Original Article

Doppler indexes of left ventricular systolic and diastolic function in relation to haemodynamic load components in a general population

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Background: The contribution of central pulsatility to left ventricular (LV) dysfunction might be mediated by the haemodynamic loads of forward (Pf) and backward (Pb) pulse waves. We investigated the relation between echocardiographic indexes of LV function and pulsatile loads derived by wave separation analysis (WSA).

Methods: In 755 participants, we assessed LV dimensions, transmitral blood flow and mitral annular tissue velocities. We derived central pulse pressure (cPP) from radial tonometric recordings and calculated Pf, Pb and their ratio (reflection magnitude) using an automated, pressure-based WSA algorithm. Despite good quality recordings, WSA failed to derive Pf and Pb in 139 participants (18.4%), in particular in older women with unfavourable haemodynamics. Thus, our analysis included 616 participants (46.1% women; mean age, 49.2 years).

Results: Age and age^2 explained most of the variance in cPP (36.9%), Pf (18.6%), Pb (41.5%) and reflection magnitude (36.7%; $P < 0.0001$) and altered the direct correlation between Pf and Pb ($P_{int} < 0.0001$). Haemodynamic loads were independently associated with sex, BMI, heart rate, mean arterial pressure, history of diabetes and use of antihypertensive drugs. In multivariable-adjusted analyses, transmitral velocities and *E*/*e*′ ratio increased with higher cPP, Pf and Pb in men and women. We also observed an age-dependent association of LV radial strain with cPP, Pf and Pb.

Conclusion: The commercial WSA algorithm holds limited clinical utility given its low feasibility in older participants with unfavourable haemodynamics. LV function indexes were similarly associated with Pf and Pb, favouring the use of the composite cPP for prediction of LV dysfunction.

Keywords: general population, haemodynamic load components, left ventricular function, wave separation analysis

Abbreviations: *a*′, the peak late diastolic mitral annular velocity; *A*, the transmitral peak late diastolic velocity; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; cPP, central pulse pressure; *e*′, the peak early diastolic mitral annular velocity; *E*, the transmitral peak early diastolic velocity; *E*/*A* ratio, *E* velocity/*A* velocity ratio; *E*/*e*′ ratio, *E* velocity/*e*′ velocity ratio; FLEMENGHO, Flemish Study on Environment, Genes and Health Outcomes; LV, left ventricle; MAP, mean arterial pressure; Pb, backward pulse wave; Pf, forward pulse wave; TDI, tissue Doppler imaging; WSA, wave separation analysis

INTRODUCTION

The properties of both the heart and the vasculature influence the capability of the body to regulate cardiac output and systemic blood pressure (BP), and to respond to changes in preload and afterload. Arterial stiffening is a common feature of aging and is exacerbated by cardiovascular risk factors such as hypertension and diabetes mellitus [1]. In stiffer arteries, aortic pulsatility is greater because of increased pulse wave propagation and reflection [1,2] and impaired aortic reservoir function [3–5]. To oppose the increased systolic afterload, the heart needs to generate greater force, spend more energy and, in the long run, adapt by adverse left ventricular (LV) remodelling [6–8].

Previous population studies showed that increased central pulsatility has detrimental effects on LV diastolic function, especially in elderly women [9–13]. Moreover, it was suggested [14,15] that the impact of central haemodynamics on LV structure and function might be mediated by the haemodynamic loads of forward (Pf) and backward (Pb) pulse waves and their ratio, that is reflection magnitude.

Information on Pf and Pb wave components of the composite central pulse waveform might be derived using

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wave separation analysis (WSA) by the rescaling and alignment of the measured aortic blood flow and central pressure curve [16]. On the other hand, Westerhof *et al.* [17] proposed WSA of pressure in its Pf and Pb wave components from the aortic pressure wave alone. In this method, unknown information on the aortic flow was approximated by a triangle with defined time intervals [17]. To date, limited information is available on feasibility and usefulness of a commercially available automated pressure-based WSA method in a population of a wide range of age. Moreover, the sex-specific association of the derived haemodynamic load components with LV dysfunction remains to be elucidated. Therefore, in a general population sample, we investigated: the performance of a commercially available automated, pressure-based WSA method to extract Pf and Pb, and the sex-specific association of echocardiographic indexes reflecting LV structure and function with the central haemodynamic load components.

METHODS

Study participants

The Ethics Committee of the University of Leuven approved the FLEMENGHO (Flemish Study on Environment, Genes and Health Outcomes) study. From August 1985 until December 2005, we randomly recruited a family-based population sample from a geographically defined area in northern Belgium as described elsewhere [18]. From 2005 to 2009, we invited 1031 former participants for a re-examination at our field centre, including echocardiography and arterial tonometry (Fig. 1). Written informed consent was obtained in 828 participants (participation rate, 80.3%). We further excluded 73 participants because of atrial fibrillation ($n = 8$), an artificial pacemaker ($n = 3$) or insufficient quality of the echocardiographic recordings ($n = 6$) or tonometry ($n = 56$).

