Sympathetic reflex control of skeletal muscle blood flow in patients with congestive heart failure: evidence for $\beta$-adrenergic circulatory control

ELI KASSIS, M.D., TAGE N. JACOBSEN, M.D., FLEMING MOGENSEN, M.D., AND OLE AMTORP, M.D.

ABSTRACT  Mechanisms controlling forearm muscle vascular resistance (FMVR) during postural changes were investigated in seven patients with severe congestive heart failure (CHF) and in seven control subjects with unimpaired left ventricular function. Relative brachioradial muscle blood flow was determined by the local $^{133}$Xe-washout technique. Unloading of baroreceptors with use of 45 degree upright tilt was comparably obtained in the patients with CHF and control subjects. Control subjects had substantially increased FMVR and heart rate to maintain arterial pressure whereas patients with CHF had decreased FMVR by 51 ± 11% (mean ± SEM, p < .02) and had no increase in heart rate despite a fall in arterial pressure during upright tilt. The autoregulatory and local vasoconstrictor reflex responsiveness during postural changes in forearm vascular pressures were intact in both groups. Further investigations were carried out in the patients with CHF. The left axillary nerve plexus was blocked by local anesthesia in the seven patients. No alterations in forearm vascular pressures were observed. This blockade preserved the local regulation of FMVR but reversed the vasodilator response to upright tilt as FMVR increased by 30 ± 7% (p < .02). Blockade of central neural impulses to this limb combined with brachial arterial infusions of phentolamine completely abolished the humoral vasoconstriction in the tilted position. Infusions of propranolol to the contralateral brachial artery that did not affect baseline values of heart rate, arterial pressure, or the local reflex regulation of FMVR reversed the abnormal vasodilator response to upright tilt as FMVR increased by 42 ± 12% (p < .02). Despite augmented baseline values, forearm venous but not arterial plasma levels of epinephrine increased in the tilted position, as did arterial rather than venous plasma concentrations of norepinephrine in these patients. The results suggest a $\beta$-adrenergic reflex mechanism elicited by spinal or supraspinal neural impulses and probably modulating a cotransmitter release in the patients with CHF.


REFLEX increases in heart rate and vascular tone are essential for the maintenance of arterial pressure during upright tilt. The stimulus for these circulatory adjustments appears to reside mainly in cardiopulmonary and arterial baroreceptors exerting afferent restraint on sympathetic efferent outflow. Recent studies in normal human beings have indicated that postural changes causing a threshold increase of vascular transmural pressure elicit an arteriolar constriction by means of a local venaarteriolar sympathetic axon mechanism. This local vasoconstrictor-reflex response has recently been shown to contribute to the maintenance of arterial pressure during postural changes.

Patients with congestive heart failure (CHF) have demonstrated abnormal vascular responses to orthostatic stress. These abnormalities have recently been related to selectively impaired baroreflex control of forearm vascular tone. A reduced baroreflex afferent inhibitory influence on brainstem vasomotor centers, may explain the neurohumoral excitation widely documented in patients with CHF. In fact, animal preparations of chronic heart failure have shown impairment of the arterial baroreflex cardiovascular control as well as a chronically reduced afferent restraint and degenerative changes of cardiopulmonary baroreceptors. However, the augmented sympathetic drive in patients with CHF is contrasted by depletion of norepinephrine in cardiac tissue and attenuated cardiac responsiveness to sympathetic efferent activity.

With the local $^{133}$Xe-washout technique for determination of blood flow, consistent results have been obtained in a recent series of studies of different human tissues. It has recently been confirmed that this
method gives reliable estimates of relative blood flow during different experimental conditions, including those with dilated veins. It is known that the veins of patients with CHF are less distensible than those of normal subjects.22, 23

Using the same method to estimate relative changes in forearm muscle vascular resistance (FMVR), we performed this study to determine circulatory adjustments to stimuli known to induce sympathetic activation in normal human subjects and to elucidate mechanisms underlying these adjustments in patients with CHF.

Methods

Patient selection. Seven male patients ranging in age from 43 to 61 years were studied. All were selected on the basis of severe CHF that was inadequately controlled by conventional treatment with digoxin and diuretics. The cause of CHF was ischemic in all patients with angiographically documented coronary artery disease. No patient was studied within 3 months of a myocardial infarction. For a minimum of 4 weeks before study, all vasodilators, calcium antagonists, and β-blocking agents were withheld while treatment with digoxin and diuretics was regulated and maintained. All patients were in sinus rhythm and had normal electrolytes, blood counts, and therapeutic serum levels of digoxin during the study. Central and peripheral hemodynamic studies were performed before noon on successive days. The study protocol was carefully explained and informed consent was obtained from all patients. The protocol was approved by the official ethical committee in Copenhagen.

