Preservation of Venous Endothelial Function in the Forearm Venous Capacitance Bed of Patients With Chronic Heart Failure Despite Arterial Endothelial Dysfunction

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OBJECTIVES
The goal of this study was to assess whether endothelial dysfunction occurs in the forearm venous capacitance bed of patients with chronic heart failure (CHF) and to determine the role of nitric oxide (NO) in modulating venous tone.

BACKGROUND
Control of venous tone is critically important in CHF. More than 70% of blood volume lies in the venous capacitance beds. Therefore, small changes in venous tone may markedly affect cardiac filling pressures and cardiac output.

METHODS
Venous tone was measured using radionuclide forearm venous plethysmography in 24 patients with CHF and 16 age-matched controls. The effect of basal NO activity on venous tone was assessed by infusing N-monomethyl-L-arginine 12 mg/min and stimulated NO using carbachol 15 μg/min. Brachial artery flow-mediated dilation was assessed by ultrasonic wall-tracking.

RESULTS
Blockade of basal NO release caused a significant and similar venoconstriction in patients (9.6 ± 1.8%, p < 0.01) and controls (6.6 ± 1.7%, p < 0.01). Carbachol-induced venodilation was significant and similar in patients (36.8 ± 3.9%, p < 0.001) and controls (40.7 ± 3.9%, p < 0.001). Brachial artery flow-mediated dilation was impaired in patients compared with controls (2.0 ± 0.6% vs. 7.5 ± 2.5%, p < 0.01).

CONCLUSIONS
Our data indicate that, despite marked impairment of the function of the arterial endothelium, there is preservation of both basal and stimulated NO release in the forearm venous capacitance bed. This may provide important insights into mechanisms of endothelial dysfunction in CHF and the potential for novel therapy. (J Am Coll Cardiol 2001;37:1062–8) © 2001 by the American College of Cardiology

Endothelial dysfunction has been demonstrated in conduit arteries and in resistance vessels in chronic heart failure (CHF) (1–4) and is mainly a consequence of reduced bioavailable nitric oxide (NO) (5). Endothelial dysfunction may contribute to increased systemic vascular resistance (6,7) and to exercise limitation by reducing skeletal muscle perfusion (8,9). There may also be an adverse impact on ventriculoarterial coupling via its effects on large artery stiffness (10).

In addition to increased arterial tone, there is also increased venous tone in untreated CHF (11,12). This has important hemodynamic consequences. Since more than 70% of blood volume lies in the venous capacitance system, it is apparent that relatively modest changes in venous tone may translocate large volumes of blood to or from the central compartment. Neural and neurohumoral factors undoubtedly contribute to the increased venous tone, but the direct role of the endothelium has not been evaluated (13,14). Work in conduit veins, such as the dorsal hand vein, suggested that the venous endothelium had little influence on venous tone (15). However, the vast majority of blood volume lies in the small veins and venules that make up the venous capacitance beds. We recently demonstrated in healthy subjects that carbachol caused a dose-dependent (maximum >40%) venodilation of the forearm venous capacitance bed, and blockade of basal NO release with N-monomethyl-L-arginine (L-NNMA) caused a 10% vеноconstriction (16). It is not known whether NO release occurs in capacitance veins in CHF. Dysfunction of the venous endothelium in CHF would have the potential to contribute to reduced venous capacitance (and, therefore, elevated venous tone). We, therefore, investigated whether NO release occurs in the forearm venous capacitance bed in patients with CHF.

METHODS

Subjects. Twenty-four patients with clinical features of CHF who had been referred to the University Hospital of Wales were studied. All patients had left ventricular ejection fraction measured by radionuclide ventriculography of ≤35% and were on stable medical therapy for ≥2 months.

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with diuretics and angiotensin-converting enzyme (ACE) inhibitors. Sixteen healthy volunteers with no risk factors for cardiovascular disease, a normal cardiovascular examination and a normal electrocardiogram were recruited as control subjects. None of the patients or controls was taking antioxidant vitamin supplements. All subjects gave written informed consent, and the study was approved by the local research ethics committee.

