Mechanisms Governing the Postural Response and Baroreceptor Abnormalities in Chronic Congestive Heart Failure: Effects of Acute and Long-term Converting-enzyme Inhibition

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SUMMARY We assessed the hemodynamic and hormonal response to tilt and the baroreceptor response in 12 patients in sinus rhythm with severe chronic congestive heart failure. We also assessed the response to acute (n = 12) and chronic (n = 8) converting-enzyme inhibition with captopril. The control tilt was characterized by high cardiac filling pressures, absence of significant peripheral pooling and apparent absence of afferent stimuli for hemodynamic and hormonal response. After acute captopril, the hemodynamic response to tilt was improved, but not normalized. The chronic response was characterized by the absence of a reflex increase of systemic vascular resistance on tilt despite peripheral pooling. Five patients developed orthostatic hypotension, but responded to acute infusion of 0.9% sodium chloride. Efferent sympathetic activity (response to cold pressor) was abnormal during the control study, but indistinguishable from normal subjects by the time of chronic captopril therapy. This paralleled an improved responsiveness of plasma catecholamines during chronic tilt. The Valsalva maneuver remained abnormal. There was a distinct absence of the normally anticipated heart rate increase on tilt, suggesting a parasympathetic abnormality.

IN BOTH normal and hypertensive persons, upright posture is associated with significant peripheral pooling. Orthostatic hypotension does not occur because reflex increase of systemic resistance and heart rate compensate for the peripheral pooling. Activation of the renin-angiotensin system and compensatory change of sympathetic and parasympathetic tone are also important adjustments. Abelmann and Fareeduddin demonstrated that the hemodynamic response to tilt in chronic congestive heart failure is atypical; that is, there was no significant peripheral pooling in the upright posture. Hence, reflex stimulation of increased systemic vascular resistance and heart rate did not appear necessary to avert orthostatic hypotension. This atypical response was attributed to intense volume expansion and vasoconstriction, but the interactions of controlling mechanisms are not known. Studies in animal models and in humans have demonstrated abnormalities of sympathetic and parasympathetic control of heart rate in chronic congestive heart failure.

Few data are available regarding the effects of vasodilator therapy on these abnormalities, although this mode of therapy is widely used. Vasodilator therapy could significantly alter the vasoconstriction, volume alterations and hormonal response that normally accompany the assumption of upright posture. This may have some influence on the reported discrepancy between supine and dynamic assessment of hemodynamic improvement during chronic vasodilator therapy of severe congestive heart failure. In the present study we reevaluated the factors contributing to the tilt response and baroreceptor function in severe chronic congestive heart failure. We assessed the effects of acute and chronic vasodilator therapy on these responses using the oral converting-enzyme inhibitor captopril.

Methods

Patients

The study included 12 patients (11 male and one female), ages 20–75 years, with New York Heart Association functional class III or IV chronic congestive heart failure. Six had idiopathic and six ischemic chronic congestive heart failure. Patients with permanent pacemaker placement or heart rhythm other than normal sinus rhythm were excluded. Vasodilator therapy was discontinued at least 4 days before this study. Because of the severity of their heart disease, digoxin and diuretic therapy were maintained throughout the study, without significant changes in dosage. During the lead-in period of the first hemodynamic study, patients were maintained on an 85-mEq sodium diet while on the metabolic ward. This diet was also administered before the chronic, 2-month hemodynamic evaluation.

Hemodynamic Study

Hemodynamics were measured in the control, acute (after 25 mg) and chronic (after 2 months, mean dose 99 ± 17 mg/day) captopril treatment phases. Hemodynamic measurements were done in the morning after an overnight fast. The morning dose of diuretic was not given before the study. Heart rate (HR) was monitored from a precordial lead. Arterial blood pressure (AP) was continuously recorded after placing a can-
nula in a radial artery. Right atrial pressure (RAP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP) and cardiac output (CO) were obtained by a Swan-Ganz catheter placed under fluoroscopic guidance. CO was corrected for body surface area. Systemic vascular resistance (SVR) was calculated from the formula

