Time-Varying Myocardial Stress and Systolic Pressure-Stress Relationship
Role in Myocardial-Arterial Coupling in Hypertension

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Background—Myocardial afterload depends on left ventricular (LV) cavity size, pressure, and wall thickness, all of which change markedly throughout ejection. We assessed the relationship between instantaneous ejection-phase pressure and myocardial stress and the effect of arterial wave reflections on myocardial stress in hypertensive and normotensive adults.

Methods and Results—We studied 42 untreated hypertensive, 42 treated hypertensive, and 42 normotensive adults with normal LV ejection fraction. Time-resolved central pressure, flow, and LV geometry were measured with carotid tonometry, Doppler, and speckle-tracking echocardiography for computation of arterial load and time-varying circumferential and longitudinal myocardial stress. In all 3 groups, peak myocardial stress typically occurred in early systole (within the first 100 milliseconds of ejection), followed by a marked midsystolic shift in the pressure-stress relationship, which favored lower late systolic stress values ($P<0.001$) relative to pressure. The mean magnitude of this midsystolic shift was quantitatively important in all 3 groups (circumferential stress, 144 to 148 kdynes/cm²) and was independently predicted by a higher LV ejection fraction and ratio of LV end-diastolic cavity to wall volume. Time of peak myocardial stress independently correlated with time of the first systolic but not with time of the second systolic central pressure peak.

Conclusions—Peak myocardial stress occurs in early systole, before important contributions of reflected waves to central pressure. In the presence of normal LV ejection fraction, a midsystolic shift in the pressure-stress relationship protects cardiomyocytes against excessive late systolic stress (despite pressure augmentation associated with wave reflections), a coupling mechanism that may be altered in various disease states. (Circulation. 2009;119:000-000.)

Key Words: hypertension • myocardium • hemodynamics

Noninvasive assessment of arterial hemodynamics and left ventricular (LV) remodeling has been shown to provide important prognostic information in various populations.1-3 LV remodeling occurs in response to a variety of pathophysiological events such as abnormalities in ventricular preload and afterload.

Clinical Perspective on p ●●●

In the presence of a normal aortic valve, LV afterload is largely dependent on the properties of the arterial tree (arterial load).1,2 In contrast to LV afterload, myocardial afterload not only is dependent on the properties of the vasculature but also is highly dependent on LV geometry.4 Myocardial afterload is appropriately described by the stress on myocardial cells, which is directly related to ventricular chamber size and ventricular chamber pressure and inversely related to wall volume (or thickness).4-6 LV myocardial stress measured at the end of ejection (end-systolic stress) has been widely used to estimate myocardial afterload noninvasively because this easily identifiable point in the cardiac cycle allows measurement of wall thickness and cavity size and an approximation of ventricular end-systolic pressure (through the use of brachial peak pressure) using nonsynchronized data. Two major problems may underlie this method: the interindividual variability in the relationship between central and brachial arterial systolic pressure5 and its limitation to a single time.
point, which may not adequately reflect time-varying phenomena. Notably, all key determinants of myocardial stress (wall thickness, cavity size, and pressure) exhibit marked variations during systole. Myocardial stress, being highly dependent on cavity size and wall thickness, is likely to be higher for any given pressure in early systole, when cavity size is close to its maximal value and wall thickness is close to its minimal value, whereas late systolic pressure may have a less pronounced effect on myocardial afterload. This is an important concept when the impact of the arterial tree on myocardial afterload is considered because distinct arterial phenomena determine early versus late systolic load on the heart. Specifically, arterial wave reflections generally arrive at the central aorta in mid to late systole, selectively increasing late systolic LV afterload and pressure.

In this study, we aimed to characterize the relationship between instantaneous ejection-phase pressure and myocardial stress in hypertensive and normotensive adults with normal LV systolic function, to test the hypothesis that arterial wave reflections do not contribute significantly to peak myocardial stress in the presence of normal cavity-emptying function, and to assess whether end-systolic stress adequately reflects the contribution of different components of arterial load to time-varying ejection-phase myocardial stress.

Methods

Study Population

We tested our hypotheses in 3 populations: treated hypertensive (T-HTN), untreated hypertensive (U-HTN), and normotensive (NT) adults. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current pharmacological treatment for hypertension. The T-HTN group consisted of 42 hypertensive adults 20 to 80 years of age who were referred for a clinical echocardiographic examination at the Hospital of the University of Pennsylvania, Philadelphia. The U-HTN group consisted of 42 individuals with untreated hypertension randomly selected from the Asklepios study, a population-based study of cardiovascular disease in Belgium that enrolled adults 35 to 55 years of age without overt cardiovascular disease randomly sampled from the Belgian communities of Erpe-Mere and Nieuwerkerken. The Asklepios cohort also was the source for 42 NT adults who were matched to the U-HTN group for age and gender. Details about the Asklepios study population and methods have been published previously. The following exclusion criteria were applied for all 3 groups: pregnancy; congestive heart failure; LV ejection fraction <50%; personal or family history of hypertrophic cardiomyopathy or echocardiographic evidence of asymmetric septal hypertrophy; wall motion abnormalities detected by echocardiography; poor transthoracic acoustic windows, likely to impede adequate quantification of time-resolved ventricular geometry; inability to provide informed consent; more than trace mitral regurgitation; and any degree of aortic stenosis. This study was approved by the University of Pennsylvania Institutional Review Board. The Asklepios study protocol was approved by the ethics committee of the Ghent University Hospital. All subjects provided informed consent.

