Brachial Artery Elastic Mechanics in Patients With Heart Failure

Daniel R. Kaiser, Kathleen Mullen, Alan J. Bank

Abstract—Studies of arterial elasticity in patients with heart failure (HF) have produced varying results. In addition, the direct effects of smooth muscle relaxation on arterial wall mechanics in these patients have not been well characterized. Nineteen patients with New York Heart Association class II to IV HF and 17 age- and size-matched normal subjects were studied by using a recently validated technique for measuring brachial arterial wall mechanics over a wide pressure range. The left brachial artery was imaged through a water-filled blood pressure cuff by use of an ultrasound wall-tracking system at baseline and after 0.4 mg sublingual nitroglycerin (NTG). Simultaneous radial artery pressure waveforms were recorded by tonometry. Transmural pressure (TP) was reduced by increasing water pressure in the cuff. Baseline area, compliance, and pulse wave velocity versus TP curves were similar in the normal subjects and the patients with HF. The incremental elastic modulus versus TP curve tended to be lower in the patients with HF. The wall-to-lumen ratio was increased in HF (P=0.05). NTG significantly shifted the area versus TP (P<0.001) and compliance versus TP (P<0.05) curves upward and the pulse wave velocity versus TP (P<0.05) curve downward in both groups. NTG also significantly (P<0.001) shifted the stress versus strain curve to the right in both groups but did not alter the incremental elastic modulus versus TP curve. We conclude that the brachial arterial wall-to-lumen ratio is increased in HF. This finding occurs together with a trend toward reduced arterial stiffness such that overall mechanical behavior of the brachial artery is preserved. Smooth muscle relaxation with NTG produces similar improvements in brachial arterial wall mechanics in normal subjects and in patients with HF. (Hypertension. 2001;38:1440-1445.)

Key Words: arteries ■ compliance ■ elasticity ■ nitroglycerin ■ muscle, smooth, vascular ■ heart failure ■ vasodilation

Large arteries act both as conduits that distribute blood to various organs and as cushions that buffer pulsatile pressure and flow. This cushion function results in steady flow at the tissue level and reduced left ventricular afterload. 

An understanding of the arterial elastic mechanics in patients with heart failure may be of particular importance because modest changes in left ventricular afterload can have profound hemodynamic and clinical effects. 

Studies assessing arterial wall mechanics in patients with heart failure have produced variable results, with some showing impaired arterial mechanical function and others showing no impairment. 

Additionally, the effects of vasodilator drugs on arterial mechanical properties have not been fully characterized. We have developed a new ultrasound technique that allows for the noninvasive assessment of arterial wall mechanics in human subjects in vivo over a wide range of distending pressures and smooth muscle tone. Thus, the present study was designed to compare brachial arterial wall mechanics in normal subjects and patients with heart failure under baseline conditions and also after smooth muscle relaxation with nitroglycerin (NTG).

Methods

Study Population

Nineteen patients with New York Heart Association (NYHA) class II to IV heart failure, age 24 to 67 years (52±2 [mean±SEM] years), and 17 normal subjects, age 33 to 68 years (51±2 years), were studied. All normal subjects were without cardiovascular disease or other systemic disease as determined by history, physical examination, routine blood tests, and ECG. Heart failure patients with hypertension (blood pressure >160/90 mm Hg), marked hypercholesterolemia (total cholesterol >250 mg/dL), unstable angina, recent (<3 months) myocardial infarction, or uncontrolled diabetes mellitus were excluded. All heart failure patients were clinically stable and without significant edema. Baseline characterization of the heart failure patients was determined by history and physical examination, routine blood tests, 6-minute walk, neurohormone measurements (norepinephrine, brain natriuretic peptide [BNP], and endothelin), and echocardiogram. The etiologies of heart failure were idiopathic dilated cardiomyopathy (n=11), ischemic cardiomyopathy (n=7), and alcoholic cardiomyopathy (n=1). Medical treatment included diuretics (89%), β-blockers (79%), ACE inhibitors or angiotensin II receptor blockers (95%), nitrates (42%), and statins (58%). Vasodilative medications were withheld for 24 to 48 hours before each study. All other medications, including diuretics and digoxin, were withheld on the morning of each study. The present study was approved by the Institutional Review Board of the University of Minnesota, Minneapolis.

