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Authors

Brumback, Lyndia C
Andrews, Leah IB
Jacobs, David R
et al.

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The association between indices of blood pressure waveforms (PTC1 and PTC2) and incident heart failure

Lyndia C. BRUMBACK[a], **Leah I.B. ANDREWS**[a], **David R. JACOBS Jr.**[b], **Daniel A. DUPREZ**[c], **Sanjiv J. SHAH**[d], **Cynthia M. DOUGHERTY**[e], **Julie O. DENENBERG**[f], **Matthew A. ALLISON**[f]

[a]Department of Biostatistics, School of Public Health, University of Washington, Seattle, Washington

[b]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota

[c]Cardiovascular Division, Department of Medicine, School of Medicine, University of Minnesota, Minneapolis, Minnesota

[d]Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois

[e]Department of Biobehavioral Nursing and Health Informatics, University of Washington School of Nursing, Department of Medicine, Division of Cardiology, Seattle, Washington

[f]Department of Family Medicine and Public Health, University of California San Diego, La Jolla, California

Abstract

Objectives: The radial artery pulse waveform is a continuous measure of pressure throughout the cardiac cycle and thus can provide more information than just systolic and diastolic blood pressures. New indices based on a Windkessel model of the waveform, PTC1 and PTC2, are related to arterial compliance and add information for prediction of incident cardiovascular disease (coronary heart disease, stroke, myocardial infarction) but their association with heart failure is unknown.

Methods: Among 6229 adults (mean age 62 years) from 4 race/ethnic groups who were initially free of clinical cardiovascular disease and heart failure in 2000–2002, we evaluated the associations of baseline PTC1 and PTC2 with incident heart failure.

Results: Mean ± standard deviation PTC1 and PTC2 were 394 ± 334 and 94 ± 46 milliseconds, respectively. During a median of 15.7 years follow-up, there were 357 heart failure events (148 with reduced, 150 with preserved, and 59 with unknown ejection fraction). After adjustment for traditional risk factors, the hazard ratio for heart failure per 1 standard deviation higher PTC2 was 0.73 (95% confidence interval: 0.63, 0.85). Higher PTC2 was also significantly associated with lower risk of heart failure with reduced ejection fraction (hazard ratio = 0.67; 95% confidence

Correspondence to: Lyndia C. Brumback, PhD, Department of Biostatistics, School of Public Health, University of Washington Box 354922, Seattle, Washington 98115. lynb@uw.edu. phone: 206-897-1942.

interval: 0.56, 0.80). There was no evidence of a significant association between PTC2 and heart failure with preserved ejection fraction or between PTC1 and heart failure.

Conclusions: The PTC2 measure of the radial artery pulse waveform may represent a novel phenotype related to heart failure, especially heart failure with reduced ejection fraction.

Condensed Abstract:

Among 6229 older adults from 4 race/ethnic groups, initially free of heart failure in 2000–2002, mean±standard deviation PTC2 was 94±46 milliseconds. During a median 15.7 years follow-up, there were 357 heart failure events (148 heart failure with reduced ejection fraction,150 with preserved ejection fraction). After adjustment for traditional risk factors, 1 standard deviation higher PTC2 was significantly associated with 27% (95% confidence interval: 15%, 37%) lower risk of heart failure and 33% (20%,44%) lower risk of heart failure with reduced ejection fraction. The PTC2 measure of the radial artery pulse waveform may represent a novel phenotype related to heart failure.

Keywords

Arterial compliance; Radial artery pulse waveform Windkessel model

Introduction

Heart failure (HF) imparts a major health-economic burden [1,2]. Among patients with HF, morbidity is high, hospital admissions are common, and survival is poor. Moreover, HF places great demands on patients, their caregivers, and healthcare systems. Early detection of predisposing factors for new onset of HF will be helpful for early diagnosis and to develop more effective preventive strategies.

For the current study, our objective was to investigate the association between recently developed indices of the radial artery pulse waveform and incident HF. This waveform is a continuous measure of pressure throughout the cardiac cycle and thus can provide more information than just systolic or diastolic blood pressures (BP), which are the 2 extreme pressures of the BP waveform. Indeed, reflection magnitude and late central systolic hypertension are indices of the waveform that have been shown to be associated with incident HF, independent of systolic and diastolic BP and other cardiovascular risk factors [3,4]. Reflection magnitude and late central systolic hypertension are obtained by transforming the radial artery pulse waveform into the aortic (central) waveform and rely on propagation wave theory [3,5].

