Late Systolic Myocardial Loading Is Associated With Left Atrial Dysfunction in Hypertension

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Background—Late systolic load has been shown to cause diastolic dysfunction in animal models. Although the systolic loading sequence of the ventricular myocardium likely affects its coupling with the left atrium (LA), this issue has not been investigated in humans. We aimed to assess the relationship between the myocardial loading sequence and LA function in human hypertension.

Methods and Results—We studied 260 subjects with hypertension and 19 normotensive age- and sex-matched controls. Time-resolved central pressure and left ventricular geometry were measured with carotid tonometry and cardiac magnetic resonance imaging, respectively, for computation of time-resolved ejection-phase myocardial wall stress (MWS). The ratio of late/early ejection-phase MWS time integrals was computed as an index of late systolic myocardial load. Atrial mechanics were measured with cine-steady-state free-precession magnetic resonance imaging using feature-tracking algorithms. Compared with normotensive controls, hypertensive participants demonstrated increased late/early ejection-phase MWS and reduced LA function. Greater levels of late/early ejection-phase MWS were associated with reduced LA conduit, reservoir, and booster pump LA function. In models that included early and late ejection-phase MWS as independent correlates of LA function, late systolic MWS was associated with lower, whereas early systolic MWS was associated with greater LA function, indicating an effect of the relative loading sequence (late versus early MWS) on LA function. These relationships persisted after adjustment for multiple potential confounders.

Conclusions—A myocardial loading sequence characterized by prominent late systolic MWS was independently associated with atrial dysfunction. In the context of available experimental data, our findings support the deleterious effects of late systolic loading on ventricular–atrial coupling. (Circ Cardiovasc Imaging. 2017;10:e006023. DOI: 10.1161/CIRCIMAGING.116.006023.)

Key Words: afterload • feature tracking • left atrial systolic function • left atrium • loading sequence • magnetic resonance imaging • myocardial contraction • wall stress

Afterload is recognized as an important determinant of myocardial function. Animal studies have demonstrated that within physiological ranges, increased afterload results in differential responses in relaxation depending on its timing. Increases in early systolic load resulted in unchanged or slightly enhanced relaxation, whereas increases in late systolic load resulted in a slow rate of diastolic ventricular pressure fall. More recently, greater late systolic central pressure was reported to be associated with impaired early diastolic relaxation in humans. These studies implicate the loading sequence as a potential mechanistic determinant of diastolic function.

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Late Systolic Wall Stress and Left Atrial Function

Chirinos et al

time-varying MWS estimations need to account for both time-varying pressure and time-varying geometry and are poorly represented by any single time point measurement. Recently, a relationship between time-varying MWS and abnormal diastolic relaxation has been demonstrated, suggesting that the systolic myocardial loading sequence is a key determinant of systolic–diastolic coupling.6–8 However, its impact on left atrial (LA) structure and function is unknown.

LA dysfunction contributes to several complications in hypertension. LA function is important to regulate and promote LV filling during diastole, contributing to cardiac output adaptations to changes in loading conditions, inotropic stimulation, and heart rate. With early/mild hypertension, conduit function of the LA decreases, whereas booster function increases.9 However, with progression of hypertensive heart disease, booster function also declines and is associated with heart failure10,11 and a poor prognosis.12 Given the clinical relevance of LA dysfunction in hypertension, a better understanding of its determinants is highly desirable.

In this study, we aimed to assess whether the myocardial loading sequence (ie, early versus late ejection-phase MWS) is associated with reduced LA function, as assessed by magnetic resonance imaging (MRI)–based measurements of atrial deformation and phasic volumes, among adults with hypertension.

Methods

Study Population

We enrolled a convenience clinical sample of 260 subjects with a history of hypertension referred for a cardiac MRI at the Corporal Michael J. Crescenz VA Medical Center. We also studied a group of age- and sex-matched control subjects without a history of hypertension, diabetes mellitus, cardiomyopathy, or vasoactive medication use (n=19). The protocol was approved by the Philadelphia VA Medical Center Institutional Review Board, and written informed consent was obtained from all participants.

Key exclusion criteria were as follows: (1) claustrophobia; (2) presence of metallic objects or implanted medical devices in body; (3) atrial fibrillation, flutter, or significant arrhythmia at the time of enrollment, which may compromise the study measurements; (4) other conditions that would make the study measurements less accurate or unreliable (ie, inability to perform an adequate breath hold for cardiac MRI acquisitions); (5) any degree of aortic stenosis, which confounds assessment of LV MWS.