$$\frac{AP - RAP}{CO} \times 80.$$ 

Pulmonary vascular resistance (PVR) was calculated from the formula

$$\frac{PAP - PCWP}{CO} \times 80.$$ 

Pressures were continuously monitored by digital display throughout the hemodynamic study. At the time of actual measurements, mean pressures were obtained by electronic damping and simultaneously recorded on a strip-chart recorder. COs were determined in triplicate. Hemodynamics were measured with the patient lying on an electronic table that was capable of head-up tilt. Upright hemodynamics were obtained by tilting the patient to 60° for 10 minutes, a level that provides the maximal hemodynamic response to acute peripheral pooling.1 Pressure transducers were attached to the table so that they remained at the same relative level of the atria, midway between the anterior and posterior chest wall. They were on a swivel so that the phlebotastic level of Rushmer18 was maintained for accurate pressure measurements during tilt.

Baroreceptor Testing

Head-up tilt is felt to be a measure of overall baroreceptor reflex response.19 Likewise, the response to the Valsalva maneuver can also assess overall baroreceptor function,19-21 and was therefore performed in all patients. Continuous recordings of the HR and AP were performed during forced expiration into a manometer, generating a constant pressure of 30 mm Hg for 15-20 seconds. Efferent sympathetic activity was assessed by the cold-pressor test.22 Continuous recordings of HR and blood pressure were obtained before, during and after immersion of the hand into ice water (0-4°C) for 1 minute. Pharmacologic testing of the baroreceptor reflexes was not performed because of the tenuous cardiac status of some of these patients.

Hormone Profile

Plasma renin activity (PRA) was estimated by radioimmunoassay of angiotensin I generated in vitro as described by Sealey and Laragh.23 In normal subjects, the range for PRA is based on a nomogram in which the PRA is related to the 24-hour urinary sodium excretion rate. A similar relationship has not been defined for congestive heart failure. The urinary sodium excretion for our patients was 48 ± 8 mEq/day; in normal persons with comparable urinary sodium excretion, the upper limit of normal is 6.0 ng/ml/hr. Plasma aldosterone (PA) was also measured by radioimmunoassay.24 Normal values for our laboratory are less than 10 ng%. Plasma norepinephrine (NE) levels were determined by radioenzymatic assay25 (normal 165 ± 66 pg/ml).

Study Design

After catheter placement, the Valsalva maneuver and cold-pressor test were performed. After a recovery period of 15 minutes, supine hemodynamic data and plasma for hormone profile were obtained. Patients were then tilted to 60° for 10 minutes, and hemodynamic data were obtained with simultaneous plasma samples for hormonal profile. Patients were then returned to the supine position for 45 minutes of recovery. Supine hemodynamic data and hormonal profiling were again obtained and served as the baseline for captopril administration. These values were not significantly different from those obtained during the initial supine measurements. Captopril was then administered as a 25-mg dose. The peak response to captopril was defined as the maximal change in AP, PCWP and cardiac index (CI), and occurred at 30-90 minutes. Hemodynamics and hormonal levels were measured at 30, 60 and 90 minutes to ensure that the peak effect was not overlooked. Patients were returned to the supine position and hemodynamics were followed for another hour. Supine hemodynamic values after tilt did not change, and the study was terminated.

Eight patients underwent hemodynamic study during the control/acute captopril phase and also after 2 months of oral captopril therapy (99 ± 17 mg/day). Furosemide dosage was 138 ± 26 mg before the initial study and 153 ± 29 mg before the chronic study. Hydrochlorothiazide (<100 mg/day) was maintained in three patients before the chronic study. On the day of the chronic hemodynamic study, the morning dose of diuretic was again withheld. The chronic hemodynamic study was performed as described above, with the following exceptions. The morning dose of captopril was given 2-3 hours before hemodynamic and hormonal determinations. After catheter placement, baroreceptor testing was then performed, and hemodynamic measurements with blood sampling for hormonal profile were obtained in both the supine and tilt positions. A greater than 10% fall of mean AP on tilt was felt to represent orthostatic hypotension. This response occurred in five of eight patients, although all patients tolerated tilt. Patients were then returned to the supine position. Those with orthostatic hypotension received 500 ml of 0.9% sodium chloride over 15 minutes through the right atrial port of the Swan-Ganz catheter. On completion of infusion, a 15-20-minute equilibration period was allowed, followed by repeat supine and tilt determinations.