**Study protocol.** The investigations were performed at the University Hospital of Wales (Cardiff) in a temperature-controlled laboratory (22 to 24°C). All studies were performed with the subject having fasted and abstained from caffeine-containing drinks for at least 6 h previously. Diuretics were withheld on the morning of the study, but other drugs were continued as normal.

**Measurement of venous tone.** Venous tone was assessed in the forearm capacitance bed by radionuclide venous plethysmography (17,18). This technique involves labeling of red blood cells with $^{99m}$Tc. At least 90% of the injected isotope is confined to the intravascular space; therefore, forearm radioactive counts are proportional to forearm blood volume. Since the vast majority of blood in the peripheral circulation is contained within the veins (19–21), changes in counts reflect changes in venous volume. Construction of a venous volume/pressure relation allows assessment of venous tone. A parallel shift of the volume/pressure relation implies a change in venous tone. The slope of the regression line obtained from the volume/pressure relation is related to venous compliance. We, and others, have previously validated this technique (16,22–24). Importantly, we have shown that the position of the volume/pressure relation is not altered by large changes in arterial inflow (16).

A cannula was inserted into the antecubital fossa of the dominant arm. Stannous fluoride (0.03 ml/kg) was injected intravenously. Red cells were then labeled using a quasi in vivo method by mixing 5 ml of the subjects blood with 750 MBq of $^{99m}$Tc pertechnetate in a syringe for 10 min. This was then reinjected through the cannula 20 to 40 min after the stannous injection.

A sphygmomanometer was placed around the nondominant upper arm. The forearm was positioned comfortably on the face of a 20-cm field-of-view gamma camera equipped with a low-energy super-high sensitivity parallel-hole collimator and with an integrated computer system (Elscint Apex 215 M). Images of the forearm were continuously acquired in 10-s frames. The cuff was inflated at 60-s intervals to produce venous occlusion pressures of 10, 20 and 30 mm Hg.

After acquisition, a region of interest was drawn around the forearm image. The counts in the region of interest were acquired in the final 30 s of each 60-s interval. The count obtained with no occluding pressure was arbitrarily taken to represent resting forearm blood volume. All subsequent readings were expressed as a percentage of this value. Measures of scintigraphic vascular volumes (in percent units) at 0, 10, 20 and 30 mm Hg were used to construct venous volume/pressure plots. The data were corrected for physical decay.

After labeling of red cells as described above, a 27-gauge unmounted steel needle (Cooper’s Engineering, Birmingham, United Kingdom) was sealed with dental wax to an epidural cannula and inserted into the brachial artery of the nondominant arm. The arm was then positioned on the gamma camera. To minimize the amount of free circulating $^{99m}$Tc, imaging was commenced at least 30 min after initial labeling. Baseline measurements were performed at least 4 min after commencing infusion of 0.9% saline (1 ml/min). A venous volume/pressure relation was recorded by sequential incremental inflation of the upper arm cuff as described above. One minute after deflation of the cuff, a further volume/pressure relation was recorded.

**Stimulated and basal NO release.** Stimulated NO activity was assessed by evaluating the effect of an intraarterial infusion of carbachol (Martindale Pharmaceuticals, Romford, United Kingdom) at a concentration of 15 μg/ml at a rate of 1 ml/min. After 4 min, a venous volume/pressure relation was performed. Saline was again infused until the count rate had returned to its resting value and a third volume/pressure relation performed during saline infusion.

Basal NO activity was next assessed by measuring the effect of intraarterial L-NMMA (Cilnafà, Läufelfingen, Switzerland), an inhibitor of nitric oxide synthase (NOS), which was infused in a concentration of 12 mg/ml at a rate of 1 ml/min. After 10 min of infusion, a venous volume/pressure relation was obtained.

To allow assessment of the relative contribution of NO to the carbachol-stimulated response, carbachol (24 μg/ml) and L-NMMA (30 mg/ml) were coinfused each at a rate of 0.5 ml/min. After 4 min a further volume/pressure relation was performed.

