Large Artery Function in Patients With Chronic Heart Failure

Studies of Brachial Artery Diameter and Hemodynamics

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Background. Although progressive chronic congestive heart failure (CHF) is associated with elevated systemic vascular resistance and increased impedance to ventricular outflow, the contribution of changes in large artery function has not been well documented in humans.

Methods and Results. We studied 45 patients with a broad range of clinical severity of CHF and compared noninvasive measurements of brachial artery diameter, flow, and pulse wave velocity with 22 normal controls of similar age. In CHF, mean arterial pressure was lower than in controls (85±1 versus 93±2 mm Hg, \( p < 0.001 \)), as were brachial artery diameter (4.07±0.10 versus 4.33±0.09 mm, \( p < 0.001 \)), flow (40.9±4.1 versus 70.9±11.5 ml·min\(^{-1} \), \( p < 0.02 \)), compliance (1.29±0.12 versus 2.00±0.18 cm\(^{-1} \)·dyne\(^{-1} \)·10\(^{-7} \), \( p < 0.002 \)), and conductance (0.49±0.05 versus 0.76±0.13 units, \( p = 0.06 \)). Limb vascular resistance (40.2±5.0 versus 20.5±3.1 units, \( p < 0.001 \)) and pulse wave velocity (10.6±0.5 versus 9.2±0.4 m·sec\(^{-1} \), \( p < 0.03 \)) were higher than in controls. Brachial artery diameter was progressively lower than in controls as severity of CHF increased (New York Heart Association class II, 4.47±0.23 mm, \( p = \text{NS} \); class III, 4.05±0.10 mm, \( p < 0.05 \); class IV, 3.71±0.28 mm, \( p < 0.05 \)). Similar changes were observed for arterial compliance (class II, 1.76±0.32 cm\(^{-1} \)·dyne\(^{-1} \)·10\(^{-7} \), \( p = \text{NS} \); class III, 1.21±0.13 cm\(^{-1} \)·dyne\(^{-1} \)·10\(^{-7} \), \( p < 0.05 \); class IV, 0.95±0.10 cm\(^{-1} \)·dyne\(^{-1} \)·10\(^{-7} \), \( p < 0.05 \)). While the lower arterial pressure and flow might be expected to passively reduce arterial diameter, this would be associated with a reduced pulse wave velocity and improved arterial compliance, yet the opposite was observed. Differences in large artery function were not likely caused by underlying atherosclerosis alone, because patients with dilated cardiomyopathy and patients with ischemic heart disease of the same sex, age, left ventricular ejection fraction, and exercise treadmill duration had similar changes in large artery function.

Conclusions. We conclude that alterations in brachial artery function are present in patients with moderate and severe CHF. The observed reduction in arterial compliance, if present diffusely throughout the arterial tree, could increase left ventricular end-systolic stress directly and through increased velocity of reflected pressure waves from the periphery. (Circulation 1991;84:2418–2425)

Large arteries serve as a conduit to deliver oxygenated blood to the body organs and as a cushion to buffer the pulsatile pressure and flow from the heart.\(^1\) Stiffness of the large arterial wall will decrease arterial distensibility. The resultant reduction in buffering effect on pulsatile pressure


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modifiers of peripheral vascular resistance. Abnormalities in the conductance vessels in humans were demonstrated by Pepine et al., who showed that input aortic impedance was increased in a small group of patients with severe CHF. These measurements were performed with pressure transducers in the ascending aorta at the time of heart catheterization. The use of such invasive catheters greatly limits the applicability of aortic impedance measurements in ordinary clinical practice. Therefore, we have used noninvasive techniques to measure brachial artery internal diameter and pulse wave velocity (PWV). Since such techniques can be used in a routine clinical setting, they allow measurements in a greater number of patients with a wider spectrum in clinical severity of CHF. We wished to determine whether abnormalities comparable with those seen at the root of the aorta are present in other parts of the large arterial tree, such as the brachial artery, in patients with CHF.

