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Increased wave reflection and ejection duration in women with chest pain and non-obstructive coronary artery disease: ancillary study from the Women's Ischemia Syndrome Evaluation (WISE)

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Abstract

Objective—Pulsatile wave reflections augment central aortic systolic blood pressure (BP) and increase systolic pressure time integral (SPTI) thereby increasing left ventricular (LV) afterload and myocardial oxygen (MVO₂) demand. When increased, such changes may contribute to myocardial ischemia and angina pectoris, especially when aortic diastolic time is decreased and myocardial perfusion pressure jeopardized. Accordingly, we examined pulse wave reflection characteristics and diastolic timing in a subgroup of women with chest pain (WISE) and no obstructive coronary artery disease (CAD).

Methods—Radial artery BP waveforms were recorded by applanation tonometry, and aortic BP waveforms derived. Data from WISE participants were compared with data from asymptomatic women (reference group) without chest pain matched for age, height, body mass index (BMI), mean arterial BP and heart rate (HR).

Results—Compared with the reference group, WISE participants had higher aortic systolic and pulse BP and ejection duration (ED). These differences were associated with an increase in, augmentation index (AIx), and reflected pressure wave systolic duration. These modifications in wave reflection characteristics were associated with an increase in SPTI and wasted LV energy (Ew) and a decrease in pulse pressure amplification, myocardial viability ratio, and diastolic pressure time fraction (DPTF).

Conclusions—WISE participants with no obstructive CAD have changes in systolic wave reflections and diastolic timing that increase LV afterload, MVO₂ demand, and Ew with the potential to reduce coronary artery perfusion. These alterations in cardiovascular function contribute to an undesirable mismatch in the MVO₂ supply/demand that promotes ischemia and chest pain and may contribute to, or increase the severity of, future adverse cardiovascular events.

Keywords

wave reflection; augmentation index; central aortic pressure; wasted LV energy; WISE study

Disclosures

None

INTRODUCTION

Up to 40% of patients undergoing non-emergency diagnostic coronary angiography for the assessment of typical chest pain have no obstructed epicardial coronary arteries [1], and this finding is observed more frequently in women [2]. Many of these patients have exertional myocardial ischemia and coronary artery endothelial dysfunction [3]. Additionally, among women, the prognosis is worse compared with that of women with normal coronary arteries and without chest pain [4–5]. Results from previous WISE studies have shown that persistent chest pain, coronary microvascular dysfunction, and increased brachial pulse pressure predict adverse cardiovascular events in these women [6–8]. WISE participants had chest pain and multiple test findings suggesting myocardial ischemia prior to referral for coronary angiography [9–12]. Coronary microvascular dysfunction, as assessed by coronary flow reserve (CFR), was present in approximately one half of the women studied, and this particular finding predicted adverse events in the presence and absence of obstructive coronary artery disease (CAD).

Myocardial ischemia occurs when there is an imbalance between myocardial oxygen supply and demand; and the ischemia is usually entirely or predominantly subendocardial. Animal models have shown that relative subendocardial ischemia can be predicted from the ratio of two pressure time areas (or integrals): the area between diastolic aortic and left ventricular (LV) pressures (DPTI) and the area beneath the systolic LV pressure curve (SPTI) [13]; these integrals can also be estimated from the aortic pressure waveform and a calculated subendocardial viability index [14].

Increased arterial stiffness increases wave reflection amplitude and aortic systolic BP, which prolongs mechanical systole (or ejection duration) and decreases diastolic pressure time [15]. These pressure changes negatively influence myocardial perfusion and CFR, reducing the myocardial oxygen (MVO_2) supply/demand ratio, which promotes subendocardial ischemia [13–16].

These adverse alterations are exaggerated in the presence of LV hypertrophy (LVH) [17]. Furthermore, reports in humans suggest that increased wave reflection amplitude promotes LVH [18,19] and predicts adverse cardiovascular outcomes [20–24]. Several reports suggest an increase in elastic artery stiffness and a decrease in brachial endothelial function in patients with exertional chest pain associated with ST-segment depression despite normal coronary angiograms [25–27]. Recent studies have shown that central aortic PP, a measure of wave reflection, more strongly relates to adverse cardiovascular outcomes than does brachial PP [28,29], therefore, measurement of central aortic pressure wave and its components may improve risk stratification [30]. Accordingly, the objective of the present study was to investigate indices of MVO_2 supply and demand non-invasively using central arterial pulse wave analysis (PWA) [31] in a subgroup of women in the WISE study.

