Practice of Epidemiology

PTC1 and PTC2: New Indices of Blood Pressure Waveforms and Cardiovascular Disease

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Systolic and diastolic blood pressures provide information about cardiovascular disease (CVD) but are only extremes of the pressure waveform during the cardiac cycle. We developed summaries of the pressure decay, called PTC1 and PTC2, that are related to arterial compliance and to an existing proprietary summary that has been shown to predict CVD. We derived the summaries from a Windkessel model (consisting of a decaying exponential plus a dampened cosine, with an intercept so they are independent of calibration with blood pressure, unlike the proprietary measures), and we estimated them using nonlinear least squares with standard, free software. Among 6,228 adults from the Multi-Ethnic Study of Atherosclerosis, initially free of CVD in 2000–2002, mean PTC2 was 94 (standard deviation, 46) milliseconds. During median 15-year follow-up, there were 911 CVD events (including 609 incidents of coronary heart disease and 270 strokes). One-standard-deviation higher PTC2 was associated with 17% (95% confidence interval: 10, 24) lower CVD risk, after adjustment for traditional risk factors. Results were similar for PTC1. PTC1 and PTC2 are relatively straightforward to compute and add information beyond traditional risk factors for prediction of CVD. Our work enables others to replicate and extend our results with waveforms from any suitable device.

blood pressure waveform; cardiovascular disease; PTC1; PTC2

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDI, Hypertension Diagnostics Inc.; MESA, Multi-Ethnic Study of Atherosclerosis; SBP, systolic blood pressure.

The pressure waveform is a continuous measure of blood pressure throughout the entire cardiac cycle. It was the first noninvasive measure of blood pressure (1, 2), preceding sphygmomanometry, but devices to record and analyze the waveform were not readily available in the late 1800s. The advent of sphygmomanometry and its ease of use led to systolic and diastolic blood pressures (SBP and DBP), the pressure extremes during the cardiac cycle, becoming the standard indices of blood pressure. Devices to collect the waveform are now more readily available, and other indices (e.g., C2, systolic and diastolic time constants, augmentation index, pulse wave velocity) have been found to add information about cardiovascular disease (CVD) beyond SBP and DBP (3–18).

C2 and a related measure, C1, are based on a “Windkessel” model (1, 19–22) of circulation that treats the arterial system as the Windkessel (German for air chamber) that

smooths intermittent blood flow from the ventricle and creates continuous blood flow to the peripheral vascular bed, like air chambers that were placed in German fire engines between the water pump and outflow hose to smooth oscillations in the pumped water and create a continuous water jet from the hose. The Windkessel model is a mechanistic, nonlinear model that includes decaying exponential and dampened cosine terms. Per Windkessel theory, C1 and C2 are related to compliance of the arteries. Higher C2, as computed by a proprietary device (Hypertension Diagnostics, Inc. (HDI), Minneapolis, Minnesota), has been found to be independently associated with lower risk of incident CVD (14, 15) in the Multi-Ethnic Study of Atherosclerosis (MESA), an ongoing cohort study of CVD (23).

In MESA, waveforms were collected at baseline (exam 1) with the HDI device and approximately 10 years later (exam 5) with a different device, so HDI’s C1 and C2 were

available from exam 1 but not exam 5. We were therefore motivated to derive C1- and C2-like indices, which we call PTC1 and PTC2, from a Windkessel model (including an intercept) of pressure decay for the overarching goals of investigating change in pressure waveforms and to better understand the association between waveforms and CVD. Using waveform data from MESA participants at exam 1, we evaluated PTC1 and PTC2 for feasibility, reproducibility, and association with CVD. To put our results into context, we provide analogous results for HDI's measures.

METHODS

Sample, covariates, and events

At MESA exam 1 in 2000–2002, 6,814 older adults who identified themselves as white, black, Hispanic, or Chinese and who were free of clinically apparent CVD were enrolled in 6 US communities/clinics (23). Participants had several procedures, including a pressure waveform measurement. A subset was selected, for quality-control purposes, to have 2 measurements of pressure waveforms collected on the same day. We have described the subsample selection (24); 131 participants had repeat measurements performed by the same technician. Participant flow is shown in Figure 1.