Echocardiographic Examination

Echocardiographic methods are detailed in the online-only Data Supplement Methods section (available at http://circ.ahajournals.org). All echocardiographic examinations were performed with Vivid-7 (GE Healthcare, Chalfont St. Giles, UK) ultrasound platforms for acquisition of LV short-axis views at the papillary muscle level and apical 2- and 4-chamber views for subsequent offline analyses. Pulsed-wave Doppler measurements of flow velocities in the LV outflow tract (LVOT) were performed and recorded placing the Doppler sample immediately proximal to the aortic valve leaflets within the centerline of the LVOT. LV end-diastolic volume and LV mass were calculated with the area-length method. LV mass was indexed for body height in meters to the allometric power of 2.7. At the University of Pennsylvania, LVOT area was measured with 3-dimensional echocardiography as described in the supplemental Methods section. Among Asklepios study participants, we computed LVOT cross-sectional area using the LVOT radius measured in the parasternal long-axis view (area = πr²). Of note, although cross-sectional area affects volumetric flow calculations, the computation of reflection magnitude (a dimensionless index) is insensitive to scaling of flow, therefore being independent of the LVOT cross-sectional area and dependent solely on the flow waveform.

Carotid Tonometry

In both centers, applanation tonometry was performed with a Millar pen-type high-fidelity tonometer (SPT 301, Millar Instruments, Houston, Tex) and dedicated hardware and software for acquisition of the arterial pulse. All carotid tonometry procedures were performed simultaneously with LVOT Doppler flow velocity recordings. Carotid pressure waveforms were calibrated according to brachial mean and diastolic pressures as detailed in the supplemental Methods section.

Pressure and Flow Analyses

Pressure and Doppler flow velocity files were processed offline with custom-designed software written in Matlab (The Mathworks, Natick, Mass) as previously described and explained in more detail in the supplemental Methods section. Time-resolved Doppler flow velocities were obtained from DICOM images and multiplied by LVOT cross-sectional area to obtain volumetric flow. Visual time alignment of pressure and flow curves was performed to maximize the concomitance of 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. An example of a pair of time-aligned pressure and flow wave forms is shown in Figure 1A. Figure 1B shows a pressure-flow loop constructed using time-aligned pressure and flow values from the same individual. Pressure and flow relations were analyzed in the frequency domain to compute the reflection coefficient and characteristic impedance of the proximal aorta as described in the online supplemental Methods section. Characteristic impedance of the proximal aorta also was calculated in the time domain as the ratio of early systolic pulsatile pressure to flow as previously described. Early systolic pulsatile changes in pressure and flow are represented by the orange line in Figure 1A and the orange arrow in Figure 1B. Reflection magnitude in the time domain was computed by the use of wave separation analysis as previously described. In this method, after separation of the pressure waveform into its forward (Pf) and backward (Pb) components, reflection magnitude is computed as the ratio of the amplitudes of Pb/Pf. Augmented pressure was calculated as the difference between the second (P2) and first (P1) systolic peak (P2−P1), as represented in Figure 1A (blue line). Augmentation index was defined as augmented pressure expressed as a percentage of pulse pressure: [(P2−P1)/pulse pressure]×100.

Speckle-Tracking Echocardiography

Speckle tracking was performed offline with an echoPAC workstation (GE Healthcare, Chalfont St Giles, UK). In the parasternal short-axis view at the papillary muscle level, the endocardium was traced in an optimal frame in which a region of interest was selected to exactly fit the wall thickness. If an exact fit could not be obtained, an alternative frame was selected until the fit was satisfactory. The software was then used to automatically track the wall at every time point in the cardiac cycle. Time-resolved numerical values derived from speckle tracking were exported from the echoPAC software.
including time-resolved radial strain. End-diastolic endocardial and epicardial areas were measured manually, and average wall thickness in end-diastole (\(h_{ED}\)) was computed as follows:

\[ h_{ED} = \sqrt{A_{EP}}/\pi - \sqrt{A_{ENDO}/\pi} \]

where \(A_{EP}\) is the epicardial area and \(A_{ENDO}\) is the endocardial area. Using \(h_{ED}\), we can then compute instantaneous average wall thickness from time-resolved average lagrangian radial strain (\(\varepsilon_{RAD,t}\)) values derived from speckle tracking:

\[ h(t) = h_{ED} \cdot \varepsilon_{RAD}(t) \]

where \(h(t)\) is wall thickness at time \(t\) and \(\varepsilon_{RAD}\) is average radial strain at time \(t\).