**Measurement of arterial endothelial function.** Conduit artery endothelial function was assessed by measurement of the endothelial response to increased shear stress. Changes in brachial artery diameter in response to reactive hyperemia were measured noninvasively using a high-resolution ultrasonic wall-tracking system (Vadirec Wall-Track System, Medical Systems, Arnhem, The Netherlands, resolution ± 3 μm) as previously described and validated by us (1). Subjects rested supine with their arm held outstretched on a pneumatic cushion. Baseline measurements of internal brachial artery diameter and blood pressure were taken after

**Abbreviations and Acronyms**

- ACE = angiotensin-converting enzyme
- ANOVA = analysis of variance
- CHF = chronic heart failure
- FMD = flow-mediated dilation
- L-NMMA = N-monomethyl-L-arginine
- NO = nitric oxide
- NOS = nitric oxide synthase
- NYHA = New York Heart Association classification
- $^{99m}$Tc = technetium-99m
10 min of supine rest. Blood pressure was measured noninvasively using photoplethysmography (Finapres, Ohmeda, Madison, Wisconsin) with a cuff on the middle finger of the arm being studied. The brachial artery was imaged using a 7.5 MHz transducer. Reactive hyperemia was produced by releasing a pediatric sphygmomanometer wrist cuff inflated to systolic pressure plus 50 mm Hg for 5 min. Internal brachial artery diameter was remeasured 60 s after cuff release.

Data analysis. FOREARM VENOUS TONE. Venous volume/pressure plots were constructed for each stage in each subject. Unstressed venous volume was defined as the intercept on the volume (y) axis. Resting unstressed venous volume in each subject was calculated as the mean of the three unstressed venous volumes during infusion of normal saline. Parallel changes in unstressed venous volume reflect changes in venous tone. The slope of the volume/pressure relation reflects compliance of the veins involved. Increases in venous tone are expressed as percentage of vasoconstriction, and decreases in venous tone as percentage of venodilation. Figure 1 is an example of volume/pressure plots obtained.

Arterial endothelial function. Results are expressed as percentage of change in diameter from baseline.

Statistics. Data are expressed as mean ± SEM. Statistical analysis was performed using a specialist data analysis package (SPSS version 10). Analysis was performed utilizing one-way analysis of variance (ANOVA) and two-way repeated measures ANOVA.

RESULTS

Subject characteristics. The baseline characteristics of the patients with CHF and controls are shown in Table 1. All the patients with CHF were taking ACE inhibitors. Other medications are shown in Table 1. There was no significant difference in the age distribution between the patients with CHF and the control group. None of the patients with CHF was diabetic, but two were smokers; two were hypertensive, and six had elevated serum cholesterol. Eight of the patients with CHF were in atrial fibrillation. Body mass index was 28.8 ± 1.4 kg/m² in the patients and 27.2 ± 0.9 kg/m² in the controls.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Patients With CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>60.1 (range 45 to 74)</td>
<td>62.2 (range 39 to 75)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>9/6</td>
<td>20/4</td>
</tr>
<tr>
<td>Smokers</td>
<td>0 (1 ex)</td>
<td>2</td>
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<tr>
<td>NYHA Class</td>
<td></td>
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<tr>
<td>Class II</td>
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<tr>
<td>Class III</td>
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<td>Class IV</td>
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<tr>
<td>Medication</td>
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<tr>
<td>HMGCoA reductase inhibitor</td>
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<tr>
<td>Aspirin</td>
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<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>14</td>
<td></td>
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<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.7 ± 0.7</td>
<td>5.9 ± 0.3</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>4.8 ± 0.1</td>
<td>7.4 ± 0.7</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>59 ± 6</td>
<td>70 ± 3</td>
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<tr>
<td>Systolic BP (mm Hg)</td>
<td>120 ± 11</td>
<td>131 ± 5</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>81 ± 5</td>
<td>77 ± 3</td>
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ACE = angiotensin-converting enzyme; BP = blood pressure; CHF = chronic heart failure; NYHA = New York Heart Association classification.
Changes in forearm venous tone. RESTING FOREARM VENOUS VOLUME. Mean forearm counts at rest were similar in the patients with CHF (714 ± 32 counts/s) and in the controls (734 ± 38 counts/s [p = NS]). The slope of the volume/pressure relationship was 5.8 ± 0.4 counts/s/mm Hg in the patients with CHF and 6.2 ± 0.9 counts/s/mm Hg in the controls (p = NS).