Ascertainment of covariates has been described (14, 25). SBP and DBP were collected as part of 1) the main MESA exam, and 2) the waveform measurement using the HDI system. The blood pressures in the main exam were the average of the second and third assessments sitting at rest, using a Dinamap oscillometer (Critikon, Tampa, Florida). HDI used a different oscillometer and a single assessment, done supine at rest. For the present study, SBP and DBP from HDI were used for the reproducibility analyses; SBP and DBP from the main exam were used for all other analyses.

Events through 2016 were obtained through questioning of participants by trained study professionals approximately annually, followed by medical record abstraction and adjudication by clinicians. We used MESA's definition of all CVD (coronary heart disease (CHD), stroke, or CVD death). Details about events are available at the MESA website (26).

Pressure waveforms

Pressure waveforms were collected with the Pulsewave CR-2000 System and Arterial Pulse Wave Sensor (HDI), consisting of a wrist stabilizer, oscillometric blood pressure cuff, and tonometer. Certified technicians used the tonometer, which was held in place by the wrist stabilizer, to measure waveforms from the radial artery. The waveforms were sampled at 200 Hertz for 30 seconds. For 6,336 participants (14), the system produced the 30 seconds of data, which were linearly calibrated using SBP and DBP from the oscillometric cuff, and summary measures (C1, C2, systemic vascular resistance). Pressure waveforms were not available for participants without summary measures, and 2 participants with summary measures did not have waveforms with matching identification numbers. Thus, waveforms were available from 6,334 participants (Figure 1).

The HDI device produces waveform data for a participant over several cardiac cycles (Figure 2), but summary measures are derived from beat-specific waveforms (i.e., the common shape that is repeated about every second and represents pressure during a cardiac cycle). Two beat-specific waveforms from each of 2 participants are shown in Figure 3; features such as 1 or more bumps during decay are discernible. The bump during decay (e.g., around 0.45 seconds in Figure 3A) is called the “dicrotic notch” and is important for HDI's C1 and C2. We obtained beat-specific waveforms by identifying the steep rises to maximum pressures in the 30-second recordings, excluding beat-specific waveforms that were greater than 2 seconds or less than 0.5 seconds. This resulted in a total of 202,235 beat-specific waveforms from 6,334 participants (or 198,152, excluding 4,083 beat-specific waveforms from 131 participants for quality control purposes), which is appropriate for the number of participants, sampling time, and average heart rate.

HDI's summaries of the pressure waveform: C1, C2, RC1, RC2

HDI (22) uses the modified Windkessel model:

$$P(t) = a_1 \exp(-a_2 t) + a_3 \exp(-a_4 t) \cos(a_5 t + a_6) \quad (1)$$

where $P(t)$ is the value of the beat-specific waveform (which has been calibrated to SBP and DBP) at time t during diastole; $t = 0$ represents the start of diastole, defined by a range of values near the “dicrotic notch”; $\exp$ is the exponential function; $\cos$ is the cosine function; and $a_1, \dots, a_6$ are parameters.

With estimates of a_2, a_4 , and a_5 , as well as systemic vascular resistance (R), which HDI estimates using information from the waveform and the participant's height, weight, and age, HDI computes:

$$C1 = \frac{2 a_4 [(a_2 + a_4)^2 + (a_5)^2]}{R a_2 [2a_4 + a_2] [(a_4)^2 + (a_5)^2]} \quad \text{and}$$

$$C2 = \frac{1}{R [2a_4 + a_2]}$$

Thus, HDI's C1 and C2 are computed from a participant's waveform and other characteristics, but C1 and C2 each multiplied by R (which we write as RC1 and RC2) are summaries of only the waveform (calibrated to SBP and DBP).

HDI's C1 and C2 are estimated from beat-specific waveforms, but HDI outputs only one estimate of C1, C2, and R from each participant's data, which could include about 30 beat-specific waveforms given that data are collected for a total of 30 seconds. Per Bratelli et al. (22), HDI's C1, C2, and R values are a weighted average using about 5–10 “representative” beat-specific waveforms.