Methods

The protocol was approved by the University Review Board for Health Sciences Research Involving Human Subjects, and all patients and subjects gave written informed consent.

Patient Population

Forty-five patients aged 27–68 years (mean±SD, 54.8±8.9 years) with clinical signs and symptoms of CHF were studied. None had a history of hypertension or hypertrophic cardiomyopathy. Their clinical characteristics are given in Table 1. Thirty-nine patients received digoxin in a mean daily dose of 0.20±0.07 mg. Forty-one patients received furosemide in doses between 20 and 1,000 mg/day with a mean daily dose of 117±156 mg. Fifteen patients with milder CHF were not on vasodilators, but 26 patients with more severe CHF were on an angiotensin converting enzyme inhibitor (24 received captopril in a mean daily dose of 47.9±34.4 mg), sometimes in combination with nitrates (n=8), and four patients were on nitrates alone as vasodilator therapy. All patients had been on a stable low-salt diet and medication dosages for at least 5 days.

Normal Controls

Twenty-two physically untrained normal controls were studied. Since age has important influences on PWV and ventricular vascular coupling, care was taken to ensure that these subjects had an age distribution similar to that of the CHF patients (52.7±12.0 years; range, 27–69 years; same frequency distribution as CHF population with \( \chi^2 = 4.29, df = 7, p = 0.75 \) for 5-year intervals). None had any history of cardiovascular disease by history, physical examination, or electrocardiogram. None were taking vasoactive medications.

Study Design

Subjects were studied in the morning in a quiet, temperature-controlled (23–24°C) cardiovascular laboratory. All fasted overnight with no caffeine or cigarettes on the morning of the study. In the CHF patients, vasodilators were withheld for at least 36 hours before the study and digoxin and diuretics were withheld on the morning of the study. Subjects lay comfortably supported in a supine or semirecumbent position to avoid symptoms of orthopnea and rested quietly for at least 30 minutes before any hemodynamic measurements were made.

Measurements

Brachial artery internal diameter and hemodynamics were measured at heart level in the nondominant arm 1–3 cm proximal to the antecubital skin crease. The transducer was moved up and down the length of the artery over a course of approximately 4–5 cm to ensure that the recordings were obtained from the middle of a straight arterial segment before the arterial bifurcation at the elbow. A bidimensional pulsed Doppler (8 MHz) zero crossing velocimeter (Alvar Electronics, Paris) was used as described by Levenson et al. This system consists of an adjustable
range-gated time system and a probe with two transducers set at a fixed angle of 120°. To minimize errors introduced by the angle of observation between the ultrasonic beam and the axis of the blood column, the probe position is adjusted with a stereotactic device so that the velocity vectors from the two transducers are equal and opposite, with the two Doppler transducers at 60° to the longitudinal axis of the blood column, thus orienting the probe perpendicular to the vessel axis. Each transducer acts alternately as an emitter and receiver. Adjustments of time delay and reception duration are made with constant steps of 0.5 μsec (0.4 mm). The time delay and reception duration represent the depth and length, respectively, of the measurement volume along the ultrasonic beam axis. The apparent echodiameter of the vessel may be deduced from the time delay of the first and last Doppler signals of systolic flow and sine of the angle between the ultrasonic beam and the vessel axis (60°). Brachial artery flow was calculated from the product of the mean velocity of blood flow across the entire diameter of the artery and the cross-sectional area of the brachial artery. Limb vascular resistance was calculated as mean arterial pressure divided by flow and is expressed in arbitrary units. Conductance of the brachial artery was calculated as flow divided by mean arterial pressure and is expressed in arbitrary units.

