Pulsatile Hemodynamics in Congestive Heart Failure


Abstract—Pulse pressure, an indirect measure of vascular stiffness and pulsatile load, predicts clinical events in congestive heart failure (CHF), suggesting that abnormal pulsatile load may contribute to CHF. This study was designed to assess more direct measures of central pulsatile load in CHF. Noninvasive hemodynamic evaluations were performed in 28 subjects with CHF and 40 controls using calibrated tonometry of the brachial, radial, femoral, and carotid arteries along with echocardiographic assessment of left ventricular outflow tract (LVOT) diameter and Doppler flow. Characteristic impedance (Zc) was calculated as the ratio of ΔP (carotid) and ΔQ (LVOT flow) in early systole. Carotid-radial (CR-PWV) and carotid-femoral (CF-PWV) pulse wave velocities were calculated from tonometry. Augmentation index was assessed from the carotid waveform. Total arterial compliance (TAC) was calculated using the area method. Brachial pulse pressure was elevated (62±16 versus 53±15 mm Hg, P=0.015) in CHF because of lower diastolic pressure (66±10 versus 73±9 mm Hg, P=0.003). CHF had higher Zc (225±76 versus 184±66 dynes · sec · cm⁻⁵, P=0.020). CF-PWV did not differ (9.7±2.7 versus 9.2±2.0, P=0.337), whereas CR-PWV was lower in CHF (8.6±1.4 versus 9.4±1.5, P=0.038). There was no difference in TAC (1.4±0.5 versus 1.4±0.6 mL/mmHg, P=0.685), and augmentation index was lower in CHF (8±17 versus 21±13%, P=0.001). CHF subjects have elevated central pulsatile load (Zc), which is not apparent in global measures such as augmentation index or TAC, possibly because of contrasting changes in central and peripheral conduit vessels. This increased pulsatile load represents an important therapeutic target in CHF. (Hypertension. 2001;38:1433-1439.)

Key Words: heart failure • hemodynamics • aorta • pulse pressure • vascular stiffness

There is growing evidence that conduit vessel stiffness contributes to the pathophysiology of congestive heart failure (CHF). Higher pulse pressure (PP) has been shown to predict an adverse outcome in patients with asymptomatic left ventricular dysfunction and CHF. Furthermore, higher PP has been shown to predict the development of CHF in previously healthy free-living elderly subjects. The seemingly paradoxical observation that prognosis worsens with higher PP in patients with CHF is presumably related to vessel stiffness, although the hemodynamic correlates of increased PP have not been evaluated in CHF.

The central conduit vessels provide an important buffering function for the necessarily pulsatile pumping of the left ventricle. Normal conduit vessels accommodate flow with a modest pressure increase. As importantly, the pressure wave travels along the conduits at a relatively low velocity so that the wave reflected from the periphery returns to the heart in diastole and augments diastolic pressure, further minimizing PP. Stiffening of conduit vessels impairs this normal coupling and adds to the load on the left ventricle. The goals of this study were to establish a method for noninvasively evaluating pulsatile hemodynamics and to assess the components of pulsatile hemodynamic load in compensated, ambulatory patients with conventionally treated mild to moderate CHF.

Methods

Study Subjects

CHF subjects were recruited as part of a multicenter trial (Candesartan in Heart Failure Assessment of Reduction in Morbidity and Mortality [CHARM]) designed to evaluate the effects of candesartan cilexetil on clinical events in CHF. Separate arms of the protocol evaluated patients with CHF and preserved or impaired left ventricular function. Noninvasive assessment of pulsatile hemodynamics was performed at a limited number of centers using the protocol detailed below. Only patients >40 years of age with complete baseline hemodynamic data sets were included in the current analysis. Because the investigators have no knowledge of the treatment assignment in this ongoing double-blind trial, the analyses presented in this preliminary report relate to baseline data only. Patients with CHF with left ventricular function that was preserved (ejection fraction >40%, n=15) or impaired (ejection fraction ≤40%, n=13) were pooled for the purposes of this analysis. The effects of this pooling were evaluated by performing separate analyses of key variables as a function of impaired versus preserved ejection fraction in the CHF cohort. Control subjects were >40 years of age and had no history of CHF, although most had coronary artery risk factors or established coronary artery disease. Protocols were...
approved by an institutional review board at each clinical center, and all subjects gave informed consent.