The HDI system outputs C1 in units of mL/mm Hg $\times$ 10, C2 in units of mL/mm Hg $\times$ 100, and R in units of

Figure 1. Participant flow, Multi-Ethnic Study of Atherosclerosis (MESA), United States, 2000–2002. Median follow-up, 15 years.

dynes·seconds·cm^{−5}. We multiplied each of C1 and C2 by R and used unit conversions to obtain RC1 and RC2 in milliseconds.

Our new indices of pressure waveforms: PTC1, PTC2

To derive our indices, we use the Windkessel model:

$$P(t) = a_0 + a_1 \exp(-a_2 t) + a_3 \exp(-a_4 t) \cos(a_5 t + a_6) \quad (2)$$

where $P(t)$ is the value of the waveform at time t during decay; $t = 0$ represents time of maximum pressure (latest time of maximum if there is not a unique time); and $a_0, a_1, \dots, a_6$ are parameters to be estimated.

We define PTC1 and PTC2 thus:

$$\text{PTC1} = \frac{2a_4[(a_2 + a_4)^2 + (a_5)^2]}{a_2[2a_4 + a_2][(a_4)^2 + (a_5)^2]} \quad \text{and} \quad \text{PTC2} = \frac{1}{2a_4 + a_2}$$

Figure 2. Observed waveform data from one participant (10 seconds of a 30-second recording), Multi-Ethnic Study of Atherosclerosis, United States, 2000–2002.

One might recognize that equation 1 and equation 2 are not identifiable because different combinations of a_3 , a_6 , and the sign of a_5 can result in the same fit. For example, $\{a_3, a_5, a_6\} = \{1, 2, \pi/2\}$ leads to the same fit as $\{-1, -2, \pi/2\}$, $\{1, -2, \pi/2 + \pi\}$, and $\{-1, 2, \pi/2 + \pi\}$ due to cosine properties. Theoretically, we do not need to use parameter constraints to ensure identifiability of PTC1 and PTC2 because they depend on only a_2 , a_4 , and the absolute value of a_5 ($|a_5|$). However, with finite sampling (200 Hertz with HDI's device), a_5 and $a_5 \pm 200 \times 2\pi k$ ($k = 1, 2, \dots$) result in the same fit and different PTC1, so we constrain $|a_5| < 200\pi$.

We obtain least squares estimates for $a_0, a_1, \dots, a_6$ using the statistical software R (R Foundation for Statistical Computing, Vienna, Austria) (27), not to be confused with systemic vascular resistance R. Specifically, we use R's `nls` function with the “conditional linearity” algorithm and a relative offset convergence criterion of $1e^{-5}$ (28). Equation 2 is a nonlinear regression model which, unlike a linear model, can be challenging to fit because it requires an iterative procedure that can fail to converge for various reasons, including inadequate starting values. Our approach exploits

the fact that conditional on a_2, a_4, a_5 , and a_6 , equation 2 is linear in the remaining parameters, which makes model fitting easier, in part because starting values for only the nonlinear parameters are required. We use a grid of values defined by $a_2 = \{0.5, 1.5, 2.5, 3.5\}$; $a_4 = \{1, 3, 5, 7, 9\}$; $a_5 = \{10, 20, 30\}$; and $a_6 = \{\pi/4, \pi/2, 3\pi/4\}$. Our R script is available at the first author's GitHub repository (29).

We used the median of PTC1 and median of PTC2 from all beat-specific waveforms from a participant's recording to create one PTC1 and PTC2 per participant. We used the median (instead of the mean) because it is less sensitive to outliers such as estimates from beat-specific waveforms that are unusual or where the fitting procedure converges to a local minimum.

Additional statistical analysis

We summarized the feasibility of PTC1 and PTC2 by the proportion of participants with waveform data where PTC1 and PTC2 were obtained, and reproducibility by Bland-Altman plots (30), and by both Pearson and Spearman correlation coefficients, given that Spearman is less sensitive to outliers. We also summarized the relationships between measures (PTC1, PTC2, RC1, RC2, C1, C2, SBP, DBP, and heart rate) with correlation coefficients.