The accuracy of the Doppler determinations has been studied with a hydraulic test device using calibrated latex tubes and found to be within 95% of the known velocity for flow velocities between 5 and 100 cm · sec⁻¹ with an intercept on the y axis of 0.035±0.015 cm, which represents an overestimate of the arterial diameter but is not significantly different from zero. In 14 subjects, estimates of brachial artery diameter were performed by the same observer under identical conditions on two occasions separated by 1–6 weeks, and the mean coefficient of variability for reproducibility of diameter in our laboratory was found to be 3.0±3.9% (mean±SD). This is comparable with the reproducibility of 7.0±2% obtained by Levenson et al. PWV was measured with paired pressure transducers (Fukuda Denshi Co.) placed lightly on the skin over the point of maximal pulsation of the brachial (approximately 1 cm proximal to the antecubital skin crease) and radial (at the wrist) arteries in the nondominant arm. The linear distance between measurement points was measured over the surface of the skin with a tape measure. Tracings were recorded at a paper speed of 150 mm · sec⁻¹. Tangents were drawn to the slope in late diastole and the most rapid upstroke during systole. The intersection of these two lines was the reference point for the foot of the pulse wave; hence, PWV was calculated as distance between measurement points divided by time delay from foot to foot of pulse waves. This foot-to-foot technique was chosen to minimize observer bias in identifying a single point such as the peak of the pulse wave contour or the start of the most rapid upstroke, both of which can be difficult to locate and thus may be associated with increased variability and reduced precision. In 10 subjects, brachioradial PWV was measured by the same observer under identical conditions on two occasions separated by 1–6 weeks. The mean coefficient of variability for the measurement was 9.9±7.3% (mean±SD).

Nonpropagative models of arterial compliance assume that all pressure changes within the arterial tree are simultaneous, but this is not known to be true in intact humans. Therefore, in the studies described below, a propagative model has been used to calculate arterial compliance as derived from the Moens-Korteweg equation. In these circumstances, arterial compliance is the product of arterial volume (or cross-sectional area per unit length) and distensibility. Volume distensibility of the brachial artery is calculated at 3.57/(PWV)² as derived according to the Bramwell-Hill formula. Thus, brachial artery compliance is similarly expressed as (πρ)/(D2PWV), where ρ is blood density (a constant, 1.06) and D is arterial diameter. The use of these derived techniques has been extensively studied in hypertension by Sfarr et al.

Arterial pressure and heart rate were measured in the contralateral arm with a semiautomated oscillographic device (Dinamap 845XT, Critikon). Mean arterial pressure was calculated as diastolic plus one third of the pulse pressure. Left ventricular ejection fraction was measured by radionuclide gated blood pool imaging. Symptom-limited exercise duration was measured on a treadmill with a modified Naughton protocol. Body mass index was calculated as mass divided by the square of the height. Limb volume of the nondominant arm up to the antecubital fossa was measured by a water displacement technique.

Plasma norepinephrine and epinephrine were measured by a radioenzymatic technique. Plasma renin activity and aldosterone (Diagnostic Products Corporation, Los Angeles) were measured by radioimmunoassay. Blood samples were obtained from an intravenous line inserted at least 20 minutes before sampling or hemodynamic measurements.

Statistical Analysis

Results are expressed as mean±SEM. Comparisons among several groups were performed using two-way analysis of variance with contrasts analyzed by Tukey’s honestly significant difference method. Comparisons between two groups were performed with a two-tailed unpaired Student’s t test. Correlations between variables were estimated by least-squares linear regression. A value of p<0.05 was taken as statistically significant.

Results

Baseline Hemodynamics

There was no significant difference between the ages of the control and CHF groups. Patients with CHF had higher heart rate, lower mean arterial
pressure, decreased brachial artery flow and velocity, and elevated limb vascular resistance (Figure 1). Brachial artery diameter was reduced in CHF to 4.07±0.10 mm versus 4.53±0.09 mm (p<0.001) in controls, while brachioradial PWV was increased to 10.6±0.5 m·sec⁻¹ versus 9.2±0.4 m·sec⁻¹ in controls (p<0.03). Thus, brachial artery compliance (1.29±0.12 versus 2.00±0.18 cm⁴·dyne⁻¹·10⁻⁷, p<0.002) was significantly reduced (Figure 2).

