Arterial Properties as Determinants of Time-Varying Myocardial Stress in Humans

Julio A. Chirinos, Patrick Segers, Thierry C. Gillebert, Amit K. Gupta, Marc L. De Buyzere, Dirk De Bacquer, Martin St John-Sutton, Ernst R. Rietzschel, on behalf of the Asklepios Investigators

See Editorial Commentary, pp 10–11

Abstract—Myocardial and arterial load are time-varying phenomena. Despite their importance in myocardial function, the arterial properties that determine time-resolved myocardial wall stress are unknown. We aimed to assess arterial properties as determinants of time-resolved myocardial stress among 1214 men and women enrolled in the Asklepios Study. Time-resolved central pressure, flow, and left ventricular geometry were measured with carotid tonometry, Doppler, and speckle-tracking echocardiography, respectively, for computation of arterial load and ejection-phase time-varying myocardial wall stress. For any given end-diastolic left ventricular geometry and cardiac output, peak myocardial stress correlated directly with systemic vascular resistance (standardized $\beta=1.12; P<0.0001$) and aortic characteristic impedance (standardized $\beta=0.17; P<0.0001$). The ejection-phase stress-time integral correlated with systemic vascular resistance (standardized $\beta=1.06; P<0.0001$), lower total arterial compliance (standardized $\beta=-0.13; P=0.0008$), and earlier return of wave reflections (standardized $\beta=-0.10; P<0.0001$) but not with reflection magnitude, whereas end-systolic wall stress correlated with systemic vascular resistance (standardized $\beta=1.06; P<0.0001$) and reflection magnitude (standardized $\beta=0.12; P<0.0001$). After adjustment for age, all of the measured arterial properties, end-diastolic left ventricular geometry, and cardiac output, women demonstrated greater peak (534 versus 507 kdyne/cm²; $P<0.0001$), end-systolic (335 versus 320 kdyne/cm²; $P<0.0001$), and ejection-phase stress-time integral (157 versus 142 kdyne·s·cm⁻²; $P<0.0001$). In conclusion, different arterial properties have selective effects on time-resolved ejection-phase myocardial wall stress, which are not apparent from single-time point measurements. Women demonstrate less efficient myocardial-arterial coupling, with higher wall stress development for any given left ventricular geometry, arterial properties, and flow output. These observations may relate to the differential susceptibility of women to heart failure. (Hypertension. 2012;60:64-70.) ● Online Data Supplement

Key Words: myocardial stress ■ arterial load ■ afterload ■ wave reflections ■ sex differences

Afterload is an important determinant of normal and abnormal myocardial function and plays an important role in various cardiovascular diseases, including heart failure and hypertensive heart disease. In the presence of a normal aortic valve, the hydraulic load opposing left ventricular (LV) ejection is primarily dependent on the properties of the arterial tree ("arterial load") and can be characterized with indices of arterial load imposed by the arterial tree. Indices of arterial load reflect the hydraulic load that the heart must overcome as a pump, and although highly informative and important, they do not directly represent actual time-varying mechanical load (stress) experienced by contractile elements in the myocardium (myocardial afterload), which, in turn, generate the LV pump function. Wall stress not only depends on arterial properties but is also profoundly affected by instantaneous LV geometry. All of the key determinants of myocardial stress (wall thickness, cavity size, and ventricular pressure, which, in turn, depends on arterial properties for any given flow delivered to the input impedance of the systemic circulation) exhibit marked variations during systole. Consequently, time-varying myocardial stress-time integral correlates with systemic vascular resistance (standardized $\beta=1.06; P<0.0001$) and reflection magnitude (standardized $\beta=0.12; P<0.0001$). After adjustment for age, all of the measured arterial properties, end-diastolic left ventricular geometry, and cardiac output, women demonstrated greater peak (534 versus 507 kdyne/cm²; $P<0.0001$), end-systolic (335 versus 320 kdyne/cm²; $P<0.0001$), and ejection-phase stress-time integral (157 versus 142 kdyne·s·cm⁻²; $P<0.0001$). In conclusion, different arterial properties have selective effects on time-resolved ejection-phase myocardial wall stress, which are not apparent from single-time point measurements. Women demonstrate less efficient myocardial-arterial coupling, with higher wall stress development for any given left ventricular geometry, arterial properties, and flow output. These observations may relate to the differential susceptibility of women to heart failure. (Hypertension. 2012;60:64-70.) ● Online Data Supplement