Data Acquisition
Subjects were studied in the supine position after ~10 minutes of rest. Using a semi-automated computer-controlled device, auscultatory blood pressure was obtained 3 to 5 times at 2-minute intervals with a goal of obtaining 3 sequential readings that agreed to within 5 mm Hg for systolic and diastolic. Arterial tonometry and ECG were obtained from the brachial, radial, femoral, and carotid arteries using a custom transducer. Next, the patient was placed in the left lateral decubitus position, and echocardiographic images of the left ventricular outflow tract were obtained from a parasternal long axis view. This was followed by duplicate acquisitions of simultaneous tonometry of the carotid artery and pulsed Doppler of the left ventricular outflow tract from an apical 5-chamber view. Finally, the body surface distances from the suprasternal notch to the brachial (SSN-B), radial (SSN-R), femoral (SSN-F), and carotid (SSN-C) recording sites were measured with a tape measure. All data were digitized during the primary acquisition (ECG and tonometry pressures at 1000 Hz, audio at 12 kHz, and video at 30 frames/s). Digital data were transferred to CD-ROM and shipped to the Core Laboratory at Cardiovascular Engineering Inc for analysis.

Data Analysis
Tonometry waveforms were signal-averaged using the ECG as a fiducial point. The averaged systolic and diastolic cuff pressures were used to calculate the peak and trough, respectively, of the signal-averaged brachial pressure waveform. Mean arterial pressure was calculated digitally by integrating the calibrated brachial pressure waveform. Diastolic and mean brachial pressures were then used to calculate the carotid, radial, and femoral pressure tracings. Pulse wave velocity to each peripheral site (brachial, radial, and femoral) was calculated from the delay between the appearance of the pressure waveform foot in the carotid and peripheral sites. The distance between recording sites was adjusted for parallel transmission in the aorta and carotid by subtracting SSN-C from SSN-B, SSN-R and SSN-F. These corrected distances were divided by the respective foot-to-foot transmission delays to give pulse wave velocity. The inflection point, \( t_i \), (Figure 1), between the peaks of the forward and reflected pressure waves was identified, and the time delay from the foot of the waveform to the inflection point was calculated as a measure of the round-trip time between the central aorta and the dominant reflecting site. Augmentation index (AI) was calculated using an equation derived by combining the Bramwell-Hill and water-hammer equations: 

\[
A_I = \frac{P_{\text{max}} - P_{\text{min}}}{P_{\text{max}} - P_{\text{ref}}}
\]

where central pulse wave velocity \( c_o \) was assumed to be equal to CF-PWV.12

Statistical Analysis
Baseline characteristics were tabulated and dichotomous variables compared using a \( \chi^2 \) statistic. Continuous variables were compared using ANOVA. Statistical models that adjusted central hemodynamic parameters for relevant covariates were constructed using a general linear model. Intraclass correlation coefficients (ICC) from the duplicate acquisitions of pressure flow data were used to assess reproducibility of key hemodynamic variables (cardiac output, \( Z_c \), \( C_l \)). For cardiac output, the single measure ICC was 0.91 (95% confidence interval [CI], 0.86 to 0.94; \( P<0.0001 \)), and the average measure ICC was 0.95 (95% CI, 0.92 to 0.97; \( P<0.0001 \)). For \( Z_c \), the single measure ICC was 0.87 (95% CI, 0.80 to 0.92; \( P<0.0001 \)), and the average measure ICC was 0.93 (95% CI 0.89 to 0.96; \( P<0.0001 \)). For \( C_l \), the single measure ICC was 0.90 (95% CI, 0.85 to 0.94; \( P<0.0001 \)), and the average measure ICC was 0.95 (95% CI, 0.92 to 0.97; \( P<0.0001 \)). Duplicate pressure-flow parameters were averaged, and the averaged value was used in subsequent analyses. Values are presented as mean ± SD except where noted. A 2-sided \( P<0.05 \) was considered significant.