CMR Imaging Protocol

Participants underwent a cardiac–MRI examination to assess LV structure and function, using a 1.5 Tesla (T) whole-body MRI scanner (Avanto or Espree; Siemens, Malvern, PA) equipped with a phase-array cardiac coil. LV volumes and ejection fraction were determined using balanced steady-state free-precession cine imaging. Typical parameters were as follows: TR=30.6 ms; TE=1.3 ms; phases=30; slice thickness =8 mm; matrix size =192×192; parallel image (integrated parallel imaging technique) factor =2. LV short-axis stack cine images were analyzed along with at least 1 long-axis view to assess time-resolved LV endocardial and epicardial contours in each cardiac phase, using CMR42 software (Circle CVI, Calgary, AB, Canada). LV wall volume was computed as the difference between epicardial and endocardial volumes at each cardiac phase. LV mass was computed as the difference between epicardial and endocardial volumes, multiplied by myocardial density. LV mass was normalized for body height in meters raised to the allometric power of 1.7.13 We measured proximal aortic flow using velocity-encoded (phase-contrast) imaging in a short-axis proximal aortic plane prescribed at or below the level of the right pulmonary artery. We acquired aortic flow during free breathing using the following parameters: TR=10 ms; TE=3.2 ms; flip angle =30°; field of view=340×340; matrix size =256×256; slice thickness =8 mm; gating=retrogressive; velocity encoding=130 cm/s (prescribed ad hoc to avoid aliasing); number of phases maximized according to heart rate. Aortic through-plane contrast images were processed with the freely available software Segment.$^{14}$

Late Systolic Wall Stress and Left Atrial Function

LA Longitudinal Strain and Volumetric Analysis

We used feature-tracking techniques for the measurement of LA phasic strain, as previously described.15 LA analyses were performed using cvi42 image analysis software (Circle Cardiovascular Imaging Inc, Calgary, Canada). LA endocardial borders were manually traced in apical 2- and 4-chamber views using LV end diastole as the point of reference. An automated tracking algorithm was applied, and the tracking of all atrial segments was confirmed. Manual adjustments were performed as needed to optimize wall tracking. An example of atrial wall tracking is shown in Figure 1 and in Movies I and II in the Data Supplement.

Values of segmental deformation were exported and further processed using custom software programmed in Python (Python Software Foundation, Wilmington, DE). We computed longitudinal atrial strain, defined as the change of atrial myocardial length throughout the atrial cycles ($L_a$) compared with its resting (or reference) length ($L_a^0$) in a relaxed state at diastasis (end of atrial diastole). Strain was computed as ($L_a−L_a^0$/$L_a^0$). We computed strain (deformation) and strain rate (SR) relative to the diastatic LA length (rather than end-diastolic length) because diastasis represents the length for LA tissue at the end of atrial diastole (reference phase). As shown in Figure 1, strain and SR were calculated to assess reservoir (total longitudinal strain), conduit (positive longitudinal strain and early-diastolic SR), and booster (negative longitudinal strain and late-diastolic SR) LA function. Maximum (LA$^{\text{MAX}}$), minimum (LA$^{\text{MIN}}$), and diastatic (LA$^{\text{DIAS}}$) LV volumes were also measured. LA expansion index, passive LA emptying fraction, and active LA emptying fraction were calculated as volumetric measures of reservoir, conduit, and booster phases, respectively. LA expansion index was calculated as (LA$^{\text{MAX}}$−LA$^{\text{MIN}}$)/LA$^{\text{MIN}}$; passive LA emptying fraction as (LA$^{\text{DIAS}}$−LA$^{\text{MIN}}$)/LA$^{\text{MAX}}$; and active LA emptying fraction as (LA$^{\text{MAX}}$−LA$^{\text{MIN}}$)/LA$^{\text{MAX}}$.

Carotid Tonometry

Carotid artery application tonometry was performed immediately before or after the cardiac MRI using a SphygmoCor-Px device (AtCor Medical), which incorporates a high-fidelity Millar application tonometer (Millar Instruments). Carotid pressure waveforms were calibrated according to brachial mean and diastolic pressure (measured with a Hewlett-Packard 78352c device; Hewlett-Packard, Palo Alto, CA), given that diastolic and mean blood pressures do not vary substantially along the arterial tree. The carotid waveform was used because it is a direct surrogate of the aortic pressure waveform; this approach, therefore, does not require the use of a generalized transfer function. We used the systolic portion of the carotid pressure waveform to assess LV pressure during ejection (Figure 2).