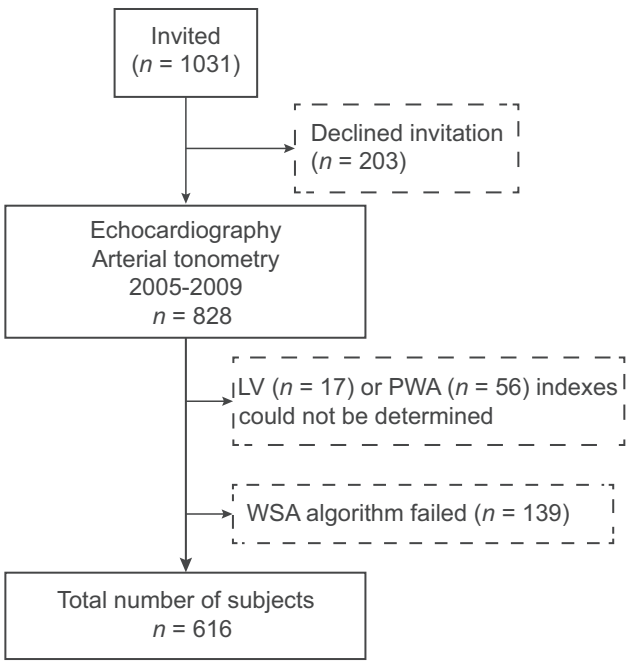

FIGURE 1 Flow chart for participants in the FLEMENGHO study. LV, left ventricular; PWA, pulse wave analysis; WSA, wave separation analysis.

Thus, we derived LV indexes from echocardiographic images and central haemodynamics from central pulse waveforms in 755 participants. Despite good quality of pulse wave recordings, however, we failed to retrieve Pf and Pb by the WSA algorithm as implemented in SphygmoCor (AtCor Medical Pty. Ltd., New South Wales, Australia) in 139 participants (failure rate, 18.4%). Therefore, current analysis included 616 participants (Fig. 1).

Echocardiography

Echocardiographic and tonometric measurements were obtained consecutively after the participants had rested for at least 15 min in supine position and had refrained from smoking, heavy exercise and drinking alcohol or caffeinated beverages for at least 2 h prior to the examination.

Echocardiographic methods are detailed in the online Supplemental Methods section, http://links.lww.com/HJH/A878. Briefly, one experienced physician (T.K.) did the ultrasound examination using a Vivid7 Pro (GE Vingmed, Horten, Norway) interfaced with a 2.5–3.5 MHz phased-array probe, in accordance to the recent recommendation [19] and as described previously [20]. With the participants in partial left decubitus and breathing normally, the observer obtained conventional 2D parasternal and apical 4, 2 and 3 chamber axis views, while ECG was recorded simultaneously. All recordings lasted at least five cardiac cycles.

Blinded to the participants' characteristics, one experienced observer (T.K.) analysed the digital echocardiograms using EchoPac software (GE Vingmed). From the long-axis parasternal view, LV internal diameter and interventricular septal and posterior wall thickness were measured at end-diastole from the two dimensionally guided M-mode tracings. Whenever optimal orientation of M-mode ultrasound beam could not be obtained, the reader performed linear measurements on correctly oriented 2D images. End-diastolic LV dimensions were used to calculate LV mass using an anatomically validated formula. Transmitral blood flow Doppler signals were used to measure peak early (E) and late (A) diastolic velocities. From pulsed-wave Tissue Doppler Imaging (TDI) recordings, we measured mitral annular peak velocities at early (e') and late (a') diastole at four acquisition sites (septal, lateral, inferior and posterior). We calculated the E/e' ratio by dividing transmitral E peak by e' averaged from the four acquisition sites. From colour Doppler myocardial data, we calculated one-dimensional longitudinal and radial regional TDI strain by comparing local myocardial velocity profiles using dedicated software as described previously [21].

Central haemodynamic loads

Brachial (peripheral) BP was the average of three consecutive readings obtained in supine position by a validated OMRON 705CP oscillometric sphygmomanometer (Omron Inc., Kyoto, Japan).