No relation was observed between brachial artery diameter and mean arterial pressure, although a positive linear relation was found between diameter and flow for all subjects (Figure 3). Arterial diameter and flow were also positively correlated for control subjects alone (r=0.57, p<0.01) and for CHF patients alone (r=0.58, p<0.001), although the slope tended to be smaller in controls (4.4×10⁻³ mm·[ml/min]⁻¹) compared with CHF patients (14.3×10⁻³ mm·[ml/min]⁻¹). Use of quadratic and cubic regression equations did not statistically improve the correlation between arterial diameter and flow. No significant differences in the relation between diameter and flow were found between patients treated and those not treated with vasodilators. Only very weak relations were found between arterial compliance and arterial pressure or flow (Figure 3). The small increase in compliance with increase in pressure and flow over the range of arterial pressures and flows measured may represent an association of low arterial pressure or flow with those patients who were sicker. There were no significant relations between brachial artery diameter, compliance, or brachioradial PWV and plasma venous norepinephrine (Figure 4) or epinephrine in patients with CHF. In patients not receiving angiotensin converting enzyme inhibitors, there were no significant relations between diameter, compliance, or PWV and plasma renin activity (3.62±0.94 ng·1⁻¹·sec⁻¹, n=21) or aldosterone level (742±154 pmol·1⁻¹, n=22).

Relation to Functional Class

When CHF patients were analyzed according to New York Heart Association class, there was a progressive decrease in diameter and compliance compared with controls (p<0.01) with increasing severity of CHF (Figure 5). While PWV tended to increase and volume distensibility tended to decrease, these changes did not reach statistical significance.

Patients in class III and class IV were more likely to be on vasodilators. There was no significant difference in age or left ventricular ejection fraction between patients on vasodilators (n=30) and those not on vasodilators (n=15). For patients on vasodilators,
mean arterial pressure was lower (82±1 versus 91±2 mm Hg, p<0.01) and treadmill duration was less (6.8±0.6 versus 13.7±1.3 minutes, p<0.001), but there were no significant differences in any measurement of brachial artery hemodynamics or distensibility.

Relation to Etiology of CHF

To investigate the contribution of underlying etiology to differences in brachial artery hemodynamics, we selected the 11 patients with dilated cardiomyopathy who had taken an exercise treadmill test and matched them by age, sex, and exercise duration with 11 patients in whom CHF was caused by ischemic heart disease. There were no differences between the two groups in age, weight, limb volume, duration of symptoms, left ventricular ejection fraction, or exercise duration. Similarly, there were no differences in brachial artery diameter (3.95±0.21 versus 4.06±0.13 mm), brachioradial PWV (10.47±0.90 versus 10.48±0.92 m · sec⁻¹), or compliance (1.13±0.08 versus 1.30±0.18 cm³ · dyn·⁻¹ · cm⁻¹).

Relation to Body Size

In CHF, body weight (71.2±1.8 kg) and body mass index (24.4±0.6 kg · m⁻²) were reduced compared with controls (80.1±3.1 kg, p<0.02 and 27.2±0.9 kg · m⁻², p<0.01, respectively). Forearm volume tended to be less in CHF, but the difference was not significant (933±26 versus 1,018±55 ml). There was no significant difference between the two groups in height (CHF, 171±1 cm; controls, 171±2 cm), distance between measurement points on the brachial and radial arteries (24.1±0.3 versus 24.9±0.3 cm), or hand volume (361±11 versus 368±22 ml). Thus, despite similar skeletal size, there was probable muscle and subcutaneous tissue wasting in CHF. When normalized for limb volume, the difference between groups in brachial artery diameter was not significant (3.21±0.09 versus 3.45±0.22 mm · l⁻¹ in controls). However, blood flow tended to remain reduced in CHF (3.30±0.38 versus 5.26±0.92 ml · 100 ml⁻¹ · min⁻¹, p=0.06).