Computation of Ejection-Phase MWS

The computation of ejection-phase MWS is schematized in Figure 2. We applied the formula developed by Arts et al.$^{15}$11 which is applicable to axisymmetric ventricles for computation of average LV MWS. This method does not neglect radially directed forces or forces generated within the wall that oppose fiber shortening, which vary significantly with cavity and wall thickness and can interfere with direct comparisons of myocardial fiber stress at different times during ejection. The formula is based on LV cavity volume ($V_{LV}$), LV wall volume ($V_w$), and pressure.

\[
\text{Fiber} \sigma = \frac{P}{\frac{1}{3} \ln \left(1 + \frac{V_w}{V_{LV}}\right)}
\]
where \( P \) = pressure, \( \ln \) = natural logarithm, \( V_w \) = wall volume, and \( V_{LV} \) = ventricular cavity volume (computed at each time point).

We computed time-varying LV cavity volume based on the integration of the proximal aortic systolic flow waveform. The time integral of the systolic flow waveform represents the cumulative ejected volume at each time point. The systolic flow time integral was, therefore, calibrated to stroke volume (computed as end-diastolic minus end-systolic LV cavity volume measured with steady-state free-precession MRI) and, in turn, was used to compute the cumulative ejected volume from the onset of ejection to each time point during ejection. The latter value was subtracted from end-diastolic LV cavity volume to compute the time-resolved LV cavity volume during ejection. LV wall volume was assumed to be constant throughout ejection, as previously demonstrated.18

To assess early versus late systolic MWS, we computed the time integrals of MWS in the first and second half of ejection, respectively, as previously described (Figure 2).6

In 5 repeated measures performed on the same day, coefficients of variation were as follows: LA expansion index, 10.9%; total longitudinal strain, 11.4%; LA passive EF, 12.5%; conduit longitudinal strain, 9.7%; early diastolic longitudinal SR, 15.6%; LA active EF, 5.9%; late diastolic longitudinal strain, 25.5%; and late diastolic

Figure 1. Representative example of measures of atrial deformation derived from atrial tissue tracking from cine steady-state free-precession magnetic resonance imaging (SSFP-MRI) images. A, The diastatic left atrial (LA) phase, in which reference points are prescribed. B, The tracking of atrial tissue, shown at a different phase of the cardiac cycle (see Movie I in the Data Supplement). C and D, Representative plots of strain and strain rate, respectively, along with measures of reservoir (R), conduit (C), and booster pump (P) function derived from strain and strain rate curves. Note that atrial diastasis was used as the reference length for all strain/strain rate measurements. SR-A indicates late diastolic (booster pump) atrial strain rate; and SR-E, early diastolic (conduit) atrial strain rate.
Late Systolic Wall Stress and Left Atrial Function

Chirinos et al

All measures of MWS (peak MWS, time to peak MWS, end-systolic stress, early ejection-phase MWS, late ejection-phase MWS, and the ratio of late/early ejection-phase MWS) demonstrated CVs<5%, whereas the time to peak fiber stress demonstrated a CV of 7.3%.

Statistical Methods

Continuous variables are presented as mean±SD and compared using t tests of analysis of variance, as appropriate. Categorical variables are presented as frequencies and percentages and compared with the χ² or Fisher’s exact test, as appropriate. Pearson correlations coefficients were computed to examine the relationship of various measures of LA structure and function. Linear regression was performed to assess the relationship between early systolic MWS, late systolic MWS (both included as independent variables), and various parameters of LA function (included as dependent variables in individual regression models) in hypertensive participants. For each parameters of LA function, we built unadjusted models (referred to as model 1), models that adjusted for age, ethnicity, and sex (model 2), and models that additionally adjusted for LA volume, body mass index, systolic blood pressure, diastolic blood pressure, diabetes mellitus, coronary artery disease, and heart failure status (model 3). For easier comparisons of the magnitude of the relationships of early and late systolic wall stress in various models, we present standardized regression coefficients (β). For a more intuitive representation of the relationship between the loading sequence and LA function, we computed the ratio of late/early MWS time integrals. Hypertensive subjects were then stratified according to tertiles of the early/late MWS–time integral ratio (<0.77, 0.77–85, and >0.85). Representative examples of pressure, flow, time-resolved LV wall/cavity ratio, and ejection-phase MWS among subjects in the lowest, mid-, and highest tertile are shown in Figures I to III in the Data Supplement, respectively.