Speckle-tracking echocardiography also was used to track the longitudinal displacement of the basal segments of the heart toward the apex in the 2- and 4-chamber views. Such displacement is directly computed by the echoPAC software in an angle-independent manner, and its time-resolved numerical values can be digitally exported for further processing. Given that the apex of the heart is stationary in these views, time-resolved ventricular length was computed by subtraction of the average displacement of the 4 basal myocardial segments examined (anterior, inferior, inferoseptal, lateral) from a manually measured end-diastolic ventricular length:

\[ L(t) = L_{ED} - D(t) \]

where \(L(t)\) is ventricular length at time \(t\), \(D(t)\) is displacement of basal segments at time \(t\), and \(L_{ED}\) is end-diastolic ventricle length. We also accounted for apical cap thickening, which makes an additional contribution to cavity longitudinal shortening, as described in detail in the supplemental Methods section.

### Assessment of Time-Resolved Myocardial Stress

Longitudinal (LS) and circumferential (CS) myocardial stress values were computed at each point in time during ejection according to Regen:

\[ LS = \frac{P_{bm}}{2h} \]

and

\[ CS = \frac{P_{bm}(2a_{bm}^2-b_{bm}^2)/h_{bm}^2}{\ln b_m - \ln b} \]

where \(P\) is pressure, \(h\) is average wall thickness, \(b_m\) is the midwall minor semiaxis (radius), and \(a_m\) is the midwall major semiaxis (length). The midwall major and minor semiaxes were computed as follows:

\[ b_m = \frac{(b_m - b)}{\ln b_m - \ln b} \]

and

\[ a_m = \frac{(a_m - a)}{\ln b_m - \ln b} \]

where \(b\) and \(a\) are minor (radius) and major (length) semiaxes of the outer (epicardial) myocardial shell and \(b_m\) and \(a_m\) are minor and major semiaxes of the ventricular cavity, respectively. In contrast to various other methods for estimation of wall stress, these formulas do 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 therefore interfere with direct comparisons of myocardial stress at different times during ejection.

### Statistical Analysis

For power calculations, we estimated that a sample size of 42 subjects was needed to achieve >85% power to detect continuous correlations associated with a coefficient of determination (\(R^2\)) >0.20, using a 2-sided hypothesis test with a significance level of 0.05. In the absence of previous studies of time-resolved ejection-phase myocardial stress that could be used as references for data distribution, such coefficients of determination (accounting for ≥20% of interindividual variability in myocardial stress) were considered to represent quantitatively important associations. Of note, our analyses were aimed at assessing the study objectives and testing the consistency of our findings within each group rather than at performing between-group comparisons. Continuous values are expressed as mean±SD or median and interquartile range (IQR) as appropriate. Proportions are expressed as percentages. Linear relationships between continuous variables were analyzed with linear regression to obtain regression slopes (\(\beta\)) and model \(R^2\) values. Normality of regression model residuals was assessed and multicollinearity of predictor variables was evaluated with eigenvalues and condition indexes. Within-group differences in end-systolic versus myocardial stress at other time points were assessed with paired \(t\) tests. All \(P\) values are 2 tailed. Statistical significance was defined as \(P<0.05\). Sample size calculations were performed with PASS for Windows (NCSS, Kaysville, Utah). All other analyses were performed with SPSS (IBM SPSS Inc, Chicago, Ill). The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

### Results

Important demographic and clinical characteristics of the study population are summarized in Table 1. Hemodynamic parameters for the study population are summarized in Table 2.
As shown, end-systolic CS was significantly lower than peak CS ($P<0.0001$), lower than mean ejection-phase CS ($P<0.0001$), and even lower than CS at aortic valve opening ($P<0.0001$) in all 3 groups. Indeed, end-systolic CS corresponded to the lowest ejection-phase value of CS in most cases (Figures 2B and 3B). Very similar results were obtained for LS (Table 3).

**Magnitude and Correlates of the Midsystolic Pressure-Stress Relationship Shift**

The magnitude of the midsystolic shift in the pressure-stress relationship was quantified within each individual as the difference in myocardial stress corresponding to the value of end-systolic pressure between early and late ejection (as represented by the length of the arrow in Figures 2D, 2E, 3D, and 3E). The mean magnitude of the midsystolic shift in the pressure-CS relationship among U-HTN, T-HTN, and NT was 144 kdynes/cm² (95% CI, 127 to 168), 148 kdynes/cm² (95% CI, 127 to 168), and 145 kdynes/cm² (95% CI, 127 to 163), respectively. However, even within each group, there was wide individual variability in the magnitude of this midsystolic shift (range, 27 to 331 kdynes/cm²). Among T-HTN, after adjustment for age, gender, body height, and body weight, the magnitude of the midsystolic shift in the pressure-CS relationship was independently predicted by LV ejection fraction ($\beta$ per 1% increase $=2.28; P=0.001$) and the ratio of LV cavity to wall volume ($\beta$ per 1% increase $=1.81; P<0.001$). Similarly, among NT subjects, in multivariate analyses, the magnitude of the midsystolic shift in the pressure-CS relationship was independently predicted by LV ejection fraction ($\beta$ per 1% increase $=3.73; P=0.001$) and the ratio of LV cavity to wall volume ($\beta$ per 1% increase $=1.74; P<0.001$). In the U-HTN group, in addition to LV ejection fraction ($\beta$ per 1% increase $=2.98; P=0.04$) and the ratio of
LV cavity to wall volume (β per 1% increase = 0.78; \( P = 0.04 \)), age emerged as an independent negative predictor of the magnitude of the mid-systolic shift in the pressure-CS relationship (β per 1-year increase = −3.78; \( P = 0.02 \)). Findings were similar for LS.