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by the Human Rights in Research Committee at the University of Minnesota, and written informed consent was obtained from all subjects.

**Measurement of Arterial Pressure, Diameter, and Wall Cross-Sectional Area**

The technique for measuring arterial elastic properties has previously been validated and described in detail. Briefly, the brachial artery was imaged through a water-filled vinyl blood cuff by using a pulsed ultrasound echo-tracking system (WTS, PIE Medical). Blood pressure waveforms were simultaneously recorded from the radial artery by using applanation tonometry (CBM 7000, Colin Instruments). Brachial artery intima-media thickness (IMT) was measured by using high-resolution B-mode ultrasonography, a technique similar to that validated for measurement of carotid artery IMT and previously published from our laboratory. Wall cross-sectional area (WCSA) was calculated as previously described. Wall thickness measurements at all other cuff pressures were then calculated with the assumption of constant WCSA.11

**Experimental Protocol**

Studies were performed in a quiet room of constant temperature (22° C to 23° C). Subjects refrained from caffeine and cigarettes on the day of the study. Forearm volume was measured by using a truncated cone formula. The left arm was positioned in an arm sling at a level slightly above that of the heart. Transmural pressure (TP) was defined as the difference between arterial pressure and water cuff pressure. Three separate measurements of 6 to 8 cardiac cycles were performed at 4 equally spaced water cuff pressures of 0 mm Hg, 1/3 diastolic pressure, 2/3 diastolic pressure, and diastolic pressure. Approximately 20 complete pressure and diameter cycles were recorded at the 4 TP levels. Ensembled pressure and area waveforms were generated from these beats at each pressure step by using custom software. The diastolic portion of the data was fit by using nonlinear regression to the arctangent model of Langewouters et al. Brachial artery compliance, stress, strain, incremental elastic modulus ($E_{inc}$), and pulse-wave velocity (PWV) were calculated as previously reported. The same procedure was repeated after 0.4 mg of sublingual NTG. Measurements were made starting 4 minutes after administration of the NTG. A previous study confirmed that the effect of NTG on arterial tone did not diminish over the study duration.

**Statistical Analysis**

Statistical analysis was performed by using SPSS version 8. The 2-tailed $t$ test for unpaired observations was used to identify differences between group parameters. Within-group comparison was performed on curves generated at baseline and after NTG administration by using a 2-way repeated-measures general linear model ANOVA (drug and pressure as conditions). Between-group comparison was performed on curves generated at baseline and also on the change in curves at baseline and after NTG by using the multivariate general linear model ANOVA (group and pressure as conditions). Statistical significance was defined as $P<0.05$. Data are presented as mean±SEM.

**Results**

**Baseline Characteristics**

Table 1 shows baseline demographic data for the subjects in the 2 study groups. The groups were well matched with respect to age, gender, height, and forearm volume. Body weight was significantly higher in the heart failure patients. There were no significant differences in blood pressure or total cholesterol between the groups. Patients with heart failure had evidence of moderate disease, with a mean NYHA class of 2.7 and a mean ejection fraction of 23%. BNP and endothelin, but not norepinephrine, levels were significantly increased in patients with heart failure. There were no significant correlations between neurohormonal levels and compliance at 100 mm Hg, $E_{inc}$ at 100 mm Hg, or wall-to-lumen ratio. Table 2 shows measurements of brachial arterial wall structure in the 2 groups. There were no significant differences in area at 100 mm Hg, unstressed area, IMT, or WCSA. The wall-to-lumen ratio was significantly ($P=0.05$) increased in the patients with heart failure.

**Brachial Arterial Wall Mechanics**

Brachial artery–TP curves (Figure 1) at baseline were similar ($P=NS$) in the normal subjects and in the patients with heart failure (although the area-TP curve tended to be slightly lower in the heart failure patients). Both normal subjects and patients with heart failure dilated significantly ($P<0.0001$) to NTG, with a mean increase in brachial artery area over the entire curve of 26.0% in the normal subjects and 23.5% in the patients with heart failure. NTG produced

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy Control (n=17)</th>
<th>CHF Patients (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area at 100 mm Hg, mm$^2$</td>
<td>17.97±1.41</td>
<td>17.09±1.77</td>
</tr>
<tr>
<td>Unstressed area, mm$^2$</td>
<td>12.59±1.41</td>
<td>11.50±1.51</td>
</tr>
<tr>
<td>IMT, mm</td>
<td>0.35±0.01</td>
<td>0.39±0.01</td>
</tr>
<tr>
<td>WCSA, mm$^2$</td>
<td>4.76±0.32</td>
<td>4.80±0.28</td>
</tr>
<tr>
<td>Wall/lumen ratio</td>
<td>0.19±0.01</td>
<td>0.23±0.01*</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *$P<0.05$. 