Procedures

Central hemodynamic measurements. The patients were studied in the supine postabsorptive state. All catheter procedures were performed under fluoroscopic control. A balloon tipped, triple-lumen thermodilution catheter (Gould SP 1435) was placed in the pulmonary artery for pressure measurements and determination of cardiac output (dilution curves of five consecutive measurements were recorded). A Cordis pigtail catheter was introduced percutaneously through the right femoral artery and positioned in the left ventricle for pressure recordings and angiography. All pressures were measured with reference to midaxillary level and were recorded with Statham P23Db transducers. Systemic vascular resistance (dyne-sec-cm⁻²) was calculated as 80 × (mean arterial pressure - right atrial pressure)/cardiac output.

Half an hour after angiography, control measurements of aortic, right atrial, and left ventricular filling pressures were performed while patients rested supine on a tilt table. Thereafter the patients were passively and slowly tilted to a 45 degree angle with the feet supported by a base platform. Pressure measurements were repeated within 5 to 7 min after initiation of tilt and with reference to the right atrium level set for each patient.

Peripheral hemodynamic measurements. On the morning of testing, the patients were placed horizontally on a tilt table. Room temperature was 22°C and remained constant during the entire investigation. The left axillary nerve plexus was percutaneously infiltrated by 40 ml mevipacaine 1% without vasocstringent. The effectiveness of this proximal nerve blockade (PNB) to the left forearm was ensured by motor paralysis, analgesia, loss of sweat secretion, and increase in skin temperature. This PNB was effective during the 4 hr period of investigation, and no complications or decreases in arterial pressure were observed. A 20-gauge polyethylene arterial catheter (Viggo FlowSwitch) was placed percutaneously in the left and right brachial arteries. An intravenous cannula was placed in a distal vein of the forearm. The arterial and local venous pressures were continuously measured with Statham P23Db transducers and recorded simultaneously with heart rate on a Siemens Elema minograph 81. After placement of the monitoring lines and induction of PNB, a 30 min rest period was allowed, during which the patients were familiarized with the protocol.

Skeletal muscle blood flow was measured by the local 133Xe-washout technique. Via a thin cannula, 0.1 ml (1 mCi) of 133Xe dissolved in isotonic saline (Radiochemical Center, Amersham, England) was injected into the brachialial muscle of each forearm. Measurements were started 20 min after the injection to avoid influences from the injection trauma on the washout rate of 133Xe. The γ-radiation of 133Xe was detected by NaI (TI) scintillation detectors placed perpendicular to the sites of injection at a distance of about 10 cm. Care was taken that the counting geometry remained constant during a single investigation. The recorded activity was fed to a universal printing γ-spectrometer (Novo Diagnostic System) with a window of acceptance adjusted around the 81 keV photopeak of 133Xe. The count rates were printed out every 5 sec without time delay.

The investigations consisted of triads of measurements on both forearms, each part of a trial lasting 5 min: (1) during reference level (ref₁), supine position with forearms studied at midaxillary line; (2) during test conditions (test); (3) after return to reference level (ref₂). Such triads of measurements were carried out before (ref₁), during, and after (ref₂) each of the following test conditions: elevation of forearms 20 cm above reference level, lowering of forearms 40 cm below reference level, and upright tilt (45 degrees) as described above, with forearms studied at heart level.

With the same radioactive depot, measurements were repeated in all patients during brachial arterial infusions of propranolol to the right forearm and brachial arterial infusions of phentolamine to the left neurally blocked forearm. Intrabrachial infusions of propranolol at 16.6 μg/min and of phentolamine at 500 μg/min in isotonic saline were carried out by means of IVAC 531 continuous nonpulsatile pumps. The total volume of infusate was 0.5 ml/min; no measurable changes in forearm blood flow have been observed during infusion of vehicle into the brachialial artery at these rates.24 Triads of measurements were repeated as described above before, during, and after the test conditions of 40 cm forearm lowering and of 45 degree upward tilt. Measurements were started after 10 min and carried out during 40 to 50 min of brachial arterial infusions of each drug.

