET-1.

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H248 LOWER LEG MICROCIRCULATION IN HEART FAILURE