Stimulated venous endothelial function. As shown in Figure 2, infusion of carbachol caused a significant reduction in venous tone in controls (40.7 ± 3.9%, p < 0.001) and in patients with CHF (36.8 ± 3.9%, p < 0.001). The degree of venodilation was similar in both groups (p = NS). There was no change in the slope of the volume/pressure relation (compliance) in either group during carbachol infusion. The maximal venodilator response to carbachol was reduced similarly by the coinfusion of L-NMMA in controls and in patients with CHF (% reduction in venous tone 49.5 ± 10.1% vs. 54.8 ± 10.1%, p = NS). This response was similar when New York Heart Association classification (NYHA) and etiology of CHF were taken into account (Table 2).

Basal venous NO activity. The response to L-NMMA is illustrated in Figure 2. Infusion of L-NMMA resulted in significant venoconstriction in both the patient (9.6 ± 1.8%, p < 0.01) and the control (6.6 ± 1.7%, p < 0.01) groups. There was no change in venous compliance in either group. There was no difference in the degree of L-NMMA-induced venoconstriction, that is, basal NO activity, between the patients with heart failure and the controls (9.6 ± 1.8% vs. 6.6 ± 1.7%, p = NS) nor when NYHA status and etiology were taken into account (Table 2).

Arterial endothelial function in response to shear stress. Flow-mediated dilation (FMD) was significantly impaired in the patients with CHF compared with controls (% FMD in CHF 2.0 ± 0.6% vs. controls 7.5 ± 2.5%, p < 0.01).

**DISCUSSION**

This study demonstrated that both basal and carbachol-stimulated NO release was preserved in patients with CHF compared with matched controls. This was in marked contrast with the impaired endothelial response to flow.

| Table 2. Effects of Etiology and Functional Class on Venous Endothelial Function |
|-------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                              | Control        | All CHF        | DCM            | IHD            | NYHA II        | NYHA III/IV    |
| n                             | 16             | 24             | 10             | 14             | 8              | 16             |
| Mean age (yrs)                | 60.1 ± 1.6     | 62.2 ± 2.4*†   | 58.1 ± 4.7*    | 65.1 ± 2.2*    | 61.8 ± 4.1*†   | 62.4 ± 3.0*†   |
| % venodilation with carbachol | 40.7 ± 3.9†    | 36.8 ± 3.9*†   | 39.1 ± 5.8*‡   | 35.1 ± 5.5*‡   | 36.6 ± 6.6*‡   | 36.9 ± 5.1*†   |
| % venodilation with coinfusion| 22.1 ± 4.8‡    | 20.3 ± 4.3*‡   | 18.8 ± 5.7‡    | 21.1 ± 6.1‡    | 16.8 ± 4.2‡    | 21.6 ± 5.7‡    |
| % venodilation with L-NMMA    | −6.6 ± 1.7†    | −9.6 ± 1.8*‡   | −12.5 ± 2.3*‡  | −7.6 ± 2.6*‡   | −9.5 ± 2.8*‡   | −9.6 ± 2.4*†   |

*p = ns compared with controls; †p < 0.01 compared with unstressed volume; ‡p < 0.01 reduction in carbachol effect.

CHF = congestive heart failure; DCM = dilated cardiomyopathy; IHD = ischemic heart disease; L-NMMA = N-monomethyl-L-arginine; NYHA = New York Heart Association classification.
mediated shear stress in the brachial arteries of these patients with CHF. This observation has important implications for our understanding of the mechanism(s) that gives rise to endothelial dysfunction in CHF. Furthermore, our data suggest that venous endothelium has the potential to significantly modulate venous tone, and, therefore, cardiac filling pressures, in CHF.