Results
Baseline characteristics are presented in Table 1. Patients with CHF tended to be older and heavier and had a higher prevalence of confirmed coronary disease than did controls. Of the CHF patients, 8 were New York Heart Association class II, 19 were class III, and 1 was class IV. CHF and control groups had comparable numbers of patients who had never smoked, whereas the CHF group had fewer active smokers. CHF subjects were more likely to be taking cardiac medications, as detailed in Table 1.

Resting hemodynamic parameters are presented in Table 2. Patients with CHF had higher central and peripheral PP despite a trend toward lower mean arterial pressure (MAP). Higher PP was attributable to lower diastolic pressure at the same systolic pressure. Heart rate tended to be higher in CHF, whereas resting cardiac output and peripheral resistance were comparable to controls in these conventionally treated, com-
overlap between the forward and reflected wave and because was substantially lower in CHF because of less temporal
pressure peak and shorter systolic ejection period (SEP),
in Table 3. Subjects with CHF had an earlier absolute
changes in central and peripheral vessel stiffness may explain
the lack of a difference in TAC.

A summary of carotid waveform morphology is presented
in Table 3. Subjects with CHF had an earlier absolute
pressure peak and shorter systolic ejection period (SEP),
although the pressures at each of these landmarks did not
differ between groups. Flow reached 95% of its peak value
(Q0.5) in a comparably short time interval in CHF and controls.
The pressure increment from diastole to the time of Q95 was greater for CHF than controls (45 ± 11 versus 36 ± 13 mm Hg,
P = 0.002), as was Pp, despite comparable flow at Q0.5
(282 ± 70 versus 262 ± 60 mL/sec, P = 0.208), which is a
manifestation of higher Zc (Table 2). The volume ejected up
to the time of Q0.5 was comparable in CHF and controls (11 ± 3
versus 11 ± 3 mL, P = 0.862). Notably, this early component
of stroke volume represented only a fraction of the total
stroke volume (20 ± 4 versus 18 ± 3%, P = 0.122), even though
it generated most of the central aortic PP as noted above.
The timing of wave reflection (t) was comparable, although AI
was substantially lower in CHF because of less temporal
overlap between the forward and reflected wave and because
of a relative decrease in global reflection (Pp/Pi). Analysis of

variance demonstrated that 77% of the variance in AI was
explained by the ratio of Pp/Pi, and the temporal overlap
between Pp and Pi (expressed as a percentage of the systolic
ejection period), with temporal overlap accounting for the
bulk of the variance. Once these parameters were considered,
there was no residual difference in AI between CHF and
controls.

Because the trend toward increased heart rate in CHF was
accompanied by a significant reduction in SEP, the relation-
ship between cardiac cycle length (CCL) and SEP was
assessed to determine if SEP was shorter because of shorter
CCL (higher heart rate) or an altered relationship between
CCL and SEP. A general linear model was constructed that
assessed the relationship between natural log transformations
of SEP and CCL, with presence of CHF as a grouping
variable. The interaction term of this analysis effectively
comparres the power of the relationship between SEP and
CCL in the 2 populations. We found both a downward shift
(main effect, P = 0.001) and a strong trend toward a steeper
slope (interaction term, P = 0.051) in this relationship in CHF
versus controls (Figure 2). This analysis demonstrates that
shorter SEP in CHF was a result of not only a higher heart
rate but also an altered relationship between SEP and CCL.