In additional series of experiments, the effect of a single dose of propranolol injected into the brachial artery or locally into the brachioradial muscle was studied during upright tilt. A depot of 0.1 ml of the 133Xe solution was mixed with 0.1 ml (10 ng) of a propranolol solution in saline (0.1 mg/liter) and injected into the brachioradial muscle. An equal depot of the 133Xe solution mixed with 0.1 ml saline was injected into the contralateral brachioradial muscle and served as a control depot. Bilateral simultaneous measurements were started 20 min after injecting the radioactive depots. A group of three consecutive measurements, each lasting 5 min, was obtained during upright tilt and during reference conditions before and after the tilt. The same triad of measurements was repeated on the control depot within 15 min after a bolus injection of 0.3 mg (0.3 ml) of propranolol into the brachial artery.

Protocol. The central and peripheral hemodynamic studies were performed in all patients before noon on successive days and at a room temperature of 22°C. The peripheral hemodynamic investigations were started after an hour rest period, during which the patients were familiarized with the techniques.
The sequence of these investigations was of the same order as described above in all patients. The responses to upright tilt before and after a single dose of propranolol injected locally or intra-arterially were recorded separately for each patient.

**Control subjects.** Seven age-matched patients who underwent routine cardiac catheterization and had normal left ventricular ejection fraction and central hemodynamics served as a control group. Brachioradial muscle blood flow regulation was studied in the sequence described above. No PNB and no intra-arterial infusion of vehicle were performed. Control subjects were not receiving vasoactive drugs before the study.

**Methodologic considerations and calculations.** When the washout of a tracer from a homogeneous tissue with homogeneous perfusion is not influenced by recirculation and is only perfusion dependent, i.e., that diffusion equilibrium is achieved within a single passage through the capillaries,26 the perfusion coefficient, \( f \), can be calculated as:

\[
f = \lambda \cdot k \cdot 100 \text{ (ml/min/100g)}
\]

where \( \lambda \) and \( k \) denote the tissue-to-blood partition coefficient (ml/g) and the fractional washout rate constant (min\(^{-1}\)), respectively.

Methodologic aspects of applying the local \(^{133}\)Xe-washout method for measurement of blood flow in skeletal muscle have been thoroughly evaluated in a number of studies.20, 24, 27, 28 Three factors are of importance for determination of resting skeletal muscle blood flow. The initial steep washout rate after intramuscular injection gives an overestimation of blood flow because of the local influence of the injection trauma lasting about 10 min.24 The later part of the washout curve, which is approximately monoexponential, is influenced by two other factors: (1) recirculation of the \(^{133}\)Xe due to venuoarteriolar shunting by diffusion27 and (2) accumulation of the \(^{133}\)Xe in fat tissue lining the veins.28 Both factors tend to reduce the washout rate of \(^{133}\)Xe, giving an underestimation of skeletal muscle blood flow by about 20% to 60% at low flow rates as during resting conditions.24 Thus it is not possible to obtain a correct estimate of resting blood flow in skeletal muscle by the local \(^{133}\)Xe technique. However, it is possible to obtain reliable estimates of relative blood flow by comparing the slopes of the approximately monoexponential washout from the same \(^{133}\)Xe depot during different test conditions if \( A \) remains constant as the relative impact of shunting by diffusion and fat accumulation remains constant within the flow rates considered. Variations in \( A \) during the test conditions of venous stasis are less than 5%.29 By relating the washout rate under test conditions to reference values obtained just before and after the test, the small spontaneous decrease in the washout rate is taken into account.3, 6, 7, 29 Studies in dog limbs have shown a close correlation between relative changes in resting muscle blood flow estimated by the local \(^{133}\)Xe washout technique and femoral blood flow measured by an electromagnetic flowmeter.21

The sources of error mentioned above were taken into account in the present study. (1) The same single depot in each brachioradial muscle was used through the entire experiment during 20 to 120 min after the intramuscular injection. Preliminary measurements on bilateral control depots in both brachioradial muscles were obtained on different days in two patients during only the supine reference conditions. After an initial steep slope, a constant shallow slope of the washout curve was observed during about 15 to 125 min after the intramuscular injection. (2) Two reference curves just before and after each test conditions were obtained. (3) To avoid variations in relative blood flow caused by other mechanisms than the test conditions, data were analyzed only when the reference washout rate before and after each test did not differ more than a maximum of 50%. (4) Reproducibility of the relative changes in blood flow during test conditions was secured by consistent results obtained on different days in the same patient, the same area for the \(^{133}\)Xe depot being used.