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dial stress is poorly represented by single time point measurements, such as end-systolic wall stress, which is most commonly measured. Understanding the determinants of myocardial stress is important because myocardial stress is the primary determinant of myocardial oxygen consumption, and systolic wall stress patterns are thought to influence hypertrophic responses and interstitial fibrosis by stretch activation of the extracellular matrix. However, the specific arterial properties and their relative importance as correlates of time-varying ejection-phase myocardial stress in humans are unknown. Similarly, although arterial properties have been compared in several studies between men and women, sex differences in time-resolved myocardial wall stress have never been studied.

In this study, we aimed to characterize the determinants of time-varying ejection-phase myocardial stress in a large sample of adults from the general population and to assess whether sex exerts an independent effect on time-resolved myocardial wall stress patterns for any given set of arterial properties.

Methods
A more detailed description of our methods can be found in the online-only Data Supplement.

Study Population
We studied men and women enrolled in the Asklepios Study, a population-based study that recruited apparently healthy, community-dwelling volunteers aged 35 to 55 years randomly sampled from the Belgian communities of Erpe-Mere and Nieuwerkerken.7 Echocardiographic studies and tonometry data were available from 2368 subjects.

To maximize the quality of our instantaneous LV geometric data, which, in turn, depends on reliable speckle tracking, we selected only cases in which optimal speckle tracking could be achieved as detailed below. This process excluded subjects with relatively poor transthoracic acoustic windows or those in which the speckle tracking algorithm did not perform optimally for adequate quantification of time-resolved ventricular geometry. Our final analyses are based on 1214 subjects.

This study was approved by the ethical committee of the Ghent University Hospital and the University of Pennsylvania Institutional Review Board. All of the subjects provided informed consent.

Echocardiographic Examination
Echocardiographic examinations were performed using a Vivid-7 ultrasound platform and included LV short-axis views at the papillary muscle level and apical 2-chamber and 4-chamber views. LV end-diastolic volume and LV mass were calculated with the area-length method. Pulsed wave Doppler measurements of flow velocities in the LV outflow tract were performed. LV outflow tract cross-sectional area was computed from LV outflow tract radius measured in the parasternal long-axis view (area=πr²).

Carotid Tonometry
LV outflow tract pulsed-wave Doppler flow velocity recordings were performed along with carotid arteryplanation tonometry using a Millar pen-type high-fidelity tonometer (SPT 301; Millar Instruments, Houston, TX).3 Carotid pressure waveforms were calibrated according to brachial mean and diastolic pressure, as described previously.3

Pressure-Flow Analyses
Pressure and Doppler flow velocity recordings were processed offline using custom-designed software written in Matlab (The Mathworks, Natick, MA), as described previously.3 Proximal aortic Zc was computed in the time domain as the slope of the early systolic pressure-flow relation as previously described.1,8 Reflection magnitude was computed using wave separation analysis.1,3 In this method, after separation of the pressure waveform into its forward and backward components, reflection magnitude is computed as the ratio of the amplitudes of the forward and backward components.1,3 Reflected wave transit time was also computed from wave separation analysis, as described previously.9 Total arterial compliance was calculated with the pulse pressure method.10 Cardiac output was computed as the product of stroke volume and heart rate. Systemic vascular resistance (SVR) was computed as mean arterial pressure/cardiac output.

Speckle Tracking Echocardiography and Assessment of Time-Resolved Myocardial Stress
Speckle tracking was performed offline using an echoPAC workstation (GE Healthcare, Chalfont St Giles, United Kingdom), as described previously.9 A region of interest was prescribed in the parasternal short-axis view at the level of the chordae tendinae to obtain an exact fit with LV wall thickness, and the software was used to automatically track the wall at every time point in the cardiac cycle. Time-resolved numeric values derived from speckle tracking were exported for further processing in custom-designed software written in Matlab. We computed time-resolved average ventricular wall thickness, cavity size, and ventricular length in an angle-independent manner, as described previously in detail.6 Time-resolved myocardial wall stress was computed according to Arts et al:11

myocardial wall (“fiber”) stress=\( P/[1/3 \ln (1+Vw/V_{LV})] \)

where \( P= \) pressure, \( \ln= \) natural logarithm, \( Vw= \) wall volume, and \( V_{LV}= \) ventricular cavity volume (computed at each time point with the area-length method).

