

Clinical Investigation

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

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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 (E_a) 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 (P_b) to forward (P_f) waves. TAC was approximated as the ratio of stroke volume (SV) to central pulse pressure. SVR was computed as mean pressure/CO. E_a 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 E_a ($P = .81$) 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; $P = .001$). P_b was also associated with an increased risk of HF after adjustment for P_f (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 E_a 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.

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With the aging of the population, the incidence of heart failure (HF) is expected to rise.¹ 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.¹ 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).^{2,3} 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.⁴ Wave reflections arise in the peripheral arterial tree when the forward wave generated by the heart encounters sites of impedance mismatch.³ 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_b) to forward waves (P_f), as a strong predictor of incident HF⁵ 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.^{6,7} However, E_a has been shown to be almost entirely dependent on heart rate and SVR,⁸ 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^{5,9} 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.¹⁰ The study was approved by the Institutional Review Boards of partici-

pating 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.¹¹ 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.¹¹

Data Collection

BP was determined at the baseline visit with the use of a standardized method.¹¹ 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.¹² 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.¹⁰ 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.¹³

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.¹⁴ 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] \times 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).¹¹ 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.¹⁴ 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/Pulsewave-CR2000 tonometry device (Hypertension Diagnostics, Eagan, Minnesota) and digitized at 200 Hz for offline 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 pressure waveforms to arrive at the central pressure waveform.¹⁵ All pressure waveforms were visually inspected by 1 investigator (JAC) for quality and physiologic consistency. We excluded averaged waveforms that met any of the following criteria: (1) a nonphysiologic appearance (usually from bigeminy, trigeminy, or contamination of the averaged signal by aberrantly-conducted complexes); (2) cardiac cycle duration variation $\geq 10\%$; (3) pulse height (beat-to-beat pulse pressure) variation $\geq 20\%$; (4) < 10 adequately recorded cycles available for signal averaging; and (5) inability to clearly identify 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 dirotic notch) and the timing of peak flow (coincident with P_1 in the pressure waveform). This subject-specific timing information was then used to produce a physiologic flow waveform. This subject-specific scaled waveform was then applied to each individual's central pressure waveform to separate the forward-traveling (P_f) and backward-traveling (reflected, P_b) waves, as previously described in detail.^{5,16} RM was calculated as:

$$RM = \frac{P_b(\text{backward wave amplitude})}{P_f(\text{forward wave amplitude})}$$

To determine MAP, a subject-specific form factor (FF) was computed for each individual based on the radial tonometric waveform, as described previously^{17,18}:

Form Factor (FF)

$$= \frac{\text{Radial Mean Pressure} - \text{Radial Diastolic Pressure}}{\text{Radial Systolic Pressure} - \text{Radial Diastolic Pressure}}$$

MAP was calculated based on BP measurements at the time of the MRI as follows: diastolic pressure + $FF \times$ (pulse pressure [PP]). SVR, expressed in Wood units, was calculated 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_a 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_a for body surface area (BSA) by dividing TAC by BSA and multiplying SVR and E_a by BSA.⁴ Such linear indexation is justified because absolute allometric exponents relating TAC, SVR, and E_a to BSA are approximately (and not significantly different from) unity.¹⁹

Assessment of Subclinical Atherosclerosis

Trained technicians performed B-mode ultrasound examination 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 of 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 quantified 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 pressures 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 \pm SD or as median (interquartile range [IQR]). Cox proportional hazards models were created to assess the independent risk for each metric of arterial load for HF. Variables 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 adjustment for markers of subclinical atherosclerosis in different vascular territories (CAC, ABI, common carotid IMT, and ascending thoracic aortic Agatston score) was performed. Finally, subjects who developed HF on the same day or after a myocardial infarction (MI) were censored at the time of the MI to mitigate any confounding between MI, the metrics of arterial load, and the development of HF. Metrics of arterial load were divided by their respective SDs before being entered into the models. Hazard ratios (HRs) presented correspond to a 1-SD increase for each metric. Log-transformation was applied to improve the normality of data distribution as needed.