Statistical Methods

Paired t-tests were used to compare the changes between supine and tilt values, as each patient served as his own control. Pooled t analysis was used for comparison of normal and congestive heart failure
populations. Correlations were obtained by linear regression analysis. All values were expressed as mean ± SEM.

Results

The Hemodynamic and Hormonal Response to Tilt

The hemodynamic and hormonal response to tilt in chronic heart failure patients is shown in table 1. On tilt, the fall in AP from 79 ± 2 to 73 ± 3 mm Hg was not significant, despite a significant fall in RAP (11 ± 2 to 2 ± 1 mm Hg), PAP (38 ± 6 to 25 ± 2 mm Hg), and PCWP (26 ± 2, to 13 ± 3 mm Hg). These values are near the upper limit of normal. Changes in CI, SI, SVR and PVR were not significant. Despite the significant fall in cardiac filling pressures, there was no reflex increase in HR on tilt. The supine baseline values for PRA (14 ± 6 ng/ml/hr), PA (43 ± 17 ng%) and NE (747 ± 249 pg/ml) are all above normal values. With tilt, however, there was no significant change in PRA (14 ± 5 ng/ml/hr), PA (41 ± 15 ng%) or NE (782 ± 227 pg/ml).

At the time of peak supine hemodynamic response to captopril, AP was reduced from 79 ± 2 to 70 ± 2 mm Hg, RAP from 11 ± 2 to 7 ± 2 mm Hg, PAP from 38 ± 6 to 32 ± 2 mm Hg, PCWP from 26 ± 2 to 19 ± 2 mm Hg, SVR from 1968 ± 125 to 1477 ± 84 dyn-sec-cm⁻², and PVR from 370 ± 45 to 303 ± 30 dyn-sec-cm⁻². CI increased from 1.57 ± 0.08 to 1.89 ± 0.09 l/min/m², and SI from 19 ± 2 to 23 ± 2 ml/beat/m². All changes were significant (p < 0.005). The supine baseline PRA was correlated with decreases in PCWP (r = −0.687) and SVR (r = −0.723) and increases in CI (r = 0.717) and SI (r = 0.667, p < 0.02). At the time of supine response to captopril, PRA increased from 14 ± 6 to 51 ± 16 ng/ml/hr (p < 0.001), PA decreased from 43 ± 17 to 18 ± 6 ng% (p < 0.001), and NE decreased from 747 ± 249 to 476 ± 71 pg/ml (p < 0.005).

During the acute response to captopril, patients were tilted. Despite the significant reduction of supine AP after captopril, orthostatic hypotension did not occur on tilt. The change of AP from 70 ± 2 to 66 ± 3 mm Hg was not significant, although the reduction of cardiac filling pressures, CI and SVI on tilt (table 1) indicated significant peripheral pooling. In response to peripheral pooling, SVR increased from 1477 ± 84 to 1758 ± 135 dyn-sec-cm⁻² (p < 0.005). There was no reflex change in HR. PRA and PA did not change significantly. In contrast to the control tilt, the increase of NE from 476 ± 71 to 615 ± 78 pg/ml during the acute captopril tilt was significant (p < 0.01).

Eight patients had both acute and chronic hemodynamic study during captopril therapy (table 2). The baseline hemodynamic characteristics of this subgroup was almost identical to those of the larger group, as was the response to tilt and acute captopril. With chronic therapy, the hemodynamic and hormonal profile of patients studied in the supine position was similar to the values after acute captopril. During chronic tilt, the reductions of cardiac filling pressures, CI, and SVI were similar to those during the acute tilt. However, AP was also significantly reduced, from 71 ± 5 to 60 ± 4 mm Hg (p < 0.005). The calculated SVR did not significantly increase in response to tilt (from 1484 ± 134 to 1536 ± 137 dyn-sec-cm⁻²). Similar to the acute tilt, there was no significant increase of PRA (32 ± 12 to 33 ± 12 ng/ml/hr) or PA (10 ± 5 to 12 ± 7 ng%) as usually seen in normal persons. However, the increase of NE in response to tilt (336 ± 69 to 407 ± 67 pg/ml) was significant (p < 0.02). Five of the eight patients developed orthostatic hypotension (table 3). The hemodynamic and hormonal profile of these patients in the supine position was not appreciably differ-
TABLE 2. Response to Tilt in Eight Patients with Congestive Heart Failure During Acute and Chronic Captopril Therapy