Statistical Analysis
Continuous values are expressed as mean±SD or median and interquartile range, as appropriate. Proportions are expressed as percentages. Relationships between continuous variables were analyzed using linear regression to obtain regression slopes (\( \beta \)) and model \( R^2 \) values. To assess myocardial efficiency to generate any given flow, all of the models included cardiac output. Therefore, these models assessed how arterial load components impact myocardial stress for any output generated by the LV. This approach also reduces the confounding effect of varying body size, body composition, and metabolic demands, all of which have direct effects on cardiac output. Models also adjusted for age, sex, and end-diastolic LV geometry (wall thickness and cavity volume). All of the \( P \) values are 2 tailed. Statistical significance was defined as \( p<0.05 \). Statistical analyses were performed using SPSS for Windows version 13 (SPSS Inc, Chicago, IL).

Results
Table S1 compares subjects enrolled in the Asklepios cohort with and without available time-resolved myocardial stress (ie, included versus not included in this study). Table 1 compares men and women included in this study. Men demonstrated higher body mass index, systolic and diastolic blood pressures, greater LV end-diastolic volume and LV mass, low-density lipoprotein cholesterol, a higher prevalence of hypertension and diabetes mellitus, and lower heart rate and high-density lipoprotein cholesterol.

A representative recording of time-resolved average short-axis ventricular wall thickness, short-axis cavity area, and cavity length are shown in Figure A through C, respectively. Figure D shows the time-resolved change in ejection-phase ventricular cavity and shell length, which results from both
displacement of the base toward the apex and apical cap thickening. Figure E and F show the time-resolved central pressure and flow for the same subject. Central pressure data can be used along with geometric data to compute time-resolved ejection-phase myocardial stress, as shown in Figure G. It can be seen that, despite a clear late systolic pressure peak, ejection-phase wall stress peaks early in ejection and subsequently declines in mid systole, which is related to the progressive LV geometric changes. Figure H demonstrates the relationship between ejection-phase pressure and stress, showing a marked shift (arrow) in the pressure-stress relationship that occurs in the midthird of ejection (represented by the dotted line), resulting in much lower stress values relative to pressure in late compared with early systole.

Peak myocardial stress was an early ejection-phase phenomenon, occurring on average at 90 ms after aortic valve opening (interquartile range, 82–100 ms). Peak myocardial stress (512 kdyne · cm⁻²; interquartile range, 457–577 kdyne · cm⁻²) was considerably greater than end-systolic myocardial stress (319 kdyne · cm⁻²; interquartile range, 278–366 kdyne · cm⁻²).

**Correlates of Peak Stress, End-Systolic Stress, and the Ejection-Phase Stress-Time Integral**

For any given end-diastolic LV geometry (LV end-diastolic volume and LV mass) and output, peak wall stress correlated directly with SVR (standardized β = 1.12; \( P < 0.0001 \)) and aortic Zc (standardized β = 0.17; \( P < 0.0001 \)) but not with reflection magnitude (Table 2). The ejection-phase stress-time integral correlated with SVR (standardized β = 1.06; \( P < 0.0001 \)), lower total arterial compliance (standardized β = 0.13; \( P = 0.008 \)), and earlier wave reflections (standardized β for reflected wave transit time = −0.10; \( P < 0.0001 \)) but not with reflection magnitude, whereas end-systolic stress was positively correlated with SVR (standardized β = 1.06; \( P < 0.0001 \)) and reflection magnitude (standardized β = 0.12; \( P < 0.0001 \)). No association was observed between end-systolic myocardial stress and Zc, total arterial compliance, or reflected wave transit time, after adjustment for other independent variables shown in Table 2.