Rationale for studying CHF patients on ACE inhibitors. Our patients were all on stable therapy with ACE inhibitors. These agents form the mainstay of treatment for CHF, and it would have been unethical to withdraw them for the period necessary for the tissue activity of these drugs to cease. The alternative strategies for studying patients not on ACE inhibitors would have been to recruit patients intolerant of ACE inhibitors or before initiation of ACE intolerant of ACE inhibitor therapy. However, most subjects intolerant of ACE inhibitors are treated with AT1 receptor antagonists, and these would have effects on angiotensin II and, thus, endothelial function. It would have been possible to study subjects before initiation of ACE inhibitors. This would also have raised difficulties in interpreting the results. These subjects would have been likely to have had markedly raised venous pressures (and volumes) compared with healthy subjects. Therefore, comparing changes in venous volume between the two groups would have been extremely difficult. A potential drawback of our strategy is that ACE inhibitors are known to improve arterial endothelial function. However, most studies in patients on long-term ACE inhibitor therapy have shown residual impairment of arterial endothelial function (1,3,9). Consistent with this, the patients with CHF in this study demonstrated marked arterial endothelial dysfunction despite treatment with ACE inhibitors. Furthermore, despite ACE inhibitor therapy, two thirds of the patients were in class III and IV, and the venous endothelial responses did not differ when analyzed according to NYHA functional class.

Endothelial dysfunction in CHF. Endothelial dysfunction plays an important role in cardiovascular pathophysiology and is believed to be predominantly due to reduced NO bioavailability (25). Endothelial dysfunction has been clearly demonstrated in both conduit arteries and resistance vessels in CHF (1–7). In conduit arteries, such as the brachial artery, there is a reduction in NO activity in response to increased shear stress. This is manifest (as in the present study) as a reduced brachial artery dilator response to increased flow (1). Similarly, dilator responses to endothelium-dependent agonists such as acetylcholine, bradykinin and carbachol have consistently been reported as having been reduced in the resistance vessels of patients with CHF (2–5). These abnormalities, which are only partially ameliorated by ACE inhibitor therapy (26), are due to a reduction in agonist-stimulated or shear-related NO activity. There are conflicting data as to whether basal NO activity is reduced in the arterial circulation of patients with CHF (3,27–30). Studies in ACE inhibitor treated patients have generally shown preservation of basal NO activity (27), whereas a study in untreated patients reported it to be markedly impaired (30).

Importantly, in this study, despite a marked reduction in brachial artery FMD, there was preservation of both basal and stimulated NO activity in the forearm venous capacitance bed of patients with CHF. One caveat is that our data are expressed in terms of percentage change in venous capacitance (or unstressed volume) from baseline. If venous capacitance were markedly reduced in the patients with CHF, then a similar percentage change in unstressed volume during L-NMMA or carbachol might nevertheless reflect a reduced absolute response. Our data do not support this. Forearm venous counts were similar in patients with CHF and controls; body mass index (and, therefore, tissue attenuation) was actually a little higher in patients. It is, therefore, highly unlikely that, in this (treated) group of patients with CHF, forearm venous volume is significantly different between the two groups. An additional caveat must be applied before concluding that stimulated NO activity is preserved. We showed that the maximal vasodilator response to carbachol was similar in patients and controls. This does not exclude a reduced response to a submaximal dose. However, it was not possible to examine doseresponse relations in the venous capacitance bed. A reduced dilator response in resistance vessels in CHF would result in lower flow rates and relatively higher carbachol concentrations in venous/venular blood for a given flow rate. However, we know that, in the arterial circulation, maximal responses to endothelium-dependent agonists are diminished (5).

Pathophysiological implications. Our observation of preserved agonist-mediated NO activity in the venous capacitance bed, despite marked impairment of shear-related NO release in the brachial artery, is intriguing. It might be argued that shear stress and agonist responses might differ, but, as noted above, agonist-mediated NO activity has also been consistently shown to be diminished in CHF, even in those treated with ACE inhibitors. The mechanism(s) of endothelial dysfunction in the arterial circulation in CHF are not fully established. It is clear that the impairment resides in the NO component. Broadly, this may be due to impairment in NO synthesis, reduction in NO bioavailability (via its oxidation to peroxynitrite) or to an abnormality of signaling pathways within smooth muscle (which may or may not be due to increased oxidative stress) (25).