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine Tilt</td>
<td>Supine Tilt</td>
<td>Supine Tilt</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>87 ± 5</td>
<td>87 ± 5</td>
<td>87 ± 5</td>
</tr>
<tr>
<td>AP (mm Hg)</td>
<td>80 ± 2</td>
<td>74 ± 4</td>
<td>84 ± 4</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>11 ± 3</td>
<td>3 ± 2</td>
<td>*</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>37 ± 3</td>
<td>26 ± 3</td>
<td>*</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>25 ± 3</td>
<td>14 ± 3</td>
<td>*</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>1.60 ± 0.09</td>
<td>1.49 ± 0.06</td>
<td>*</td>
</tr>
<tr>
<td>SI (ml/beat/m²)</td>
<td>19 ± 2</td>
<td>18 ± 1</td>
<td>*</td>
</tr>
<tr>
<td>SVR (dyn-sec-cm⁻²)</td>
<td>1916 ± 136</td>
<td>2122 ± 194</td>
<td>*</td>
</tr>
<tr>
<td>PVR (dyn-sec-cm⁻²)</td>
<td>377 ± 54</td>
<td>370 ± 39</td>
<td>*</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>13 ± 7</td>
<td>13 ± 7</td>
<td>*</td>
</tr>
<tr>
<td>PA (ng%)</td>
<td>30 ± 14</td>
<td>24 ± 9</td>
<td>*</td>
</tr>
<tr>
<td>NE (pg/ml)</td>
<td>591 ± 113</td>
<td>620 ± 139</td>
<td>*</td>
</tr>
</tbody>
</table>

*p ≤ 0.02.

Abbreviations: See table 1.

event from that of the larger group of eight patients. With tilt, AP was reduced from 72 ± 6 to 57 ± 4 mm Hg (p < 0.001). This was associated with significant reductions in cardiac filling pressures, CI and SVI. There was no significant reflex increase of HR or calculated SVR. Furthermore, there was no significant change of PRA (41 ± 14 to 42 ± 14 ng/ml/hr) or PA (8 ± 5 to 8 ± 5 ng%), although the increase of NE (303 ± 88 to 394 ± 94 pg/ml) was significant (p < 0.05). After tilt, the patients were returned to the supine position and 500 ml of 0.9% sodium chloride were administered. After reequilibration, the supine hemodynamic and hormonal profile was not significantly different from that before saline infusion. On repeat tilt after saline infusion, the orthostatic hypotension was abolished and the change of AP from 76 ± 8 to 73 ± 8 mm Hg was not significant. The fall of cardiac filling pressures, CI and SVI on tilt remained significant, however, so that the increase of calculated SVR from 1455 ± 229 to 1722 ± 229 dyn-sec-cm⁻² was significant (p < 0.001). HR, PRA and PA did not change on tilt. NE increased from 308 ± 77 to 385 ± 91 pg/ml (p < 0.05).

The relationship of decrease in CI and decrease of mean AP in response to tilt during chronic captopril therapy is shown in figure 1. A linear relationship was noted, indicating that reflex increase of SVR to avert orthostasis was absent. The values for five patients who had orthostatic hypotension during chronic captopril tilt with subsequent abolition of orthostasis after sodium chloride infusion are also in figure 1. After the infusion, these five patients had less than a 10% decrease of mean AP on repeat tilt, similar to the other patients.