A complementary approach to summarizing the pressure waveform relies on the Windkessel theory [6–9] and yields indices C1 and C2, which are sometimes called large and small arterial compliance. C1 and C2, as computed by Hypertension Diagnostics Inc. (HDI), have been shown to be associated with incident HF [10]. However, these C1 and C2 are functions of the waveform and participant characteristics including systolic and diastolic BPs, which makes it difficult to discern their added value beyond the pressure extremes, and they are difficult to replicate. We recently developed novel indices of the waveform, PTC1 and PTC2, which are based on the Windkessel theory and related to arterial compliance (inverse of

arterial stiffness) but are different from Hypertension Diagnostics Inc.'s C1 and C2 in 3 important ways: 1) they are neither explicit functions of blood pressure nor are they affected by arbitrary linear calibration of the pulse waveform to blood pressure, 2) they are derived from a clearly defined portion of the arterial waveform, and 3) they can be computed from waveforms obtained with a suitable device using free, standard software [11]. The indices are named PTC1 and PTC2 because they are analogous to C1 and C2, are related to Compliance, and share similarities with Time Constants derived from Pressure profiles. Higher PTC1 and PTC2 have been shown to be associated with lower risk of cardiovascular disease (specifically, coronary heart disease, myocardial infarction, stroke) [11], but their associations with heart failure have not yet been evaluated.

In this paper, we report the association of both PTC1 and PTC2 with incident HF in the Multi-Ethnic Study of Atherosclerosis [12] to gain a more complete understanding of the association between BP waveforms and HF. We also explore their association with HF subtypes i.e. HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF).

Methods

Sample, Covariates, and Events

Participants for this analysis were from the Multi-Ethnic Study of Atherosclerosis (MESA), a prospective cohort study of cardiovascular disease [12]. At the first MESA exam in 2000–2002, 6814 older adults who identified themselves as White/Caucasian, Black/African American, Hispanic, or Chinese American, and were free of clinically apparent cardiovascular disease, were enrolled at six communities in the United States. We used radial artery pulse waveforms and other covariates from the first exam, as well as follow-up for events since the first exam.

Information about cardiovascular risk factors and medication use was obtained with standardized questionnaires. Resting blood pressure was measured 3 times with a Dinamap oscillometer (Critikon™, Tampa, FL), and the average of the last 2 measurements were used to define systolic and diastolic BP. Serum cholesterol, high density-lipoprotein cholesterol, and glucose were measured after a 12-hour fast. Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dL or hypoglycemic medication use [13]. Physical activity was measured as total intentional exercise, in met-minute/week [14]. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula [15].

Events through 2017 were obtained through questioning of participants by trained study professionals approximately annually, followed by medical record retrieval and abstraction, and then adjudication by clinicians. HF was defined as symptoms, such as shortness of breath or edema, plus diagnosis of HF by a physician and documented medical treatment for HF. Subtype of HF based on left ventricular ejection fraction (LVEF) was defined for participants who had an adjudicated diagnosis of HF and an evaluation of LVEF by echocardiography at the time of HF diagnosis that could be obtained from review of medical records. HF with preserved EF, HFpEF, was defined as LVEF ≥ 45%, while HF with reduced EF, HFrEF, was defined as HF with LVEF<45%, consistent with other studies [16–19].