**Sex Differences in Myocardial Stress**

Table 3 compares end-systolic myocardial stress, peak myocardial stress, and the stress-time integral between men and women. Estimated marginal means and 95% CIs were computed, after adjustment for age, all measured arterial properties (SVR, proximal aortic characteristic impedance, total arterial compliance, reflection magnitude, and reflected wave transit time), stroke volume, heart rate, and end-diastolic LV geometry (LV end-diastolic volume and wall thickness). Women demonstrated greater peak (531 versus 509 kdyne/cm²; \( P < 0.0001 \)), end-systolic (336 versus 319 kdyne/cm²; \( P < 0.0001 \)), and a greater ejection-phase stress-time integral (155 versus 143 kdyne · s · cm⁻²; \( P < 0.0001 \)). Further adjustments for body size did not appreciably change the results (data not shown).

**Discussion**

Using a combination of arterial tonometry, Doppler echocardiography, and speckle-tracking echocardiography, we assessed the arterial correlates of time-resolved ejection-phase myocardial stress noninvasively in a large population of middle-aged adults. We assessed various arterial hemodynamic properties as predictors of myocardial stress at different times in the ejection phase, demonstrating that specific arterial properties have differential effects on time-resolved myocardial wall stress, which are not apparent from single-time point measurements. We found that, for any given end-diastolic LV geometry and volume flow output, peak stress is determined by SVR and aortic Zc but not by wave reflection magnitude. The ejection-phase stress-time integral was determined by SVR, lower total arterial compliance, and earlier wave reflections, whereas end-systolic stress was largely a function of SVR and reflection magnitude. Interestingly, after adjustment for all of the measured arterial properties and for common measures of end-diastolic LV geometry, women demonstrated greater peak and mean myocardial stress.

Our study demonstrates the importance of the microvasculature and the aortic root as determinants of peak myocardial stress. Our findings are consistent with (and are best interpreted in the context of) previous data showing that myocardial...
Dial stress is an early systolic phenomenon that occurs when quasidiastolic geometry and systolic pressure coexist, ~90 ms after the opening of the aortic valve, a time point that corresponds roughly with the first systolic pressure peak. The early systolic aortic pulsatile pressure rise (and amplitude of the forward wave) for any given flow delivered through the aortic valve is governed by aortic Zc, which, in turn, depends on ascending aortic wall stiffness but is also highly sensitive to aortic size. Therefore, aortic Zc but not wave reflections (which influence afterload in mid-to-late systole) emerged as a determinant of peak stress. Our findings are consistent with previous observations that indicate that most of the overall central pressure rise (pulse pressure) is achieved during early systole, at a time when only ~25% of the stroke volume has been ejected.
been ejected, and, therefore, important changes in wall thickness/cavity ratio (a key determinant of wall stress for any given pressure) have not yet occurred. Importantly, however, we showed that SVR was a strong correlate of peak systolic stress, before the reflected wave exerts a significant influence on myocardial wall stress. For any given reflection magnitude, reflected wave transit time modestly influenced the stress-time integral, whereas the magnitude of reflections was a determinant of end-systolic stress. This is expected from the fact that, with progressively shorter reflected wave transit time, progressively greater proportions of the reflected wave overlap with ventricular ejection, increasing LV afterload.

The observation that wave reflections do not influence early, peak stress is important for the interpretation of animal and clinical data, which strongly suggest that wave reflections are important determinants of LV hypertrophy and dysfunction. Jointly, these findings further suggest that the loading sequence may be more important than absolute stress levels, per se. Although we found absolute wall stress to be lower in late systole, the myocardium may be particularly vulnerable to even small wall stress increases during this period of time. This may be because of intrinsic differences in cellular processes between early and late ejection. During early ejection, active development of fiber cross-bridges occurs in the electrically activated myocardium, and peak myocardial wall stress occurs, whereas a transition from contraction to relaxation may occur at the myocardial level in mid-to-late systole, during which increases in load may lead to more hypertrophy and abnormal diastolic relaxation. The differential effect of time-varying myocardial afterload on cellular processes taking place in early and late ejection under the stress curve was associated with a higher SVR, lower total arterial compliance, and earlier wave reflections.