In an unadjusted linear regression model, P_b equals $0.84 \times P_f$, with an intercept not significantly different than unity. Given the strong correlation between P_b and P_f ($r = 0.98$; $P < .0001$), we determined residual values for the observed P_b versus the predicted P_b for any given P_f ($P_{b,res}$). These residual values were used to determine the impact of P_b after taking the magnitude of P_f into account. A type I error rate of $\leq .05$ was taken to be significant. All analyses were performed 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

Table 1. Baseline Demographic, Clinical, Anthropomorphic, and Laboratory Data for Study Participants

Variable	Overall Population (n = 4345)
Age (y), median (IQR)	61.0 (53.0–69.0)
Male, n (%)	2109 (48.5)
Race, n (%)	
White	1658 (38.2)
Black	1080 (24.9)
Chinese	589 (13.6)
Hispanic	1018 (23.4)
Height (m), mean ± SD	1.66 ± 0.10
Weight (kg), mean ± SD	77.03 ± 16.11
Body mass index (kg/m ²), mean ± SD	27.71 ± 4.95
Diabetes, n (%)	505 (11.7)
Estimated glomerular filtration rate (mL/min/1.73 m ²), mean ± SD	78.52 ± 15.85
Urine microalbumin:creatinine ratio (μg/mL), median (IQR)	5.2 (3.3–10.2)
Total cholesterol (mg/dL), mean ± SD	194.17 ± 35.23)
LDL cholesterol (mg/dL), mean ± SD	117.01 ± 31.24
HDL cholesterol (mg/dL), mean ± SD	51.02 ± 14.87
Triglycerides, median (IQR)	113.0 (78.0–163.0)
Statin use, n (%)	619 (14.3)
Current smoking, n (%)	1531 (35.2)
Hypertension, n (%)	1826 (42.0)
Hypertension medication, n (%)	1512 (34.8)
Brachial systolic blood pressure (mmHg), mean ± SD	134.02 ± 20.55
Brachial diastolic blood pressure (mmHg), mean ± SD	77.43 ± 11.06
Brachial mean arterial pressure (mmHg), mean ± SD	100.82 ± 14.00
Aortic systolic blood pressure (mmHg), mean ± SD	127.42 ± 19.27
Aortic diastolic blood pressure (mmHg), mean ± SD	75.02 ± 10.25
Aortic pulse pressure (mmHg), mean ± SD	52.40 ± 14.60
Heart rate (beats/min), mean ± SD	63.79 ± 9.84
Markers of subclinical atherosclerosis	
Ankle-brachial index, mean ± SD	1.12 ± 0.11
Maximum common carotid intimal-medial thickness (mm), mean ± SD	0.86 ± 0.18
Coronary artery calcium Agatston score, median (IQR)	0 (0–70.29)
Ascending thoracic aorta Agatston calcium score, median (IQR)	0 (0–0)
Arterial parameters	
SVR (Wood units), mean ± SD	18.76 ± 5.68
Indexed SVR (Wood units × m ²), mean ± SD	34.37 ± 10.11
TAC (mL/mm Hg), mean ± SD	1.78 ± 0.63
Indexed TAC (mL/mm Hg/m ²), mean ± SD	0.96 ± 0.31
RM, (mean ± SD)	0.84 ± 0.05
P _f (mm Hg), mean ± SD	30.65 ± 8.58
P _b (mm Hg), mean ± SD	25.70 ± 7.35
Residual P _b given P _f , mean ± SD	0 ± 1.53
Effective arterial elastance (mm Hg/mL), mean ± SD	1.40 ± 0.41
Indexed effective arterial elastance (mm Hg × m ³ /mL), mean ± SD	2.55 ± 0.70
Form factor, mean ± SD	0.41 ± 0.04

IQR, interquartile range; P_b, magnitude of backward wave; P_f, magnitude of forward wave; RM, reflection magnitude; SVR, systemic vascular resistance; TAC, total arterial compliance.

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_b Versus P_f and Incident Heart Failure

[Table 3](#) presents models in which RM was replaced by its components: P_f and P_{b, res}. Consistent with [Table 2](#), neither SVR nor TAC bore significant relationships to HF. In contrast, P_{b, res} was a significant predictor of incident HF. After age and sex adjustment, increasing P_{b, res} was associated with increased HF risk (HR for each SD increase 1.39, 95% CI 1.14–1.69; *P* = .001); whereas, P_f was not (*P* = .43). The relationship between P_{b, res} and HF was maintained after adjustment for demographic, clinical, and laboratory risk factors (model 2: P_{b, res} HR 1.39, 95% CI 1.15–1.69; *P* = .001; P_f *P* = .19). Further adjustment for markers of subclinical atherosclerosis did not alter these relationships (model 3: P_{b, res} HR 1.43, 95% CI 1.17–1.75; *P* = .001; P_f *P* = .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_a and HF was assessed in analogous models. E_a was not significantly associated with HF ([Table 4](#)). Additional models were created in which RM and E_a were both included ([Supplemental Table 3](#)). In all models, RM was independently associated with HF risk (*P* = .001), whereas E_a 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

