Clinical Investigation

Pulsatile Load Components, Resistive Load and Incident Heart Failure: The Multi-Ethnic Study of Atherosclerosis (MESA)

PAYMAN ZAMANI, MD, MTR, 1 SCOTT M. LILLY, MD, PhD, 2 PATRICK SEGERS, PhD, 3 DAVID R. JACOBS Jr., PhD, 4 DAVID A. BLUEMKE, MD, PhD, MsB, 5, 6 DANIEL A. DUPREZ, MD, PhD, 7 AND JULIO A. CHIRINOS, MD, PhD 1

Pennsylvania; Columbus, Ohio; Ghent, Belgium; Minnesota; Bethesda and Baltimore, Maryland; and Minnesota

ABSTRACT

Background: Left ventricular (LV) afterload is composed of systemic vascular resistance (SVR) and components of pulsatile load, including total arterial compliance (TAC), and reflection magnitude (RM). RM, which affects the LV systolic loading sequence, has been shown to strongly predict HF. Effective arterial elastance (Ea) is a commonly used parameter initially proposed to be a lumped index of resistive and pulsatile afterload. We sought to assess how various LV afterload parameters predict heart failure (HF) risk and whether RM predicts HF independently from subclinical atherosclerosis.

Methods: We studied 4345 MESA participants who underwent radial arterial tonometry and cardiac output (CO) measurements with the use of cardiac MRI. RM was computed as the ratio of the backward (Pb) to forward (Pf) waves. TAC was approximated as the ratio of stroke volume (SV) to central pulse pressure. SVR was computed as mean pressure/CO. Ea was computed as central end-systolic pressure/SV.

Results: During 10.3 years of follow-up, 91 definite HF events occurred. SVR (P = .74), TAC (P = .81), and Ea (P = .81) were not predictive of HF risk. RM was associated with increased HF risk, even after adjustment for other parameters of arterial load, various confounders, and markers of subclinical atherosclerosis (standardized hazard ratio [HR] 1.49, 95% confidence interval [CI] 1.18–1.88; P = .001). Pb was also associated with an increased risk of HF after adjustment for Pf (standardized HR 1.43, 95% CI 1.17–1.75; P = .001).

Conclusions: RM is an important independent predictor of HF risk, whereas TAC, SVR, and Ea are not. Our findings support the importance of the systolic LV loading sequence on HF risk, independently from subclinical atherosclerosis. (J Cardiac Fail 2016;22:988–995)

Key Words: Wave reflections, compliance, vascular resistance, heart failure.
With the aging of the population, the incidence of heart failure (HF) is expected to rise. Some of the strongest risk factors for the development of HF include hypertension, diabetes, and atherosclerotic disease, making their appropriate treatment an important part of HF prevention. Clarifying the role of novel modifiable risk factors is of paramount importance to stem the tide of new HF cases.

Blood pressure (BP) represents the complex interplay between cardiac function and the opposition to flow imposed by the arterial system (arterial load). Arterial load is complex and can be understood in terms of its resistive (ie, systemic vascular resistance [SVR]) and pulsatile (total arterial compliance [TAC], characteristic impedance of the aorta, and indices of wave reflections) components. Wave reflections arise in the peripheral arterial tree when the forward wave generated by the heart encounters sites of impedance mismatch. Wave reflections travel back to the heart, increasing mid-to-late systolic load. We have recently identified reflection magnitude (RM), the ratio of the reflected (P_r) to forward waves (P_f), as a strong predictor of incident HF independently from BP and multiple confounders. However, BP is not an index of arterial load, because the latter depends on the ratio of pressure to flow. Whether RM predicts HF independently from indices of load that account for the flow generated by the heart (stroke volume or cardiac output [CO]) is unknown.

Effective arterial elastance (E_a), the ratio of end-systolic pressure to stroke volume (SV), is a commonly used parameter of arterial load. E_a was initially proposed as a lumped index of “effective” resistive and pulsatile afterload. However, E_a has been shown to be almost entirely dependent on heart rate and SVR, therefore insensitive to pulsatile load, including the left ventricular (LV) loading sequence imposed by wave reflections.