### Table 2. Correlates of Peak Wall Stress, End-Systolic Wall Stress, and the Ejection-Phase Stress-Time-Integral*

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Independent Variables</th>
<th>Standardized Regression Coefficient</th>
<th>Partial R</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak myocardial stress (model R²=0.63)</td>
<td>Systemic vascular resistance</td>
<td>1.12</td>
<td>0.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Proximal aortic Zc</td>
<td>0.17</td>
<td>0.11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Total arterial compliance</td>
<td>-0.07</td>
<td>-0.04</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Reflected wave transit time</td>
<td>0.07</td>
<td>0.09</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Reflection magnitude</td>
<td>-0.04</td>
<td>-0.05</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Stroke volume</td>
<td>1.25</td>
<td>0.61</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Heart rate</td>
<td>0.76</td>
<td>0.55</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>End-systolic myocardial stress (model R²=0.46)</td>
<td>Systemic vascular resistance</td>
<td>1.06</td>
<td>0.48</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>Proximal aortic Zc</td>
<td>0.04</td>
<td>0.02</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>Total arterial compliance</td>
<td>0.004</td>
<td>0.002</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>Reflected wave transit time</td>
<td>-0.03</td>
<td>-0.03</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>Reflection magnitude</td>
<td>0.12</td>
<td>0.12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Stroke volume</td>
<td>0.89</td>
<td>0.41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Heart rate</td>
<td>0.59</td>
<td>0.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardial ejection-phase stress time-integral (model R²=0.66)</td>
<td>Systemic vascular resistance</td>
<td>1.06</td>
<td>0.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Proximal aortic Zc</td>
<td>0.07</td>
<td>0.04</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>Total arterial compliance</td>
<td>-0.13</td>
<td>-0.08</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Reflected wave transit time</td>
<td>-0.10</td>
<td>-0.12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Reflection magnitude</td>
<td>0.02</td>
<td>0.02</td>
<td>0.45</td>
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<tr>
<td></td>
<td>Stroke volume</td>
<td>1.13</td>
<td>0.58</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Heart rate</td>
<td>0.37</td>
<td>0.31</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

LV indicates left ventricular.

*All of the models are also adjusted for age, sex, end-diastolic LV cavity size, and end-diastolic LV wall thickness.

### Table 3. Differences Between Men and Women in Ejection-Phase Myocardial Wall Stress

<table>
<thead>
<tr>
<th>Myocardial Stress Parameter*</th>
<th>Women (n=551)</th>
<th>Men (n=663)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak stress, kdyne/cm²</td>
<td>534 (527 to 541)</td>
<td>507 (500 to 513)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ejection-phase stress-time integral, kdyne · cm⁻² · s⁻¹</td>
<td>156 (154 to 159)</td>
<td>143 (140 to 145)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>End-systolic stress, kdyne/cm²</td>
<td>331 (326 to 337)</td>
<td>323 (318 to 328)</td>
<td>0.027</td>
</tr>
<tr>
<td>Adjusted*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak stress, kdyne/cm²</td>
<td>534 (528 to 539)</td>
<td>507 (502 to 511)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ejection-phase stress-time integral, kdyne · cm⁻² · s⁻¹</td>
<td>157 (155 to 158)</td>
<td>142 (141 to 144)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>End-systolic stress, kdyne/cm²</td>
<td>335 (330 to 340)</td>
<td>320 (316 to 325)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

LV indicates left ventricular.

*Values are estimated marginal means (95% CIs) after adjustment for age and all measured arterial properties (systemic vascular resistance, proximal aortic characteristic impedance, total arterial compliance, reflection magnitude, and reflected wave transit time), stroke volume, heart rate, and end-diastolic LV geometry (LV end-diastolic volume and LV wall thickness).
should be a focus of further research. Future studies in this regard may have important implications for our understanding of hypertensive heart disease and heart failure with preserved ejection fraction.

An important finding of our study is that, after adjustment for all of the measured arterial properties and for common measures of end-diastolic LV geometry, women demonstrated greater peak and mean myocardial stress. This indicates that, for any given end-diastolic geometry and comprehensively measured arterial hemodynamic function, any given cardiac output was associated with higher myocardial stress, which suggests a less efficient myocardial-arterial coupling in women compared with men. These observations are novel and may be related to the differential susceptibility of women to heart failure. However, this was not investigated nor proven in the current study, and the observed relationships between arterial properties and time-resolved myocardial stress in this middle-aged population may differ from those observed in older subjects or those with established heart failure. Further studies should assess whether our observations hold true in older women, who are at higher risk for heart failure.