Because there were trends toward differences in age, weight,
and MAP, models were constructed to adjust for these
covariates (Table 4). Each covariate had a significant
relationship with Zc and CI, whereas weight and MAP were
related to TAC. The associations between CHF and abnormal
central pulsatile hemodynamics (Zc, CI) were strengthened
after adjusting for these covariates. Additionally, a trend to
lower TAC in CHF was found, suggesting that the lack of
difference in unadjusted TAC was at least partially attribut-
able to lower MAP and higher body weight in CHF subjects.

### TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHF (n=28)</th>
<th>Non-CHF (n=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61±10</td>
<td>57±10</td>
<td>0.100</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172±9</td>
<td>171±8</td>
<td>0.769</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>86±18</td>
<td>77±14</td>
<td>0.033</td>
</tr>
<tr>
<td>Male, %</td>
<td>82</td>
<td>81</td>
<td>1.000</td>
</tr>
<tr>
<td>Medical history, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary disease</td>
<td>79</td>
<td>43</td>
<td>0.003</td>
</tr>
<tr>
<td>Angina</td>
<td>68</td>
<td>16</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior MI</td>
<td>61</td>
<td>19</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>61</td>
<td>16</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>43</td>
<td>19</td>
<td>0.054</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>25</td>
<td>22</td>
<td>...</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>57</td>
<td>21</td>
<td>...</td>
</tr>
<tr>
<td>Active smoker</td>
<td>18</td>
<td>57</td>
<td>0.003*</td>
</tr>
<tr>
<td>Current medications, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>57</td>
<td>22</td>
<td>0.005</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>14</td>
<td>5</td>
<td>0.390</td>
</tr>
<tr>
<td>Nitrites</td>
<td>29</td>
<td>3</td>
<td>0.004</td>
</tr>
<tr>
<td>Converting-enzyme inhibitor</td>
<td>54</td>
<td>8</td>
<td>0.001</td>
</tr>
<tr>
<td>Digoxin</td>
<td>46</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Diuretics</td>
<td>64</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Lipid-lowering agent</td>
<td>57</td>
<td>22</td>
<td>0.005</td>
</tr>
<tr>
<td>Aspirin</td>
<td>71</td>
<td>30</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Overall χ² for smoking status.

### TABLE 2. Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHF</th>
<th>Non-CHF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral systolic</td>
<td>128±16</td>
<td>126±19</td>
<td>0.584</td>
</tr>
<tr>
<td>Peripheral pulse pressure</td>
<td>62±16</td>
<td>53±15</td>
<td>0.015</td>
</tr>
<tr>
<td>Central systolic</td>
<td>126±17</td>
<td>124±22</td>
<td>0.584</td>
</tr>
<tr>
<td>Central pulse pressure</td>
<td>61±16</td>
<td>51±17</td>
<td>0.019</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>66±10</td>
<td>73±9</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean pressure</td>
<td>88±10</td>
<td>94±12</td>
<td>0.060</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>65±11</td>
<td>60±9</td>
<td>0.061</td>
</tr>
<tr>
<td>Cardiac output, mL/s</td>
<td>60±15</td>
<td>58±14</td>
<td>0.550</td>
</tr>
<tr>
<td>Peripheral resistance, DSC</td>
<td>2085±560</td>
<td>2270±570</td>
<td>0.188</td>
</tr>
<tr>
<td>Characteristic impedance, DSC</td>
<td>225±76</td>
<td>184±66</td>
<td>0.020</td>
</tr>
<tr>
<td>Proximal aortic compliance, CD</td>
<td>0.56±0.26</td>
<td>0.72±0.30</td>
<td>0.031</td>
</tr>
<tr>
<td>TAC, mL/mm Hg</td>
<td>1.38±0.51</td>
<td>1.43±0.58</td>
<td>0.685</td>
</tr>
<tr>
<td>Pulse wave velocities, m/s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid-brachial</td>
<td>7.4±1.0</td>
<td>8.0±1.0</td>
<td>0.119</td>
</tr>
<tr>
<td>Carotid-radial</td>
<td>8.6±1.4</td>
<td>9.4±1.5</td>
<td>0.038</td>
</tr>
<tr>
<td>Carotid-femoral</td>
<td>9.7±2.7</td>
<td>9.2±2.0</td>
<td>0.337</td>
</tr>
</tbody>
</table>