In the present study, we expand on our previous work by assessing (1) how RM compares to other metrics of arterial load (SVR, TAC, E_a) as a predictor of incident HF in the general population, and (2) how various indices of arterial load relate to incident HF after adjustment for subclinical atherosclerosis.

**Methods**

**Study Sample**

The Multi-Ethnic Study of Atherosclerosis (MESA) enrolled 6,814 men and women aged 45–84 years of diverse ethnic backgrounds from 6 centers across the United States. Subjects self-reported their ethnicity as African-American, Asian-American (predominantly Chinese), Caucasian, or Hispanic. All subjects were free of clinical cardiovascular disease by self-report at baseline. Subjects were enrolled from 2000 to 2002 and contacted every 9–12 months for assessment of clinical end points. All participants were followed through December 31, 2011. Follow-up telephone interviews were completed in 92% of living participants, and medical records were obtained for 98% of hospital admissions. The study was approved by the Institutional Review Boards of participating centers, and every participant signed an informed consent.

**HF Event Adjudication**

Two physicians independently reviewed copies of medical records and death certificates for hospitalizations and outpatient cardiovascular diagnoses. End points were classified with the use of prespecified criteria. The diagnosis of HF was established by “definite” criteria, which required clinical symptoms (eg, dyspnea) or signs (eg, edema), a physician’s diagnosis, and medical treatment for HF in addition to objective evidence: (a) pulmonary edema/congestion on chest X-ray and/or (b) a dilated LV or poor function on echocardiography or ventriculography, or LV diastolic dysfunction.

**Data Collection**

BP was determined at the baseline visit with the use of a standardized method. Brachial systolic (SBP) and diastolic (DBP) BPs were also obtained before and after the magnetic resonance imaging (MRI) scan while the subject was on the MRI table, with the results averaged. There was good correlation between the BP obtained at the time of the MRI and the standardized BP measurements from the baseline visit (SBP: r = 0.66, P < .0001; DBP: r = 0.61; P < .0001). Mean arterial pressure [MAP]: r = 0.62, P < .0001). Serum cholesterol was obtained after a 12-hour fast. Diabetes mellitus was defined as a fasting glucose ≥126 mg/dL or use of diabetic medications. Hypertension was defined according to the Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.

**Assessment of Cardiac Output**

Cardiac MRI was performed with the use of 1.5-Tesla field strength systems to determine LV mass and volume as previously described. Short-axis images of the LV were acquired with the use of a gradient-echo cine sequence (time to repetition/time to echo 8–10 ms/3–5 ms, flip angle 20°, 6 mm slice thickness, 4 mm gap, flow compensation, in-plane resolution 1.4–1.6 mm [frequency] × 2.2–2.5 mm). Endocardial and epicardial borders were traced with the use of a semiautomated method (MASS 4.2; Medis, Leiden, the Netherlands). Myocardial volume was defined as the difference between epicardial and endocardial areas for all slices at end-diastole, multiplied by the sum of slice thickness and the interslice gap. SV was determined as the difference between end-diastolic and end-systolic volumes. This method of LV quantification has been shown to have excellent reproducibility.

CO was determined by multiplying the SV with the heart rate at the time of the MRI.

**Hemodynamic Measurements**

Radial arterial waveform recordings were obtained at the baseline visit in the supine position. In all study centers, 30
seconds of data were recorded with the use of the HDI/ 
Pulseeave-CR2000 
tonometer device (Hypertension 
Diagnostics, Eagan, Minnesota) and digitized at 200 Hz for 
online processing. Custom-designed software was written in 
Matlab (Mathworks, Natick, Massachusetts) for analysis of 
waveforms and to generate an averaged waveform for each 
individual, as previously described in detail.5 A generalized 
transfer function was subsequently applied to radial artery pres-
sure waveforms to arrive at the central pressure waveform.15 
All pressure waveforms were visually inspected by 1 inves-
tigator (JAC) for quality and physiologic consistency. We 
excluded averaged waveforms that met any of the following 
criteria: (1) a nonphysiologic appearance (usually from bi-
genomaly, trigeminy, or contamination of the averaged signal 
by aberrantly-conducted complexes); (2) cardiac cycle du-
ration variation ≥10%; (3) pulse height (beat-to-beat pulse 
pressure) variation ≥20%; (4) ≤10 adequately recorded cycles 
available for signal averaging; and (5) inability to clearly iden-
tify key landmarks of the pressure waveform required for wave 
separation using an averaged physiologic flow approach.