Within the triad of measurements from the same \(^{133}\)Xe depot, \( \lambda \) was assumed to remain constant and relative blood flow during test conditions was calculated as:

\[
f_{\text{test}} / f_{\text{ref}} = k_{\text{test}} / k_{\text{ref}}
\]

where \( k_{\text{test}} \) is the washout rate constant obtained during test conditions, \( k_{\text{ref}} \) is the average value of \( f_{\text{test}} \) and \( f_{\text{ref}} \). The \( k \) value was calculated from the regression analysis (least-squares method) of the count rates transformed logarithmically and corrected for background activity.

Relative vascular resistance during test conditions was calculated as:

\[
R_{\text{test}} / R_{\text{ref}} = (\Delta P_{\text{test}} / \Delta P_{\text{ref}}) / (k_{\text{ref}} / k_{\text{test}})
\]

where \( \Delta P_{\text{test}} \) is the mean perfusion pressure \( (P_a - P_v) \) during test conditions and \( \Delta P_{\text{ref}} \) is the average value of perfusion pressures obtained during the two reference conditions before and after the test.

**Determination of plasma catecholamine concentrations.** Plasma concentrations of norepinephrine and epinephrine were determined by the double-isotope derivative technique22 and use of a high-performance liquid chromatographic system (Waters Associates, Milford, MA). Normal resting levels of norepinephrine and epinephrine were 0.4 to 1.9 and 0.07 to 0.44 nmol/liter, respectively. Venous and brachial arterial blood samples were obtained simultaneously from the forearm 1 hr after resting in supine position and within 9 to 10 min of initiating upright tilt.

**Statistics.** The results are given as mean ± SEM. The Wilcoxon signed-rank test was used. Comparison between patients and control subjects was performed by the Wilcoxon rank-sum test. A .05 level of significance was set.

**Results**

**Central hemodynamics.** The seven patients had classic symptoms of dyspnea, fatigue, orthopnea, and paroxysmal nocturnal dyspnea for a mean of 18 months before the study. Baseline hemodynamic measurements confirmed the presence of severely impaired left ventricular performance with low stroke volume and increased pressures and dimensions (table 1). Control subjects had an angiographic left ventricular ejection fraction of 75 ± 4% and normal central hemodynamics.

**Hemodynamic responses to postural changes** (table 2). During forearm elevation 20 cm above reference levels, the brachial perfusion pressure \( (P_a - P_v) \) decreased by about 14 and 15 mm Hg in patients with CHF and in control subjects, respectively. Forearm lowering 40 cm below reference levels caused parallel increments in arterial and venous transmural pressures, the latter corresponded to 33 ± 2 and 30 ± 1 mm Hg in patients and control subjects, respectively. During 45 degree upright tilt, both right atrial and left ventricular filling pressures decreased substantially in patients with CHF.
and in control subjects. However, control subjects had increased heart rate and maintained arterial mean pressure whereas patients with CHF showed no increase in heart rate in the tilted position.

Regulation of FMVR during postural changes. The decrease in brachial perfusion pressure observed in the elevated forearm elicited no relative change in brachioradial muscle blood flow (0 ± 1%) in patients with CHF and control subjects whose FMVR decreased by about 16% and 17%, respectively.

The increased venous transmural pressure observed in the lowered forearm elicited a decrease in muscle blood flow of 25 ± 3% (p < 0.02) in control subjects and of 19 ± 6% (p < 0.02) in patients with CHF, corresponding to substantial increments in FMVR that were similar in both groups (figure 1).

During 45 degree upright tilt with the forearm at heart level, blood flow decreased by 43 ± 5% (p < 0.02) corresponding to an increase in FMVR of 60 ± 10% (p < 0.02) in control subjects, whereas in patients with CHF blood flow increased by 76 ± 24% (p < 0.02) corresponding to a decrease in FMVR of 51 ± 11% (p < 0.02) (figure 1).

Mechanisms underlying vasodilatation during upright tilt in patients with CHF. An example of the 133Xe-washout curves obtained in one patient is shown in figure 2 and the compiled data of the 133Xe studies are shown in figures 3 and 4.

Effects of local β-adrenoceptor blockade. During 10 to 50 min of brachial arterial infusions of propranolol at 16.6 μg/min, no alterations in the baseline values of heart rate or arterial and venous pressures were observed. Measurements obtained during this period revealed a vasoconstrictor response to venous pressure elevation of about 32 mm Hg in the lowered forearm (figure 3, B) that did not substantially differ from the control.