Our study has limitations. We did not measure ventricular pressure invasively but rather used noninvasive central arterial pressure measurements. Although ventricular and central pressures correspond closely during ejection, ventricular pressure is slightly higher than aortic pressure in early ejection and slightly lower in late ejection because of acceleration and deceleration of flow, respectively. Similarly, pressure is not uniform in the ventricle given the development of small intraventricular pressure gradients attributed to early systolic flow acceleration and late systolic flow deceleration. However, these differences are small compared with the absolute pressure changes during systole. The fact that we took carotid pressure as a surrogate for aortic pressure is also a limitation, inherent to the noninvasive nature of our study in a large general population sample. Although the carotid pressure is considered a good surrogate for aortic pressure, differences between the carotid and aortic pressure waveforms may have affected our computations of aortic input impedance. Although our simplified calculations of myocardial stress can be affected by asymmetrical ventricular geometry, all of the subjects in this study had normal LV systolic function without regional wall motion abnormalities. However, we acknowledge that the true 3D geometry of the LV is variable and not fully accounted for by simplified geometric models. Finally, we had to rely on high-quality instantaneous geometric data derived from speckle tracking, which led to the exclusion of a large number of subjects. Despite this limitation, differences between subjects included and not included in this analysis were small and unlikely to have importantly influenced the correlation patterns observed. Finally, our cross-sectional study cannot address effects of arterial load on chronic ventricular remodeling, which would, in turn, influence operating patterns of wall stress.

Perspectives
Our study provides, for the first time, data regarding the relative importance of specific arterial hemodynamic properties on LV wall stress in humans, demonstrating differential effects of commonly measured arterial properties on time-varying wall stress. Our study also reports sex differences in time-resolved wall stress, which require further investigation in relation to their potential link with sex differences in susceptibility to heart failure. Our study underscores the importance of time-resolved assessments of myocardial afterload (wall stress), which should provide novel insights regarding the role of early versus late systolic wall stress in biological processes, such as LV hypertrophy, systolic and diastolic myocardial functions, and the risk of heart failure in humans. This should be the focus of future studies. The noninvasive assessment of time-resolved wall stress is feasible at a large scale, complements information derived from arterial pressure-flow analyses, and provides further insight into ventricular-arterial interactions.

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Disclosures
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References


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**Novelty and Significance**

**What Is New?**

- We characterize the impact of specific arterial properties on time-resolved myocardial wall stress in middle-aged adults.
- Women demonstrate higher myocardial wall stress for any given set of arterial properties and flow output.

**What Is Relevant?**

- Myocardial wall stress is highly relevant because it is what cardiomyocytes “experience” during the ejection phase.

**Summary**

The findings help us understand the physiology/pathophysiology of ventricular-arterial interactions.

Specific arterial properties systematically influence time-resolved myocardial wall stress. After accounting for differences in arterial properties, women demonstrate higher myocardial wall stress than men.
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Supplemental Methods

Study population
We studied men and women enrolled in the Asklepios study, a population-based study which recruited apparently healthy, community-dwelling volunteers aged 35 to 55 years randomly sampled from the Belgian communities of Erpe-Mere and Nieuwerkerken, as previously described. ¹ Echocardiographic studies and tonometry data were available from 2,368 subjects. None of the participants had a history of congestive heart failure or echocardiographic evidence of hypertrophic cardiomyopathy, segmental wall motion abnormalities or significant valvular heart disease.

In order to maximize the quality of our instantaneous LV geometric data, which in turn depends on reliable speckle tracking, we selected only cases in which optimal speckle tracking could be achieved as detailed below. This process excluded subjects with relatively poor trans-thoracic acoustic windows or those in which the speckle tracking algorithm did not perform optimally for adequate quantification of time-resolved ventricular geometry. Our final analyses are based on 1,214 subjects.

This study was approved by the ethical committee of the Ghent University Hospital and the University of Pennsylvania Institutional Review Board. All subjects provided informed consent.