During an 8-s period, trained observers recorded radial arterial waveforms by applanation tonometry, using a high-fidelity SPC-301 micromanometer (Millar Instruments, Inc., Houston, Texas, USA) interfaced with a computer running the SphygmoCor software version 9. Recordings were

discarded whenever the systolic or diastolic variability of consecutive waveforms exceeded 5% or whenever the signal amplitude was below 80 mV. From the radial wave, SphygmoCor software calculated the aortic pulse wave by means of a validated transfer function using brachial DBP and mean arterial pressure (MAP, defined as $DBP + 0.40 \times [SBP - DBP]$) [22]. Central pulse pressure (cPP) was calculated as the difference between central SBP and DBP. From the central waveform, Pf and Pb wave amplitudes were derived using the triangular-flow pressure-based WSA algorithm as implemented in SphygmoCor software (Supplemental Figure S1, http://links.lww.com/HJH/A878). Reflection magnitude was defined as $100 \times Pb/Pf$.

The automated pressure-based WSA algorithm failed to derive Pf and Pb in 139 participants despite good quality of pulse wave recordings. In these participants, reflection index ($n = 85$), augmentation index ($n = 21$) or the time point of the first shoulder of the central waveform (T1; $n = 33$) were outside the acceptable ranges as defined in the commercially available software (Supplemental Table S1, http://links.lww.com/HJH/A878). We opted to exclude these recordings from further analysis, as there is to date no standardized way to manually adjust the automatically retrieved values of the error-causing indexes. The participants in whom the pressure-based WSA algorithm failed, as compared with those in whom the pulsatile components could be separated successfully, were more likely to be women (73.3 versus 46.1%, $P < 0.0001$), hypertensive (55.4 versus 38.0%, $P = 0.0002$), older (58.2 versus 49.2 years, $P < 0.0001$), and had higher cPP ($P < 0.0001$), MAP ($P = 0.011$) and augmentation pressure ($P < 0.0001$; Supplemental Table S2, http://links.lww.com/HJH/A878). Across age quartiles, the WSA algorithm successfully derived Pf and Pb in 92% from the first (<41 years), 91% from the second (41–51 years), 76.4% from the third (51–61 years) and 69.6% from the fourth (>61 years) quartile.

Other measurements

We administered a standardized questionnaire to collect detailed information on medical history, lifestyle and intake of medications. Hypertension was defined as a BP of at least 140 mmHg systolic or 90 mmHg diastolic and/or the use of antihypertensive drugs. Body mass index (BMI) was weight in kilograms divided by the square of height in meters. Diabetes mellitus was determined by self-report, a fasting glucose level of at least 126 mg/dl, or the use of antidiabetic agents.

Statistical methods

For database management and statistical analysis, we used SAS software version 9.4 (SAS Institute, Cary, North Carolina, USA). We compared means and proportions by a z-test and χ^2-test, respectively. Significance was $P < 0.05$ on two-sided tests. First, we performed forward stepwise regression to determine clinical correlates of the WSA-derived haemodynamic load components. Age, age^2, sex, BMI, heart rate, MAP, history of diabetes, smoking, alcohol consumption, and antihypertensive drug intake were considered as covariables in stepwise regression. We set the P value for variables to enter and stay in the stepwise regression models at 0.10 and 0.05, respectively. We extrapolated the relationship between Pb and Pf at fixed levels of age whereas adjusting for important covariables.

Second, by use of a mixed model, we further assessed multivariable-adjusted associations between echocardiographic indexes reflecting left heart structure and function (dependent variables) and central haemodynamic load components. All mixed models were adjusted for sex, age, body height and weight, heart rate, MAP and antihypertensive treatment while accounting for family relationships. We reported association sizes as the change in LV structure and function indexes, in absolute units, per standard deviation increase in the arterial indexes. All principal assumptions of multiple linear regression (linearity and additivity, statistical independence, homoscedasticity and error normality) were fulfilled. In continuous analyses, we extrapolated the multivariable-adjusted relationship between radial LV strain and hemodynamic indexes at fixed levels of age. We also performed a log-likelihood ratio test to compare the goodness-of-fit of the basic multivariable-adjusted models with and without the central haemodynamic load indexes.

RESULTS

Characteristics of participants

The 616 participants with successfully derived Pf and Pb included 284 (46.1%) women and 234 (38.0%) hypertensive participants of whom 133 (56.8%) were on antihypertensive drug treatment. The mean age of all participants was 49.2 ± 15.0 years. Tables 1 and 2 list the clinical, haemodynamic and echocardiographic characteristics of the participants by sex.

Compared with women, men had higher brachial SBP and DBP and lower heart rate ($P \leq 0.0003$; Table 1). Men also reported more frequently regular alcohol consumption and history of coronary heart disease ($P \leq 0.017$). Furthermore, Pf ($P < 0.0001$), but not Pb ($P = 0.56$), was significantly lower in women than in men. Consequently, women had significantly higher reflection magnitude as compared with men ($P < 0.0001$).

