The Contribution of Local Factors to the Elevated Venous Tone of Congestive Heart Failure

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ABSTRACT Since the concept of an elevated venous tone in congestive heart failure (CHF) has been recently questioned, the venous volume of the elevated calf at a venous pressure of 30 mm Hg (VV[30]) was determined in 18 normal volunteers (N) and 10 CHF patients with a mercury-in-rubber strain gauge plethysmograph. CHF patients had a significantly lower VV[30] at rest and after intra-arterial phentolamine (2 mg) than normal subjects, suggesting that in these patients a state of peripheral venoconstriction existed (rest–N: 4.63±0.17, CHF: 1.7±0.23 ml/100 ml, $P < 0.01$; pre- and postphentolamine–N: 4.85±0.21 to 4.95 ±0.31, CHF: 2.26±0.29 to 2.68±0.38 ml/100 ml, $P < 0.01$). Of note is that alpha adrenergic blockade failed to increase VV[30] significantly in N, but did increase it in CHF ($P < 0.05$), suggesting that part of the decreased VV[30] in CHF in due to an augmented sympathoadrenal discharge. When sodium nitrite (30 mg) was given as a single intra-arterial injection before or after phentolamine or when given in four successive doses at 3-min intervals, the VV[30] of CHF patients was never increased to more than 3.62±0.42 ml/100 ml and was always less than N ($P < 0.01$). Importantly, VV[30] in CHF after these interventions was even significantly less than that of N before intervention ($P < 0.05$), suggesting that factors other than local active smooth muscle venoconstriction were operative in CHF to lower VV[30]. It is suggested that perhaps clinically undetectable edema and an elevated tissue pressure may account for these differences.

INTRODUCTION

Previously it has been suggested that patients with congestive heart failure have an increased venous tone (1–6). This has been thought to be secondary to an exaggerated sympathoadrenal discharge (6). This increased venous tone in heart failure has been considered to be one of the major mechanisms by which such patients exhibit an elevated systemic venous pressure, especially during exercise (6). Recently, the concept of increased neurogenically mediated venous tone in heart failure has been questioned, and it has been implied that venous tone in heart failure may not be elevated (7). Similarly, the circulatory role of the sympathetic nervous system in heart failure has been questioned (8, 9). Therefore, the purpose of these studies was to reevaluate the state of the systemic veins in heart failure especially in terms of the local factors that might contribute to alterations in venous tone.

METHODS

Studies were performed on 18 normal volunteers between the ages of 21 and 45 yr and 10 patients with rheumatic heart disease and congestive heart failure (New York Heart Association Functional Class III–IV) between the ages of 35 and 51 yr. Normal subjects were student volunteers or patients admitted to the Sacramento Medical Center for cardiac evaluation who were found to have minimal heart disease or to be disease free. All protocols were evaluated and approved by the Chancellor's Advisory Committee on Research Involving Human Subjects. The subjects wore light clothing and felt comfortably warm at a room temperature of 72–74°F. Venous volume of the elevated calf at a venous pressure of 30 mm Hg (VV[30]) [1] was measured with a single strand mercury-in-rubber strain gauge plethysmograph by the equilibration technique (10–12). With this technique venous occlusion was produced by suddenly inflating a 13-cm wide cuff placed around the thigh to a pressure of 30 mm Hg after appropriate determination of cuff zero. Equilibration of venous pressure with cuff pressure was permitted for 3 min at which time the venous volume remained constant. In all instances it was determined that before venous congestion all veins were collapsed and the venous pressure in the elevated calf was reduced to less than 1 mm Hg. In a number of subjects an arterial needle was inserted into the femoral artery through which sodium nitrite (Eli Lilly and Company, Indianapolis, Ind.) and/or phentolamine

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[1] *Abbreviation used in this paper:* VV[30], venous volume of the elevated calf at a venous pressure of 30 mm Hg.