METHODS

WISE is a National Heart, Lung and Blood Institute (NHLBI) sponsored study that aims to improve diagnostic evaluation and understanding of pathological mechanisms of ischemic heart disease in women. Details of protocol and design of the WISE study have been previously published [32,33]. Briefly, between 1996 and 2000, 936 women aged 18–84 years undergoing clinically indicated diagnostic coronary artery angiography were enrolled. Major exclusion criteria were comorbidity which would compromise follow up, pregnancy, contraindications to provocative diagnostic testing, cardiomyopathy, New York Heart Association class III–IV congestive heart failure, recent myocardial infarction, significant valvular or congenital heart disease, and a language barrier to questionnaire testing. Baseline

evaluation included physical examination and comprehensive clinical and laboratory data. Data were collected at the Data Coordinating Center and entered on standardized forms. Qualitative and quantitative coronary angiographic analyses were performed by the Angiographic Core Lab masked to patient data [33]. Any coronary artery luminal diameter stenosis >50% was defined as obstructive CAD, 20–50% as mild CAD, and <20% as no CAD. A CAD severity score was defined as an aggregate of percent stenosis, extent and location of stenosis, and degree of collateral vessels. In general, CAD severity scores ≤5 indicate no luminal narrowing. Scores >5 and ≤10 usually reflect “minimal” CAD (no stenosis >50%), scores 11–20 reflect nonobstructive stenosis, and scores >20 usually are found in patients with 3-vessel CAD (all vessels with at least one stenosis >50%).

A subgroup of women (N=59) underwent non-invasive central aortic PWA studies as described below, and they are the subject of this ancillary study. These women were from the University of Florida site, and all gave informed consent to add this testing to the WISE testing, which was approved by the local Institutional Review Board. Data from these WISE participants were compared with a reference group of asymptomatic women (N=59) matched for age, height, BMI, mean arterial BP, and heart rate. All of these women were volunteers selected from a larger group to match the demographic characteristics of the WISE participants. They were in sinus rhythm, and none had a diagnosis of CAD, diabetes, or previous cardiovascular event such as myocardial infarction or stroke. Systolic hypertension was defined as a brachial cuff systolic BP of at least 140 mmHg. Diabetes mellitus was defined as a plasma glucose level of at least 7.0 mmol/L fasting or at least 11.1 mmol/L at 2 hours after glucose load, or as the use of anti-diabetic drugs or insulin. Pertinent demographic data from both groups are summarized in Table 1.

All of the WISE participants in this ancillary study had chest pain and were free from obstructive CAD (>50% lesion in ≥1 epicardial vessel); 17 had minimal CAD (mean severity score 8.44).

Long acting vasoactive drugs were withdrawn at least 48 hours and short acting vasoactive drugs were withdrawn at least 24 hours before data collection. Noninvasive data were collected at least 2 hours after a meal and/or intake of coffee (or smoking) with the subject supine in the same quiet, temperature-controlled room after a rest period of at least 10 minutes.

Peripheral cuff blood pressure measurement

Brachial SBP, DBP, and PP were measured in the left arm using a validated, automatic oscillometric BP monitor (Omron R3, Omron Healthcare, Kyoto, Japan) and an appropriate size BP cuff. Three measurements were taken at least 2 minutes apart, and the latter two averaged and used in data analysis.

Central aortic pulse waveform analysis

Assessment of arterial wall properties, wave reflection characteristics, and event timing were performed noninvasively using the SphygmoCor system (AtCor Medical, Sydney, Australia). Radial artery BP waveforms were recorded at the left wrist, using applanation tonometry. After 20 sequential waveforms were acquired and ensemble averaged, a validated generalized mathematical transfer function was used to synthesize the central aortic BP waveform [34–36]. Indices of LV afterload, MVO₂ demand and coronary artery perfusion were derived from the central aortic BP waveform using PWA [31,34]. Morphologies of the aortic BP wave and its components are illustrated in Figure 1. The merging point of forward and reflected waves (the inflection point, P_i) is identified on the pressure waveform. (P_i – P_d) is amplitude of the forward wave generated by LV ejection and