### Temporal Relationship of Pressure Events to Peak Myocardial Stress
The relationships between P1 (peak of the incident wave), P2 (peak of the reflected wave), and myocardial stress values for an individual with negative (P2<P1) and an individual with prominent positive (P2>P1) late systolic pressure augmentation are shown in Figures 2A, 2D, 2E, 3A, 3D, and 3E.

The time of peak CS correlated directly with the time of the first systolic peak (P1) among T-HTN (\( r = 0.52 \)), U-HTN (\( r = 0.51 \)), and NT (\( r = 0.68 \)) subjects, respectively (all \( P < 0.001 \)), which persisted after adjustment for ejection duration (\( P < 0.01 \)). In contrast, the time of the second systolic peak (P2; resulting from wave reflections) did not correlate with the time of peak CS after adjustment for ejection duration in any of the 3 groups (\( P > 0.05 \)). In multivariate models that included time of P1, time of P2, and ejection duration, time of P1 (but not time of P2) was an independent predictor of time of peak CS in all 3 groups. Similarly, the time of the inflection point (“foot” of the reflected wave) was not predictive of the time of peak stress (\( P > 0.05 \)).

### End-Systolic Stress Versus Peak Myocardial Stress: Role of Wave Reflections
The ratio of peak systolic to end-systolic CS was highly variable (range, 1.27 to 2.58), indicating that there is wide interindividual variability in the correspondence between end-systolic and peak CS. The ratio of peak systolic to end-systolic CS significantly decreased with increasing wave reflection coefficient among T-HTN (\( r = -0.57, P < 0.001 \)), U-HTN (\( r = -0.35, P = 0.02 \)), and NT (\( r = -0.48, P = 0.002 \)), indicating that prominent wave reflections are associated with higher end-systolic CS relative to peak CS. This relationship was independent of age, gender, LV mass index, LV end-diastolic volume, systemic vascular resistance, and aortic characteristic impedance. Similar results were obtained relative to LS.

### Discussion
Using a combination of arterial tonometry and contemporary echocardiographic techniques, we assessed time-resolved ejection-phase myocardial stress noninvasively. Our study...
Figure 2. Ejection-phase pressure (A), CS (B), LS (C), pressure-CS relationship (D), and pressure-LS relationship (E) from an individual with negative augmentation index. Early ejection, mid ejection, and late ejection are given by dotted, dashed, and solid lines, respectively. Note the early myocardial stress peak, followed by a marked shift in the pressure-stress relationship, resulting in low myocardial stress values in late systole relative to pressure. The magnitude of this shift is represented by the blue arrow in D and E. P1 and P2 represent first (incident wave) and second (reflected wave) pressure peaks. AVO indicates aortic valve opening; AVC, aortic valve closure.
Figure 3. Ejection-phase pressure (A), CS (B), LS (C), pressure-CS relationship (D), and pressure-LS relationship (E) from an individual with prominent pressure augmentation in late systole. Early ejection, mid ejection, and late ejection are given by dotted, dashed, and solid lines, respectively. Note the early myocardial stress peak, followed by a marked shift in the pressure-stress relationship, resulting in low myocardial stress values in late systole despite prominent pressure augmentation from wave reflections. The magnitude of this shift is represented by the arrow in D and E. P1 and P2 represent first and second pressure peaks. AVO indicates aortic valve opening; AVC, aortic valve closure.
demonstrates that, in hypertensive and normotensive adults with normal LV ejection fraction, peak myocardial stress occurs in early systole, before important contributions of the reflected wave to central pressure. We quantified and characterized, for the first time, a marked midsystolic shift in the pressure-stress relationship, which may serve to protect cardiomyocytes against excessive late systolic stress (despite pressure augmentation associated with wave reflections), a coupling phenomenon that may be altered in various disease states. We also report that end-systolic myocardial stress, a widely used index of myocardial afterload, does not adequately reflect the contribution of different components of arterial load to overall ejection-phase myocardial stress in this population. Specifically, the relationship between end-systolic and time-resolved myocardial stress is markedly affected by wave reflections because wave reflections selectively increase myocardial stress in late systole.

Our study has important implications for the noninvasive assessment of myocardial afterload. Stress on the myocardium (which reflects the tension of cardiomyocytes) represents a key physical stimulus for various physiological responses, including gene expression, extracellular remodeling, and stretch-activated ion channel function.11–15 Myocardial stress is also a major determinant of the pump function of the heart and myocardial oxygen consumption.16 In contrast to ventricular afterload, which in the presence of a normal aortic valve depends almost entirely on the vasculature,2 myocardial afterload (stress) is highly dependent of myocardial wall volume (or thickness) and cavity size.4 Therefore, in contrast to ventricular afterload, which can be completely characterized by analyses of pressure-flow relationships in the proximal aorta,2,7 assessment of myocardial afterload requires knowledge of instantaneous pressure, wall thickness, and cavity size.4 Contemporary speckle-tracking techniques combined with arterial tonometry allow measurements of such parameters with high temporal resolution during the ejection phase, during which peak myocardial stress occurs.