### Determination of Arterial Load Parameters

After application of the generalized transfer function, the 
subject-specific central pressure waveform was analyzed to 
determine the duration of flow (onset of pressure until the di-
crotic notch) and the timing of peak flow (coincident with 
Pp in the pressure waveform). This subject-specific timing in-
formation was then used to produce a physiologic flow wave-
form. This subject-specific scaled waveform was then 
\n\[
RM = \frac{Pb(ba(wave amplitude))}{Pf (forward wave amplitude)}
\]

To determine MAP, a subject-specific form factor (FF) was 
computed for each individual based on the radial tonomet-
metric waveform, as described previously17,18:

\[
FF = \frac{Radial Mean Pressure − Radial Diastolic Pressure}{Radial Systolic Pressure − Radial Diastolic Pressure}
\]

MAP was calculated based on BP measurements at the 
time of the MRI as follows: diastolic pressure + FF × (pulse 
pressure [PP]). SVR, expressed in Wood units, was calcu-
lated as the ratio of MAP to CO, both obtained during the 
MRI. Calculation of SVR using the blood pressure from the 
baseline exam did not alter our findings (data not shown). 
TAC was approximated as the ratio of the SV to the central 
PP obtained using arterial tonometry. E, was computed as 
the ratio of central end-systolic pressure to SV.8 Given that 
arterial load is highly dependent on body size,4 we indexed 
TAC, SVR, and E, for body surface area (BSA) by dividing 
TAC by BSA and multiplying SVR and E, by BSA.4 Such 
linear indexation is justified because absolute allometric 
exponents relating TAC, SVR, and E, to BSA are approxi-
mate (and not significantly different from) unity.19

### Assessment of Subclinical Atherosclerosis

Trained technicians performed B-mode ultrasound exami-
nation of both common carotid arteries. Maximum common 
carotid intima-media thickness (IMT) was calculated as the 
mean of the maximum IMT of the near and far walls 
bilaterally.20 Coronary artery calcium (CAC) was measured 
using computerized tomography and referenced to a phantom 
known calcium concentration that was included in the field 
of view. Each participant was scanned twice to determine the 
average phantom-adjusted Agatston score.20 During these scans, 
calcification within the thoracic aorta was measured and quan-
tified as for CAC.12 The ankle brachial index (ABI) was 
determined for each lower extremity using a hand-held Doppler 
probe. The numerator was set as the higher of the 2 pres-
sures between the dorsalis pedis and posterior tibial arteries 
for each leg. The denominator was the higher brachial artery 
pressure between both arms. The lower ABI of the 2 legs was 
recorded.21,22

### Statistical Methods

Baseline characteristics of the cohort are presented as 
mean ± SD or as median (interquartile range [IQR]). Cox pro-
portional hazards models were created to assess the 
independent risk for each metric of arterial load for HF. Var-
iables known to predict HF were included in sequential models 
to adjust for potential confounders.1 Given the known risk of 
HF conferred by atherosclerotic disease,1 additional adjust-
ment for markers of subclinical atherosclerosis in different 
vascular territories (CAC, ABI, common carotid IMT, and as-
cending thoracic aortic Agatston score) was performed. Finally, 
subjects who developed HF on the same day or after a myo-
cardial infarction (MI) were censored at the time of the MI 
to mitigate any confounding between MI, the metrics of ar-
terial load, and the development of HF. Metrics of arterial 
load were divided by their respective SDs before being entered 
to the models. Hazard ratios (HRs) presented correspond 
\n\[
RM = Pf(ba(wave amplitude))−Pf (forward wave amplitude)
\]

\[
1 − 0.05 was taken to be significant. All analyses were per-
formed with the use of Stata 13.1 (Statacorp, College Station, 
Texas).
Results

Baseline demographic, laboratory, anthropomorphic, and clinical data are presented in Table 1. Of the 6336 subjects enrolled in MESA who had radial tonometry, 5989 (95%) had sufficiently reliable digitized tonometric records to permit calculation of RM. Of these individuals, 1582 did not have information on CO, 42 did not have BP measurements during the cardiac MRI, and 20 were lost to follow-up, leaving a final cohort of 4345 subjects. Subjects were followed for a median of 10.3 years (IQR 9.7–10.8 y). A total of 91 definitive HF events occurred over this time period (2.1%).