$(P_s - P_i)$ is amplitude of the reflected wave from the lower body (augmented pressure). Aortic augmentation index (AIx) is defined as reflected wave amplitude, $(P_s - P_i)$, divided by aortic PP [$(P_s - P_i)/(\text{PP}) \times 100$], and expressed as a percentage [37]. The time from the beginning upstroke of the synthesized aortic systolic BP waveform (P_d) to the upstroke of the reflected wave (inflection point, P_i) is the round-trip travel time (T_r) of the pressure wave to and from the major reflecting site in the lower body [34,37]. Time from inflection point to the incisura (or dicrotic notch) is the systolic duration of the reflected wave (SDR) [37]. When the reflected wave returns during systole, as seen in Figure 1, the aortic BP is augmented and, therefore, the LV must generate enough energy to overcome this added boost in pressure and opposition to emptying. This energy (E_w), which takes into account both amplitude and systolic duration of the reflected wave, is wasted since it does not contribute to blood flow production and was obtained as the area under the systolic portion of the reflected wave [38]. $\text{SPTI} = \Delta\text{SPTI} + E_w$ was estimated as the area under the systolic portion of the aortic BP wave above zero, and DPTI was estimated as the area under the diastolic portion of the BP wave above zero. The ratio of these two area variables, DPTI/SPTI , represents the MVO_2 supply and demand ratio and is termed the myocardial viability ratio [39]. The fraction (F) of time during the cardiac cycle the heart spends in systole (systolic pressure time fraction [SPTF]) and diastole (diastolic pressure time fraction [DPTF]) was calculated as $\text{SPT}/(\text{cycle length})$ and $\text{DPT}/(\text{cycle length})$, respectively. Subendocardial perfusion is dependent upon the ratio DPTF/SPTF and is associated with aortic stiffness and wave reflection amplitude [40,41].

Only women with high-quality recordings, defined as acceptable curves on visual inspection with an in-device quality index of $>80\%$, were included in the analysis. The latter was derived from an algorithm including average pulse height, pulse height variation, diastolic variation, and the maximum rate of rise of the peripheral waveform.

Statistics

Data for each group were summarized as means and standard deviations for continuous variables. Hemodynamic variables were compared using the unpaired two-tailed Student t test. $P < 0.05$ was considered significant.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

Subjects

Pertinent variables collected from the reference group women and WISE participants are summarized in Tables 1 and 2. Case matching resulted in no significant differences in age (one-half of the women in either group were over 50 years of age), height, BMI, heart rate, or mean arterial BP between the two groups. Forty-four of the WISE participants had normal coronary angiograms and CAD severity scores, 12 had minimal stenosis and severity scores >5 and <10 , and three had severity scores >10 and <20 indicating non-obstructive stenosis. It was assumed that all women in the control reference group had no significant CAD. Thirty-one percent of WISE participants and 22% of control reference group women were previous smokers (Table 1). Twenty-four percent of the WISE group and 30% of the control group were post menopausal, while almost one-half of both groups were on hormone replacement therapy (HRT). Systolic hypertension was present in 20% of women in WISE and 19% in the control group. Seventy-two percent of women in the WISE group and 69% in the control group were overweight ($\text{BMI} > 25 \text{ kg/m}^2$). A small portion of women in each group was on antihypertensive (WISE 27%; Controls 24%) and lipid lowering (WISE 15 %;

Controls 12%) medication, however, these drugs had been withdrawn before data collection; four controls and six WISE women were on vasodilators and 10 in each were on a diuretic.

Components of peripheral and central blood pressure

The in-device quality index ranged from 82% to 100% for aortic pressure waves. Average values of measured and derived variables from the aortic BP wave in the reference group of women and WISE participants are summarized in Table 2. In general, these values are slightly higher in the reference group than those previously published for normal subjects [42] in this age group while those in the WISE group (age 53 ± 10 years) were significantly higher. Composite data from the two groups indicate that brachial SBP (130 ± 19 vs 125 ± 15 mmHg, $P=0.13$), DBP (80 ± 10 vs 78 ± 11 mmHg, $P=0.20$), and PP (49 ± 13 vs 47 ± 9.7 mmHg, $P=0.30$) were similar in the two groups of women. Conversely, central aortic SBP (121 ± 17 vs 115 ± 15 mmHg, $P=0.04$) and PP (40 ± 11 vs 36 ± 7.9 mmHg, $P=0.05$) were greater in the WISE participants compared with reference group women (Table 2).