Although LA volume was not significantly different between the tertiles, there were significant differences in...
Late Systolic Wall Stress and Left Atrial Function

all measures of LA function. LA conduit function was progressively reduced among subjects in the mid- and highest tertile, compared with subjects in the lowest tertile. In contrast, indices of LA booster pump function were reduced only in the highest tertile of late/early MWS. Reservoir function (which is influenced by both conduit and booster pump function) exhibited an intermediate trend, with progressive reductions from the lowest to the highest tertile, which were more clear (and statistically significant) in the highest tertile.

Correlation of Early and Late Systolic MWS With LA Function in Multivariable Models

The results of regression models in which early and late systolic MWS are examined as independent predictors of LA reservoir, conduit, and booster pump function were presented in Tables II to IV in the Data Supplement, respectively. In these models, early systolic MWS was consistently related to higher LA reservoir, conduit, and booster pump function, whereas late systolic MWS was consistently related to reduced LA reservoir, conduit, and booster pump function. These relationships remained significant and only modestly attenuated after adjustment for age, sex, and race (model 2) or after further adjustment for LA volume, body mass index, systolic and diastolic blood pressure, presence of diabetes mellitus, coronary artery disease, use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, spironolactone, and diuretics.

Interestingly, the values of the standardized regression coefficients for both early and late systolic MWS were lower...
in models that assessed parameters of booster pump LA function (Table IV in the Data Supplement) than the values obtained in models that assessed parameters of LA conduit or reservoir function (Tables II and III in the Data Supplement). Nevertheless, these relationships remained significant and only modestly attenuated after adjustment for demographic factors (model 2) and after further adjustment for LA volume and multiple potential confounders (model 3).

**Discussion**

In this study, we assessed the relationship between the myocardial loading sequence (early versus late MWS) and LA dysfunction in adults with hypertension. LA function was assessed from classic phasic LA volumes, as well as novel measurements of LA myocardial deformation (strain). We report, for the first time, that a myocardial loading sequence characterized by prominent late systolic wall stress (relative to early systolic wall stress) is independently associated with reduced reservoir, conduit, and booster pump LA function. In the context of available experimental data, our findings support the deleterious effects of late systolic LV loading on systolic–diastolic coupling.

LA structure and function represent highly clinically relevant phenotypes in hypertensive patients. The prognostic importance of phasic LA function, independent of LA size, is increasingly recognized.6–12,20 Furthermore, there is a differential clinical course of reservoir and conduit function versus booster pump function in hypertension. Eshoo et al10 reported that among mild untreated hypertensive subjects, reservoir and conduit LA function was decreased, whereas booster function was increased. As hypertensive heart disease progresses, however, booster pump function also decreases,10,11 which is associated with an increased risk of cardiovascular morbidity and mortality in population-based and hypertensive cohorts.20,21 Our findings indicate that even average levels of late systolic load (late/early MWS time integral ratios >0.77) are associated with reduced conduit LA function, compared with subjects with low levels of late/early load, with further reduction seen at higher levels of late/early MWS (ratios >0.85). In contrast, only subjects in the highest tertile of late/early MWS (late/early MWS time-integral ratios >0.85) demonstrated reduced LA booster pump function. Because reservoir function is influenced by both conduit and booster pump function, the observed trend in indices of reservoir function was progressive from the lowest to the highest tertile, but more clear in the highest tertile.

In multivariable analyses, we found that in models that adjust for late systolic load, early systolic load is associated with increased LA function, indicating that it is not only the absolute load but the myocardial loading sequence that determines LA dysfunction in hypertension. These findings advance our understanding of systolic–diastolic coupling in the intact heart. Causal links between the systolic loading pattern and abnormal diastolic function have been shown in experimental settings.22,23 Interestingly, the pattern of systolic load,22,24,25 rather than the absolute afterload itself,26 seems to be the most important determinant of diastolic function. The intact ejecting LV has been shown to respond to late systolic load with delayed relaxation in animal1,24 and human25 experiments. Similarly, late systolic MWS has been shown to be associated with impaired diastolic relaxation in a large middle-aged community-based sample6 and in subjects with hypertension.7

MWS represents the time-varying mechanical load on the myocardium, which is determined by complex interactions between myocardial contractile elements, instantaneous LV geometry, and the time-varying hydraulic load imposed by the arterial tree.5,7,8 As such, MWS integrates the influence of arterial load and LV structure and function on myocardial load.