Values are mean±SD. DSC indicates dyne · sec · cm⁻²; CD, 10⁻⁵ · cm² · dyne⁻¹
TABLE 3. Waveform Morphology

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHF</th>
<th>Non-CHF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing from foot, ms</td>
<td></td>
<td></td>
<td>0.819</td>
</tr>
<tr>
<td>Flow peak (Qp)</td>
<td>67±10</td>
<td>67±11</td>
<td></td>
</tr>
<tr>
<td>Inflection point (t)</td>
<td>123±35</td>
<td>112±29</td>
<td>0.183</td>
</tr>
<tr>
<td>Pressure peak (tpmax)</td>
<td>165±53</td>
<td>207±32</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic ejection period (tse)</td>
<td>293±39</td>
<td>323±24</td>
<td>0.001</td>
</tr>
<tr>
<td>Pressures, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure at Qp5</td>
<td>111±14</td>
<td>109±18</td>
<td>0.544</td>
</tr>
<tr>
<td>Pressure at inflection point</td>
<td>117±15</td>
<td>113±19</td>
<td>0.363</td>
</tr>
<tr>
<td>Peak pressure</td>
<td>126±17</td>
<td>124±22</td>
<td>0.584</td>
</tr>
<tr>
<td>End-systolic pressure</td>
<td>96±12</td>
<td>101±15</td>
<td>0.156</td>
</tr>
<tr>
<td>AI, %</td>
<td>8±17</td>
<td>21±13</td>
<td>0.001</td>
</tr>
<tr>
<td>Forward wave (Pf), mm Hg</td>
<td>50±12</td>
<td>40±14</td>
<td>0.002</td>
</tr>
<tr>
<td>Reflected wave (Pr), mm Hg</td>
<td>21±6</td>
<td>22±8</td>
<td>0.560</td>
</tr>
<tr>
<td>Pp/Pf amplitude ratio, %</td>
<td>42±7</td>
<td>55±9</td>
<td>0.001</td>
</tr>
<tr>
<td>Pp/Pf temporal overlap, %</td>
<td>57±13</td>
<td>65±9</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Values are mean±SD.

To determine whether the presence of coronary disease contributed to the differences in central conduit stiffness, the adjusted models for Zc and Cl were repeated, evaluating only CHF (n=22) and control patients (n=17) with documented CAD. Zc adjusted for age, weight, and MAP remained significantly higher in CHF versus non-CHF patients (229±57 versus 186±57 mmHg·sec·cm⁻³·m⁻²; P<0.05), but there was no longer a significant difference in Cf (0.55±0.22 versus 0.64±0.22×10⁻⁵ cm²/dyne, P=0.220). Additionally, patients with CHF and no CAD (n=6) were compared with those with CHF and CAD (n=22). After adjusting for age, weight, and MAP, there were no differences in Zc (229±67 versus 224±64 mmHg·sec·cm⁻³·m⁻²; P=0.877) or Cf (0.52±0.20 versus 0.56±0.19×10⁻⁵ cm²/dyne, P=0.650) in CHF patients without versus those with CAD, respectively. Taken together, these observations suggest that the presence or absence of coronary disease was not an explanation for the finding of increased Zc in patients with CHF.

The effects of left ventricular function on pulsatile hemodynamics in CHF were assessed by comparing variables presented in Tables 2 and 3 in CHF subjects with impaired (n=13) versus preserved (n=15) left ventricular function. The only difference found was a trend toward a shorter systolic ejection period in those patients with impaired left ventricular function (278±34 versus 306±39 milliseconds, P=0.059).