The response of left ventricular function to tilt is shown in figure 2. During the control study, despite significant reductions of PCWP on tilt, SVI changed minimally. With both acute and chronic captopril therapy, left ventricular function is improved in both the supine and tilt positions. Patients who were orthostatic

TABLE 3. Orthostatic Hypotension During Chronic Captopril Therapy in Five Patients

<table>
<thead>
<tr>
<th></th>
<th>Before saline</th>
<th>Tilt</th>
<th>After saline</th>
<th>Tilt</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>80 ± 6</td>
<td>85 ± 9</td>
<td>80 ± 6</td>
<td>85 ± 8</td>
</tr>
<tr>
<td>AP (mm Hg)</td>
<td>72 ± 6</td>
<td>57 ± 4</td>
<td>76 ± 8</td>
<td>73 ± 8</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>4 ± 1</td>
<td>0 ± 1</td>
<td>6 ± 2</td>
<td>*</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>27 ± 2</td>
<td>13 ± 2</td>
<td>30 ± 2</td>
<td>*</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>13 ± 2</td>
<td>3 ± 1</td>
<td>16 ± 2</td>
<td>*</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.18 ± 14</td>
<td>1.81 ± 18</td>
<td>2.18 ± 13</td>
<td>1.91 ± 10</td>
</tr>
<tr>
<td>SI (ml/beat/m²)</td>
<td>28 ± 2</td>
<td>21 ± 3</td>
<td>29 ± 3</td>
<td>*</td>
</tr>
<tr>
<td>SVR (dyn-sec-cm⁻²)</td>
<td>1442 ± 210</td>
<td>1478 ± 216</td>
<td>1455 ± 229</td>
<td>*</td>
</tr>
<tr>
<td>PVR (dyn-sec-cm⁻²)</td>
<td>288 ± 33</td>
<td>278 ± 79</td>
<td>291 ± 24</td>
<td>258 ± 59</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>41 ± 14</td>
<td>42 ± 14</td>
<td>37 ± 14</td>
<td>36 ± 15</td>
</tr>
<tr>
<td>PA (ng%)</td>
<td>8 ± 5</td>
<td>8 ± 5</td>
<td>6 ± 3</td>
<td>7 ± 4</td>
</tr>
<tr>
<td>NE (pg/ml)</td>
<td>303 ± 88</td>
<td>394 ± 94</td>
<td>308 ± 77</td>
<td>*</td>
</tr>
</tbody>
</table>

*p ≤ 0.05.

Abbreviations: See table 1.
Figure 1. The relationship of the extent of peripheral pooling (change in cardiac index [\(\%\Delta CI\)]) and orthostatic hypotension (change in mean arterial pressure [\(\%\Delta MAP\)]) were strongly correlated (\(p < 0.02\)). There was no reflex increase in systemic vascular resistance in patients with extensive peripheral pooling. Five of the eight patients had greater than 10% fall of arterial pressure on tilt. On repeat tilt, after infusion of sodium chloride, there was less than 10% fall in MAP despite comparable degrees of peripheral pooling. With sodium repletion in these five, all eight patients receiving chronic captopril therapy then demonstrated less than 10% decrease of MAP on tilt, even though CI ranged from +2 to -21%. CHF = congestive heart failure.

during chronic tilt were also shown in figure 2. Their response to tilt had the steepest slope, and the PCWP/SVI relationship subsequent to sodium chloride infusion appeared to coincide with the preinfusion function curve.

Reflex Changes During Captopril Therapy of Congestive Heart Failure

Figure 3 is a summary of the response to cold pressor stimulation in congestive heart failure. During the control study, HR, systolic blood pressure and diastolic blood pressure were essentially unchanged after 1 minute of hand immersion in ice water. With acute captopril, neither HR nor diastolic blood pressure increased significantly; the small increase of systolic blood pressure was significant (\(p < 0.05\)). During chronic captopril therapy, however, cold pressor stimulation resulted in significant increase of HR, systolic blood pressure, and diastolic blood pressure (\(p < 0.01\)). These increases did not differ significantly from those of age-matched normal subjects.

During the control Valsalva maneuver, a typical "square-wave" heart failure blood pressure response was observed, with no HR change. Eight patients performed the Valsalva maneuver during control, acute captopril and chronic captopril therapy (table 4). Unlike the response in normal subjects, neither pulse pressure or HR changed during phase II or phase IV, for both control and acute captopril studies. With chronic captopril therapy, pulse pressure narrowed during phase II, from 57 ± 11 to 39 ± 3 mm Hg (NS). During phase IV, there was no blood pressure overshoot, and HR did not change.

The pulse pressure/HR relationship during tilt is shown in figure 4. The change of pulse pressure on tilt ranged from 47% to -32% at the various stages of therapy. Despite this wide range, the HR change on tilt was within 10% of supine values in most instances, and was equally distributed in the positive and negative range.