(500x142)

**TABLE 1.** Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy Control Subjects (n=17)</th>
<th>CHF Patients (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women, n</td>
<td>13/4</td>
<td>14/5</td>
</tr>
<tr>
<td>Age, y</td>
<td>51±2</td>
<td>52±2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78±3</td>
<td>91±4*</td>
</tr>
<tr>
<td>Height, cm</td>
<td>176±2</td>
<td>176±2</td>
</tr>
<tr>
<td>FAV, mL</td>
<td>972±61</td>
<td>990±56</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>123±3</td>
<td>127±4</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>71±2</td>
<td>69±2</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>59±3</td>
<td>67±3*</td>
</tr>
<tr>
<td>NYHA class</td>
<td>...</td>
<td>2.7±0.2</td>
</tr>
<tr>
<td>Duration of heart failure, y</td>
<td>...</td>
<td>4.2±0.6</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>...</td>
<td>23±1</td>
</tr>
<tr>
<td>6-min walk, m</td>
<td>...</td>
<td>446±36</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>17±2</td>
<td>26±3*</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.98±0.05</td>
<td>1.28±0.12*</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>167±8</td>
<td>188±12</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>193±22</td>
<td>243±39</td>
</tr>
<tr>
<td>Endothelin, pg/mL</td>
<td>2.4±0.2</td>
<td>3.9±0.4†</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>17±4</td>
<td>191±38†</td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure; FAV, forearm volume; BP, blood pressure; and BUN, blood urea nitrogen. Values are mean±SEM.

$*P<0.05$; †$P<0.01$. 

\[ \text{(500x142)} \]
modest changes in systemic hemodynamics, with heart rate changing from 63 to 65 bpm \((P=\text{NS})\), systolic blood pressure changing from 125 to 119 mm Hg \((P<0.05)\), and diastolic blood pressure changing from 70 to 65 mm Hg \((P<0.05)\).

Compliance-TP curves (Figure 2) were also similar \((P=\text{NS})\) under baseline conditions in both groups. NTG significantly increased compliance in both groups \((P<0.05)\). The increase in compliance over the entire pressure range was similar in normal subjects (63%) and patients with heart failure (81%). Stress-strain curves are shown in Figure 3. There was a small nonsignificant rightward shift of the baseline stress-strain curve in patients with heart failure compared with normal subjects. Stress-strain curves significantly \((P<0.0001)\) shifted to the right after NTG in a similar fashion in both groups. \(E_{\text{inc}}\)-TP curves are shown in Figure 4. Under baseline conditions, the \(E_{\text{inc}}\)-TP curve tended to be higher \((P=\text{NS})\) in the normal subjects than in the patients with heart failure. After NTG administration, there was no significant change in the \(E_{\text{inc}}\)-TP curves in either group.

Figure 1. Area versus TP curves at baseline in normal subjects (■) and heart failure patients (○) and after 0.4 mg sublingual NTG in normal subjects (□) and heart failure patients (○). The curves at baseline were not significantly different between normal subjects and patients with heart failure. Smooth muscle relaxation with NTG significantly and similarly increased brachial artery area over the entire pressure range in both groups \((P<0.0001)\).

Figure 2. Compliance versus TP curves at baseline in normal subjects (■) and heart failure patients (○) and after 0.4 mg sublingual NTG in normal subjects (□) and heart failure patients (○). The curves at baseline were not significantly different between normal subjects and patients with heart failure. NTG significantly increased compliance in both groups \((P<0.05)\).