Wave reflection indices

There was an increase in central aortic SBP and PP among WISE participants, resulting from a deleterious effect on wave reflection characteristics. The amplitude, ($P_s - P_i$) (12 ± 5.2 vs 9.3 ± 4.3 mmHg, $P=0.002$), and duration, SDR (194 ± 22 vs 173 ± 23 msec, $P=0.001$), of the reflected wave were both greater in WISE participants compared with the reference group (Table 2). These differences in wave reflection characteristics produced a higher AIx (30 ± 7.4 vs 24 ± 8.7 %, $P=0.001$) and caused a reduction in PP amplification (1.2 ± 0.12 vs 1.3 ± 0.13 , $P=0.01$).

Indices of MVO₂ demand

The changes in arterial wave reflection characteristics produced a significant elevation in pulsatile LV afterload and were associated with an increase in indices of MVO₂ demand. The increase in wave reflection amplitude and duration in the WISE participants caused the LV to generate more wasted energy (2466 ± 1197 vs 1767 ± 891 dyne-sec-cm⁻², $P=0.001$) compared with the reference group. Also, the elevated systolic pressure and prolongation of ejection duration (330 ± 23 vs 309 ± 23 msec, $P=0.001$) in WISE participants caused an increase in estimated SPTI (2542 ± 412 vs 2335 ± 411 mmHg-sec/min, $P=0.007$) and SPTF (0.39 ± 0.04 vs 0.37 ± 0.04 , $P=0.01$) compared with the reference group.

Determinants of MVO₂ supply (coronary artery perfusion)

Heart rate (71 ± 9.5 vs 72 ± 10 beats/min, $P=0.46$) (Table 1) and cardiac cycle length (866 ± 122 vs 852 ± 121 msec, $P=0.51$) (Table 2) were normal and similar in the two groups of women. However, coronary artery perfusion time fraction (DPTF) was reduced in WISE participants (0.61 ± 0.04 vs 0.63 ± 0.04 , $P=0.01$) compared with reference group women, which, along with the increase in SPTF, was associated with a reduction in MVO₂ supply/demand (1.6 ± 0.30 vs 1.7 ± 0.29 , $P=0.02$) and myocardial viability ratio (1.3 ± 0.24 vs 1.5 ± 0.22 , $P=0.001$).

DISCUSSION

These are the first data from the WISE focusing on the central aortic pressure waveform and may help to explain results from previous reported observations. The study by Saito et al [16] showed a strong inverse relationship between arterial AIx and CFR. O'Rourke [14] hypothesized in 2008 that future WISE studies would show that treatment which modifies indices of wave reflection would improve CFR. The study by Pauly et al [7] proved this to be true; the ACE-1 inhibitor quinapril did, indeed, improve CFR. In the present study, we

investigated indices of arterial wave reflection and time intervals (systolic and diastolic) in a sample of women with symptoms and signs of ischemia and angiographically normal epicardial coronary arteries (or with non-obstructive atherosclerotic disease) participating in the WISE. Data from this study group were compared with those collected from a reference group of women without symptoms and signs of ischemia or history of CAD or diabetes matched for age, height, BMI, mean arterial BP and heart rate in addition to clinical characteristics that may alter arterial pathophysiology (Table 1). Our findings confirm and extend previous reports suggesting an association between increased arterial stiffness and chest pain in individuals with normal coronary arteries (or with non-obstructive atherosclerotic disease) [24–27,43].

The central arterial BP wave is composed of a forward traveling wave generated by LV ejection and a later arriving reflected (or backward) wave from the periphery [34]. A chronic increase in elastic artery stiffness and the migration of the reflected wave from diastole into systole is the primary cause of increased PP in subjects with degeneration and hyperplasia of the elastic arterial wall. An increase in smooth muscle tone in peripheral arteries can shorten reflection site distance and increase wave reflection amplitude and systolic and pulse pressure in central elastic vessels. Also, a minor decrease in DPT plus an increase in augmented pressure may have as much negative effect on coronary blood flow and CFR as a severe coronary artery stenosis [44]. All of the above hemodynamic variables can be obtained from PWA of the central aortic pressure wave.