Echocardiographic examination
Echocardiographic examinations were performed using a Vivid-7 ultrasound platform and included LV short axis views at the papillary muscle level and apical 2-chamber and 4-chamber views. LV end-diastolic volume and LV mass were calculated with the area-length method.

Pulsed wave Doppler measurements of flow velocities in the LV outflow tract were performed and recorded placing the Doppler sample immediately proximal to the aortic valve leaflets within the centerline of the LV outflow tract. We computed LV outflow tract cross sectional area from LV outflow tract radius measured in the parasternal long axis view (area=πr²).

Carotid tonometry
LV outflow tract pulsed-wave Doppler flow velocity recordings were performed along with carotid artery applanation tonometry using a Millar pen-type high-fidelity tonometer (SPT 301; Millar Instruments, Houston, Texas, USA) and dedicated hardware and software for acquisition of the arterial pulse as previously described.¹ Carotid pressure wave forms were calibrated according to brachial mean and diastolic pressure as previously described.¹

Pressure-flow analyses
Pressure and Doppler flow velocity files were processed off-line using custom-designed software written in Matlab (The Mathworks, Natick, MA) as previously described.¹² Given the finite delay between aortic and carotid pressure phenomena, visual time alignment of carotid pressure and LV outflow curves was performed to maximize the following criteria: concordance of the rapid systolic upstroke of pressure and flow, concordance of the pressure dichrotic notch and cessation of flow, zero value of the phase angle of higher-frequency harmonics (7th to 10th) of input impedance, and linearity of the early systolic pressure-flow
relationship. Proximal aortic characteristic impedance ($Z_c$) was computed in the time domain as the ratio of early systolic pulsatile pressure/flow as described by Mitchell et al.\textsuperscript{1,4} As previously described in detail,\textsuperscript{1} the pressure wave was separated into its forward ($P_f$) and backward ($P_b$) traveling component (i.e., the reflected wave):\textsuperscript{1,3,5-7}

$$P_f = (P + Q \times Z_c)/2$$
$$P_b = (P + Q \times Z_c)/2$$

The ratio of the amplitudes of $P_b$ and $P_f$ ($P_b/P_f$) yields the reflection magnitude. Reflected wave transit time (RWTT) was computed from wave separation analysis as the moment in time where $P_b$ adds to the forward wave as previously described.\textsuperscript{8} Total arterial compliance was calculated with the pulse pressure method, which is based on maximizing the fit between measured pulse pressure and pulse pressure predicted by the 2-element windkessel model using measured aortic flow as input.\textsuperscript{9}

**Speckle tracking echocardiography and assessment of time-resolved myocardial stress**

Speckle tracking was performed offline using an echoPAC workstation (GE Healthcare; Chalfont St. Giles, UK) as previously described.\textsuperscript{2} Briefly, a region of interest was prescribed in the parasternal short axis view at the level of the chordae tendineae to obtain an exact fit with LV wall thickness and the software was used to automatically track the wall at every time point in the cardiac cycle. Only cases in which reliable tracking of endocardial and epicardial borders was ascertained visually in both long and short axis views and in which $\leq 1$ segment was labeled by the automated software as unreliably tracked were processed further. Time-resolved numerical values derived from speckle tracking were exported from the echoPAC software for further processing in custom-designed software written in Matlab (The Mathworks, Natick, MA). We computed time-resolved average ventricular wall thickness, cavity size and ventricular length in an angle-independent manner as previously described in detail.\textsuperscript{2} Time-resolved myocardial wall stress was computed according to Arts\textsuperscript{10}:

$$\text{Myocardial Wall ("Fiber") Stress} = \frac{P}{1/3 \ln (1 + V_W/V_{LV})}$$

where $P$=pressure, $\ln$=natural logarithm, $V_W$=wall volume and $V_{LV}$=ventricular cavity volume (computed at each time point with the area-length method). In analogy to the Regen formula,\textsuperscript{11} previously used by our group to separately compute time-resolved circumferential and longitudinal wall stress from time-resolved ventricular length and short-axis diameter, the Arts formula does not neglect radially-directed forces or forces generated within the wall that oppose fiber shortening, which vary significantly with cavity and wall thickness and can interfere with direct comparisons of myocardial stress at different times during ejection. We used the Arts formula for this study because results using longitudinal and circumferential components computed with the Regen method were highly consistent (and essentially identical to those presented here) and because the Arts formula is readily applicable to future studies using 3-dimensional techniques that directly assess ventricular cavity and wall volumes.
**Statistical analysis**