(Regitine, Ciba Pharmaceutical Company, Summit, N. J.) could be injected. In nine normal subjects and seven patients with congestive heart failure, venous volume was determined before and after the intra-arterial injection of 2 mg of phentolamine. In 13 normal subjects and 10 patients with heart failure, sodium nitrite (30 mg) was injected intra-arterially at the 3rd min of venous congestion which was continued until 6 min at which time the venous volume was measured. In nine normal subjects and six patients with heart failure, sodium nitrite was injected during the 3rd min of venous congestion after repeat alpha adrenergic blockade with phentolamine, and venous volume was determined after the 6th min of venous congestion. In six normal subjects and four patients with congestive heart failure, the venous collection cuff was left inflated to 30 mm Hg for 15 min. Sodium nitrite was injected at the 3rd, 6th, 9th, and 12th min of venous equilibration. In all instances when a pharmacologic agent was injected during an equilibration period and it was necessary to prolong the equilibration beyond 3 min, venous volume was determined during a comparable control equilibration period during which an equal volume of saline was injected. In all instances the base-line limb volume was allowed to return to pre-venous collection levels between interventions. The venoconstriction associated with the application of ice to the forehead was evaluated in six normal and three heart failure subjects before and after phentolamine. In five normal subjects ouabain (0.5 mg) was given slowly intravenously over 10 min and venous volume determined 30 min after the completion of the injection. In one additional heart failure subject, VV[30] was determined in both lower limbs before and 5 h after intravenous ethacrynic acid (0.5 mg/kg). One lower limb was maintained in a position 30 cm above heart level and the other was subjected to mild venous congestion by inflation of a thigh cuff to 30 mm Hg while the limb remained at heart level. Statistical analysis between groups and in individuals after an intervention was performed by utilizing the appropriate Student t test.

RESULTS

Venous volume of the normal subjects was 4.63±0.17 ml/100 ml, a value that was significantly different from the patients with congestive heart failure, whose venous volume averaged 1.70±0.23 ml/100 ml ($P < 0.01$). In normal subjects phentolamine increased VV[30] from 4.85±0.21 to 4.95±0.31 ml/100 ml ($P > 0.5$) whereas phentolamine significantly increased VV[30] in the heart failure patients (from 2.26±0.29 to 2.68±0.38 ml/100 ml ($P < 0.05$) (Fig. 1). After phentolamine the difference in VV[30] between the normal and heart failure patients persisted. When 30 mg of sodium nitrite was injected intra-arterially during the 3rd min of a 6-min equilibration, VV[30] increased in normal subjects (from 4.54±0.21 to 5.26±0.23 ml/100 ml, $P < 0.01$) and in patients with congestive heart failure (from 1.56±0.25 to 2.42±0.25 ml/100 ml, $P < 0.01$) (Fig. 2B). There was no significant change in VV[30] in either group from the 3rd to the 6th min of a control equilibration period during which a comparable volume of saline was injected (Fig. 2A). After the injection of sodium nitrite, the differences between the normal subjects and heart failure patients were still significantly different ($P < 0.01$) (Fig. 2). When the injection of sodium nitrite was repeated after a second intra-arterial phentolamine administration, there was still a significant difference between the normal subjects (VV[30]: 5.15±0.28 ml/100 ml) and the patients with congestive heart failure (VV[30]: 2.54±0.41 ml/100 ml, $P < 0.01$). When sodium nitrite (30 mg) was injected four times in order to attempt to produce complete venodilation, the differences between the normal subjects and the heart failure patients persisted (Fig. 3B). After the last injection of sodium nitrite, VV[30] of the normal subjects was 6.41±0.55 ml/100 ml and in the heart failure patients it was 3.62±0.42 ml/100 ml, $P < 0.01$. During a control 15-min equilibration

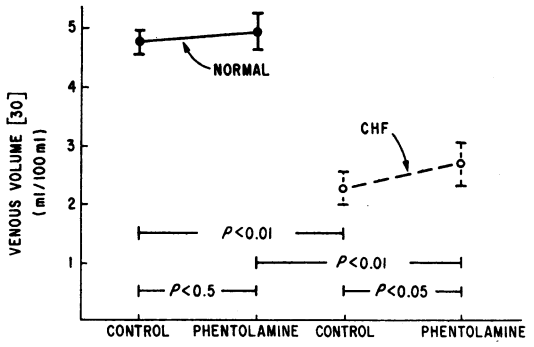

FIGURE 1 Venous volume of the elevated calf at a venous collection pressure of 30 mm Hg (±SEM) in normal subjects (●—●) and patients with congestive heart failure (CHF) (○--○) before (control) and after intra-arterial phentolamine. Brackets and P values indicate the groups between which comparisons were made.