The associations between medication usage and key hemodynamic parameters (Zc, Cf, TAC, CR-PWV) were also assessed in the CHF cohort. Adjustments for trends or differences in these variables as a function of medication usage were then included in general linear models. We found that B-blocker usage was associated with lower CR-PWV (P=0.042), digoxin usage was associated with a trend toward higher Cf (P=0.184), and TAC (P=0.149), diuretic usage was associated with higher TAC (P=0.012), converting enzyme inhibitor usage was associated with a lower CR-PWV (P=0.019) and a trend to higher Cf (P=0.104), and aspirin usage was associated with a trend to lower CR-PWV (P=0.171). As a result of these analyses, the multivariate model for Zc was unchanged, whereas usage of digoxin and converting-enzyme inhibitor were added to the model for Cf, and usage of digoxin and diuretic were added to the model for TAC. After making these additional adjustments, the differences in Cf and TAC between CHF and control were strengthened, as would be expected from the univariate analyses. In contrast, the difference in CR-PWV between CHF and control was no longer significant. Thus, differential use of therapeutic agents does not explain the differences in central aortic stiffness (Zc, Cf) but may explain the reduced stiffness in peripheral conduits (CR-PWV).

**Discussion**

This study is the first to provide a detailed noninvasive evaluation of pulsatile hemodynamic load in conventionally...
treated, ambulatory patients with CHF. We found abnormalities in the proximal aortic pressure-flow (Zc) and pressure-area (Cf) relationships, indicating increased functional stiffness of the central conduits in CHF. In contrast, distal (muscular) conduit vessels tended to be less stiff (lower CR-PWV) in CHF. These contrasting changes in central and peripheral conduits may have resulted in the attenuated difference in TAC that was observed. Furthermore, decreased stiffness in the peripheral conduits, compared with controls, may have contributed to the diminished global reflection coefficient (Pp/Pt) by providing for a more gradual transition from relatively low impedance central conduits to intermediate impedance peripheral conduits to high impedance resistance vessels. The diminished reflection coefficient and a shorter SEP resulted in a marked reduction in carotid AI in CHF, despite clear evidence of increased central pulsatile load. Thus, in this small cohort of ambulatory patients with conventionally treated CHF, we found moderate abnormalities in pulsatile hemodynamic load (Zc, Cf) that were not evident in global measures of pulsatile load (TAC, AI). The resulting increase in pulsatile load on the heart may explain the relationship between higher PP and increased clinical events in patients with CHF.

Prior studies of central pulsatile hemodynamics in CHF utilized invasive techniques, studied smaller numbers of patients, and focused largely on younger patients with idiopathic cardiomyopathy. In these prior invasive studies, there is no clear consensus on the status of pulsatile load. Failure to detect a small but potentially important difference in Zc in these studies may relate to the invasive techniques utilized, to the control population (patients with “atypical chest pain” and normal coronary arteries, which may include patients with Syndrome X), to between-group differences in MAP, to the relatively young age of the subjects, or to frequency domain versus time domain assessment of Zc. The prior studies, which used a frequency-domain approach, differ in their choice of the frequency band used to compute Zc. The studies of Kromer, Laskey, and Merillon used 4 Hz as the lower limit for averaging and failed to show a difference in CHF, whereas an earlier study by Pepine used 2 Hz and found a difference. The higher cutoff of 4 Hz in the later studies was chosen “because the values of (impedance moduli) at lower frequencies are increased in patients with heart failure”. Laskey et al presented (in their discussion) values for Zc computed over the 2 to 12 Hz band and found Zc to be 16% higher in CHF (versus the 9% difference presented in their main results). Clearly, this empirical selection of frequency band (4 to 12 Hz) biased in favor of the null hypothesis by systematically eliminating harmonics known to be higher in CHF. We have avoided this limitation by using a time domain assessment of Zc. We also assessed Zc by 2 alternative frequency domain approaches and found comparable differences between CHF and controls when Zc was computed by averaging harmonics from 2 to 10 Hz (P=0.010) or by averaging all harmonics after and including the first impedance minimum (P=0.008). Values for Zc computed by these 3 techniques were highly correlated (R=0.948 to 0.994), confirming that the time domain approach provides a valid assessment of Zc, while offering the distinct advantage of being conceptually more accessible to those unfamiliar with frequency domain techniques. Despite the foregoing technical differences between prior studies, Zc was numerically higher in the CHF group in each study (Kromer, 5%; Laskey, 9% or 16% if 2 Hz is used; Merillon, 11%; and Pepine, 47%), whereas the differences were statistically significant only in the study by Pepine and in our study (22%). Additional work will be needed to resolve these controversies, and in this regard, a major strength and focus of our work is the noninvasive approach that we have developed, which can be readily implemented by others in studies designed to further assess baseline pulsatile hemodynamics and the effects of interventions in CHF.