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

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). CI, confidence interval; HR, hazard ratio; other 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_a do not. These relationships were unaltered by adjustment for known clinical and laboratory risk factors for HF, such as age, hypertension, smoking, diabetes, and renal function.^{1,23–26} Finally, because atherosclerosis is a major risk factor for HF and relates to arterial hemodynamic properties,^{1,27} we performed additional adjustment for markers of subclinical atherosclerosis. In these models, the hazard ratios for RM, $P_{b,res}$, and P_f were largely unchanged. This suggests that the risk of HF associated with RM and $P_{b,res}$ operate through mechanisms other than atherosclerosis. Furthermore, the importance of RM in all models suggests that the relationship between P_f and P_b (ie, the greater the P_b relative to P_f), rather than their absolute amplitudes, is the significant factor for in-

cident HF. Importantly, when assessed simultaneously in regression models, $P_{b,res}$ bore a significant relationship with definite HF events, whereas P_f did not. Because P_b and P_f impose their hemodynamic effects on the LV at different times during systole (early systole for P_f and late systole for P_b), 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.^{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

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

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

Metric of Load	Model 1		Model 2		Model 3	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Effective arterial elastance	1.16 (0.99–1.36)	.064	1.02 (0.84–1.23)	.86	0.98 (0.79–1.20)	.81

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.⁴ Proximal aortic Z_c defines the early systolic pressure-flow relationship and is an important determinant of early (within the 1st 100 ms) ventricular afterload and PP.^{28–30} TAC represents the “total” compliance of the arterial system, although it is in large part composed of the compliance of the large conduit arteries.⁴ RM is the ratio of the incident (ie, forward, P_f) pressure wave generated by LV contraction to that of the reflected (ie, backward, P_b) pressure waves generated when the forward wave encounters sites of impedance mismatch.³¹ Importantly, P_b and RM selectively impose their load on the LV during mid-to-late systole and bear little relation to early ventricular wall stress.²⁸ Although P_b 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.³² Furthermore, given that P_b represents a portion of P_f that is reflected, the amplitude of P_b should always be interpreted while taking P_f into account (either by computing the residual component of P_b for a given P_f , or by computing RM, which is the ratio of P_b/P_f).

Earlier animal and human studies demonstrate that the loading sequence (early vs late load) is an important determinant of LV hypertrophy and fibrosis,^{33,34} diastolic dysfunction,^{35–39} and HF risk.^{5,9} 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.^{5,9} 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_a), 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_a , 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_a does not reflect pulsatile load and does not bear any relationship to arterial wall stiffness.⁸ E_a is indeed an almost perfect function of the product of systemic vascular resistance and heart rate⁸ and intrinsically neglects important information about pulsatile load and the loading sequence. Recent American Heart Association guidelines recommend against the use of E_a for the assessment of LV pulsatile load or arterial stiffness.⁴⁰ Given the important limitations of E_a , 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^{41,42} 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 ([Supplemental Table 5](#)), limiting the generalizability of our conclusions. We used a pseudoflow approach to perform wave separation,¹⁶ 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_b/P_f). Furthermore, because time-resolved flow measurements were not available, we could not calculate the Z_c for each subject. However, the latter primarily affects P_f , 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 (HF_rEF) versus preserved (HF_pEF) ejection fractions, and the pathophysiologic mechanisms between these may be different. The relationship between RM and HF_pEF versus HF_rEF 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 $P_{b,res}$, bear important relationships to the development of HF that persist despite comprehensive adjustment for SVR, TAC, and measures of atherosclerosis. E_a , 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