We evaluated the association between the measures and CVD (as well as its components CHD and stroke separately) with Cox proportional hazards models (31). Model 1 was adjusted for age category, sex, race/ethnicity, and clinical site. To evaluate whether the waveform indices add information about events beyond traditional risk factors, we evaluated their association with further adjustment for SBP, DBP, heart rate, use of antihypertensive medication, high-density lipoprotein cholesterol, total cholesterol, smoking status, diabetes mellitus, and total intentional exercise (model 2). The *P* values for the hazard ratios from model 2 test the added value of the waveform indices beyond traditional risk factors for prediction of events (32). Because there were

Figure 3. Beat-specific waveforms (gray points) and fitted pressure decay (black lines), Multi-Ethnic Study of Atherosclerosis, United States, 2000–2002. A) Two beat-specific waveforms from Figure 2; combined estimates of PTC1 and PTC2 are 398 and 75 milliseconds, respectively. B) Two beat-specific waveforms from another participant; combined estimates of PTC1 and PTC2 are 299 and 94 milliseconds, respectively.

Table 1. Baseline Characteristics (*n* = 6,228 Participants), Multi-Ethnic Study of Atherosclerosis, United States, 2000–2002

Characteristic	%	Mean (SD)
Age, years		
45–54	29	
55–64	28	
65–74	29	
75–84	14	
Male sex	48	
Race/ethnicity		
White	38	
Chinese	12	
Black	27	
Hispanic	23	
Systolic blood pressure, mm Hg		127 (21)
Diastolic blood pressure, mm Hg		72 (10)
Heart rate, beats/minute		63 (10)
Use of antihypertensive medication	37	
Total cholesterol, mg/dL		194 (36)
High-density lipoprotein cholesterol, mg/dL		51 (15)
Cigarette smoking status		
Never	51	
Former	36	
Current	13	
Diabetes mellitus	13	
Total intentional exercise, MET-minutes/week		1,537 (2,297)
C1, mL/mm Hg × 10 ^a		13.4 (5.6)
C2, mL/mm Hg × 100 ^a		4.5 (2.8)
RC1, milliseconds ^a		1,567 (579)
RC2, milliseconds ^a		51 (26)
PTC1, milliseconds ^b		393 (334)
PTC2, milliseconds ^b		94 (46)

Abbreviations: MET, metabolic equivalent; SD, standard deviation.

^a RC1 and RC2, from Hypertension Diagnostics, Inc.^b PTC1 and PTC2, new indices of pressure waveforms.

many non-CVD deaths with no prior CVD (437 among 6,228 participants), which could lead to bias due to informative censoring (33), we also evaluated the association with the composite event (CVD or non-CVD death) where non-CVD deaths are events rather than reasons for censoring; associations with the composite event were consistent with associations with CVD, suggesting that the competing risk issue is of less concern.

RESULTS

PTC1 and PTC2 were obtained for all 6,334 (100%) participants with waveform data, including 131 participants

Table 2. Correlation Between Repeat Measurements (*n* = 131), Multi-Ethnic Study of Atherosclerosis, United States, 2000–2002

Measure	Pearson Correlation Coefficient	Spearman Correlation Coefficient
PTC1 ^a	0.61	0.75
PTC2 ^a	0.92	0.87
RC1 ^b	0.58	0.62
RC2 ^b	0.74	0.68
SBP	0.90	0.89
DBP	0.86	0.85

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

^a PTC1 and PTC2, new indices of pressure waveforms.^b RC1 and RC2, from Hypertension Diagnostics, Inc.

with repeat measurements. Examples of fitted models are shown in Figure 3.

Of the 6,334 participants with waveforms (and PTC1 and PTC2), 6,228 had complete information on other covariates and events (Table 1). The means and medians were 393 (standard deviation, 334) and 332 (interquartile range, 237–468) milliseconds for PTC1, 94 (standard deviation, 46) and 85 (interquartile range, 64–113) for PTC2, 1,567 (standard deviation, 579) and 1,470 (interquartile range, 1,193–1,805) for RC1, and 51 (standard deviation, 26) and 44 (interquartile range, 31–64) for RC2.

Among the 131 participants with repeat measurements for quality-control purposes, the Spearman correlation was 0.75 for PTC1 and 0.87 for PTC2, similar to SBP (Table 2). The mean difference between repeat measurements was 18 (standard deviation, 222) milliseconds for PTC1 and 1.1 (standard deviation, 22) milliseconds for PTC2 (Figure 4).