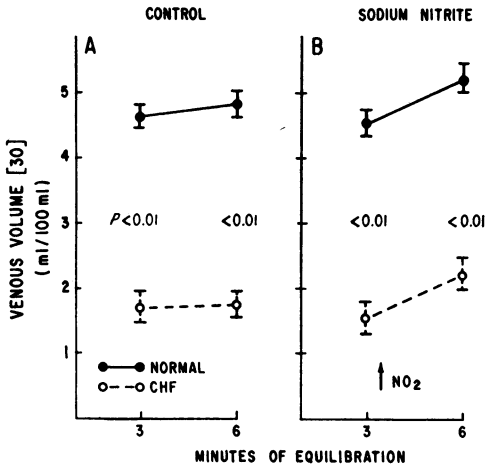

FIGURE 2 Venous volume (±SEM) determined at minutes three and six of a 6-min equilibration period. In panel B intra-arterial sodium nitrite (NO_2) (30 mg) was injected at minute three; in panel A a comparable volume of saline was injected. P values indicate comparisons between normal and heart failure groups (CHF).

period without nitrite, VV[30] increased significantly beyond the 3rd min in the normal individuals (from 4.71±0.27 to 5.42±0.43 ml/100, $P < 0.01$), but failed to increase in the patients with heart failure (from 2.05 ±0.30 to 2.14±0.37 ml/100 ml, $P > 0.3$). From analysis of the data in Fig. 3, it was difficult to determine whether maximal nitrite-induced venodilation had occurred or whether both groups of subjects were responding to the later injections of nitrite in a similar manner. Therefore, the percent change in VV[30] following each injection of sodium nitrite was calculated (Fig. 4). After the first dose of the drug, there was a significantly greater increase in VV[30] in the heart failure subjects (+ 33.5±5.6%) as compared to the normal subjects (+ 15.6±2.0%, $P < 0.01$). After each subsequent injection, the differences were less so that after the fourth injection the percent increase in venous volume is similar for both groups (Fig. 4). After the administration of ouabain (0.5 mg), normal subjects decreased their VV[30] from 5.57±0.44 ml/100 ml to 5.32±0.40 ml/100 ml ($P < 0.05$). In these normal subjects the VV[30] following ouabain was still significantly different from that observed in patients with congestive heart failure ($P < 0.01$). Intra-arterial phentolamine significantly attenuated the venoconstrictor response to the application of ice to the forehead in the nine subjects studied by 44% ($P < 0.01$). In the six normal subjects VV[30] fell 0.87 ml/100 ml before phentolamine and 0.51 ml/100 ml after phentolamine. In the three heart failure subjects the values were 0.46 and 0.18 ml/100 ml, respectively. In the one heart failure subject who received ethacrynic acid a 1,900 ml diuresis was obtained. VV[30] rose from 1.56 to 2.48 ml/100 ml in the continuously elevated leg, whereas it was unchanged in the limb subjected to mild congestion (1.33 to 1.30 ml/100 ml).

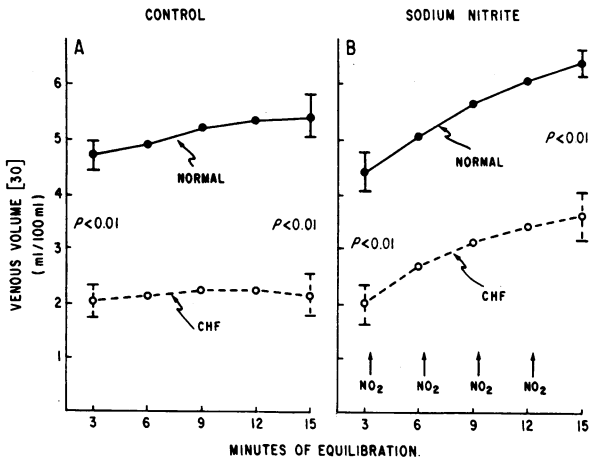

FIGURE 3 Venous volume (±SEM) determined every 3 min during a 15-min equilibration. In panel B four doses of sodium nitrite (NO_2) were injected intra-arterially at the arrows. In panel A saline was injected at comparable times. P values indicate comparisons between normal (●—●) and heart failure (CHF) (○ - - ○) groups.

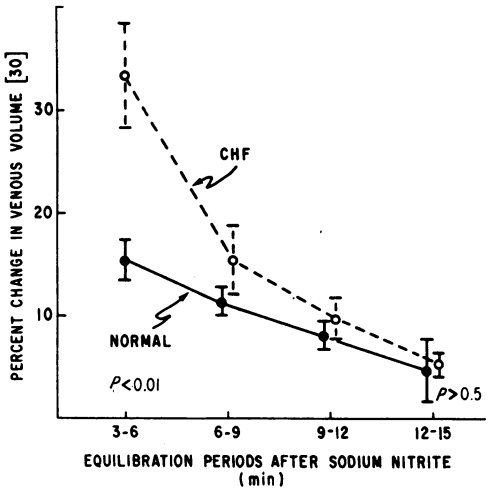

FIGURE 4 Percent change in venous volume after each of the four injections of sodium nitrite calculated from the data depicted in Fig. 3. P values indicate comparisons between normal (●—●) and heart failure (CHF) (○ - - ○) groups.