Figure 3. Stress versus strain curves at baseline in normal subjects (■) and heart failure patients (○) and after 0.4 mg sublingual NTG in normal subjects (□) and heart failure patients (○). There was a small nonsignificant rightward shift of the baseline stress-strain curve in patients with heart failure compared with normal subjects. NTG significantly shifted the baseline stress-strain curve rightward similarly in both groups, resulting in a large decrease in isometric wall stress \((P<0.0001)\).

Figure 4. \(E_{\text{inc}}\) versus TP curves at baseline in normal subjects (■) and heart failure patients (○) and after 0.4 mg sublingual NTG in normal subjects (□) and heart failure patients (○). Under baseline conditions, the \(E_{\text{inc}}\)-TP curve tended to be higher \((P=\text{NS})\) in the normal subjects than in the heart failure patients. After NTG administration, there was no significant change in the \(E_{\text{inc}}\)-TP curves in either group.

Discussion
In the present study, we measured brachial arterial wall mechanics in vivo over a wide range of pressures and smooth muscle tone for the first time in human subjects with heart failure. We demonstrate that brachial arterial wall mechanics are normal under baseline conditions. The wall-to-lumen ratio is increased in patients with heart failure, which is consistent with vascular remodeling. Normal subjects and patients with heart failure vasodilate and demonstrate relatively similar improvements in arterial wall mechanics after smooth muscle relaxation with NTG.
Baseline Arterial Structure and Wall Mechanics

The major difference between the baseline brachial artery properties in the 2 groups was an increased wall-to-lumen ratio in the patients with heart failure. This occurred as a result of a mildly (not statistically significantly) decreased cross-sectional area and a mildly increased IMT and WCSA in the patients with heart failure. These data suggest that the brachial arteries in the patients with heart failure underwent eutrophic (or mildly hypertrophic) inward remodeling.13,14 The vessel size tended to be smaller, but the WCSA was the same or slightly increased. This increase in wall-to-lumen ratio would be expected to result in reduced arterial compliance in the heart failure patients if the stiffness of the wall components remained unchanged. In the present study, baseline arterial compliance was normal to minimally increased in the patients with heart failure, whereas \( E_{inc} \), a measure of intrinsic arterial stiffness, tended to be decreased in the patients with heart failure. These findings suggest that the remodeling process occurred in concert with a trend toward reduced arterial stiffness such that overall mechanical behavior of the brachial artery was preserved.

Endothelin levels were significantly increased in the patients with heart failure, and this neurohormone can cause vascular hypertrophy and remodeling.15 Abnormalities in the endothelial NO pathway are common in patients with heart failure,16,17 and this abnormality along with reduced blood flow to the periphery could also have contributed to the remodeling noted.18 Vascular remodeling in association with a trend toward reduced vessel stiffness could occur via a number of possible mechanisms, including changes in the ratio or absolute amounts of collagen and elastin, changes in collagen type, or alterations in the mechanical connections or arrangement of wall components. Vascular remodeling has been described in humans with heart failure both in the carotid arteries (increased IMT with normal lumen size)4 and in the microvasculature (increased arteriolar hyalnosis and basement membrane thickening).19

Previous studies of muscular arterial mechanical function have produced varying results. Radial artery compliance in heart failure patients was decreased in one study6 but increased in another study.7 Ramsey et al8 found no difference in brachial artery distensibility or iliac artery PWV in patients with heart failure. Arnold et al9 demonstrated that brachial artery diameter and calculated compliance were decreased and that PWV was increased in patients with heart failure. The present study results differ from those of Arnold et al for several possible reasons. It is possible that our patients were not as sick. Mean ejection fraction was higher (23% versus 19%) and NYHA class was slightly lower (2.7 versus 3.0) in the present study. There was evidence to suggest tissue wasting in the study of Arnold et al, inasmuch as body weight and body mass index were decreased and forearm volume tended to be less despite similar height. These abnormalities were not present in our patients, and in fact, body weight was increased in our heart failure group despite similar height. Muscle and subcutaneous tissue wasting may have resulted in reduced blood flow and decreased brachial artery size in the study of Arnold et al. The reduced brachial artery size alone may have accounted for the reduction in compliance and PWV.20