Prior work has demonstrated an important link between PP and adverse events in patients with impaired ventricular function and overt CHF. The relationship between PP and events was independent of MAP, providing indirect evidence that abnormal conduit vessel stiffness plays a role in the pathophysiology of CHF. Indeed, in the Studies in Left Ventricular Dysfunction (SOLVD) study, higher PP predicted adverse events in the setting of an inverse relationship between mean pressure and adverse events. It is possible that these 2 associations share a common pathophysiology. Neurohumoral activation is known to occur in patients with left ventricular dysfunction, even before the onset of overt CHF. As cardiac output falls, the vasoconstricting effects of neurohumoral activation increase resistance vessel tone and maintain MAP. This same neurohumoral activation presumably increases vascular smooth muscle mass and tone and fibrosis, resulting in increased conduit stiffness and PP. Such a direct relationship between neurohumoral activation and increased vessel stiffness has been demonstrated in CHF, although another study found no relationship between Zc and neurohumoral levels.

Endothelial function is known to be abnormal in CHF and this abnormality is associated with impaired control of arterial distensibility. Reduced NO availability and impaired endothelial function in CHF is related to chronic reduction in shear stress and increased cytokine production, which downregulate endothelial NO synthase (eNOS), as well as increased oxidative stress, which reduces NO availability. The resulting abnormality in endothelial function provides a rationale for our finding of increased vessel stiffness in CHF. In contrast, the basis for lower CR-PWV in our CHF subjects is unclear, although our analyses suggest that the use of concomitant medications may have contributed. However, standard therapy was not randomly assigned in this study so therapy-related analyses must be interpreted with caution, as differences may represent either therapeutic effect or confounding by indication. These findings of contrasting changes in central and peripheral conduits in CHF underscore the importance of assessing local vessel properties in differing vascular regions. There is considerable diversity in conduit vessel structure and function and response to vasoactive agents. We were able to assess regional differences in conduits by prospectively defining a select number of complementary parameters. Thus, Zc and Cf assess proximal and overall properties of the aorta, respectively, whereas CR-PWV assesses a segment of predominantly muscular
conduit. In contrast, global parameters, such as TAC, provide a composite measure of central and peripheral conduit stiffness and thus may fail to detect important regional changes in subjects such as our CHF patients, with divergent changes in central and peripheral vessel stiffness.

It is important to note that we have used 2 different parameters (Zc and PWV) to assess stiffness of central and peripheral vessels. The divergent change seen may be attributable to the differential dependence of these parameters on vessel geometry. PWV is proportional to the square root of [wall elastance/radius], whereas Zc is proportional to the square root of [wall elastance/fifth power of radius]. Thus, changes in vessel diameter have a much more dramatic effect (≈5×) on Zc than on PWV. This dependence on geometry may explain why the moderate difference (+22%) in Zc was accompanied by a statistically insignificant increase in CF-PWV (5%). However, CF-PWV fails to assess the most proximal segment of the aorta, because of parallel transmission in the carotid and proximal aorta, and CF-PWV is influenced by transmission in the iliac and femoral arteries, whose properties differ dramatically from those of the proximal aorta. These differences may also contribute to the differential changes in Zc and CF-PWV.