Arterial Load and Definitive Heart Failure

Proportional hazards models relating RM, SVR, and TAC to incident HF are presented in Table 2. After adjustment for confounding variables, resistive load (SVR) was not associated with increased HF risk in any model. TAC was similarly not associated with incident HF. In contrast, RM bore important relationships to HF in an age and sex–adjusted model (model 1: HR 1.52, 95% CI 1.21–1.90; P < .001). After adjustment for additional demographic, clinical, and laboratory data, each SD increase in RM remained associated with incident HF (model 2: HR 1.47, 95% CI 1.17–1.84; P = .001). This relationship was unaltered by inclusion of the markers of subclinical atherosclerosis (model 3: HR 1.49, 95% CI 1.18–1.88; P = .001). Censoring individuals who had an MI on the same day or before the development of HF did not meaningfully alter these relationships (Supplemental Table 1).

P\text{\textsubscript{b}} Versus P\text{\textsubscript{f}} and Incident Heart Failure

Table 3 presents models in which RM was replaced by its components: P\text{\textsubscript{b}} and P\text{\textsubscript{f,res}}. Consistent with Table 2, neither SVR nor TAC bore significant relationships to HF. In contrast, P\text{\textsubscript{f,res}} was a significant predictor of incident HF. After age and sex adjustment, increasing P\text{\textsubscript{f,res}} was associated with increased HF risk (HR for each SD increase 1.39, 95% CI 1.14–1.69; P = .001); whereas, P\text{\textsuperscript{f}} was not (P = .43). The relationship between P\text{\textsubscript{f,res}} and HF was maintained after adjustment for demographic, clinical, and laboratory risk factors (model 2: P\text{\textsubscript{f,res}} HR 1.39, 95% CI 1.15–1.69; P = .001; P\text{\textsuperscript{f}} = .19). Further adjustment for markers of subclinical atherosclerosis did not alter these relationships (model 3: P\text{\textsubscript{f,res}} HR 1.43, 95% CI 1.17–1.75; P = .001; P\text{\textsuperscript{f}} = .17), nor did censoring individuals who developed an MI on the same day or before the onset of HF (Supplemental Table 2).

Arterial Elastance, Mean Arterial Pressure, and HF

The association between E\text{\textsubscript{e}} and HF was assessed in analogous models. E\text{\textsubscript{e}} was not significantly associated with HF (Table 4). Additional models were created in which RM and E\text{\textsubscript{e}} were both included (Supplemental Table 3). In all models, RM was independently associated with HF risk (P = .001), whereas E\text{\textsubscript{e}} was not (P > .20).

Finally, models were created in which SVR was replaced by MAP alone (Supplemental Table 4). MAP was independently associated with HF in an age and sex–adjusted model (model 1: HR for each SD increase 1.33, 95% CI 1.09–1.63; P = .005); however, further adjustment rendered the relationship non-significant (model 2: P = .26; Model 3: P = .38). RM retained its significant independent association with HF risk in these models (P = .001).
Table 2. Proportional Hazards Models for SVR, TAC, and RM per SD Increase

<table>
<thead>
<tr>
<th>Metric of Load</th>
<th>Model 1</th>
<th></th>
<th></th>
<th>Model 2</th>
<th></th>
<th></th>
<th>Model 3</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td></td>
</tr>
<tr>
<td>Indexed SVR</td>
<td>0.94 (0.74–1.19)</td>
<td>.59</td>
<td></td>
<td>0.98 (0.78–1.22)</td>
<td>.85</td>
<td></td>
<td>0.96 (0.76–1.21)</td>
<td>.74</td>
<td></td>
</tr>
<tr>
<td>Indexed TAC</td>
<td>0.77 (0.56–1.06)</td>
<td>.11</td>
<td></td>
<td>0.93 (0.68–1.28)</td>
<td>.66</td>
<td></td>
<td>0.96 (0.70–1.32)</td>
<td>.81</td>
<td></td>
</tr>
<tr>
<td>RM</td>
<td>1.52 (1.21–1.90)</td>
<td>&lt;.001</td>
<td></td>
<td>1.47 (1.17–1.84)</td>
<td>.001</td>
<td></td>
<td>1.49 (1.18–1.88)</td>
<td>.001</td>
<td></td>
</tr>
</tbody>
</table>