### Table 1
Clinical and hemodynamic characteristics of patients with CHF

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Duration of symptoms (mo)</th>
<th>HR (bpm)</th>
<th>LVEF (%)</th>
<th>LVEDV (ml)</th>
<th>LVEDP (mm Hg)</th>
<th>Mean RAP (mm Hg)</th>
<th>Mean PAP (mm Hg)</th>
<th>Mean AP (mm Hg)</th>
<th>CI (l/min/m²)</th>
<th>SVR (dyne-sec-cm⁻²)</th>
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<td>55</td>
<td>8</td>
<td>83</td>
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<td>42</td>
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<tr>
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HR = heart rate; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVEDP = left ventricular end-diastolic pressure; RAP = right atrial pressure; PAP = pulmonary arterial pressure; AP = aortic pressure; CI = cardiac index; SVR = systemic vascular resistance.

### Table 2
Mean values (± SEM) of arterial, venous, and cardiac filling pressures and heart rate during supine position and postural changes in seven patients with CHF and seven control subjects (C)

<table>
<thead>
<tr>
<th></th>
<th>CHF (mm Hg)</th>
<th>C (mm Hg)</th>
<th>CHF (bpm)</th>
<th>C (mm Hg)</th>
<th>CHF (mm Hg)</th>
<th>C (mm Hg)</th>
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<th>C (mm Hg)</th>
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<tbody>
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<td>Supine</td>
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<td>96</td>
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<td>88</td>
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<td>(1)</td>
<td>(7)</td>
<td>(2)</td>
<td>(1)</td>
<td>(2)</td>
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<tr>
<td>Forearm elevation (20 cm)</td>
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<td>81</td>
<td>9</td>
<td>7</td>
<td>89</td>
<td>71</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(6)</td>
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<td>(2)</td>
<td>(6)</td>
<td>(1)</td>
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<td>Forearm lowering (40 cm)</td>
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<td>37</td>
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<td></td>
<td>(5)</td>
<td>(2)</td>
<td>(3)</td>
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<td>(5)</td>
<td>(1)</td>
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<tr>
<td>Upright tilt (45°)</td>
<td>73</td>
<td>96</td>
<td>0</td>
<td>1</td>
<td>89</td>
<td>80</td>
<td>1</td>
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<tr>
<td></td>
<td>(6)</td>
<td>(3)</td>
<td>(2)</td>
<td>(2)</td>
<td>(7)</td>
<td>(2)</td>
<td>(2)</td>
<td>(2)</td>
<td>(3)</td>
<td>(2)</td>
</tr>
</tbody>
</table>

$P_a =$ mean brachial arterial pressure; $P_v =$ mean forearm venous pressure; RAP = mean right atrial pressure; LVFP = left ventricular filling pressure.

*Ap < .02 vs supine values.
response (figure 3, A). However, this administration of propranolol elicited a decrease in blood flow of 46 ± 5% (p < .02) corresponding to an increase in FMVR of 42 ± 12% (p < .02) during upright tilt (figures 2, B, and 4, B). Despite this vasoconstrictor response, both mean and systolic arterial pressures decreased from 95 ± 6 and 128 ± 10 mm Hg in the supine position to 70 ± 7 and 99 ± 9 mm Hg in the tilted position while heart rate and arterial pulse pressure were maintained at predrug values.

Brachioradial muscle vascular responses to upright tilt were reproducible both before and after a single dose of propranolol injected either intra-arterially (0.3 mg) or locally into the muscle (10 ng). Muscle blood flow increased by 56 ± 10% corresponding to a decrease in FMVR of 48 ± 10% in the tilted position before propranolol. Upright tilt after the brachial arterial or intramuscular propranolol injection elicited a decrease in blood flow of 40 ± 5% or 46 ± 8% corresponding to an increase in FMVR of 37 ± 4% or 51 ± 6%, respectively.

FIGURE 1. Mean relative change ± SEM in blood flow and FMVR during 40 cm lowering of forearm and 45 degree upright tilt with forearm at heart level in control subjects (hatched columns) and in patients with CHF (open columns).