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

References

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62:e147–239.
2. Segers P, Stergiopoulos N, Westerhof N. Quantification of the contribution of cardiac and arterial remodeling to hypertension. *Hypertension* 2000;36:760–5.
3. Chirinos JA, Segers P. Noninvasive evaluation of left ventricular afterload: part 1: pressure and flow measurements and basic principles of wave conduction and reflection. *Hypertension* 2010;56:555–62.
4. Chirinos JA, Segers P. Noninvasive evaluation of left ventricular afterload: part 2: arterial pressure-flow and pressure-volume relations in humans. *Hypertension* 2010;56:563–70.
5. Chirinos JA, Kips JG, Jacobs DR Jr, Brumback L, Duprez DA, Kronmal R, et al. Arterial wave reflections and incident cardiovascular events and heart failure: MESA (Multiethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2012;60:2170–7.
6. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. *Am J Physiol* 1983;245:H773–80.
7. Sunagawa K, Maughan WL, Sagawa K. Optimal arterial resistance for the maximal stroke work studied in isolated canine left ventricle. *Circ Res* 1985;56:586–95.
8. Chirinos JA, Rietzschel ER, Shiva-Kumar P, De Buyzere ML, Zamani P, Claessens T, et al. Effective arterial elastance is insensitive to pulsatile arterial load. *Hypertension* 2014;64:1022–31.
9. Chirinos JA, Segers P, Duprez DA, Brumback L, Bluemke DA, Zamani P, et al. Late systolic central hypertension as a predictor of incident heart failure: the Multi-ethnic Study of Atherosclerosis. *J Am Heart Assoc* 2015;4:e001335.
10. Martin SS, Blaha MJ, Blankstein R, Agatston A, Rivera JJ, Virani SS, et al. Dyslipidemia, coronary artery calcium, and incident atherosclerotic cardiovascular disease: implications for statin therapy from the Multi-ethnic Study of Atherosclerosis. *Circulation* 2014;129:77–86.
11. Bluemke DA, Kronmal RA, Lima JA, Liu K, Olson J, Burke GL, et al. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-ethnic Study of Atherosclerosis) study. *J Am Coll Cardiol* 2008;52:2148–55.
12. Al-Mallah MH, Nasir K, Katz R, Takasu J, Lima JA, Bluemke DA, et al. Thoracic aortic distensibility and thoracic aortic calcium (from the Multi-ethnic Study of Atherosclerosis [MESA]). *Am J Cardiol* 2010;106:575–80.
13. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997;157:2413–46.
14. Natori S, Lai S, Finn JP, Gomes AS, Hundley WG, Jerosch-Herold M, et al. Cardiovascular function in Multi-ethnic Study of Atherosclerosis: normal values by age, sex, and ethnicity. *AJR Am J Roentgenol* 2006;186:S357–65.
15. Karamanoglu M, O'Rourke MF, Avolio AP, Kelly RP. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. *Eur Heart J* 1993;14:160–7.
16. Kips JG, Rietzschel ER, de Buyzere ML, Westerhof BE, Gillebert TC, van Bortel LM, et al. Evaluation of noninvasive methods to assess wave reflection and pulse transit time from the pressure waveform alone. *Hypertension* 2009;53:142–9.
17. Zamani P, Bluemke DA, Jacobs DR Jr, Duprez DA, Kronmal R, Lilly SM. Resistive and pulsatile arterial load as predictors of left ventricular mass and geometry: the multi-ethnic study of atherosclerosis. *Hypertension* 2015;65:85–92.
18. Segers P, Mahieu D, Kips J, Rietzschel E, de Buyzere M, de Bacquer D, et al. Amplification of the pressure pulse in the upper limb in healthy, middle-aged men and women. *Hypertension* 2009;54:414–20.
19. Chirinos JA, Rietzschel ER, de Buyzere ML, de Bacquer D, Gillebert TC, Gupta AK. Arterial load and ventricular-arterial coupling: physiologic relations with body size and effect of obesity. *Hypertension* 2009;54:558–66.
20. Folsom AR, Kronmal RA, Detrano RC, O'Leary DH, Bild DE, Bluemke DA, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-ethnic Study of Atherosclerosis (MESA). *Arch Intern Med* 2008;168:1333–9.
21. Criqui MH, McClelland RL, McDermott MM, Allison MA, Blumenthal RS, Aboyans V, et al. The ankle-brachial index and incident cardiovascular events in the MESA (Multi-ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2010;56:1506–12.
22. Ix JH, Katz R, Peralta CA, de Boer IH, Allison MA, Bluemke DA, et al. A high ankle brachial index is associated with greater left ventricular mass MESA (Multi-ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2010;55:342–9.
23. Wilhelmsen L, Rosengren A, Eriksson H, Lappas G. Heart failure in the general population of men—morbidity, risk factors and prognosis. *J Intern Med* 2001;249:253–61.
24. Butler J, Kalogeropoulos A, Georgiopoulos V, Belue R, Rodondi N, Garcia M, et al. Incident heart failure prediction in the elderly: the health ABC heart failure score. *Circ Heart Fail* 2008;1:125–33.
25. Kalogeropoulos A, Georgiopoulos V, Kritchevsky SB, Psaty BM, Smith NL, Newman AB, et al. Epidemiology of incident heart failure in a contemporary elderly cohort: the health, aging, and body composition study. *Arch Intern Med* 2009;169:708–15.
26. Pfister R, Cairns R, Erdmann E, Schneider CA. A clinical risk score for heart failure in patients with type 2 diabetes and macrovascular disease: an analysis of the PROactive study. *Int J Cardiol* 2013;162:112–6.
27. Tsao CW, Pencina KM, Massaro JM, Benjamin EJ, Levy D, Vasan RS, et al. Cross-sectional relations of arterial stiffness, pressure pulsatility, wave reflection, and arterial calcification. *Arterioscler Thromb Vasc Biol* 2014;34:2495–500.
28. Chirinos JA, Segers P, Gillebert TC, Gupta AK, de Buyzere ML, de Bacquer D, et al. Arterial properties as determinants of time-varying myocardial stress in humans. *Hypertension* 2012;60:64–70.
29. Mitchell GF, Conlin PR, Dunlap ME, Lacourcière Y, Arnold JM, Ogilvie RI, et al. Aortic diameter, wall stiffness, and wave reflection in systolic hypertension. *Hypertension* 2008;51:105–11.
30. Mitchell GF, Lacourcière Y, Ouellet JP, Izzo JL Jr, Neutel J, Kerwin LJ, et al. Determinants of elevated pulse pressure in middle-aged and