DISCUSSION

In this study it was demonstrated that the VV[30] of patients with congestive heart failure was considerably reduced when compared to normal subjects (Figs. 1–3). The finding of a decreased venous volume at a constant venous pressure would suggest that the limb veins of these patients appear to be constricted when compared to normal individuals. In utilizing the equilibration technique with a mercury-in-rubber plethysmograph for the determination of the venous tone, it is most important that the limb be elevated so that the veins are collapsed and are at similar low initial pressures in both groups of subjects (11). If the heart failure patients were to start at a venous pressure which was significantly positive, venous volume would have been considerably underestimated because the venous pressure volume curve is extremely compliant in the lower ranges of pressure (11). That this was not the case was carefully insured in all patients with congestive heart failure. The lower leg was elevated above heart level until the veins collapsed and the venous pressure was less than 1 mm Hg. Therefore, these studies appear to confirm earlier observations that venous tone is elevated in patients with congestive heart failure (5, 6).

One explanation for the increase in venous tone might be the digitalis preparations that all heart failure patients were receiving. It has been previously noted

that digitalis produces both an arteriolar and venoconstriction in normal subjects (13, 14). The usual response of heart failure patients is a venodilation. It has been suggested that this venodilation is a reflex-mediated reduction in sympathetic adrenergic tone following the enhancement of cardiac performance produced by the glycoside (14). In these studies it was demonstrated that the magnitude of the direct venoconstriction produced by ouabain in normal subjects, though significant, is still quite minimal and could not explain the rather large 60% reduction in venous volume seen in the patients with congestive heart failure. Acetylstrophanthidin has also been shown to potentiate the effects of both neurogenically liberated and humoral norepinephrine (15). The studies reported here do not answer the question whether digitalis glycosides might account for part of the observed reduction in venous volume by this mechanism.

What then might account for the higher venous tone in these patients? When phentolamine was administered to block the effects of endogenously released as well as circulating catecholamines, it was demonstrated that normal subjects increased their venous volume minimally. This is consistent with the idea that in normal subjects there is an insignificant degree of sympathetically mediated resting venous tone. On the other hand, patients with heart failure demonstrate a significant 18.6% increase in VV[30] (Fig. 2). This is twice that observed by Wood after ganglionic blockade (6), a procedure that would not eliminate the effects of circulating catecholamines. The current studies suggest that part of the increase in venous tone seen in congestive heart failure could possibly be explained by increased alpha adrenergic stimulating activity. Although Wood only showed a slight increase in venous volume with ganglionic blockade (6), when his data are analyzed statistically, they appear to be significant at the 2% level. These findings would suggest that in his subjects with heart failure there was a minimal increase in neurogenically mediated venous tone. Since our data demonstrate a greater increase in venous volume with phentolamine blockade, circulating catecholamines may be playing at least an equally important role in reducing limb venous volume in these patients with symptomatic heart failure. Whether the potentiation by digitalis of catecholamine venoconstriction (15) is leading to an overestimation of the sympathoadrenal influences on venous tone in heart failure cannot be readily answered, since it is unknown how effective phentolamine is as an alpha blocking agent in the presence of digitalis. In the present studies only partial blockade of neurogenic venoconstriction was achieved by the phentolamine; however, it appeared to attenuate the venoconstrictor response to ice application better in heart failure than in normal subjects.

It is important to note that there is still a major difference in venous volume between the normal subjects and the patients with heart failure following alpha adrenergic blockade which persists even when a potent smooth muscle-relaxing agent, sodium nitrite, was injected alone or after phentolamine blockade (Fig. 2). When four doses of sodium nitrite were administered at 3-min intervals during a 15-min period of venous collection, there was a continuous increase in venous volume in both the normal subjects and the patients with congestive heart failure; however, the differences between the groups still persisted (Fig. 3). The reason for the repeated injections of sodium nitrite was to insure that a maximum venodilator stimulus had been achieved. That this probably was the case was indicated by the observations of the percent change in venous volume after each injection (Fig. 4). It can be seen that at the beginning of the injections the heart failure patients dilated their veins significantly more than the normal subjects. However, after the last injection of sodium nitrite, both groups of subjects were responding similarly. Although these data suggest that maximal venodilation probably occurred, an adequate distribution of the venodilator agents to the constricted skin circulation could not be assured with absolute certainty, even though these agents are very potent arteriolar dilators. The subjects were comfortably warm, but no thermal stress was applied to increase skin blood flow because of the potential deleterious effect it might have had to the heart failure subjects (16).