Pressure Waveforms, PTC1, and PTC2

Stored waveforms were available from the first MESA exam for 6334 participants. Pressure waveforms were collected with the Pulsewave CR-2000 System and Arterial Pulse Wave Sensor (HDI, Hypertension Diagnostics Inc. Eagan, Minnesota, USA). The device, consisting of a tonometer which is held in place on the radial artery by a wrist stabilizer, samples waveforms at 200 Hertz for a total of 30 seconds (approximately 30 cardiac cycles). PTC1 and PTC2 were computed from the stored pressure waveforms as previously described [11]. Briefly, pressure decay during a single cardiac cycle was described by the following Windkessel model:

$$P(t) = a_0 + a_1\exp(-a_2 t) + a_3\exp(-a_4 t)\cos(a_5 t + a_6)$$

where P(t) is the pressure at time t during decay; t=0 represents time of maximum pressure; and $a_0, a_1, \ldots, a_6$ are parameters estimated by nonlinear least squares. PTC1 and PTC2 corresponding to a single cardiac cycle were then computed as: PTC1 $= \frac{2\,a_4\left[(a_2 + a_4)^2 + (a_5)^2\right]}{a_2\left[2a_4 + a_2\right]\left[(a_4)^2 + (a_5)^2\right]}$ and PTC2$= \frac{1}{2a_4 + a_2}$

Figure 1 shows an observed waveform corresponding to a cardiac cycle and fitted pressure decay based on the Windkessel model. We used the median of each PTC1 and PTC2 across all cardiac cycles for each participant. The reproducibility, as measured by the Spearman correlation coefficient between measurements from 131 participants with two sets of 30 second waveform data collected on the same day by the same technician, was 0.75 for PTC1 and 0.87 for PTC2; for comparison, the reproducibility of systolic and diastolic BPs from those same participants were 0.89 and 0.85, respectively [11].

Statistical analysis

Cox proportional hazard models were used to evaluate the association between first HF event and PTC1 and PTC2, separately. Participants without HF were censored at their time of last follow-up or death. For analysis of subtypes of HF, e.g. HFpEF and HFrEF, participants without the known subtype of interest were censored at the time of other known subtype or HF event if LVEF was not available to distinguish subtype, last follow-up, or death. This is consistent with handling of competing events [20]. For each event, we considered 2 models: Model 1 included adjustment for age, gender, race/ethnicity, and clinical site; Model 2 included further adjustment for systolic BP, diastolic BP, heart rate, use of anti-hypertensive medication, high density lipoprotein cholesterol, total cholesterol, use of cholesterol-lowering medication, estimated glomerular filtration rate, smoking status, diabetes mellitus, exercise, body mass index, socioeconomic status (education), and access to healthcare (health insurance). We explored whether the association between HF and each of PTC1 and PTC2 differed by race/ethnicity but found no evidence of modification. Since there were many deaths with no prior HF (625 among 6229 participants) which could lead to bias due to informative censoring [20], we also evaluated the association with death without prior HF where death is an event rather than reason for censoring and with the composite (death or HF); the associations were consistent with associations with HF. We used

cumulative incidence functions to visually describe the association between quartiles of PTC2 and HF and also death without prior HF. We restricted our analysis to participants with complete information on pressure waveforms (PTC1 and PTC2), follow-up for events, and baseline covariates. A two-sided p-value of less than 0.05 was considered statistically significant.

Results

Among the 6814 MESA participants, PTC1 and PTC2 were computed from 6334 available waveforms. Covariates and information about events were also available for 6229. Among the participants with complete information, 38% were White/Caucasian, 12% Chinese American, 27% Black/African American, and 23% Hispanic (Table 1). The mean age at baseline was 62 years (standard deviation = 10 years), and 52% were female. The mean (standard deviation) was 394 (334) milliseconds for PTC1 and 94 (46) milliseconds for PTC2.

There were 357 incident HF events from the 6229 participants with a median follow-up of 15.7 years (interquartile range: 11.8 years, 16.5 years). Cumulative incidence of HF (and also death without prior HF) was graded across quartiles of PTC2 (Figure 2). PTC2 was associated with HF but there was no evidence of a significant association between PTC1 and HF (Table 2). With adjustment for age, gender, race/ethnicity and clinical site (Model 1), a 1-SD higher PTC2 was associated with a 29% lower risk (hazard ratio (HR) = 0.71, 95% confidence interval (CI): 0.62, 0.81, P<0.0001). After further adjustment (Model 2), higher PTC2 remained significantly associated with a lower risk of incident HF (HR = 0.73, 95% CI: 0.63, 0.85, P < 0.0001. Specifically, a 1-SD higher PTC2 was associated with a 27% lower risk.