The mechanism by which late systolic load acutely impacts diastolic function remains incompletely understood. Although absolute MWS tends to be lower in late systole,
the myocardium may be particularly vulnerable to even small MWS increases during this period. This may be because of intrinsic differences in cellular processes between early and late ejection. Loading during active cross-bridge formation (early systolic load) increases the number of interacting cross-bridges (cooperative activity), a physiological mechanism that allows adequate matching of the number of cross-bridges with systolic load. However, when increased load occurs after the onset of myocardial relaxation, the number of interacting cross-bridges can no longer adapt, which results in a mismatch between the number of cross-bridges and load, and an increased stress imposed on individual cross-bridges.

Figure 3. Measures of left atrial (LA) reservoir, conduit, and booster pump function in hypertensive subjects in the lower, middle, and higher tertile of the late/early myocardial wall stress (MWS)–time integral ratio. Higher levels of this ratio indicate greater late systolic load relative to early systolic load. ANOVA indicates analysis of variance.
note, the timing of transition from myocardial fiber contraction to relaxation differs from the timing of transition from ventricular systole to diastole, normally occurs early during the ejection phase, and is related to the descending limb of the myocyte cytoplasmic calcium transient. In addition to the acute effect of late systolic load on diastolic function demonstrated in various studies, late systolic load has been shown to induce more LV remodeling and fibrosis than early systolic load. LV fibrosis may increase diastolic passive stiffness of the LV, imposing excessive load on the atrial myocardium, ultimately contributing to LA dysfunction.

Interestingly, in our study, the myocardial loading sequence was more strongly associated with parameters of conduit and reservoir LA function, although the loading sequence was also associated with reduced LA booster pump LA function, with lower booster pump function observed in subjects in the highest tertile of MWS. A potential explanation for a weaker association between the loading sequence and booster pump function (relative to conduit and reservoir function) relates to the effect of atrial contraction on LV early systolic load. It has been shown that booster pump function imparts kinetic energy to LV inflow in late diastole, which is preferentially preserved by blood that passes directly from inflow to outflow in a single cardiac cycle (referred to as direct flow). During early LV contraction, this direct flow has the greatest amount of kinetic energy, has the shortest distance to the LV outflow tract, and is moving in a favorable direction relative to the LV outflow tract, effectively unloading the LV during early systole. Therefore, booster pump function reduces early systolic LV load, which may induce preferential shortening over fiber stress generation in early systole. This mechanism (which is specific to booster pump function) may confound/attenuate the relationship between worse LA function and a loading pattern characterized by lower early and greater late systolic MWS.

Our study raises the possibility that manipulating the loading sequence may lead to increased LA function in hypertension. Arterial wave reflections selectively increase mid to late systolic LV load and MWS. However, the effect of wave reflections on MWS is influenced by the LV contraction pattern. Normally, brisk force development and fiber shortening occur in early systole, which is followed by a dynamic reconfiguration of LV geometry that results in a midsystolic reduction in MWS relative to LV pressure, thus, protecting the cardiomyocytes against excessive load in late systole (a period of increased vulnerability). However, in the presence of contractile abnormalities that compromise early systolic ejection, the dynamic geometric reconfiguration of the LV that favors a reduced MWS relative to pressure is less efficient, increasing late systolic MWS and facilitating the ill effects of wave reflections. A reduction in late systolic MWS may, therefore, be accomplished by (1) interventions that reduce the hemodynamic load induced by wave reflections (such as inorganic nitrates or other nitric oxide donors) or (2) interventions that alter the contraction pattern, which could be accomplished by manipulating myocardial contractility, chronic LV remodeling, or by enhancing shortening deactivation, which has recently been proposed as a mechanism linking late systolic MWS with impaired relaxation. Our observational study was not designed to assess whether manipulating the loading sequence enhances LA function, which should be the focus of future studies.