Model 1 adjusted for age and sex (n = 4345; 91 heart failure events). Model 2 adjusted for age, sex, diabetes, diagnosis of hypertension, treatment with antihypertensive medications, race, estimated glomerular filtration rate, log microalbumin:creatinine ratio, and heart rate (n = 4318; 91 heart failure events). Model 3 adjusted for age, sex, diabetes, diagnosis of hypertension, treatment with antihypertensive medications, race, estimated glomerular filtration rate, log microalbumin:creatinine ratio, heart rate, ankle-brachial index, maximum common carotid intimal-media thickness, log Agatston coronary artery calcium score, and log Agatston ascending thoracic aorta calcium score (n = 4263; 90 heart failure events). Abbreviations as in Table 1.

Discussion

In this community-based study of adults free from cardiovascular disease, we demonstrate that RM bears important independent relationships to incident HF, whereas SVR, TAC, and E, do not. These relationships were unaltered by adjustment for age and sex, hypertension, smoking, diabetes, and renal function.\(^\text{12,20}\) Finally, because atherosclerosis is a major risk factor for HF and relates to arterial hemodynamic properties,\(^\text{27,28}\) we performed additional adjustment for markers of subclinical atherosclerosis. In these models, the hazard ratios for RM, \(P_{\text{res}}\), and \(P_b\) were largely unchanged. This suggests that the risk of HF associated with RM and \(P_{\text{res}}\) operate through mechanisms other than atherosclerosis. Furthermore, the importance of RM in all models suggests that the relationship between \(P_b\) and \(P\), (ie, the greater the \(P_b\) relative to \(P\)), rather than their absolute amplitudes, is the significant factor for incident HF. Importantly, when assessed simultaneously in regression models, \(P_{b,\text{res}}\) bore a significant relationship with definite HF events, whereas \(P_c\) did not. Because \(P_b\) and \(P\) impose their hemodynamic effects on the LV at different times during systole (early systole for \(P_b\) and late systole for \(P_c\)), this finding reinforces the importance of the LV loading sequence on HF.

In the absence of aortic stenosis, the arterial system imposes the load opposing LV ejection during systole. Arterial load is composed of several components that influence the interaction between the LV and the arterial system. The resistive load, summarized by SVR, is largely determined by the arterioles and is the primary determinant of the absolute level of overall wall stress experienced by the myocyte during ejection for any given ventricular geometry.\(^\text{4,28}\) Pulsatile load, on the other hand, is complex but can be described by a number of different arterial properties: characteristic impedance of the proximal aorta (\(Z_c\)), TAC, RM, and reflection timing, which

Table 3. Proportional Hazards Models for Resistive Versus Pulsatile Load per SD Increase

<table>
<thead>
<tr>
<th>Metric of Load</th>
<th>Model 1</th>
<th></th>
<th></th>
<th>Model 2</th>
<th></th>
<th></th>
<th>Model 3</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td></td>
</tr>
<tr>
<td>Indexed SVR</td>
<td>0.97 (0.76–1.23)</td>
<td>.79</td>
<td></td>
<td>1.04 (0.83–1.30)</td>
<td>.75</td>
<td></td>
<td>1.02 (0.80–1.29)</td>
<td>.89</td>
<td></td>
</tr>
<tr>
<td>Indexed TAC</td>
<td>0.87 (0.59–1.29)</td>
<td>.49</td>
<td></td>
<td>1.12 (0.76–1.67)</td>
<td>.56</td>
<td></td>
<td>1.17 (0.79–1.74)</td>
<td>.44</td>
<td></td>
</tr>
<tr>
<td>(P_s) adjusted for (P_b) (mm Hg)</td>
<td>1.39 (1.14–1.69)</td>
<td>.001</td>
<td></td>
<td>1.39 (1.15–1.69)</td>
<td>.001</td>
<td></td>
<td>1.43 (1.17–1.75)</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>(P_b) (mm Hg)</td>
<td>1.11 (0.86–1.44)</td>
<td>.43</td>
<td></td>
<td>1.22 (0.91–1.64)</td>
<td>.19</td>
<td></td>
<td>1.24 (0.91–1.68)</td>
<td>.17</td>
<td></td>
</tr>
</tbody>
</table>

