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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;*■■*:*■■–■■)

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 HF[5] 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 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.[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] × 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