Of the 357 HF events, 148 (41%) were HFrEF, 150 (42%) were HFpEF, and 59 did not have known EF at the time of HF diagnosis. PTC2 was associated with HFrEF; a 1 SD higher PTC2 was associated with a 33% (95% CI: 20%, 44%) lower risk of HFrEF after adjustment for traditional risk factors. There was no evidence of a significant association between PTC2 and HFpEF after adjustment for traditional risk factors, or between PTC1 and either subtype (Table 2).

Discussion

In this relatively large multi-ethnic cohort of older adults free of overt cardiovascular disease in 2000–2002 recruited from 6 communities across the United States, higher arterial compliance, as measured by PTC2, was associated with lower incidence of HF. Higher PTC2 was also significantly associated with lower incidence of HFrEF. The direction and magnitude of the association of PTC2 with HFpEF was similar but not statistically significant.

We did not find an association between PTC1 and HF. While the hazard ratio estimates were close to 1 (no association), the confidence intervals were wide so we cannot rule out an association. Both PTC1 and PTC2 are functions of the pressure waveform. Some have argued that C1 and C2, which are analogous to PTC1 and PTC2, represent large and small

artery compliance or “vessel capacitive compliance” and “combined resonance and reflective properties of compliant vessels”, respectively [7]. It is possible that compliance of the small arteries is a greater factor in heart failure than the larger arteries. As shown in Brumback et al. [11], PTC1 appears to be less reproducible than PTC2. It is also possible that measurement error could have contributed to bias and/or lack of statistical significance of the association between PTC1 and HF.

We defined HFrEF and HFpEF using a LVEF cutoff of 45% consistent with other recent studies [16–19]. When we defined HFrEF as LVEF<40% and HFpEF as LVEF>50% consistent with the AHA guidelines [5], we obtained similar conclusions. However, of the 357 events, 62 (about 20%) had an LVEF between 40% and 50%, 13 had an LVEF of exactly 45%, and 59 had EF unknown at the time of HF. It is worthwhile for studies to explore the sensitivity of conclusions to the definition of HFrEF and HFpEF.

Our results complement other studies of HF and pressure waveforms. They are consistent with Chirinos et al. [3–4] who found a significant association between HF and indices of the waveform based on reflection wave theory. Chirinos et al. found a significant association between incident HF and reflection magnitude in 5960 MESA participants during median follow-up of 7.6 (117 HF events) [3], and between HF and late systolic hypertension in 6124 MESA participants during 8.5 years of follow-up (135 HF events) [4]. Redheuil et al. [21] studied the association between incident HF and ascending aortic distensibility using magnetic resonance imaging at baseline among 3,675 MESA participants during 8.5 years of follow-up (88 HF events). Distensibility was associated with HF but not after adjustment for traditional cardiovascular risk factors. Information about subtype of HF was not available in Chirinos et al [3–4] or Redheuil et al. [21]. Caughey et al [22] evaluated the association between incident HF and echocardiographic arterial compliance, defined by the ratio of echocardiographic velocity time integral (a surrogate for stroke volume) and brachial arterial pulse pressure, during 13 years follow-up in 1887 Black adults in the United States (322 HF events) in the Atherosclerosis Risk in Communities (ARIC) study. They found higher echocardiographic arterial compliance was associated with lower risk of HF. Pandey et al. [16] examined the association of carotid-femoral pulse wave velocity at baseline with the incidence of HF, HFrEF and HFpEF during 11.4 years follow-up in 2290 participants (390 HF events, 145 HFrEF, 162 HFpEF) in the Health, Aging, and Body Composition (ABC) study. They did not find an association between arterial stiffness, as measured by pulse wave velocity and HF or its subtypes HFrEF and HFpEF after adjustment for traditional cardiovascular risk factors. Thus, our study adds to the literature on HF, pressure waveforms, and arterial compliance.

This is the first study to evaluate the association between both PTC1 and PTC2 with incident HF and to explore the association between radial artery pressure waveforms and HFrEF and HFpEF. Radial artery pulse waveforms are relatively easy to collect, requiring a simple tonometer. Furthermore, standard software is freely available to estimate PTC1 and PTC2. Code to compute PTC1 and PTC2 is available via GitHub: github.com/LBrumback/PTC1andPTC2. Other strengths of our study include a relatively large sample of adults with different race/ethnicities, standardized data collection across six communities, and a cohort design so we know the PTC1 and PTC2 measurements precede the HF event.