Model 1 adjusted for age and sex (n = 4345; 91 heart failure events). Model 2 adjusted for age, sex, diabetes, diagnosis of hypertension, treatment with antihypertensive medications, race, estimated glomerular filtration rate, log microalbumin:creatinine ratio, and heart rate (n = 4318; 91 heart failure events). Model 3 adjusted for age, sex, diabetes, diagnosis of hypertension, treatment with antihypertensive medications, race, estimated glomerular filtration rate, log microalbumin:creatinine ratio, heart rate, ankle-brachial index, maximum common carotid intimal-media thickness, log Agatston coronary artery calcium score, and log Agatston ascending thoracic aorta calcium score (n = 4263; 90 heart failure events). Abbreviations as in Tables 1 and 2.

Table 4. Proportional Hazards Models for Indexed Arterial Elastance per SD Increase

<table>
<thead>
<tr>
<th>Metric of Load</th>
<th>Model 1</th>
<th></th>
<th></th>
<th>Model 2</th>
<th></th>
<th></th>
<th>Model 3</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td></td>
</tr>
<tr>
<td>Effective arterial elastance</td>
<td>1.16 (0.99–1.36)</td>
<td>.064</td>
<td></td>
<td>1.02 (0.84–1.23)</td>
<td>.86</td>
<td></td>
<td>0.98 (0.79–1.20)</td>
<td>.81</td>
<td></td>
</tr>
</tbody>
</table>

Model 1 adjusted for age and sex (n = 4345; 91 heart failure events). Model 2 adjusted for age, sex, diabetes, diagnosis of hypertension, treatment with antihypertensive medications, race, estimated glomerular filtration rate, log microalbumin:creatinine ratio, and heart rate (n = 4318; 91 heart failure events). Model 3 adjusted for age, sex, diabetes, diagnosis of hypertension, treatment with antihypertensive medications, race, estimated glomerular filtration rate, log microalbumin:creatinine ratio, heart rate, ankle-brachial index, maximum common carotid intimal-media thickness, log Agatston coronary artery calcium score, and log Agatston ascending thoracic aorta calcium score (n = 4263; 90 heart failure events).
is itself determined by aortic pulse-wave velocity and the distance between the LV and the reflection sites. Proximal aortic Z, defines the early systolic pressure-flow relationship and is an important determinant of early (within the 1st 100 ms) ventricular afterload and PP. TAC represents the “total” compliance of the arterial system, although it is in large part composed of the compliance of the large conduit arteries. RM is the ratio of the incident (ie, forward, P) pressure wave generated by LV contraction to that of the reflected (ie, backward, P) pressure waves generated when the forward wave encounters sites of impedance mismatch. Importantly, P, and RM selectively impose their load on the LV during mid-to-late systole and bear little relation to early ventricular wall stress. Although P, is represented as one discrete number, it represents the summation of myriad reflected waves that are generated as the forward wave propagates throughout the arterial system. Furthermore, given that P, represents a portion of P, that is reflected, the amplitude of P, should always be interpreted while taking P, into account (either by computing the residual component of P, for a given P, or by computing RM, which is the ratio of P/P). Early animal and human studies demonstrate that the loading sequence (early vs late load) is an important determinant of LV hypertrophy and fibrosis, diastolic dysfunction, and HF risk. Our previous work in this cohort demonstrated that RM and the presence of prominent late systolic hypertension (defined as the ratio of late to early pressure-time integrals during systole) are strongly predictive of incident HF, independent of the absolute BP. However, whether this is independent from arterial load indices that are dependent on both arterial pressure and the flow (or SV) generated by the heart is unknown. We demonstrate that RM, but not commonly used arterial load indices (SVR, TAC, and E), is predictive of incident HF. Similarly, we extend our previous observations by showing that RM is predictive of incident HF independent of subclinical atherosclerosis.