Discussion

The overall response to upright tilt in congestive heart failure patients was unlike that reported in the normal and hypertensive population: whether it was atypical or abnormal, however, is unclear. Orthostatic hypotension did not occur, but the normal compensatory mechanisms that protect blood pressure from the gravitational stress of peripheral pooling were not activated. Abelmann and Fareeduddin\(^{9,10}\) suggested that part of this atypical response is due to volume overload. In our study, despite significant decreases in cardiac filling pressures, these pressures were greater than those of normal subjects. However, the reduction of filling pressures on the tilt may represent a relative change. Furthermore, the normally anticipated decrease in CI and SVI on tilt, which signifies peripheral
pooling, did not occur. This absence of significant peripheral pooling may therefore represent an inadequate stimulus for reflex responses; hence the absence of significant increase of HR or SVR during tilt. In normal and hypertensive subjects, significant activation of the renin-angiotensin-aldosterone axis and sympathetic stimulation of NE release occur as a compensatory response for the stress of upright posture.2,5-8,26-30 In patients with congestive heart failure, a similar compensatory increase during tilt was not observed. This may represent maximum stimulation of their release, either inappropriately, or as an attempted compensatory response. It may also represent an absence of afferent signal for their release. In normal subjects, renin release is stimulated by reduction of atrial pressure (low-pressure receptors),29 or combined reduction of atrial and arterial (high-pressure recep-

tors) pressure.31 Based on the present study, congestive heart failure patients demonstrated no increase in PRA during the gravitational stress of tilt, despite significant reduction of atrial pressure, and, in some patients during chronic therapy, AP.

These abnormalities are of further importance because almost no data are available regarding the hemodynamic response to upright tilt during vasodilator therapy in chronic congestive heart failure. This may have some relationship to the difference in degree of hemodynamic improvement when supine and dynamic assessments are compared during the chronic vasodilator therapy of heart failure.17 The response to tilt after acute captopril may be a reflection of both improved overall cardiac status as well as a direct effect of pharmacologic intervention. The main observations were
that RAP, PAP and PCWP fell to normal levels in the upright position. Despite significant peripheral pooling, no orthostatic hypotension was observed due to reflex increase in SVR. Despite converting-enzyme blockade (increased PRA and decreased PA after captopril), the normal increase of PRA and PA were absent on tilt, although such a response to tilt has been reported in hypertensive patients receiving captopril. Supine plasma NE levels were decreased after acute captopril. More important, the increase of NE during the postcaptopril tilt was similar to that anticipated for normal subjects. The absence of increased renin-angiotensin-aldosterone activity on tilt may be an afferent lack of responsiveness, since sympathetic activity improved and this may be a major stimulus for renin release. The compensatory increase of SVR during the acute captopril tilt may represent improved responsiveness, mediated by the sympathetic nervous system, incomplete blockade of angiotensin-mediated vasoconstriction, or a combination of both. The extent of renin-angiotensin blockade during tilt is difficult to assess by PRA and PA levels alone, because their responsiveness was abnormal even during the control tilt.

The response to tilt during chronic vasodilator therapy with captopril was more complex. Despite a comparable reduction of cardiac filling pressure and peripheral pooling, the reduction of blood pressure that occurred with tilt during chronic therapy was more marked. There was an absence of reflex increase of SVR, demonstrated by the linear relationship between the percent decrease of CI vs percent decrease of mean AP on tilt. Although improved responsiveness of plasma NE on tilt continued during chronic therapy, this was not sufficient to avert orthostatic hypotension. Diminished intravascular and total body sodium may have played a role in this chronic orthostatic hypotension. Clinically, all but one patient reported relief of symptoms by at least one functional class. There was a reduction in weight, peripheral edema and pulmonary congestion. Cardiac filling pressures, especially in the upright position, were substantially and significantly reduced compared with control values. The tendency for sodium retention by abnormally elevated aldosterone levels would be diminished, due to the significant reduction of PA levels during chronic captopril therapy. Acute and chronic sodium depletion with loop diuretics intensifies the participation of the renin angiotensin aldosterone system in congestive heart failure. During sodium depletion, there is increased dependency of vascular tone on the renin-angiotensin system; therefore, renin-angiotensin blockade may limit vascular responsiveness to gravitational stress. The explanation for reversal of orthostatic hypotension with sodium chloride infusion is not clear, as CI and filling pressures did not change appreciably, and the greatest improvement was in calculated SVR. In congestive heart failure patients receiving both chronic diuretic and captopril therapy, attention should be given to signs and symptoms of orthostatic hypotension. This may adversely affect exercise tolerance, regional perfusion, and objective assessment of response to therapy, since patients with congestive heart failure generally have chronic low blood pressure.