Effects of NTG

Sublingual NTG produced significant dilation of the brachial artery in both study groups. NTG also tended to produce improvements in arterial wall mechanical properties in both groups, including improvements in isobaric arterial compliance, \( E_{inc} \), and PWV. A number of studies have demonstrated that smooth muscle relaxation improves arterial wall properties in normal subjects.8,21,22 Vasodilator drug administration to patients with heart failure has generally resulted in beneficial effects on pulsatile arterial function. Both nitroprusside2,23–25 and dobutamine26 improve ventricular-vascular coupling through a reduction of wave reflection and (in some studies) a decrease in aortic characteristic impedance. The effects of changes in smooth muscle tone on arterial stiffness are variable27 and complex. Smooth muscle relaxation decreases stiffness by decreasing tension in the smooth muscle itself and in its associated series elastic component.28 Smooth muscle relaxation increases stiffness by increasing tension in the parallel collagen and elastin fibers that are recruited as vessel size increases. The net effect on stiffness depends on the relative magnitude of these 2 opposing effects. In the present study, NTG had no significant effect on \( E_{inc} \) in either study group. Therefore, the improvements in compliance and PWV after NTG were predominantly due to increases in vessel size rather than changes in vessel stiffness. A similar finding occurred in an intravascular study of brachial arterial wall mechanics in normal subjects performed in our laboratory.22 In contrast, a study of brachial wall mechanics in young normal subjects (by using the technique followed in the present study) showed that NTG significantly reduced \( E_{inc} \).9

Potential Limitations

It is possible that the increased wall-to-lumen ratio and the trend toward decreased \( E_{inc} \) in the patients with heart failure was a result of increased basal vasoconstrictor tone rather than remodeling.29 However, if vascular tone was

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**Figure 5.** PWV versus TP curves at baseline in normal subjects (■) and heart failure patients (●) and after 0.4 mg sublingual NTG in normal subjects (○) and heart failure patients (▲). Baseline PWV was similar (\( P=NS \)) in the 2 groups and decreased significantly and similarly in both groups after NTG administration (\( P<0.05 \)).
increased without remodeling in the patients with heart failure, then the vasodilator response (which was near maximal) should have been greater in the heart failure patients compared with the normal subjects. In addition, the heart failure patients had a larger body weight and tended to have a larger forearm volume. Thus, one would expect that the brachial artery area after NTG administration would be greater in the heart failure patients if remodeling was not a factor. Finally, the E\textsubscript{inc} would likely not have tended to be reduced because acute intra-arterial norepinephrine administration to normal subjects of similar age produced marked vasoconstriction but did not shift the brachial artery E\textsubscript{inc}-TP curve.\textsuperscript{22} Another possible explanation for the increased wall-to-lumen ratio observed in the heart failure group may be due to previous hypertension (present in 42% of the heart failure patients). However, the heart failure patients had a history of only mild hypertension and were normotensive at the time of the study. Prior studies of hypertensive patients have shown an increased wall-to-lumen ratio in muscular conduit arteries.\textsuperscript{30}

The present study addressed arterial wall mechanics in only a muscular artery, the brachial artery. This artery was studied because it can be readily imaged through a water-filled cuff and hence studied over a wide pressure range. The ability to determine unstressed area enabled us to measure true strain (and hence E\textsubscript{inc}) for the first time in vivo in patients with heart failure. The findings described in the present study cannot necessarily be extrapolated to elastic arteries, such as the carotid or the aorta.

The normal subjects were similar to the heart failure patients in gender, size, and age. These details are important because each of these factors can influence arterial mechanical properties.\textsuperscript{31–33} In particular, arterial size (which correlates fairly tightly with measures such as height and forearm volume) is a major determinant of mechanical properties, such as compliance and PWV,\textsuperscript{20} independent of vessel stiffness.

The heart failure patients were on chronic vasoactive medical therapy. Vasodilator medications were withheld for 24 to 48 hours before each study. Withholding medication for longer periods of time was not felt to be acceptable because of the risk of clinical deterioration. It is possible that some of the acute effects of these medications could still be present, but reduced in magnitude, at the time of the study. It is also possible that chronic inhibition of the renin-angiotensin system with drugs improved the brachial arterial wall mechanics.\textsuperscript{34} Although this is a possible explanation, with present day therapy, it is very difficult to find chronic heart failure patients who are not being treated with renin-angiotensin blockers. Therefore, the present study represents the arterial mechanics in stable heart failure patients on standard chronic medication.

Acknowledgments
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References
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