FIGURE 2. Example of $^{133}$Xe-washout curves obtained in a patient with CHF before (left), during (middle), and after (right) 45 degree upright tilt during control conditions (A) and after local $\beta$-receptor blockade (B), proximal nervous blockade ('A), and proximal nervous blockade combined with local $\alpha$-receptor blockade ('B). Figures in parentheses denote the washout rate constant per minute ($k$, $\times 10^3$ ± 1 SD).
Effects of PNB. Half an hour after PNB of the limb, motor paralysis, analgesia, and an increase in skin temperature were present and lasted through the entire experiment. Baseline values of heart rate and arterial and venous pressures were preserved. No relative change in muscle blood flow was elicited by a decrease of 15 ± 1 mm Hg in perfusion pressure of the elevated forearm; however, FMVR decreased by about 15%. No substantial changes were observed in the increase of vascular transmural pressure of the lowered forearm or in the consequent vascular responses (figure 3, 'A). PNB did not affect the control values of vascular pressures and heart rate during upright tilt. However, the vascular responses were reversed as muscle blood flow decreased by 30 ± 5% (p < .02) corresponding to an increase in FMVR of 30 ± 7% (p < .02) (figures 2, 'A, and 4, 'A).

Effects of PNB combined with local $\alpha$-receptor blockade. Additional brachial arterial infusions of phentolamine at 500 $\mu$g/min to the neurally blocked limb elicited no change in supine values of heart rate and vascular pressures. The given dose of the drug completely abolished the vasoconstrictor response to venous stasis in the lowered forearm as blood flow increased by 7 ± 5% and FMVR decreased by 4 ± 3% (figure 3, 'B). The vasoconstriction in the tilted position was also abolished as blood flow and FMVR decreased by 6 ± 5% and 1 ± 4%, respectively (figures 2, 'B, and 4, 'B).

Plasma concentrations of catecholamines (table 3). Supine values of venous plasma catecholamines were within the normal range in control subjects; those for epinephrine were maintained but those for norepinephrine increased during upright tilt. Patients with CHF had augmented supine values of circulating catecholamines, which for epinephrine were significantly lower in venous than in brachial arterial plasma. During upright tilt, patients with CHF had an attenuated increment in venous but not arterial plasma levels of norepinephrine; they had an increase in the venous plasma levels of epinephrine and maintained the arterial levels. The tilt venous and arterial plasma epinephrine concentrations were not substantially different.

**Discussion**

Circulating baseline levels of the neurotransmitter, norepinephrine, and the adrenal hormone, epinephrine, were elevated in the patients with CHF. Despite

<table>
<thead>
<tr>
<th>TABLE 3</th>
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<tbody>
<tr>
<td><strong>Mean plasma levels of catecholamines (± SEM) during the supine and tilted positions in control subjects (venous) and patients with CHF (venous and arterial)</strong></td>
</tr>
<tr>
<td>Norepinephrine (nmol/l)</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Supine</td>
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<td>Control subjects</td>
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<td>0.93</td>
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<td>(0.08)</td>
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<td>Patients with CHF</td>
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<td>Arterial</td>
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</table>

$^a$p < .02, tilt vs supine.
$^b$p < .02, arterial vs venous.
augmented sympathetic efferent outflow to neuroeffector junctional clefts, which may facilitate further neurohumoral excitation in CHF,\textsuperscript{11-15} arterial hypotension during simulated orthostatic stress has recently been observed in a subset of patients with CHF\textsuperscript{10} as it was in our patients. The results of the present study seem to indicate that the arterial hypotension is not a primarily effect of upright tilt but is subsequent to a vasodilator reflex arc intended probably to improve cardiovascular performance in patients with CHF.

The cardiovascular response normally intended to maintain arterial pressure during the gravitational forces of upright tilt is mainly related to a reflex arc originating from cardiopulmonary and arterial baroreceptors.\textsuperscript{1} Evidence obtained so far suggests that digitalis at a therapeutic dose in man selectively augments arterial baroreflex-mediated effects\textsuperscript{30} and augments cardiopulmonary baroreflex-mediated vasoconstrictor responses.\textsuperscript{31} Moreover, short-term administration of digitalis may normalize vascular responses to orthostatic stress in patients with moderate-to-severe CHF.\textsuperscript{10} Despite conventional therapy, our patients presented classic symptoms and signs of severe CHF and had abnormal responses to upright tilt. The patients studied had therapeutic serum levels of digoxin and were not hypovolemic as judged by the normal hematocrit and electrolytes. These patients had dilated rather than constricted resistance vessels of skeletal muscle during the orthostatic stress.