There are some limitations of our study. We did exclude participants with missing data which can result in bias and/or less precision. However, our resulting complete sample still included over 90% (6229 of 6814) of participants. While we considered many covariates, there may be other unmeasured covariates which could explain the observed association between PTC2 and HF. PTC1 and PTC2 are based on the theoretical Windkessel model and have been compared to HDI's C1 and C2 [11] but they have not been compared to other measures of vascular compliance. It would be useful to compare PTC1 and PTC2 to pulse wave velocity but the latter is not available in MESA.

In summary, we show that higher arterial compliance, as measured by PTC2, is associated with lower incidence of HF among older adults. The radial arterial pulse waveform, especially PTC2, may represent an important phenotype for HF. Validation of our findings in other population-based studies is warranted.

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Abbreviations:

BP	blood pressure
CI	confidence interval
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
LVEF	left ventricular ejection fraction
MESA	Multi-Ethnic Study of Atherosclerosis
SD	standard deviation

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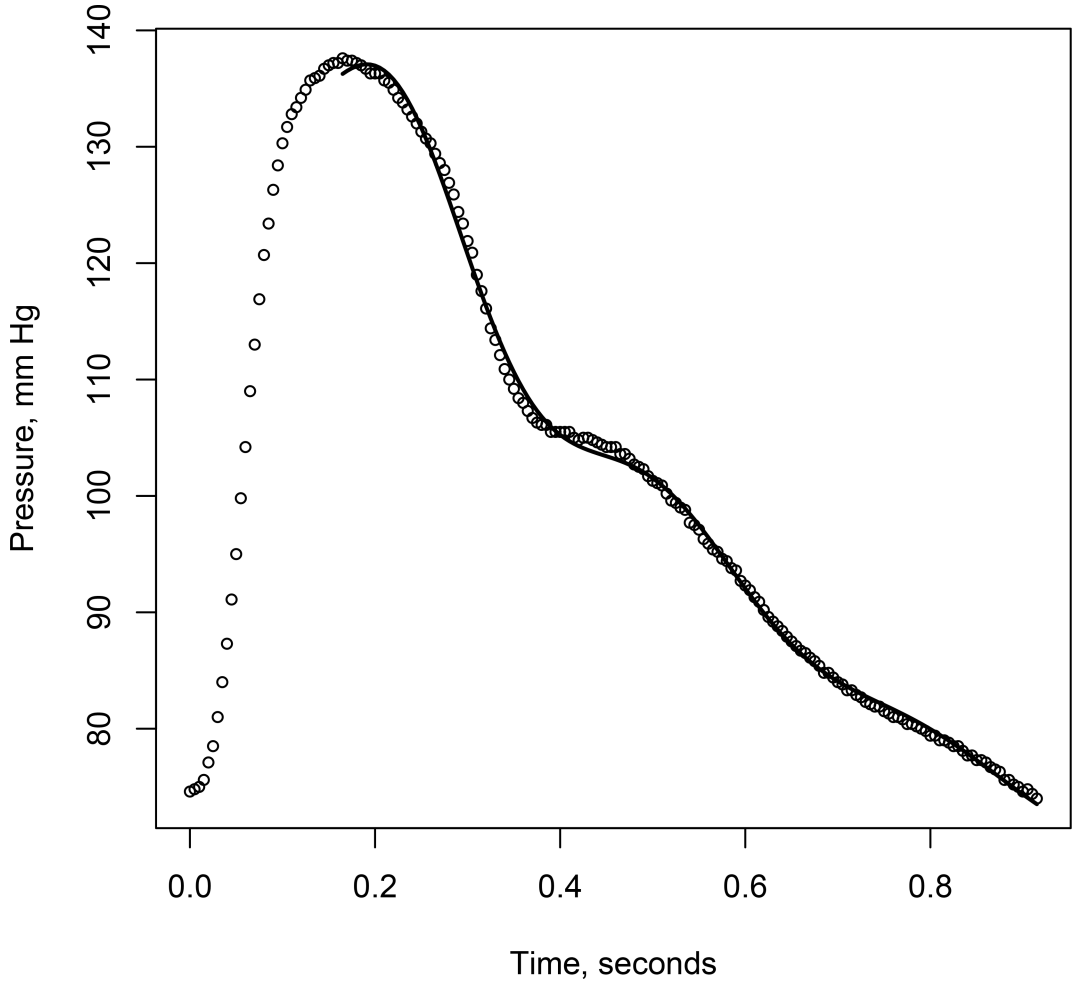