It is unclear whether NO synthesis in arteries and arterioles is impaired in CHF. Plasma levels of asymmetric dimethylarginine are increased in CHF (31). Asymmetric dimethylarginine is an endogenous inhibitor of L-arginine cellular uptake and binding to eNOS. This might be expected to reduce NO synthesis rates. Conversely, it has been reported that plasma nitrate may be increased in CHF although this may be due to reduced renal excretion (32).

Oxidative stress is increased in CHF (33). Both short lived lipid-derived free radicals and longer-lived products of
lipid peroxidation are increased in proportion to the functional severity of the CHF, and antioxidant defenses are diminished (34–36). Increased oxidative stress may be directly toxic to endothelium as reactive oxygen species can combine with NO to form peroxynitrite, which has toxic effects (37). Furthermore, reactive oxygen species may cause signaling pathway abnormalities in vascular smooth muscle (38). The marked improvement in endothelium-dependent vasodilation after acute and chronic oral vitamin C administration implies an important role for oxidative stress in the endothelial dysfunction (34,39) although recent data suggest that vitamin C may also have other relevant effects (40).

What insights may the preservation of function of the venous endothelium in CHF provide into pathophysiology? In saphenous vein rings, eNOS messenger RNA was lower than it was in internal mammary artery rings, arguing against increased NO synthesis in veins (41). However, there is no data on NO synthesis from the functionally more important small veins and venules that we have studied. Furthermore, asymmetrical dimethylarginine levels are increased in venous as well as in arterial blood in patients with CHF. It may seem logical that, since lipid-derived free radicals and thiobarbituric acid reactive substances are increased in venous blood in patients with CHF, the venous endothelium would also be exposed to a similar degree of oxidative stress as the arterial circulation. However, it is the local levels of the short-lived radicals, superoxide and hydrogen peroxide, that are relevant in terms of the underlying pathophysiology of endothelial dysfunction, not the longer-lived markers of oxidative stress. A recent study reported that saphenous vein rings demonstrated a markedly reduced capacity to generate superoxide via the NAD(P)H oxidase enzyme system in response to angiotensin II stimulation compared with internal mammary artery rings (42). Thus, local levels of oxidative stress may be lower in veins than they are in arteries. While our observations do not prove such a mechanism, they are consistent with it.

**Clinical implications.** On the face of it, our observation that forearm venous capacitance was not lower in patients with CHF than it was in controls may seem surprising. In untreated CHF, venous tone is increased (and venous capacitance reduced) in the same way that systemic vascular resistance is increased (43,44). However, we know that in patients treated with ACE inhibitors, systemic vascular resistance falls to normal levels (44). It is, therefore, perfectly consistent that the same changes might occur in venous capacitance. Indeed, in severe CHF, optimal therapy may require a reduction in venous tone or systemic vascular resistance to below “normal” levels (44). Therefore, our observation that the venous endothelium is capable of responding normally to agonists raises the potential of novel therapy to lower venous tone. Nebivolol, for example, is a beta-adrenergic blocking agent that has vasodilator actions via increasing NO synthesis (45). The action of agents such as this on venous tone in patients with CHF needs to be tested as further reductions in venous tone might be expected to be associated with beneficial hemodynamic changes in certain patients with CHF. In addition, this study raises the highly intriguing question of why venous endothelial function is preserved despite the presence of marked arterial endothelial dysfunction. An understanding of the mechanisms involved may allow new strategies for improving arterial endothelial function.

**Study limitations.** We cannot necessarily extrapolate our data to other large venous capacitance beds such as the splanchnic bed. Assessment of this bed would be highly invasive given the need for local infusion of carbachol and L-NMMA. As discussed above, these results need to be interpreted in light of concurrent drug treatment including ACE inhibitors.

**Conclusions.** Despite marked impairment of shear-related NO activity in the brachial artery, both basal and agonist-mediated NO activity were preserved in the forearm venous capacitance bed of patients with CHF receiving treatment with ACE inhibitors. Potential mechanism(s) for this “protection” has been discussed but remains to be determined. Our findings have important clinical implications suggesting that endothelium-dependent agonists may have the potential to lower venous tone and, thus, improve central hemodynamics.

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