Our study should be interpreted in the context of its strengths and limitations. Our relatively large sample, the application of methods suitable for time-resolved MWS estimations, and use of volume-independent measures of LA function (derived from semiautomated measures of LA myocardial longitudinal deformation) are strengths of our study. Similarly, our assessment of LV wall and cavity volumes for MWS computations was based on steady-state free-precession cine-MRI; unlike 2D echocardiography (which we used in previous studies), this method does not rely on geometric assumptions. Furthermore, we used novel tissue-tracking algorithms to assess LA strain (deformation), a more direct measure of LA myocardial function. We found that the loading sequence was associated with LA function in all 3 domains (reservoir, conduit, and booster); these associations were consistently demonstrated with various measures of LA function in each domain and were robust to adjustment for potential confounders. The high consistency and robustness of our results adds confidence to our findings. Our study also has several limitations. Our observational study can only demonstrate associations and does not prove causality. Although the administration of a vasoactive drug, such as nitroglycerin, could be introduced to induce changes in the loading sequence in an experimental design, concomitant effects of the drug on preload, or the atrial myocardium would confound assessments of the cause–effect relationship between changes in the loading sequence and atrial function. Residual confounding cannot be excluded; therefore, unmeasured mechanisms (such as neurohormonal factors or genetic polymorphisms) may lead to noncausal associations between time-resolved MWS patterns and LA function. We used a convenience sample to recruit our study participants at a VA Medical Center. Therefore, our study population was composed predominantly of males, and it may not be adequate to extrapolate these findings to women, younger, or community based samples of hypertensive adults. Our control group was small, which could have led to type II error in some comparisons with the hypertensive group.

In summary, we assessed the relationship between the myocardial loading sequence (early versus late MWS) and LA dysfunction in adults with hypertension. We found that a LV myocardial loading sequence characterized by prominent late systolic MWS (relative to early systolic MWS) is independently associated with reduced reservoir, conduit, and booster pump LA function in hypertensive adults. We found that conduit function progressively decreased from the lowest to the highest tertile of late/early ejection-phase MWS, whereas booster pump function was selectively reduced in the highest tertile of late/early ejection-phase MWS. Time-varying MWS represents an integrated index of myocardial–ventricular–arterial coupling. In the context of available experimental data from previous studies, our findings suggest that time-varying systolic MWS influences atrial function and is, thus, important for ventricular–arterial
coupling. Future mechanistic studies regarding the role of the loading sequence on systolic–diastolic coupling may enhance our understanding of the pathophysiology of abnormal myocardial function and may aid in identifying potential targets or interventions to improve LV diastolic relaxation and systemic adaptations to adverse patterns of systolic load.

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Disclosures
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CLINICAL PERSPECTIVE

Myocardial wall stress (the load that cardiomyocytes experience) during ejection cannot be derived solely from blood pressure. The systolic loading sequence underlies ventricular–arterial coupling in health and disease and likely underlies the development of maladaptive left ventricular hypertrophy and progression to heart failure. We assess myocardial wall stress during ejection using a combination of arterial tonometry and cardiac magnetic resonance imaging in patients with hypertension and in normotensive controls. We also measured left atrial function with cardiac magnetic resonance imaging. Our study demonstrates that early-systolic myocardial wall stress correlates positively, whereas late systolic wall stress correlates negatively with left atrial function. A loading sequence characterized by a prominent late systolic load (relative to early systolic load) is associated with impaired reservoir, conduit, and booster pump left atrial function. Our study supports the role of the systolic loading sequence as a determinant of atrial function in hypertension. The systolic loading sequence represents a suitable therapeutic target to improve diastolic function and atrial function in hypertension, which should be tested in future trials.
Late Systolic Myocardial Loading Is Associated With Left Atrial Dysfunction in Hypertension


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SUPPLEMENTAL MATERIAL

**TITLE:** Late Systolic Myocardial Loading is Strongly Related to Left Atrial Dysfunction in Hypertension

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Supplemental results

Correlations between LA volumes and various measures of LA function

A correlation matrix including LA volume and various measures of reservoir, conduit and booster pump function are shown in supplemental Table 1. The rows corresponding to the domains of LA structure and function are color coded (blue=reservoir; green=conduit; red=booster pump; white=LA volume). LA volume was correlated with “worse” LA reservoir and booster pump function. However, LA volume was not associated with measures of conduit function. In general, correlations within each domain of LA function (conduit and booster pump) were stronger than those with measures in the other domain. Given that reservoir function is influenced by both conduit and booster pump function, measures of both conduit and booster pump function were correlated with measures of reservoir function.
Supplemental Tables.