Continuous values are expressed as mean±standard deviation or median and interquartile range (IQR) as appropriate. Proportions are expressed as percentages. Relationships between continuous variables were analyzed using linear regression to obtain regression slopes (β) and model R² values. Normality of regression model residuals was assessed and multicollinearity of predictor variables was evaluated with Eigenvalues and condition indices and addressed with log-transformation of variables or mean-centering as needed. In order to assess myocardial efficiency to generate any given flow, all models included cardiac output. Therefore, these models assessed how arterial load components impact myocardial stress for any output generated by the LV. This approach also reduces the confounding effect of varying body size, body composition and metabolic demands, all of which have direct effects on cardiac output. Models also adjusted for age, gender and end-diastolic LV geometry (wall thickness and cavity volume). All probability values are 2-tailed. Statistical significance was defined as alpha<0.05. Statistical analyses were performed using SPSS for Windows v13 (SPSS Inc., Chicago, IL).

**Supplemental Results**

*Comparison of Asklepios cohort subjects included vs. not included in this study*

Table S1 compares subjects enrolled in the Asklepios cohort with and without available time-resolved myocardial stress (i.e., included vs. not included in this study). Males represented a higher proportion of subjects included in this study. There were minimal but statistically significant differences in age, body weight, body height, body mass index and LV end-diastolic volume index between subjects included in this study versus those not included in this sub-study. There were no significant differences in the prevalence of hypertension, diabetes mellitus, LV mass index, LV wall thickness, or LV ejection fraction between the 2 sub-populations.
References


Table S1. General characteristics of Asklepios study subjects included and not included in this study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Included in this sub-study (n=1,214)</th>
<th>Not included in this sub-study (n=1,310)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Years †</td>
<td>45.1 (40.5-50.2)</td>
<td>46.5 (41.5-51.5)</td>
</tr>
<tr>
<td>Male Gender, % †</td>
<td>54.6</td>
<td>42.8</td>
</tr>
<tr>
<td>Body height, m †</td>
<td>170 (164-177)</td>
<td>168 (162-175)</td>
</tr>
<tr>
<td>Body weight, Kg ‡</td>
<td>72 (62.8-82.4)</td>
<td>74.1 (63.1-84.7)</td>
</tr>
<tr>
<td>Body Mass Index, Kg/m² †</td>
<td>24.8 (22.7-27.2)</td>
<td>25.6 (23-29.2)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg ‡</td>
<td>133 (123-142)</td>
<td>130 (121-140)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg ‡</td>
<td>77 (70-86)</td>
<td>76 (69-83)</td>
</tr>
<tr>
<td>Heart rate, bpm †</td>
<td>66 (59-73)</td>
<td>64 (58-71)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>27</td>
<td>30.5</td>
</tr>
<tr>
<td>Diabetes Mellitus, %</td>
<td>1.2</td>
<td>2.0</td>
</tr>
<tr>
<td>LDL-cholesterol, mg/dL</td>
<td>127 (107-152)</td>
<td>127 (107-152)</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dL</td>
<td>61 (51-74)</td>
<td>62 (51-75)</td>
</tr>
<tr>
<td>Current Smoking, %</td>
<td>21.6</td>
<td>20.1</td>
</tr>
<tr>
<td>Left ventricular mass, g</td>
<td>143 (115-176)</td>
<td>140 (111-176)</td>
</tr>
<tr>
<td>Left ventricular mass index, g/BSA in m² ‡</td>
<td>76.4 (65.4-90)</td>
<td>74.6 (63.7-87.5)</td>
</tr>
<tr>
<td>Left ventricular end-diastolic volume index (mL/ BSA in m²) †</td>
<td>57 (49-67)</td>
<td>53 (46-63)</td>
</tr>
</tbody>
</table>

* Values indicate median (IQR) or percentage. † P<0.0001; ‡ P<0.05.