Up to 40% of non-emergency patients with typical chest pain present with normal epicardial coronary arteries (or with nonobstructive atherosclerotic disease), the majority of which are women; men presenting with chest pain usually have CAD [5]. In a proportion of these patients, angina is attributed to coronary artery endothelial and/or microvascular dysfunction [3,6,12,45,46]. Other studies have suggested that arterial stiffness and wave reflection may be increased in patients with signs and symptoms of ischemia in the absence of CAD and higher values of stiffness are predictive of CAD in mixed gender studies [17–21,27]. These studies consistently show that elastic artery stiffness increases in relation to the severity of CAD [17–19]. Also, other studies have shown an inverse relation between arterial wave reflection and endothelial function of the coronary microvascular circulations [47].

To our knowledge, this is the first report to examine wave reflection characteristics and diastolic timing in women with chest pain and angiographically normal epicardial coronary arteries (or with nonobstructive atherosclerotic disease). We found in this study, using PWA of the non-invasively obtained central aortic BP waveform, that WISE participants have adverse alterations in large conduit arterial properties, wave reflection characteristics, and indices of MVO₂ supply and demand.

Pulse BP (peripheral and central) and to a lesser degree SBP are dependent upon heart rate, ejection duration, peak flow and arterial stiffness while mean pressure is dependent upon arteriolar caliber and peripheral resistance. Central and peripheral BP are not the same, and cardiovascular risk factors can exert differential effects on the various pressure components [34]. Both SBP and PP increase markedly, while diastolic and mean BP decrease slightly as the pressure wave travels from the heart toward the periphery. This “amplification” (brachial PP/central PP) of the pressure pulse is due to greater stiffness of peripheral muscular arteries (compared to central elastic arteries) and enhanced wave reflection amplitude, which depends upon the difference between elastic moduli of the respective arteries and distance to major reflecting sites [34]. As a consequence, these two pulsatile BP components are greater in arteries of the extremities than in the central aorta. This difference is important since the major organs (e.g., brain, heart, and kidney) are exposed to central arterial BP and not brachial BP. Also, increased central aortic stiffness and vasoactive drugs cause a markedly

different effect on central pulse pressure than on peripheral pulse pressure. Therefore, brachial SBP and PP measured with a sphygmomanometer in the arm are not always reliable measures of central aortic SBP and PP.

We found in this subgroup of the WISE study that central systolic augmented pressure resulting from increased reflected wave amplitude was elevated and amplification of the pulse was reduced. Reflected wave amplitude and PP amplification are directly related to arterial stiffness and inversely related to major reflecting site distance [34]. Therefore, it was assumed from these observations that arterial stiffness was abnormally elevated in the WISE cohort. This contention is supported by other studies that found an increase in arterial stiffness in patients with chest pain and non-obstructed coronary arteries [25–27]. The increase in wave reflection may be related to chronic inflammation [25], superoxide generation in the arterial wall [48], and/or peripheral and coronary artery endothelial dysfunction [26, 27]. Previous studies in humans and animals have shown that exogenous inhibition of nitrite oxide (NO) and oxidative stress cause an increase in elastic artery stiffness as measured by pulse wave velocity (PWV) [48,49]. In support of this, recent studies showed that AIx was positively associated with plasma levels of asymmetric dimethyl-arginine, an endogenous inhibitor of endothelial NO synthase [49], and inversely associated with global endothelial function [50].

Our results support the fact that wave reflection amplitude can alter the aortic pressure wave and pulsatile LV afterload independent of changes in brachial cuff BP. This mechanism probably explains why central aortic BP is a better predictor of cardiovascular events and outcome than peripheral BP [28, 29, 51].