The observed decreases in cardiac filling pressures during upright tilt were comparable in the patients with CHF and control subjects. Since these pressures were elevated in the patients, cardiopulmonary baroreceptors might have been less sensitive to a pressure decrease from high to less high levels than to a fall to low levels. Such a possibility may explain an attenuated and not reversed vasoconstriction in the tilted position. However, the patients and control subjects had comparable supine values of arterial pressure, but the patients developed a state of arterial baroreceptor hypotension during upright tilt and the expected circulatory adjustments failed to occur.\textsuperscript{1, 16, 30} Despite an apparently adequate level of reflex stimulus to the baroreceptors, the responses observed in the tilted position were severely deranged in these patients. Impairment of the cardiopulmonary and arterial baroreflex control in CHF has been reported in human\textsuperscript{10} and animal\textsuperscript{14} studies.

Studies of the baroreflex afferent limb have disclosed degenerative changes in neurofibrillar end plates of arterial baroreceptors in patients with CHF.\textsuperscript{32} Similar changes in cardiopulmonary baroreceptors combined with abnormally reduced afferent activity from these receptors have been disclosed in animal preparations of heart failure.\textsuperscript{17, 18} Abnormally reduced baroreceptor afferent restraint on sympathetic efferent outflow\textsuperscript{1} may account for the augmented baseline plasma levels of catecholamines in our patients, but the question is whether it explains the abnormal vasodilator response to upright tilt. Circulatory homeostasis is a complex supraspinal integration of afferent impulses from various receptor sites.\textsuperscript{1} Microneurographic studies in normal human subjects have shown the differentiated sympathetic outflow to skeletal muscle and subcutaneous vascular beds to become uniform after lidocaine blockade of vagus and glossopharyngeal nerves in the neck.\textsuperscript{33} Such a temporary baroreceptor deafferentation has also been shown to cause the appearance of an abnormal sympathetic reflex.\textsuperscript{33}

We did not study the supraspinal restraint of baroreflex parasymathetic afferents but carefully investigated the sympathetic efferent limb effects on FMVR as an effector organ. It seems difficult to attribute the decrease in FMVR during upright tilt in the patients with CHF to nonspecific depression of vascular reactivity.\textsuperscript{34} The vasodilatation observed in these patients seems to be specific to the reflex stimulus of upright tilt, since the patients had a normal vasoconstrictor response to sympathetic reflex stimulation evoked by forearm lowering.

Despite the increased sympathetic vasoconstrictor activity, venous pressure elevation in the 40 cm lowered forearm elicited vasoconstriction in the patients with CHF as in control subjects. With the $^{133}$Xe-washout technique, studies of different human tissues have shown that a threshold increase in venous transmural pressure of about 25 mm Hg or more elicits $\alpha$-adrenergic arteriolar constriction by means of a local sympathetic axon mechanism.\textsuperscript{2-7} This vasoconstrictor axon reflex has also been demonstrated during blockade of central sympathetic outflow to the limb.\textsuperscript{6, 7, 21} The vasoconstriction during venous pressure elevation has been abolished after short-term denervation of the entire sympathetic nerve tree of the limb with use of PNB combined with blockade of vascular $\alpha$-adrenoreceptors.\textsuperscript{6, 21} The observations in our patients are in agreement with those in normal human subjects\textsuperscript{2-7}: the vasoconstrictor response to venous stasis in the lowered forearm was preserved after PNB and was completely abolished after additional intra-arterial infusions of phentolamine.

The given dose of phentolamine induced no systemic effect and was within the range previously reported to achieve vascular $\alpha$-receptor blockade when given intra-arterially to the human limb.\textsuperscript{6, 35} PNB of the fore-
arm did not only abolish but reversed the vasodilator response to upright tilt in our patients. Brachial arterial levels of norepinephrine increased during upright tilt in these patients, and the dose of phentolamine given to the neurally blocked forearm completely abolished the vasoconstriction in the tilted position. Taken together, these observation suggest that the vasoconstrictor response to upright tilt after PNB is a humoral, α-nor-epinephric effect.

As observed during forearm elevation 20 cm above heart level, the skeletal muscle vascular bed was not maximally dilated after PNB. The fall in perfusion pressure of the elevated forearm elicited a decrease in FMVR while the blood flow was maintained at a constant level. These circulatory adjustments were of similar magnitude and direction at baseline and after PNB. The observations suggest that intrinsic vascular mechanisms underlying autoregulation of blood flow were operative in the patients with CHF and were essentially unaffected by neural vasoconstrictor activity. Autoregulatory mechanisms might have supported the vascular responses to upright tilt, since brachial perfusion pressure decreased by about 12 mm Hg in these patients (table 2). If this were the case, autoregulation of blood flow should also have been observed in the tilted position after PNB.