Discussion

In this group of patients covering a broad spectrum of clinical heart failure, we have shown evidence for increased stiffness and reduced compliance of the brachial artery. This extends previous observations in humans on the vascular physiology of heart failure in small arteries and arterioles and proximal aorta and complements other noninvasive observations on peripheral large arteries in healthy subjects. Our studies were limited to the brachial artery, but if these changes were present throughout the large arterial tree, they could increase impedance to left ventricular performance in heart failure. Abnormalities in the aorta and carotid baroreceptor have been documented in patients with heart failure and throughout the arterial tree in both proximal and more distal arteries in animal models of failure. In hypertension, abnormalities in large artery compliance have been observed in both the carotid and brachial arteries by using the same methodology as described in our current study. Whether diffuse changes are seen throughout the large arterial tree in heart failure in humans awaits confirmation in further studies. Increased stiffness in the peripheral arteries could cause the reflected pressure wave to return earlier to the heart, possibly before aortic valve closure. Increases in left ventricular end-systolic pressure could contribute to progressive left ventricular dilatation and failure and reduced survival.

Mechanisms of Large Artery Changes

The changes in arterial compliance that we observed (approximately 36%) were comparable with
If the changes in the brachial artery were merely passive secondary to changes in forearm size, blood flow, or blood pressure, it would have been expected that the arterial wall might remain more distensible with a reduction in brachioradial PWV and improved compliance.28 However, the opposite was found to be the case. Despite a lower arterial pressure and reduced diameter, both of which would be expected to increase compliance if the arterial wall remained normal, brachioradial PWV was increased and compliance reduced in heart failure. Thus, the observed changes probably represent specific alterations in vascular function associated with the pathophysiology of heart failure, so that the effect of increased stiffness of the arterial wall is greater than the effect of reduced arterial pressure and diameter and the net outcome is reduced arterial compliance. Although vasodilators were withheld for at least 36 hours in patients who were receiving them, we cannot exclude a lingering vasodilating effect from these drugs. However, this would probably have caused us to underestimate the changes we observed.

The specific cause of increased stiffness and reduced compliance of the brachial artery in heart failure has not been defined in this study. Although changes in arterial distensibility may be secondary to the process of atherosclerosis,29 in our study similar changes were seen whether the etiology of heart failure was coronary artery disease or idiopathic dilated cardiomyopathy. Furthermore, our observations were made in the upper limb, where atherosclerosis is uncommon. Zelis et al16 have suggested that significant salt and water retention impairs the ability of small arteries and arterioles to vasodilate to a metabolic stimulus and have shown increased sodium content in the aorta and femoral artery of dogs with heart failure.30 Although the vast majority of patients in the present study were on diuretics and none had gross edema at the time of arterial measurements, some contribution of salt and water retention to the arterial stiffness remains possible. The sympathetic nervous system can cause marked vasoconstriction of

**FIGURE 4.** Plots of brachial artery diameter, compliance, and brachioradial pulse wave velocity (PWV) plotted against plasma venous norepinephrine levels in all patients with heart failure (○, no vasodilators; ▼, vasodilators).

those seen in established hypertension.27 No patients in our study had a history of hypertension. The changes in arterial diameter appeared to parallel the concurrent changes in forearm volume presumably caused by tissue wasting in more severe heart failure.

**FIGURE 5.** Bar graphs showing brachial artery diameter, compliance, volume distensibility, and brachioradial pulse wave velocity (PWV) in normal subjects and patients with heart failure separated by New York Heart Association (NYHA) clinical classification. Values are expressed as mean ± SEM. Mean value of each column is given as X. *p<0.05 vs. normal.
arterioles, but there was no association between arterial diameter, compliance, or PWV and norepinephrine levels in our patient population. However, plasma venous norepinephrine levels reflect abnormal clearance as well as increased release of norepinephrine and therefore are only a crude indicator of sympathetic nervous system activity. With worsening heart failure, the renin-angiotensin system becomes activated, and either systemic or local release of angiotensin could have contributed to the brachial artery changes in our patients, although the majority of patients with more severe heart failure and large artery changes in our study were already receiving an angiotensin converting enzyme inhibitor. Endothelium-derived relaxing factor does modulate large artery size, and responses are impaired in the femoral artery of a dog model of heart failure. The slope of the relation between arterial diameter and flow in our study tended to be smaller in controls than in patients with CHF; this could be consistent with impaired release or function of relaxing factors at lower flow rates in heart failure. However, our study was not designed to test this hypothesis. The influence of other regulatory hormones such as vasopressin, prostaglandins, bradykinin, and atrial natriuretic factor on large arteries in heart failure has not been defined in humans.