- older subjects with uncomplicated systolic hypertension: the role of proximal aortic diameter and the aortic pressure-flow relationship. *Circulation* 2003;108:1592–8.
31. Westerhof N, Sipkema P, van den Bos GC, Elzinga G. Forward and backward waves in the arterial system. *Cardiovasc Res* 1972;6:648–56.
 32. Westerhof N, Westerhof BE. Wave transmission and reflection of waves: “The myth is in their use.” *Artery Res* 2012;6:1–6.
 33. Kobayashi S, Yano M, Kohno M, Obayashi M, Hisamatsu Y, Ryoke T, et al. Influence of aortic impedance on the development of pressure-overload left ventricular hypertrophy in rats. *Circulation* 1996;94:3362–8.
 34. Hashimoto J, Westerhof BE, Westerhof N, Imai Y, O’Rourke MF. Different role of wave reflection magnitude and timing on left ventricular mass reduction during antihypertensive treatment. *J Hypertens* 2008;26:1017–24.
 35. Hori M, Inoue M, Kitakaze M, Tsujioka K, Ishida Y, Fukunami M, et al. Loading sequence is a major determinant of afterload-dependent relaxation in intact canine heart. *Am J Physiol* 1985;249:H747–54.
 36. Kohno F, Kumada T, Kambayashi M, Hayashida W, Ishikawa N, Sasayama S. Change in aortic end-systolic pressure by alterations in loading sequence and its relation to left ventricular isovolumic relaxation. *Circulation* 1996;93:2080–7.
 37. Chirinos JA, Segers P, Rietzschel ER, de Buyzere ML, Raja MW, Claessens T, et al. Early and late systolic wall stress differentially relate to myocardial contraction and relaxation in middle-aged adults: the Asklepios study. *Hypertension* 2013;61:296–303.
 38. Gillebert TC, Lew WY. Influence of systolic pressure profile on rate of left ventricular pressure fall. *Am J Physiol* 1991;261:H805–13.
 39. Gillebert TC, Sys SU, Brutsaert DL. Influence of loading patterns on peak length-tension relation and on relaxation in cardiac muscle. *J Am Coll Cardiol* 1989;13:483–90.
 40. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, et al. Recommendations for improving and standardizing vascular research on arterial stiffness: a scientific statement from the American Heart Association. *Hypertension* 2015;66:698–722.
 41. Brutsaert DL, Sys SU. Relaxation and diastole of the heart. *Physiol Rev* 1989;69:1228–315.
 42. Gillebert TC, Leite-Moreira AF, De Hert SG. Load dependent diastolic dysfunction in heart failure. *Heart Fail Rev* 2000;5:345–55.