Among the 6,228 participants with complete information, the Pearson correlation coefficients between PTC1 and each of PTC2, RC1, RC2, C1, C2, SBP, DBP, and heart rate were 0.25, –0.10, 0.15, 0.00, 0.19, –0.15, –0.02, –0.10, respectively (Table 3). The correlation between PTC2 and RC2 was 0.59. Spearman correlation coefficients were similar.

There were 911 CVD events from the 6,228 participants, with a median follow-up of 15 (interquartile range: 11–16) years. Both PTC1 and PTC2 were associated with incident CVD (Table 4). With adjustment for age, sex, race/ethnicity, and clinical site (model 1), 1-standard-deviation-higher PTC1 was associated with a 14% (95% confidence interval: 7, 20) lower risk of CVD; 1-standard-deviation-higher PTC2 was associated with a 23% (95% confidence interval: 16, 29) lower risk of CVD. After further adjustment for traditional risk factors (model 2), both PTC1 and PTC2 remained associated with events; 1-standard-deviation-higher PTC2 was associated with a 17% (95% confidence interval: 10, 24) lower risk of CVD. Results were similar for each of the components of CVD (CHD and stroke), although the associations with stroke were only marginally significant after adjustment for traditional risk factors. Results for HDI's RC2 were relatively similar to PTC2, but we did not find

Figure 4. Bland-Altman plots for PTC1 and PTC2 ($n = 131$), comparing estimates from two 30-second recordings collected on the same day, Multi-Ethnic Study of Atherosclerosis, United States, 2000–2002. A) PTC1, mean of differences = 18 (standard deviation, 222) milliseconds. B) PTC2, mean of differences = 1.1 (standard deviation, 22) milliseconds.

evidence that HDI's RC1 was significantly associated with CVD, unlike PTC1.

DISCUSSION

We derived C1- and C2-like indices of pressure waveforms, PTC1 and PTC2, based on a Windkessel model of pressure decay. We computed the new indices for all 6,334 MESA participants with stored waveform data. PTC1 and PTC2 provided additional information about pressure during the cardiac cycle as evidenced by their low correlations with SBP, DBP, and heart rate, and they each added information about incident CVD beyond traditional risk factors. Higher PTC1 and PTC2 were independently associated with lower risk of CVD and its component CHD. The direction and magnitude of the estimated association with stroke was

similar to the other outcomes but the confidence intervals for stroke were wider, consistent with fewer events (270 for stroke versus 911 for CVD and 609 for CHD).

The reproducibility of PTC2 was similar to SBP but the reproducibility of PTC1 was not as good. Reproducibility might be improved by increasing the sampling rate or by using an average across multiple 30-second recordings during a very short time period (where the tonometer is removed and placed back on the artery between recordings).

The correlation between PTC1 and HDI's RC1 was -0.10 and between PTC2 and HDI's RC2 was 0.59 . One might be surprised that PTC1 and PTC2 are not more similar to HDI's RC1 and RC2, but inspection of data collection/processing/model leads to an appreciation of the differences. First, equation 2, from which PTC1 and PTC2 are derived, includes an intercept, a_0 , and equation 1, from which HDI's

Table 3. Pearson Correlation Between Different Measures at Baseline ($n = 6,228$), Multi-Ethnic Study of Atherosclerosis, United States, 2000–2002

PTC1 ^a	PTC2 ^a	RC1 ^b	RC2 ^b	C1 ^b	C2 ^b	SBP	DBP	HR
PTC1	0.25	-0.10	0.15	0.00	0.19	-0.15	-0.02	-0.10
	PTC2	-0.07	0.59	0.13	0.62	-0.28	-0.03	-0.01
		RC1	0.14	0.85	0.12	-0.15	0.07	-0.32
			RC2	0.29	0.94	-0.25	0.00	-0.09
				C1	0.41	-0.37	-0.07	-0.29
					C2	-0.36	-0.09	-0.08
						SBP	0.61	0.04
							DBP	0.14
								HR

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

^a PTC1 and PTC2, new indices of pressure waveforms.