Human studies have indicated that vascular β-adrenoceptors may take part in regulation of skeletal muscle blood flow in resting forearm during contralateral isometric handgrip.36 Animal studies have shown a β2-adrenergic mechanism operating in various vascular beds during the stress of hemorrhagic shock and subserving improvement of the tissue perfusion and cardiovascular performance.37,38 In the patients with heightened sympathetic tone due to CHF, the sympathetic stimulation of the orthostatic stress might have activated vascular β-adrenoceptors. To test this hypothesis, brachial arterial infusions of propranolol were carried out and no systemic effects were elicited by the drug. The infusate volume was at a rate shown not to alter forearm blood flow,25 and the given dose of propranolol was similar to that reported to achieve vascular β-adrenoceptor blockade in the human limb.39 Although the drug preserved the α-adrenergic vasoconstrictor response to venous pressure elevation in the lowered forearm, it elicited vasoconstriction in the tilted position and muscle blood flow decreased by 46%. This vasoconstriction might have increased the concentration of propranolol delivered to the forearm during upright tilt, since the drug concentrations in blood and tissue would depend on the blood flow. Therefore a single intra-arterial dose of propranolol was given and not only attenuated but also reversed the vasodilator response to upright tilt. Furthermore, a local injection of propranolol into the labeled area elicited vasoconstriction in the tilted position. A local anesthetic action of propranolol (10 mg/liter) has been shown,40 whereas β-adrenoceptor blocking properties of the drug have been achieved at a lower plasma concentration of 0.1 mg/liter.41

Propranolol is not known to possess intrinsic sympathomimetic properties. Although it is not a selective β-antagonist, its effect on the skeletal muscle vascular bed in the present study seems most likely to be mediated by β2-adrenoceptors on the blood vessel wall. The consistent observations made during the propranolol studies, together with those made during the blockade of neutral efferent impulses to the forearm, suggest that a central neural mechanism is elicited by upright tilt to modulate an apparently β2-adrenergic vasodilatation in the patients with CHF.

The tilt-induced neurogenic vasodilatation in our patients may involve a cotransmitter role for epinephrine. There is increasing evidence that circulating epinephrine is taken up into adrenergic nerve terminals, stored, and eventually released with norepinephrine into the junctional clefts on the blood vessel wall.42-44 In normal human subjects, a cotransmitter role for epinephrine has been reported to augment neurogenic vasoconstriction by activation of primarily prejunctional β2-adrenoceptors that facilitate the release of norepinephrine.44 The patients with CHF had augmented circulating epinephrine levels that were higher in arterial inflow than in venous effluents of the forearm. Such an extraction of epinephrine in the supine resting position may be ascribed to intact neuronal membrane uptake system in the human limb.15 This neuronal uptake is not operating during the time the neurotransmitter release is evoked by central neural impulses, a time at which prejunctional adrenoceptors on the neuronal membrane exert negative (α2) or positive (β2) feedback control of transmitter release.42,43

Our data provide no direct evidence for a cotransmitter release of epinephrine from forearm adrenergic nerve terminals during upright tilt in the patients with CHF. Despite the tilt-induced increment in muscle blood flow that would tend to decrease the concentration of the blood-borne catecholamine, plasma epinephrine levels increased in venous outflow from the forearm during upright tilt while they were almost maintained in the arterial inflow in these patients. The sympathetic stimulation of upright tilt in control subjects did not affect the normal plasma concentrations of this adrenal hormone. It is tempting to speculate that
long-term exposure to augmented neurotransmitter vasoconstrictor activity in the patients with CHF may increase the β-adrenergic responsiveness of skeletal muscle resistance vessels to catecholamines or that, in contrast to its effect in normal subjects, epinephrine at higher concentrations might exert predominantly postjunctional rather than prejunctional β₂ effects.

Circulatory homeostasis during the course of CHF may apparently be maintained by a delicate balance between α-adrenergic vasoconstrictor and β-adrenergic vasodilator neural efferent pathways. The net hemodynamic significance subjected to central integration of responses[1] seems to be determined by the severity of impairment of the afferent restraint from cardiopulmonary and arterial baroreceptors.

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References


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Erratum

An error appeared in the abstract. The sentence beginning five lines from the bottom should have read: “Exercise-induced regional wall motion improved in the training group.”

E Kassis, T N Jacobsen, F Mogensen and O Amtorp

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