Using such techniques, we found that time-resolved analyses during ejection provide important information on myocardial afterload that cannot be captured by a single end-systolic measurement. We found that after an early systolic peak in myocardial stress, there is a variable, but generally pronounced, shift of the pressure-stress relationship during midsystole, which results in lower values of myocardial stress for any given pressure value during late systole. Therefore, in normotensive and hypertensive adults with normal LV systolic function, late systolic pressure augmentation (associated with wave reflections) is associated with myocardial stress values that are far lower than those observed in early systole, despite higher absolute late systolic pressure values. Our findings indicate that this midsystolic shift in the pressure-stress relationship protects cardiomyocytes against late systolic stress (despite late systolic pressure augmentation induced by wave reflections). Even among subjects with normal LV systolic function, we found this shift to be highly dependent on the magnitude of fractional cavity emptying and ventricular geometry (ie, increasing with an increasing ratio of end-diastolic cavity to wall volume). These findings indicate that a normal/high ejection fraction is a key requirement for this shift to occur and suggest that a prominent midsystolic shift may allow the ventricle to compensate for increased myocardial stress levels that tend to occur with increasing end-diastolic cavity size relative to wall volume. Therefore, our findings are likely to have implications beyond the hypertensive state. In subjects with depressed LV ejection fraction, the midsystolic shift in the pressure-stress relationship may be blunted, making the myocardium more sensitive to wave reflections arriving to the central aorta during systole.

In conditions such as severe mitral regurgitation, ventricular unloading into the left atrium may promote an earlier and/or more pronounced shift in the pressure-stress relationship, which may allow the ventricle to compensate for increased wall stress levels associated with eccentric LV remodeling. Blunting of this mechanism may occur with valve replacement, which may affect the sensitivity of the myocardium to reflected waves. Our findings indicate that even in the presence of a normal ejection fraction, the midsystolic shift in the pressure-stress relationship occurs in various degrees in normotensive and hypertensive adults, which may make some individuals more susceptible than others to the adverse consequences of reflected waves on the myocardium. In particular, our findings of an independent association between older age and a less pronounced midsystolic shift in the pressure-stress relationship among untreated hypertensive adults raise the possibility that older hypertensive subjects may be more susceptible to the adverse consequences of reflected waves on the myocardium. These and other related hypotheses should be tested in future research.

| Table 3. Mean Within-Group Differences (95% CIs) Between End-Systolic Myocardial Stress and Myocardial Stress During Other Time Points in the Ejection Phase |
|-------------------------------------------------|-----------------|-----------------|
|                                                   | T-HTN, kdynes/cm² | U-HTN, kdynes/cm² | NT, kdynes/cm² |
| **Circumferential myocardial stress**             |                  |                  |                |
| End-systolic vs peak ejection-phase CS*           | 168 (138–198)    | 135 (122–148)    | 139 (129–149)  |
| End-systolic vs mean ejection-phase CS*           | 96 (80–111)      | 73 (65–80)       | 77 (68–85)     |
| End-systolic vs CS at aortic valve opening*       | 27 (12–43)       | 43 (28–57)       | 47 (35–59)     |
| **Longitudinal myocardial stress**                |                  |                  |                |
| End-systolic vs peak ejection-phase LS*           | 92 (75–108)      | 77 (70–84)       | 82 (73–91)     |
| End-systolic vs mean ejection-phase LS*           | 52 (43–60)       | 41 (37–45)       | 44 (39–49)     |
| End-systolic vs LS at aortic valve opening*       | 17 (9–26)        | 28 (20–36)       | 31 (24–38)     |

*P<0.0001 for all within-group differences.
It is important to note that our findings do not contradict the importance of wave reflections in hypertension and cardiovascular disease. As previously noted, various cardiac disease states may facilitate the deleterious effects of reflected waves on the myocardium. Reflected waves induce late systolic pressure augmentation and therefore increase central pressure pulsatility, which appears to contribute to the pathophysiology of renal disease, stroke, and aortic wall damage. Furthermore, wave reflections are key determinants of the relationship between central and brachial systolic pressure, a phenomenon that is clinically relevant and cannot be assessed with conventional sphygmomanometry. Indeed, measures of central systolic, pulse, or augmented pressure (resulting from wave reflections) have been shown to predict adverse cardiovascular outcomes in various populations. Wave reflections also may be involved in prolonging the contractile effort of the myocardium and may adversely affect LV relaxation. Finally, it should be noted that our findings are not in disagreement with the well-established end-systolic pressure-volume relationship of the LV, in which an increase in end-systolic pressure relates in an approximately linear fashion to increased end-systolic volume in variably loaded hearts. We speculate that various candidate mechanisms may link time-varying, early-peaking myocardial stress to LV time-varying elastance (and end-systolic elastance), including the force-velocity relation, the Frank-Starling mechanism, and cellular mechanisms by which early systolic load may affect the degree of subsequent fiber shortening. This should also be addressed in future research. Regardless of these mechanisms, the end-systolic pressure-volume relation implies that increases in end-systolic pressure affect end-systolic volume, particularly in situations in which LV contractility is impaired (and end-systolic elastance is decreased), which is consistent with the fact that wave reflections do affect LV pump function, as is apparent from the known effects of wave reflections on late systolic flow.