Supplemental Table 1. Correlation between measures of LA structure and function

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<th>Booster Pump Function</th>
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† Absolute values were used (i.e., higher values indicate higher function and lower values indicate lower function)

* P<0.01 (2-tailed).
Supplemental Table 2: Early and Late Systolic Myocardial Wall Stress Time-Integrals as predictors of left reservoir function

<table>
<thead>
<tr>
<th></th>
<th>Early systolic Ejection-phase MWS-TI</th>
<th>Late systolic Ejection-phase MWS-TI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standardized Beta Coefficient</td>
<td>$P$ value</td>
</tr>
<tr>
<td><strong>LA expansion index</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.739</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.716</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.716</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Reservoir (total) longitudinal strain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.993</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.966</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.914</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Model 1: Unadjusted
Model 2: Adjusted for age, sex, and race
Model 3: Adjusted for variables in Model 2 plus LA volume, body mass index, systolic and diastolic blood pressure, presence of diabetes mellitus, coronary artery disease, use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, spironolactone, and diuretics.
Supplemental Table 3: Early and Late Systolic Myocardial Wall Stress Time-Integrals as predictors of left atrial conduit function

<table>
<thead>
<tr>
<th></th>
<th>Early systolic Ejection-phase MWS-TI</th>
<th>Late systolic Ejection-phase MWS-TI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standardized Beta Coefficient</td>
<td>$P$ value</td>
</tr>
<tr>
<td><strong>LA passive Ejection Fraction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.751</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.787</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.672</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td><strong>Conduit longitudinal Strain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.045</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.053</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.827</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td><strong>Early diastolic longitudinal Strain Rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.878</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.911</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.828</td>
<td>$&lt;0.0001$</td>
</tr>
</tbody>
</table>

*Absolute value (i.e., lower value indicates lower function)

Model 1: Unadjusted
Model 2: Adjusted for age, sex, and race
Model 3: Adjusted for variables in Model 2 plus LA volume, body mass index, systolic and diastolic blood pressure, presence of diabetes mellitus, coronary artery disease, use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, spironolactone, and diuretics.
Supplemental Table 4: Early and Late Systolic Myocardial Wall Stress Time-Integrals as predictors of left atrial booster pump function

<table>
<thead>
<tr>
<th></th>
<th>Early systolic Ejection-phase MWS-TI</th>
<th>Late systolic Ejection-phase MWS-TI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standardized Beta Coefficient</td>
<td>P value</td>
</tr>
<tr>
<td>LA active Ejection Fraction</td>
<td>0.446</td>
<td>0.004</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.397</td>
<td>0.012</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.46</td>
<td>0.003</td>
</tr>
<tr>
<td>Late diastolic longitudinal Strain amplitude*</td>
<td>0.498</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.441</td>
<td>0.005</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.656</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late diastolic longitudinal Strain rate (atrial kick)*</td>
<td>0.396</td>
<td>0.012</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.363</td>
<td>0.022</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.474</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Absolute value (i.e., lower value indicates lower function)

Model 1: Unadjusted
Model 2: Adjusted for age, sex, and race
Model 3: Adjusted for variables in Model 2 plus LA volume, body mass index, systolic and diastolic blood pressure, presence of diabetes mellitus, coronary artery disease, use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, spironolactone, and diuretics.
Supplemental Figures and Figure Legends.

Supplemental Figure 1. Representative examples of pressure, flow, time-resolved LV wall/cavity ratio, and ejection-phase myocardial wall stress in subjects with a low late/early MWS (L/E MWS) time-integral (lower tertile)
Supplemental Figure 2. Representative examples of pressure, flow, time-resolved LV wall/cavity ratio, and ejection-phase myocardial wall stress in subjects with an intermediate late/early MWS (L/E MWS) time-integral (middle tertile)
Supplemental Figure 3. Representative examples of pressure, flow, time-resolved LV wall/cavity ratio, and ejection-phase myocardial wall stress in subjects with a high late/early MWS (L/E MWS) time-integral (highest tertile)
Legends for online video files

**Online Video 1.** Example of atrial wall tracking using feature tracking in CMR-42 software.

**Online Video 2.** Example of atrial wall tracking using feature tracking in CMR-42 software.