Figure 1:
Observed pressure waveform (points) and Windkessel model of pressure decay (line). PTC1 = 571 milliseconds. PTC2 = 107 milliseconds.

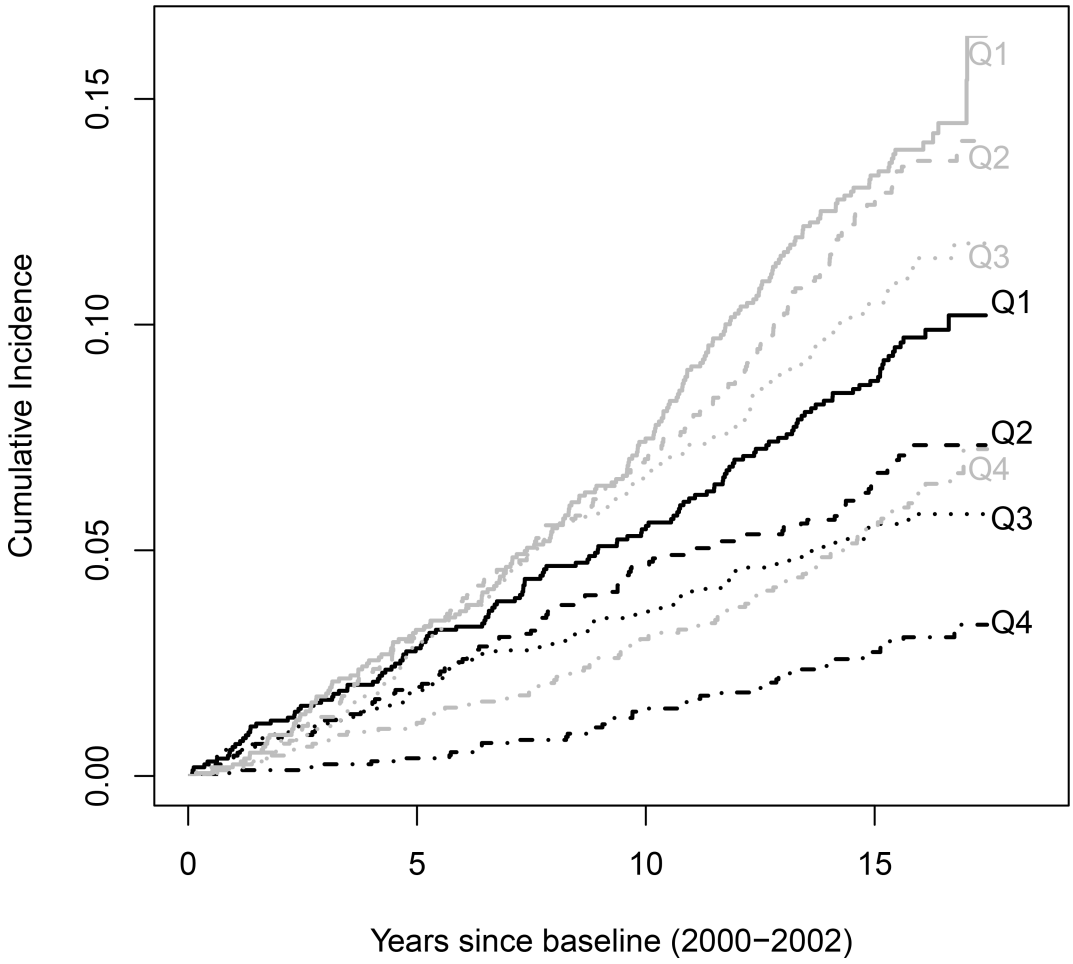

Figure 2:
Cumulative incidence of heart failure (black) and the competing event death before heart failure (gray) by quartiles of PTC2. Q1: PTC2 < 64 ms; Q2: 64 ms< PTC2 <85 ms; Q3: 85 ms < PTC2 < 113 ms; Q4: PTC2 > 113 ms. (Multi-Ethnic Study of Atherosclerosis 2000–2002, with median follow-up of 15.7 years)