We demonstrate that E, an index commonly assumed to incorporate both resistive and pulsatile load, is not related to HF risk in the general population. We recently demonstrated that E, does not reflect pulsatile load and does not bear any relationship to arterial wall stiffness. E, is indeed an almost perfect function of the product of systemic vascular resistance and heart rate and intrinsically neglects important information about pulsatile load and the loading sequence. Recent American Heart Association guidelines recommend against the use of E, for the assessment of LV pulsatile load or arterial stiffness. Given the important limitations of E, it is not surprising that it did not predict incident HF in this cohort.

The mechanism whereby late-load adversely affects the myocardium is incompletely understood. It is known that the myocardium can better adapt to loads imposed early in systole by increasing myofilament cross-bridge formation. In contrast, loads imposed late in systole do not lead to increased cross-bridges, instead increasing the load on each individual cross-bridge. This could lead to an earlier onset, but slowed rate, of relaxation and potentially the activation of unfavorable signaling pathways that promote maladaptive hypertrophy. Further work is needed to understand the molecular mechanisms by which late systolic load may affect myocardial remodeling and failure.

**Study Limitations**

Our work must be interpreted in the context of its strength and limitations. Strengths of this MESA substudy include its large size and detailed phenotypic analysis of its participants including tonometry, cardiac MRI, adjudicated definite HF events, and a comprehensive assessment of subclinical atherosclerosis in numerous territories. Several limitations should also be noted. Given the large number of phenotypic measures, about one-third of the overall MESA cohort were excluded from this substudy owing to incomplete data, limiting the generalizability of our conclusions. We used a pseudoflow approach to perform wave separation, because flow was not directly measured. The physiologic waveform applied to each subject’s central pressure waveform was generated in a younger population than in this substudy of MESA. This technique, and the lack of invasively derived flow waveforms, may have introduced noise into the quantification of RM (and P/P). Furthermore, because time-resolved flow measurements were not available, we could not calculate the Z, for each subject. However, the latter primarily affects P, which was included in regression models. We approximated TAC as the ratio of SV to central PP. This method neglects venous run-off of blood during systole, although adjustment for SVR in the models should diminish this source of error. Additionally, our use of FF to derive individual MAP recordings relied on radial tonometry measurements that were then applied to the brachial BP. This neglects differences in brachial-to-radial PP amplification. Because this method was applied in all individuals, however, it is unlikely to have introduced significant bias. Finally, we were not able to distinguish between HF events that occurred with reduced (HFrEF) versus preserved (HFpEF) ejection fractions, and the pathophysiologic mechanisms between these may be different. The relationship between RM and HFpEF versus HFrEF should be the focus of future research.

**Conclusion**

In a large multiethnic cohort of individuals free of incident cardiovascular disease, we demonstrate that metrics of late systolic load, namely RM and P, bear important relationships to the development of HF that persist despite comprehensive adjustment for SVR, TAC, and measures of atherosclerosis. E, in contrast, did not predict incident HF. We also demonstrate that SVR was not associated with HF risk, further highlighting the importance of pulsatile versus resistive load on LV performance. Our findings demonstrate the importance of the loading sequence during systole on the
LV, with greater risk for HF conferred by loads applied during mid-to-late systole, which is consistent with previous experimental and human observations.

Disclosures

Dr Chirinos has received consulting fees from OPKO Healthcare, Bristol-Myers Squibb, Merck, Microsoft Research, and Fukuda Denshi, receives research funding from the National Institutes of Health, Veterans Affairs Administration, American College of Radiology Network, Bristol-Myers Squibb, and Fukuda Denshi, and is named as inventor in a University of Pennsylvania patent application for the use of inorganic nitrate/nitrite for HFpEF. The other authors report no potential conflicts of interest.

Appendix: Supplementary Data

Supplemental data related to this article can be found at doi:10.1016/j.cardfail.2016.04.011.

References