Our study has limitations. We did not measure ventricular pressure invasively but assumed time-aligned central arterial pressure measurements to correspond to ventricular pressure in the presence of a normal aortic valve. 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 as a result of acceleration and deceleration of flow, respectively. However, these differences are small compared with the absolute pressure and the overall ventricular pressure changes during systole. Furthermore, this small measurement error would actually tend to mask (rather than accentuate) the marked reduction in end-systolic stress relative to early ejection-phase stress. Although our simplified calculations of myocardial stress can be affected by asymmetric ventricular geometry, all subjects in this study had normal LV systolic function without regional wall motion abnormalities. However, we acknowledge that the true 3-dimensional geometry of the LV is variable and not fully accounted for by simplified geometrical models. Of note, estimation of end-systolic stress, the most widely used noninvasive method to assess myocardial afterload, is also subject to such limitations.

Conclusions

Myocardial stress is highly dynamic during the ejection phase, given its dependency on LV size, pressure, and wall thickness, all of which are time-varying parameters. Peak myocardial stress is an early systolic phenomenon, followed by a marked shift in the pressure-stress relationship in midsystole, so that myocardial stress in late systole is lower than in early systole for any given pressure. This phenomenon may serve to protect cardiomyocytes from wave reflections. We propose that this shift is important for adequate coupling between the myocardium, the left ventricle, and the arterial tree. Finally, attempts to assess overall myocardial stress with a single end-systolic value tend to neglect the selective effects of early versus late systolic arterial load on myocardial load. Myocardial afterload results from complex interactions between cardiomyocytes, LV geometry, and the time-varying load imposed by the arterial tree. The study of such myocardial-ventricular-arterial interactions is likely to yield valuable insights into the pathophysiology of various disease states, including hypertensive heart disease, heart failure, and regurgitant valvular lesions.

Disclosures

None.

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**CLINICAL PERSPECTIVE**

Myocardial wall stress is important in the pathophysiology of many clinical cardiac conditions, including hypertensive heart disease, heart failure, and valvular heart disease. Myocardial stress depends on left ventricular cavity size, wall thickness, and pressure, all of which change markedly throughout ejection. Therefore, end-systolic wall stress may not adequately represent time-varying phenomena. We used arterial tonometry combined with contemporary echocardiographic techniques to assess myocardial stress throughout ejection noninvasively in normotensive and hypertensive adults. We found that peak myocardial stress typically occurred very early during ejection, followed by a marked midsystolic shift in the pressure-stress relationship, which favored lower late systolic stress values relative to pressure. The magnitude of this shift was important and independently predicted by a higher left ventricular ejection fraction and ratio of left ventricular end-diastolic cavity to wall volume. In addition, among individuals with untreated hypertension, older age was independently associated with a less pronounced midsystolic shift in the pressure-stress relationship. We conclude that in the presence of a normal left ventricular ejection fraction, a midsystolic shift in the pressure-stress relationship protects cardiomyocytes against excessive late systolic stress, a coupling mechanism that may be altered in various common clinical conditions such as heart failure with low ejection fraction. We demonstrate that the noninvasive assessment of time-resolved myocardial stress provides important information that cannot be gained by assessment of end-systolic stress alone and is likely to yield, through future research, valuable insights into the pathophysiology of prevalent cardiac diseases, including hypertension, heart failure, and valvular heart disease.
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SUPPLEMENTAL METHODS

Echocardiographic examination

An echocardiographic examination was performed with Vivid-7 ultrasound platforms (GE Healthcare; Chalfont St. Giles, UK). The echocardiographic views used from both centers for assessment of instantaneous LV geometry were identical. These included a parasternal short-axis view at the papillary muscle level and apical 2-chamber and 4-chamber views. All offline analyses of echocardiographic images with speckle tracking were performed at the University of Pennsylvania as described in detail below. Pulsed wave Doppler measurements of flow velocities in the LV outflow tract were performed and recorded at high sweep speed (100-200 mm/sec). The Doppler sample was placed immediately proximal to the aortic valve leaflets within the centerline of the LV outflow tract. LV end-diastolic volume and LV mass were calculated with the area-length method. LV mass was indexed for body height in meters to the allometric power of 2.7.