The augmentation in late central aortic SBP and PP increases LV afterload, wasted LV energy, SPTI, and MVO₂ demand, and decreases systolic coronary blood flow. According to previous studies MVO₂ requirements are closely related to SPTI [52–54]. Wasted LV energy is that component of SPTI which is attributable to wave reflection. Furthermore, wasted LV energy is also deleterious to the circulation since it causes a reduction in ejected blood volume during blood flow deceleration. Previous studies have shown that long term exposure of the LV to elevated arterial stiffness and energy expenditure causes LVH and eventually leads to cardiac failure [38, 55].

At a given arterial pressure, subendocardial perfusion is dependent upon the ratio between the time the heart is in diastole and the duration of a complete cardiac cycle. This ratio is defined as the DPTF [40,41]. The DPTF indicates the duration of absence of compression of intramural vessels during a heartbeat and has been used as input into theoretical models on coronary artery perfusion [56]. The participants in the WISE substudy had a longer ejection duration than reference group women. This prolonged ejection duration decreased diastolic time and DPTF indicating reduced blood supply to the subendocardium. This adverse change in timing of cardiac cycle components and presumed decrease in coronary artery perfusion during both systole and diastole coupled with the increase in LV afterload causes a mismatch in ventricular/vascular coupling and an imbalance in the supply/demand ratio. This contention is supported by reduction in both DPTF/SPTF and the myocardial viability ratio in the WISE participants. This scenario is exaggerated during exercise and thus can cause angina at a lower workload even in individuals with normal coronary arteries [34, 44]. In patients with angina and normal coronary arteries DPTF is less both at rest and during exercise than that in normal individuals [34, 44, 57]. Indeed, a decrease in DPTF can have the same effect as an increase in coronary artery stenosis [44], especially in individuals with increased LVH. Furthermore, women with chest pain and normal coronary arteries may exhibit endothelial dysfunction and/or coronary microvascular dysfunction [6, 46] as observed in about half of WISE participants. These adverse alterations in LV load, diastolic

pressure time, and possibly coronary microvasculature dysfunction may explain why women with signs and symptoms suggestive of myocardial ischemia but without obstructive CAD are at elevated risk for cardiovascular events compared with asymptomatic women [7].

In summary, this study shows for the first time that, compared with reference women, women with chest pain and normal or non-obstructed coronary arteries have higher LV afterload and abbreviated diastolic pressure time. These hemodynamic alterations probably cause a mismatch in ventricular/vascular coupling and an imbalance between MVO₂ supply and demand resulting in myocardial ischemia and angina. Therefore, these women are more likely to develop cardiovascular disease sooner than their normal counterparts [46].

Limitations

This ancillary study has some limitations worthy of mention. Although the sample is limited to women and much larger than some previous reports, measurements were made at only one point in time. The possibility exists that with repeated measurements over time the data may change. Furthermore, no direct measure of arterial stiffness such as pulse wave velocity was attempted. Only surrogates of arterial stiffness and indices of wave reflection and time intervals were measured. Although the results strongly imply an increase in arterial stiffness, it is not known, with certainty, which arterial segment is altered (e.g., central elastic arteries or peripheral muscular arteries or both). The surrogates (Tr, AIx and PP amplification) we used are only rough estimates of arterial stiffness. Both AIx and PP amplification were different in WISE participants and suggested an increase in arterial stiffness. Also, these variables have been shown to be markers of adverse cardiovascular events [20, 58]. Tr was the same for both groups; in general increased arterial stiffness or a reduction in reflection site distance causes a decrease in Tr. Since Tr is related to ejection duration [59], arterial stiffness can change without a change in Tr. Indeed, if Tr is corrected for ejection duration then there is a decrease in this variable. However, LV pulsatile afterload and systolic time fraction (indicators of myocardial oxygen demand) clearly are increased, and diastolic time fraction (indicator of myocardial perfusion) is decreased. The cause of these changes in arterial stiffness and wave reflection characteristics could be a change in arterial wall properties of the elastic arteries or a change in smooth muscle tone of the muscular arteries and arterioles (microcirculation). Also, the possibility of selection bias exists, so these results should not be generalized to other groups. Furthermore, use of a reference group of presumed normal women without angiography to exclude CAD is a limitation, however, their demographic characteristics were matched to those of the WISE participants. Antihypertensive medication was similar in the two groups (16 in WISE vs 14 in the reference group). We attempted to collect data from a representative sample of the global WISE study. The antihypertensive agent was a diuretic in ten women in each group. Diuretics have little effects, if any, on the complex interplay between central and peripheral pressure waveforms. The others were taking a vasodilator. Excluding these drugs did not alter the results. Finally, it would be informative to collect similar data on arterial properties and wave reflection characteristics in a group of age-matched men with chest pain and normal coronary arteries.