Table 1:

Baseline Characteristics (Multi-Ethnic Study of Atherosclerosis, 2000–2002). N=6229

Characteristic	mean ± SD or (%)
Age (years)	62 ± 10
Gender, Female	3256 (52%)
Race/Ethnicity	
White/Caucasian	2365 (38%)
Chinese American	764 (12%)
Black/African American	1678 (27%)
Hispanic	1422 (23%)
Clinic/Community	
Wake Forest University	1031 (17%)
Columbia University	1006 (16%)
Johns Hopkins University	828 (13%)
University of Minnesota	985 (16%)
Northwestern University	1102 (18%)
University of California Los Angeles	1277 (21%)
Education	
Less than HS	1135 (18%)
Completed HS/GED	1131 (18%)
Some College	1770 (28%)
Bachelor's Degree	1069 (17%)
Graduate/Professional School	1124 (18%)
Health Insurance	5656 (91%)
Heart Rate (Beats/Min)	63 ± 10
Systolic Blood Pressure (mmHg)	126 ± 21
Diastolic Blood Pressure (mmHg)	72 ± 10
Use of Antihypertension Medication	2304 (37%)
Body Mass Index (kg/m^2)	28 ± 5
Total Intentional Exercise (met-min/wk)	1537 ± 2296
Cigarette Smoking	
Never	3162 (51%)
Former	2270 (36%)
Current	797 (13%)
Total Cholesterol (mg/dL)	194 ± 36
HDL Cholesterol (mg/dL)	51 ± 15
Use of Cholesterol-Lowering Medication	998 (16%)
Estimated glomerular filtration rate ($ml/min/1.73\ m^2$)	78 (16)
Diabetes Mellitus	787 (13%)
PTC1 (ms)	394 ± 334
PTC2 (ms)	94 ± 46

Table 2:

Association of pressure waveform (PTC1 and PTC2) with heart failure. (Multi-Ethnic Study of Atherosclerosis 2000–2002, with median follow-up of 15.7 years). Hazard ratios, per standard deviation [a]. N = 6229

	Heart Failure HFrEF, HFpEF, and HF without known EF 357 events			Heart Failure with Reduced Ejection Fraction (HFrEF) 148 events			Heart Failure with Preserved Ejection Fraction (HFpEF) 150 events		
	Hazard Ratio	**95% CI**	**p-value**	**Hazard Ratio**	**95% CI**	**p-value**	**Hazard Ratio**	**95% CI**	**p-value**
Model 1 [b]									
PTC1	0.95	0.83, 1.08	0.43	1.02	0.85, 1.23	0.83	0.90	0.72, 1.12	0.35
PTC2	0.71	0.62, 0.81	<0.0001	0.67	0.57, 0.78	<0.0001	0.82	0.65, 1.03	0.09
Model 2 [c]									
PTC1	1.02	0.90, 1.17	0.72	1.07	0.90, 1.28	0.45	0.99	0.79, 1.24	0.93
PTC2	0.73	0.63, 0.85	<0.0001	0.67	0.56, 0.80	<0.0001	0.88	0.69, 1.11	0.27

PTC1 and PTC2, indices of pressure waveforms; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction. CI, confidence interval. Ejection fraction was not available at the time of HF for 59 participants.

[a] Standard deviations: PTC1, 334 milliseconds; PTC2, 46 milliseconds

[b] Model 1: adjusted for age, gender, race/ethnicity and clinical site.

[c] Model 2: Model 1 with additional adjustment for baseline systolic blood pressure, diastolic blood pressure, heart rate, use of anti-hypertensive medication, high-density lipoprotein cholesterol, total cholesterol, use of cholesterol-lowering medication, estimated glomerular filtration rate, smoking status, diabetes mellitus, exercise, body mass index, education, and health insurance