At the University of Pennsylvania, a 3-dimensional full volume parasternal dataset was acquired for subsequent off-line measurement of LV outflow tract (LVOT) area using a dedicated offline workstation (GE Healthcare; Chalfont St. Giles, UK), in which multiplanar reconstructions of the full-volume dataset were performed. In a mid-systolic phase, 2 orthogonal planes parallel to the LV outflow tract long axis were selected. An additional plane was aligned to be orthogonal to both long-axis planes and translated to the position immediately proximal to the aortic valve leaflets, corresponding to the minimal cross-sectional area, which was digitally traced. For echocardiograms from Asklepios study participants, we computed LVOT cross sectional area using the LVOT radius (r=diameter/2) measured in the parasternal long axis view (area=πr²). Although the accuracy of the latter method may be affected by deviations from
LVOT circularity (i.e., LVOT eccentricity)², which impacts volumetric flow calculations, the computation of reflection magnitude (a dimensionless index) is insensitive to scaling of flow, therefore being independent of the LVOT cross-sectional area and thus dependent solely on the flow wave form³.

**Carotid tonometry**

All carotid tonometry procedures were performed simultaneously with LV outflow tract Doppler flow velocities. In both centers, applanation tonometry was performed with a Millar pentype high-fidelity tonometer (SPT 301; Millar Instruments, Houston, Texas, USA) and dedicated hardware and software for acquisition of the arterial pulse. At the University of Pennsylvania, a SphygmoCor Vx System (AtCor Medical; Sydney, Australia) was used. At Ghent University, the hardware platform was designed and custom built around the modular National Instruments SC-2345 signal acquisition hardware.⁴⁻⁵ Pressure data was digitally recorded and processed identically for both study sites using custom-designed software written in Matlab (The Mathworks, Natick, MA). Carotid pressure wave forms were calibrated according to brachial mean and diastolic pressure measured with oscillometric devices (University of Pennsylvania: Hewlett Packard 78352c, Hewlett Packard, Palo Alto, CA; Asklepios study: Omron HEM-907 device, Omron Healthcare Co. Ltd., Kyoto, Japan). We used mean and diastolic pressure rather than diastolic and systolic pressure since mean and diastolic pressures exhibit little variation between the arm and the central arteries, in contrast to systolic pressure, which increases (variably) from the aorta to the brachial artery due to the phenomenon of pulse pressure amplification⁶.
**Pressure and flow analyses**

Time-resolved numerical values of an ensemble averaged carotid pressure waveform were used along with LVOT flow velocities exported in raw DICOM format from the echoPAC workstation. Both pressure and flow velocity files were processed off-line using custom-designed software written in Matlab (The Mathworks, Natick, MA). For each cardiac cycle, the onset and end of systolic ejection were visually delineated on the DICOM images with two cursors, after which the contours in the systolic phase were automatically traced using the transition in pixel intensity above a user-defined threshold value as previously described. Instantaneous flow velocities were multiplied by LV outflow tract cross-sectional area to obtain volumetric flow. Visual time-alignment of pressure and flow curves was performed in order to maximize the following criteria: (a) Concordance of the rapid systolic upstroke of pressure and flow; (b) Concordance of the pressure dichrotic notch and cessation of flow; (c) Zero value of the phase angle of higher-frequency harmonics ($7^{th}$ to $10^{th}$) of input impedance; (d) Linearity of the early systolic pressure-flow relationship.

For analyses in the frequency domain, the pressure and flow wave forms were decomposed into their harmonic components using a Fourier transform and the modulus of input impedance ($Z_{in}$) was calculated as the ratio of the magnitude (amplitude) of pressure and flow harmonics. Characteristic impedance of the proximal aorta ($Z_c$) was calculated in the frequency domain as the average modulus of the 3rd to 10th harmonics of $Z_{in}$. The reflection coefficient in the frequency domain was calculated as: $(Z_{in} - Z_c)/(Z_{in} + Z_c)$ and expressed as the amplitude of its first harmonic (heart frequency) as previously described. Characteristic impedance of the proximal aorta was also calculated in the time domain as the ratio of early systolic pulsatile pressure/flow as previously described. Early systolic pulsatile changes in
pressure and flow are represented by the orange line in figure 1A and the orange arrow in figure 1B. Reflection magnitude in the time domain was computed using wave separation analysis \(^4,6\). In this method, after separation of the pressure waveform into its forward (Pf) and backward (Pb) components, reflection magnitude is computed as the ratio of the amplitudes of Pb/Pf \(^4,6\).

Augmented pressure was calculated as the difference between the second (P2) and first (P1) systolic peak (P2-P1), as represented in figure 1A (blue line). Augmentation index was defined as augmented pressure expressed as a percentage of pulse pressure \([(P2-P1) / \text{Pulse pressure}] \times 100\). Since the second systolic peak results from wave reflections\(^6\), whereas the first systolic peak results from the incident wave, the augmentation index increases with wave reflections\(^6\). A negative augmentation index indicates that the second systolic peak does not augment peak pressure in systole (i.e., P2<P1).

**Speckle tracking echocardiography**

Speckle tracking was performed offline using an echoPAC workstation (GE Healthcare; Chalfont St. Giles, UK). In the parasternal short axis view at the papillary muscle level, the endocardium was traced in a user-selected frame. The width of the region of interest was then prescribed to exactly fit the wall thickness. Since the software allows for user-prescribed finite increases in the thickness of the region of interest, occasionally the true wall thickness in a particular frame lies between 2 user-defined intervals. In these cases, we chose an alternative frame with a slightly different wall thickness until the user-defined region of interest corresponded exactly to the thickness of the wall. We took particular care in performing speckle tracking of the entire wall because there is a (small) gradient of radial strain between the endocardium and epicardium; therefore, interrogating the entire wall provides the greatest
accuracy for overall (mean wall) radial strain, which is used for computations of instantaneous wall thickness as detailed below.