Implications of Large Artery Changes in Heart Failure

In hypertension, abnormalities in large artery compliance have been observed in both the carotid and brachial arteries with the same methodology as described in our current study. Since the specific technique used is noninvasive, measurements are limited to those conductance arteries that are close to the skin surface. Other noninvasive techniques have been used to examine other large conductance vessels such as the aorta. However, few data are available on the function of conductance vessels throughout the large artery tree in heart failure. Our observations have been limited to the brachial artery.

Although large artery compliance is also reduced in hypertension, not all vasodilator treatments improve large artery function in that disease. Those that do may be more likely to cause regression of left ventricular hypertrophy and nitrates have been shown to improve large arterial function in hypertension. Angiotensin converting enzyme inhibitors and nitrates have been shown to improve large arterial function in hypertension, and although the pathophysiology of the vascular changes may be different, it remains possible that these vasodilators could have specific benefits in heart failure through improved large artery function in addition to reducing preload, systemic vascular resistance, and mitral regurgitation. Angiotensin converting enzyme inhibitors have been shown to reduce left ventricular dilatation and improve function in both animals and humans after myocardial infarction. In these clinical cases of asymptomatic left ventricular dysfunction, the drug has been introduced at a very early stage, presumably before excessive detrimental neurohormonal activation has occurred. The mechanism of action of the drug in these circumstances remains speculative, but a contribution through improved large artery function is possible. In patients with heart failure, nitroprusside has been shown to diminish potentially adverse effects of reflected pressure waves during exercise.

Limitations

Our techniques were noninvasive, but the results are consistent with invasive studies in humans. One previous study of PWV in heart failure failed to find a significant difference from age-similar controls. Their heart failure patient population was not well defined, however, and our study showed that the increase in PWV is accentuated with worsening severity of heart failure. Furthermore, they studied arteries in the lower and not the upper limb. We performed our studies on the brachial artery because it can be approached with ease noninvasively and has been studied extensively in hypertension. We do not know whether similar changes are seen with heart failure in other conductance vessels such as the carotid and femoral arteries. We also do not know whether the degree of severity of arterial change is the same between the proximal aorta and peripheral arteries within the same patient. Changes in the proximal aorta would be expected to alter impedance to left ventricular outflow directly, whereas changes in the peripheral arteries may have a greater effect on the reflected pressure wave, which, on returning to the heart, may augment aortic pressure and increase left ventricular end-systolic stress if the aortic valve is still open. Because the relative proportions of smooth muscle, elastin, and collagen vary along the length of the arterial conductance vessels and these changes may be associated with alterations in arterial distensibility, it remains to be shown whether the changes described in the present study of heart failure in humans are uniform throughout the large arterial tree. It is of interest that the compliance of the distal but not the proximal arterial circulation was increased by nitroprusside, nitroglycerin, and hydralazine in an animal study without heart failure using an electrical analogue model of the circulation.

Conclusions

We have shown reduced diameter and compliance of the brachial artery in patients with moderate to severe heart failure. Although our observations are limited to the brachial artery, if similar changes were found to be present throughout the large arterial tree, it is possible that they could increase impedance to left ventricular performance. It is anticipated that vasodilator therapy to improve large artery function could reduce left ventricular end-systolic stress, and this mechanism of action might be an important contributor to clinical improvement. The noninvasive techniques described may allow serial measurements to be made over time to monitor changes in large artery function after the introduction of vasodilator therapy.
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References


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