^b C1, C2, RC1, and RC2, from Hypertension Diagnostics, Inc.

Table 4. Association of Waveform Indices With Events (Hazard Ratios per Standard Deviation^a ($n = 6,228$)), Median Follow-up 15 Years, Multi-Ethnic Study of Atherosclerosis, United States, 2000–2002

Index	All CVD ^b (911 Events)			CHD (609 Events)			Stroke (270 Events)		
	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value
<i>Model 1^c</i>									
PTC1	0.86	0.80, 0.93	0.0001	0.85	0.78, 0.93	0.0004	0.84	0.73, 0.97	0.02
PTC2	0.77	0.71, 0.84	<0.0001	0.76	0.69, 0.83	<0.0001	0.80	0.68, 0.94	0.006
RC1	0.91	0.85, 0.98	0.02	0.91	0.83, 0.99	0.04	0.98	0.86, 1.11	0.7
RC2	0.80	0.73, 0.87	<0.0001	0.79	0.72, 0.88	<0.0001	0.80	0.68, 0.94	0.005
<i>Model 2^d</i>									
PTC1	0.91	0.84, 0.99	0.02	0.90	0.82, 0.99	0.04	0.87	0.74, 1.02	0.09
PTC2	0.83	0.76, 0.90	<0.0001	0.81	0.73, 0.90	<0.0001	0.87	0.73, 1.03	0.10
RC1	1.02	0.95, 1.09	0.6	1.02	0.94, 1.11	0.6	1.05	0.92, 1.19	0.5
RC2	0.87	0.80, 0.94	0.0007	0.86	0.78, 0.95	0.004	0.86	0.74, 1.02	0.08

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

^a Standard deviations: PTC1, 334 milliseconds; PTC2, 46 milliseconds; RC1, 579 milliseconds; RC2, 26 milliseconds. PTC1 and PTC2 are new indices of pressure waveforms; RC1 and RC2 are from Hypertension Diagnostics, Inc.

^b CHD, stroke, and other CVD death.

^c Model 1 adjusted for age, sex, race/ethnicity, and clinical site.

^d Model 2: model 1 with additional adjustment for baseline systolic blood pressure, diastolic blood pressure, heart rate, use of antihypertensive medication, high-density lipoprotein cholesterol, total cholesterol, smoking status, diabetes mellitus, and exercise.

C1 and C2 are derived, does not. This means that PTC1 and PTC2, unlike HDI's RC1 and RC2, are not affected by the scale on which waveforms are collected or by arbitrary linear calibration to blood pressure. In other words, when the model includes a_0 (with a_1 and a_3), the same estimates of a_2 , a_4 , and a_5 (and thus PTC1 and PTC2) are obtained whether the data are calibrated such that the maximum and minimum are SBP and DBP, or some other linear calibration. Without the intercept, the estimates of a_2 , a_4 , and a_5 depend on the calibration. (If this is not obvious, consider in simple linear regression, the estimated slope will be different with and without the intercept in the model except in the special case when the estimated intercept is 0.) Second, in equation 2, $P(0)$ is defined as maximum pressure, which is clearly defined, whereas in equation 1, $P(0)$ is defined by the pressure, which yields the best model fit, out of a range of pressures near the dicrotic notch. The latter is problematic because 1) the dicrotic notch is not necessarily well-defined, and 2) it results in choosing the data to fit the model rather than the model to fit the data, which could lead to bias. There are other differences between our method and HDI's, but the 2 above (and that we use all beat-specific waveforms and HDI uses 1/6–1/3) are probably the most significant. Our approach to estimating C1- and C2-like summaries is consistent with the Windkessel model as described by others (19, 21).

We estimated a PTC1 and PTC2 from each beat-specific waveform and then combined them (using the median) into 1 PTC1 and 1 PTC2 per participant, instead of computing an “ensemble average” waveform from the beat-specific waveforms and then estimating PTC1 and PTC2. This is

important because, in an ensemble average, the features (peaks, valleys, dicrotic notch) will be attenuated if the features across beat-specific waveforms are not aligned in time, and this attenuation could affect the resulting PTC1 and PTC2.