Once the region of interest was selected, the software was used to automatically track the wall at every time point in the cardiac cycle. Time-resolved numerical values for X-Y coordinates corresponding to the mid-distance between endocardium and epicardium were exported from the echoPAC software along with time-resolved radial strain. End-diastolic endocardial and epicardial areas were measured manually and average wall thickness in end-diastole ($h_{ED}$) was computed as follows\textsuperscript{1}:

$$h_{ED} = \sqrt{\frac{A_{EPI}}{\pi}} - \sqrt{\frac{A_{ENDO}}{\pi}}$$

where $A_{EPI}$ is epicardial area and $A_{ENDO}$ is endocardial area. Using $h_{ED}$, instantaneous average wall thickness could then be computed from time-resolved average Lagrangian radial strain ($\epsilon_{RAD}$) values derived from speckle tracking:

$$h(t) = h_{ED} \times \epsilon_{RAD}(t)$$

where $h(t)$ is wall thickness at time $t$ and $\epsilon_{RAD}$ is average radial strain at time $t$.

Speckle tracking echocardiography was also used to track the longitudinal displacement of the basal segments of the heart towards the apex in the 2 and 4-chamber views. Using the speckle tracking algorithm in echoPAC, such displacement is directly computed in an interrogation angle-independent fashion and its time-resolved numerical values can be digitally exported for further processing. Given that the apex of the heart is stationary in these views, time-resolved ventricular length was computed by subtraction of the average displacement of the 4 basal myocardial segments examined (anterior, inferior, inferoseptal, lateral) from a manually measured end-diastolic ventricular length:
\[ L(t) = L_{ED} - D(t) \]

where \( L(t) \) is ventricular length at time \( t \), \( D(t) \) is displacement of basal segments at time \( t \) and \( L_{ED} \) is end-diastolic ventricular length. Of note, this method (in contrast to tissue Doppler imaging) is angle-independent, because the speckle-tracking software automatically computes displacement of individual segments along the longitudinal axis of the left ventricle (rather than absolute displacement).

Because the length of the cavity decreases slightly more than the length of the epicardial shell due to contraction of the apex, we accounted for this difference in our computations. We manually measured apical cap thickness in end diastole (\( APXh_{ED} \)) as from the apical 4-chamber view. Using \( APXh_{ED} \), instantaneous apical wall thickness was then estimated from time-resolved apical Lagrangian strain (\( \epsilon \)) values derived from speckle tracking:

\[ APXh(t) = APXh_{ED} \times \epsilon(t) \]

where \( APXh(t) \) is wall thickness at time \( t \) and \( \epsilon \) is average strain (thickening) at time \( t \). An example of time-resolved cavity and epicardial shell length are shown in supplemental figures 1A and 1B. In figure 1A, the blue line represents the displacement of the base towards the apex and the red line represents the additional long-axis shortening of the cavity due to apical thickening. Figure 1B shows the instantaneous (time-resolved) length of the cavity and epicardium (shell) computed by subtracting the respective degree of absolute shortening from end-diastolic measured cavity and epicardial length. In figure 1B, the red area indicates instantaneous apical thickness.
Assessment of time-resolved fiber stress

Longitudinal (LS) and circumferential (CS) fiber stress values were computed at each point in time during ejection according to Regen\textsuperscript{8}:

\[
\text{LS} = \frac{P \ b_m}{2h}
\]
\[
\text{CS} = \frac{P \ b_m (2a_m^2 - b_m^2)}{2h a_m^2}
\]

where \( P \) is pressure, \( h \) is average wall thickness, \( b_m \) is the midwall minor semiaxis (radius) and \( a_m \) is the midwall major semiaxis (length). The midwall major and minor semiaxes are computed as the logarithmic means of cavity and outer semiaxes:

\[
b_m = \frac{(b_o - b_c)}{(\ln b_o - \ln b_c)}
\]
\[
a_m = \frac{(a_o - a_c)}{(\ln a_o - \ln a_c)}
\]

where \( b_o \) and \( b_c \) are minor semiaxes (radius) of the outer (epicardial) myocardial shell and the ventricular cavity, whereas \( a_o \) and \( a_c \) are major semiaxes (length) of the outer (epicardial) myocardial shell and the ventricular cavity, respectively.

In contrast to various other methods for estimation of wall stress, these formulae do 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 therefore interfere with direct comparisons of myocardial stress at different times during ejection\textsuperscript{8}.
Supplemental Figure Legends.

**Figures 1A and 1B.** Figure 2A shows ejection-phase longitudinal displacement of the base (blue line) and absolute increase in apical thickness (red) derived from speckle tracking echocardiography. Figure 2B shows the time-resolved length of the cavity and epicardial shell. The red area represents the instantaneous apical cap thickness.
Supplemental Figures 1A-B.
Supplemental References

1. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18(12):1440-1463.