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FIGURE 1.

A synthesized central aortic pressure waveform. P_i indicates the merging (or inflection) point of the forward and reflected waves. The early part of the ascending aortic pressure wave of amplitude $(P_i - P_d)$ is generated by left ventricular (LV) ejection. The later part of the pressure wave with amplitude $(P_s - P_i)$ is generated by the reflected wave arriving during systole and adding to the forward pressure wave. Pulse pressure (PP) = $(P_i - P_d) + (P_s - P_i) = (P_s - P_d)$ and augmentation index (AIx) = $(P_s - P_i)/PP$. Tr is the round-trip travel time of the pressure wave from the LV to the periphery and back; SDR is systolic duration of the reflected wave; ED is ejection duration; DPT is diastolic pressure time. The area under the systolic portion of the reflected wave (dark shaded area) is defined as LV wasted energy (E_w). $SPTI = \Delta SPTI + E_w$ and is the area under the systolic portion of the pressure wave and DPTI is the area under the diastolic portion of the pressure wave.

Table 1

Demographic and clinical characteristics of reference group and WISE participants

	Reference Group (N=59)	WISE Participants (N=59)	P
Age (years)	50±13	53±10	0.24
Height (cm)	163±6.0	164±7.5	0.30
HR (beats/min)	72±10	71±9.5	0.46
BMI (kg/m ²)	28±6.7	30±7.0	0.08
BMI >25 (%)	69	72	
>50 years of age (%)	51	53	
Hypertensive (%)	19	20	
Postmenopausal (%)	30	24	
Current HRT use (%)	42	49	
Antihypertensive medication (%)	24	27	
Previous smoker (%)	22	31	
Lipid lowering medication (%)	12	15	
Diabetes (%)	0	12	

BMI, body mass index; HR, heart rate; HRT, hormone replacement therapy.

Table 2

Pertinent variables of the reference group and WISE participants

	Reference Group (N=59)	WISE Participants (N=59)	P
Brachial SBP (mm Hg)	125±15	130±19	0.13
Brachial DBP (mm Hg)	78±11	80±10	0.20
Brachial PP (mm Hg)	47±9.7	49±13	0.30
(P _i – P _d) (mm Hg)	27±5.4	28±7.4	0.47
Tr (msec)	137±14	137±8.6	0.95
Aortic SBP (mm Hg)	115±15	121±17	0.04
Aortic MP (mm Hg)	95±12	99±12	0.09
Aortic PP (mm Hg)	36±7.9	40±11	0.05
PP amplification	1.3±0.13	1.2±0.12	0.01
Ejection duration (msec)	309±23	330±23	0.001
(P _s – P _i) (mm Hg)	9.3±4.3	12±5.2	0.002
AIx (%)	24±8.7	30±7.4	0.001
SDR (msec)	173±23	194±22	0.001
Wasted LV Energy (dyne-sec-cm ⁻²)	1767±891	2466±1197	0.001
SPTI (mmHg-sec/min)	2335±411	2542±412	0.007
DPTI/SPTI	1.5±0.22	1.3±0.24	0.001
Cardiac Cycle Length (msec)	852±121	866±122	0.51
SPTF	0.37±0.04	0.39±0.04	0.01
DPTF	0.63±0.04	0.61±0.04	0.01
DPTF/SPTF	1.7±0.29	1.6±0.30	0.02

AIx, aortic augmentation index; BP, blood pressure; DBP, diastolic BP; DPTF, diastolic pressure time fraction; DPTI, diastolic pressure time index; DPTI/SPTI, myocardial viability ratio; MP, mean BP; PP, pulse BP; (P_i – P_d), unaugmented BP (or forward wave amplitude); (P_s – P_i), reflected wave amplitude; SDR, systolic duration of reflected wave; SBP, systolic BP; SPTI, systolic pressure time index; SPTF, systolic pressure time fraction; Tr, travel time of wave to and from the lower body.