These studies reconfirm the presence of an increased venous tone in heart failure (1–6, 17) and help to delineate some of the possible causes. These studies did not evaluate the possibility of increased levels of nonadrenergic constrictor agents which might contribute to the increased venous tone. They do suggest this phenomenon can partially be explained by increased circulating catecholamines or increased sympathetic adrenergic impulses to the veins. However, most of the increase in venous tone appears to be secondary to local factors. It is quite possible that the increased salt content seen in the arteries of animals with experimental congestive heart failure is also present in the veins (18, 19). This may impart them with an increased venous stiffness and resistance to venodilator stimuli. On the other hand, there could be an intrinsic abnormality of the venous smooth muscle that prevents it from dilating normally.

Perhaps one explanation for this failure of the veins to respond normally to venodilator stimuli can be seen in Fig. 3A. It was noted that after 15 min of venous

congestion in the normal subjects, the volume of the calf continued to increase. This was undoubtedly due to the transcapillary migration of fluid secondary to the increased capillary pressure resulting from the venous congestion. Care was taken to insure that the base-line limb volume had returned to control between interventions to prevent a net accumulation of such fluid. On the other hand, patients with congestive heart failure did not increase their calf volume when venous congestion was prolonged from 3 to 15 min. Although the lower extremities were not overtly edematous, it is possible that clinically undetectable edema may have been present in the muscle or cutaneous tissues. It has been previously noted that tissue pressure while negative in nonedematous states becomes significantly positive with the onset of edema (20, 21). It is quite possible that a positive tissue pressure in the lower extremities of these patients could have significantly impeded fluid transfer from the capillaries to the interstitial space with prolonged venous congestion. The nitrite-induced arteriolar dilation could have allowed for a greater transmission of systemic pressure to the exchange vessels, leading to a greater fluid filtration. This could account for the similar percent increases in limb volume in the two groups after the later doses of nitrite seen in Fig. 4. Therefore, from these data it is suggested that local factors and specifically interstitial edema may be one of the major factors contributing to an elevated venous tone in heart failure. Such local factors could also explain the discrepancy noted two decades ago between the magnitude of venoconstriction that can be elicited by endogenous and exogenous norepinephrine and that present in heart failure (22, 23). Even then it was suggested that sympathetically mediated venoconstriction was not the sole cause of the reduced peripheral venous volume seen in heart failure (5).

Three further pieces of information would also suggest that chronic venous congestion may be an important local factor in reducing limb venous volume in heart failure. A preliminary report has stated that venous congestion at 70 mm Hg for 3 h can reduce venous volume of an extremity by 22% (24). Conversely another preliminary report has shown that external limb compression with a volume plethysmograph can improve venous distensibility 30% in edematous limbs of nephrotic patients (25). Lastly, in the one patient studied 5 h after diuresis, venous volume increased in an elevated limb but not in a limb in which mild venous pressure elevation was maintained.

The findings of this study are not inconsistent with the study of Zitnik, Lorenz, and Shepherd regarding whether or not neurogenic venous tone is elevated in heart failure (7). In their studies they used the isolated hand technique and determined that there was no significant change in the isovolumic hand after ganglionic blockade with trimethaphan. It is quite likely that patients with significant heart failure who are not symptomatic at rest will not show an increase in neurally mediated venous tone. Our studies were done in patients with symptomatic heart failure who were uncomfortable at rest. Thus, an increased venous tone which is adrenergically mediated might be expected; however, our studies could not differentiate neurogenic from circulation components. On the other hand, studies by Wood et al. suggest that although neurogenic venous tone may be elevated, it probably contributes minimally to the reduced venous volume of heart failure. Importantly, it appears that local factors are majorly operative to partially compress veins and reduce limb venous volume. Such factors would not be seen by using the isolated hand technique for the evaluation in venous tone, since one can only measure directional changes in venous tone with an intervention (26). It is not useful for the evaluation of basal levels of venous tone such as can be determined by the equilibration technique used in the present studies. Thus, with the latter method it was demonstrated that local factors may be the most significant contributors to the observed reduced limb venous volume in heart failure. More important is that these findings are the first report that local factors other than intravascular venous pressure may be important in the determination of regional venous volume.

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