We applied our procedure to 202,235 beat-specific waveforms from 6,334 participants. We acknowledge that there was a relatively small number of “problematic” waveforms, where the procedure with our initial grid of starting values failed to converge or converged to a local minimum, or where equation 2 is inappropriate (in part because a simpler model, with $a_1 = 0$ or $a_3 = 0$, would suffice), as evidenced by negative beat-specific PTC1 or PTC2 or beat-specific waveforms where the range of the fitted values for either $a_1 \exp(-a_2 t)$ or $a_3 \exp(-a_4 t) \cos(a_5 t + a_6)$ was effectively 0. Of the 6,334 participants, more than 90% had fewer than 10% problematic waveforms, and less than 1% had greater than 50% problematic waveforms. When we used a larger, different grid of starting values, we obtained reasonable estimates for many of these problematic beat-specific waveforms. (We also verified for many participants without problematic waveforms that we obtained the same PTC1 and PTC2 estimates with both our initial grid of starting values and the larger grid.) In general, it is good practice to check for potential convergence issues in estimating nonlinear models, including the Windkessel model. Future work could investigate better or more efficient sets of starting values for the nonlinear estimation procedure for equation 2.

When measurements are collected from different sources (e.g., separate lab, device), there can be issues with matching measurements from the different sources. There were 2

participants with HDI's C1 and C2 but not stored waveforms, and 294 for whom waveforms were obtained by HDI, but C1 and C2 were not computed by HDI, and the waveforms were not stored. It is possible that these participants (plus 184 for whom waveforms were not obtained and 106 without covariate/event information) would affect our conclusions if they could be included in our analysis, but it is less likely given that they represent less than 10% of the sample.

We named the new indices PTC1 and PTC2 for a few reasons. We chose the suffixes "C1" and "C2" because PTC1 and PTC2 are analogous to C1 and C2 and related to arterial compliance under the Windkessel theory, as described in the landmark paper by Goldwyn and Watt (19). Consistent with Windkessel theory, we found that higher PTC1 and PTC2 were associated with lower risk of CVD. HDI's C1 and C2 have been called large and small artery compliance (elasticity), and C2 has been termed "oscillatory" or "reflexive," although these terms are controversial (34, 35). While the "C" could stand for compliance, we also chose "TC" because PTC1 and PTC2 are functions of a_2 and a_4 , which are related to time constants in exponential models. We chose the prefix "P" for pressure.

Others (16–18) have derived diastolic and systolic time constants (τ_{dias} and τ_{sys}), or their inverse rate constants, by combining Windkessel and wave transmission theories. The combination of these theories generates a reservoir pressure waveform whose diastolic part is used to estimate τ_{dias} . Other investigators (16–18) have estimated τ_{dias} using a Windkessel model consisting of a single exponential decay term with or without an intercept (simpler than the Windkessel model in equation 2), which thus generates only 1 diastolic time constant. Behnam et al. (18) have also estimated τ_{dias} using another approach that generates a "pressure-varying" diastolic time constant which is subsequently summarized by its value at mean arterial pressure. Thus, these τ_{dias} share similarities with PTC1 and PTC2, and like PTC1 and PTC2, higher τ_{dias} has been shown to be associated with lower risk of CVD, although statistical significance has not always been demonstrated with τ_{dias} . The systolic time constant τ_{sys} , which is related to the systolic part of the calculated reservoir waveform and thus less similar to PTC1 and PTC2, has also been shown to be associated with CVD. It could be useful to combine equation 2 with wave transmission theory, to obtain a τ_{sys} , in addition to PTC1 and PTC2.

In summary, we developed C1- and C2-like indices, PTC1 and PTC2, from pressure waveforms for our overarching goals of investigating change in pressure waveforms and to better understand the association between waveforms and CVD. Using radial artery waveforms from over 6,000 participants from the Multi-Ethnic Study of Atherosclerosis, we showed that PTC1 and PTC2 are feasible to compute and independently associated with incident CVD (CHD, in particular). Future work will investigate 10-year change in these indices. Because our method is straightforward to implement with standard, freely available software, we hope that our results will be replicated and extended with other waveforms. The waveforms could be from other existing studies which have stored waveform data or new studies and could be collected using any suitable device for measuring

pressure waveforms, including possibly future personal fitness devices.

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