Overall, left ventricular function improved during acute and chronic captopril therapy in the supine position and on tilt. During captopril therapy, not only supine but also upright left ventricular function were improved compared with the supine control values. That is, in the upright position during chronic therapy, improved flow was possible at a much lower range of filling pressures compared with the control study.

Studies have demonstrated abnormalities of both the sympathetic and parasympathetic contributions to the baroreceptor reflex in both animal studies and clinical studies of congestive heart failure. These abnormalities may begin to appear before the onset of clinical decompensation. As all of our patients had failed to respond to conventional therapy before captopril, it is reasonable to assume that the findings in our patients are typical of those in patients with severe chronic congestive heart failure, especially during decompensation.

The cold pressor test is a measure of efferent sympathetic response to noxious stimulation. The typical response is a significant increase of HR, systolic blood pressure and diastolic blood pressure. Although all of our patients reported painful stimulation with submersion of their hand in ice water, the normal efferent sympathetic response was not observed. Although acute captopril therapy was associated with some improvement of the systolic blood pressure response, overall improvement was most marked during chronic therapy. These findings, together with the observation of increased plasma NE during tilt, suggest improved sympathetic responsiveness during chronic vasodilator therapy with captopril. However, despite a wide range of pulse-pressure change on tilt during both acute and chronic therapy, HR changed only slightly. Degenerative changes have been documented in the neuronal end-plates of the aortic arch and carotid sinuses in heart failure. This may result in an abnormal or blunted HR response during tilt. In the present study, there was evidence of absent afferent stimulus and blunted efferent sympathetic response during the control and acute captopril tilt. However, other explanations should be considered for the absence of HR response during chronic therapy, when orthostatic hypotension on tilt should provide an adequate afferent stimulus, and efferent sympathetic responsiveness was improved. Given these data, a parasympathetic defect would seem likely.

Several studies have demonstrated a decreased HR with atropine in patients with congestive heart failure. In a study of patients with Chagas' disease, the absence of appropriate tachycardia on tilt was felt to represent an absence of parasympathetic withdrawal, and sinus node denervation has been implicated in the parasympathetic abnormalities seen with congestive cardiomyopathy. Because of the design of our study, we did not administer atropine. However, a parasympathetic abnormality, together with altered afferent stimulus and sympathetic responsiveness, may variably contribute to the absence of an appropriate HR.
response to tilt, depending on the state of cardiac decompensation. Congestive heart failure patients may develop tachycardia during standard exercise testing. This may represent a more intense form of stimulation or an overriding mechanism of stimulation. In both hypertension and congestive heart failure studies with vasodilating drugs, the response of HR has been used to help classify these compounds according to site of action; that is, the increase of HR indicates an arterial site of action, and absence of an HR increase indicates both arterial and venous sites of vasodilatation. Based on the above data, such theoretical considerations may not apply to patients with severe congestive heart failure.

Captopril therapy was associated with an overall favorable improvement of hemodynamics both acutely and chronically, in both supine and tilt positions. However, saline-responsive orthostatic hypotension was observed in some patients during chronic therapy, but the mechanism for saline responsiveness is unclear. This finding suggests that chronic reduction of diuretic dosage may be necessary in many heart failure patients during converting-enzyme inhibition. During captopril therapy, there was a reduction of supine plasma norepinephrine levels; however, the response of plasma norepinephrine to tilt was improved with both acute and chronic therapy. This was associated with improvement of the efferent sympathetic response to cold pressor stimulation. This suggests that the autonomic changes reported in chronic heart failure may not be irreversible.

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