Our finding of differential changes in Zc and TAC underscores the importance of utilizing propagative models of the arterial system that account for the diverse and distributed properties of the arterial tree. We have characterized pulsatile load using a pressure-flow term (Zc) that describes the interaction between early systolic pressure and flow, along with measures of propagation velocity in central (carotid-femoral) and peripheral (carotid-radial) conduits, and measures of the timing and amplitude of reflected waves. We have shown that the early systolic rise in pressure, when most of PP is attained despite a fraction of stroke volume having been delivered, is the result of an interaction between flow and Zc, not volume and TAC. Flow into the arterial system in early systole is far too brisk (relative to propagation velocity) for equilibration with TAC to occur. Thus, one must model the arterial system as a smaller proximal compliance and a larger distal compliance with finite propagation velocity between the (functional) chambers, or one can simply acknowledge that this early rise in pressure is the result of a pressure-flow interaction dictated by aortic inflow and Zc.

As previously noted, AI was markedly lower in CHF than in controls. Lower AI in CHF was attributable to diminished relative amplitude of the reflected wave (Pp/Ps) (see above) and diminished temporal overlap between the forward and reflected wave, because of shorter SEP. The reduction in SEP was greater than expected from the trend to higher heart rate in the CHF group (Figure 2). We speculate that this disproportionate reduction in SEP at nominal heart rates (>60 bpm) may be a manifestation of impaired myocyte contractility, altered Ca2+ kinetics, or dysfunctional contraction in hypertrophied, fibrotic hearts with impaired electrical activation. Because the factors that contributed to lower AI in CHF were not directly related to central conduit vessel stiffness, AI was a poor indicator of central aortic stiffness in CHF.

A number of important limitations of our study need to be emphasized. Our CHF cohort is relatively diverse, in terms of both clinical characteristics and therapy. This diversity may have introduced bias into the results or obscured additional important differences between CHF and controls. The control group is relatively large but is also diverse, in part because of a desire to study comparable groups of patients that differed only in the absence or presence of CHF. The controls were studied at a single site, whereas CHF patients were studied at multiple sites. Again, this may have biased the results, although all sites were carefully trained to perform the studies, and only complete, high-quality studies were included in the present analysis. Counterbalancing these limitations are several strengths of our study. We have demonstrated a method whereby pulsatile hemodynamics can be evaluated noninvasively in a multicenter clinical setting, providing an opportunity to evaluate the pulsatile hemodynamic effects of various therapies with potential conduit vessel effects. We have also underscored the importance of separately evaluating both central and peripheral conduit function rather than relying on global measures that may fail to detect important regional abnormalities in conduit function.

The finding of increased central conduit stiffness in patients with CHF is important for 2 reasons. First, this observation provides a pathophysiological basis for the seemingly paradoxical relationship between increased PP and higher clinical event rates in CHF. We have shown that increased PP in CHF is an indicator of stiff central conduit vessels and elevated pulsatile load. Second, this abnormal loading of the heart represents a potential therapeutic target. The concept of vasodilator therapy in CHF is not new, but the benefits of “vasodilators” have generally been interpreted in the context of their effects on peripheral resistance. It is now becoming apparent that it may be possible and perhaps desirable to selectively modify the properties of the central conduits in an attempt to reduce pulsatile load on the heart without further reducing MAP, which may already be tenuous in patients with advanced heart failure.

Acknowledgment

This project was funded in part by Astra-Zeneca.

References


Pulsatile Hemodynamics in Congestive Heart Failure

Hypertension. 2001;38:1433-1439
doi: 10.1161/hy1201.098298

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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