Women compared with men had smaller left atrial and LV volumes as well as LV dimensions and mass, yet higher LV radial strain, ejection fraction, transmitral E and A peak velocities and E/e' ratio ($P \leq 0.0095$; Table 2).

Correlates of haemodynamic load components

In unadjusted analyses, peripheral PP, cPP, Pf and Pb increased curvilinearly with age ($P < 0.0001$; Fig. 2). Table 3 and Supplemental Table S3, http://links.lww.com/HJH/A878 list the overall and sex-specific haemodynamic indexes by age quartiles, respectively.

Table 4 shows the correlates of the central haemodynamic load indexes as identified in stepwise regression analyses. As expected, most of the variance in peripheral PP (41.9%), cPP (36.9%), Pf (18.6%) and Pb (41.5%) was explained by age and age^2. In addition, cPP and Pb increased independently and significantly with women, MAP, history of diabetes mellitus and antihypertensive

TABLE 1. Clinical and haemodynamic characteristics of 616 participants

Characteristics	Men ($n=332$)	Women ($n=284$)
Anthropometrics		
Age (years)	49.1 ± 14.9	49.3 ± 15.0
Body mass index (kg/m^2)	26.7 ± 3.78	26.4 ± 4.85
Brachial SBP (mmHg)	130.0 ± 15.0	125.2 ± 17.5‡
Brachial DBP (mmHg)	82.0 ± 9.32	77.3 ± 8.69‡
Brachial PP (mmHg)	48.0 ± 12.6	48.0 ± 15.1
MAP (mmHg)	98.0 ± 9.85	93.3 ± 10.1‡
Heart rate (beats/minute)	62.2 ± 9.32	65.7 ± 9.96‡
Questionnaire data		
Current smoking, *n* (%)	75 (22.6)	51 (18.0)
Drinking alcohol, *n* (%)	202 (60.8)	62 (21.8)‡
Hypertensive, *n* (%)	135 (40.7)	99 (34.9)
Treated for hypertension, *n* (%)	66 (19.9)	67 (23.6)
β-Blockers, *n* (%)	36 (10.8)	35 (12.3)
ACE-I or ARB, *n* (%)	26 (7.8)	20 (7.0)
CCB or α-blockers, *n* (%)	12 (3.6)	10 (3.5)
Diuretics, *n* (%)	21 (6.3)	37 (13.0)†
History of CHD, *n* (%)	14 (4.2)	3 (1.1)*
History of diabetes, *n* (%)	13 (3.9)	12 (4.2)
Central haemodynamics		
Central PP (mmHg)	44.1 ± 14.0	43.2 ± 15.6
Pf (mmHg)	33.6 ± 9.58	30.1 ± 9.47‡
Pb (mmHg)	21.0 ± 7.80	21.4 ± 8.75
Reflection magnitude (%)	62.8 ± 17.0	70.8 ± 17.3‡

Values are mean (±SD) or number of participants (%). ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BP, blood pressure; CCB, calcium-channel blocker; CHD, coronary heart disease; MAP, mean arterial pressure; Pb, backward wave amplitude; Pf, forward wave amplitude; PP, pulse pressure.
$^{*}P \leq 0.05$.
$^{\dagger}P \leq 0.01$.
$^{\ddagger}P \leq 0.001$.

TABLE 2. Echocardiographic characteristics of 616 participants

Characteristics	Men ($n=332$)	Women ($n=284$)
Left atrial volume		
Crude volume (ml)	47.5 ± 13.6	37.2 ± 10.5‡
Indexed to BSA (ml/m^2)	23.8 ± 6.35	21.1 ± 5.03‡
Indexed to body height^2 (g/m^2)	15.4 ± 4.61	14.0 ± 3.98‡
LV geometry		
Internal diameter (cm)	5.28 ± 0.44	4.82 ± 0.39‡
Posterior wall (cm)	0.95 ± 0.14	0.83 ± 0.13‡
Septal wall (cm)	1.04 ± 0.16	0.91 ± 0.15‡
Relative wall thickness	0.38 ± 0.07	0.36 ± 0.06†
LV Mass		
Crude mass (g)	199.2 ± 45.3	144.1 ± 36.1‡
Indexed to BSA (g/m^2)	100.3 ± 21.6	81.9 ± 17.7‡
Indexed to body height$^{2.7}$ (g/m$^{2.7}$)	43.8 ± 11.4	38.6 ± 10.5‡
EDV index (ml/m^2)	68.6 ± 12.6	62.5 ± 10.5‡
ESV index (ml/m^2)	22.4 ± 7.11	18.9 ± 5.54‡
LV systolic function		
Ejection fraction (%)	67.7 ± 7.20	69.8 ± 6.83‡
TDI longitudinal strain[b] (%)	22.2 ± 3.69	22.4 ± 3.52
TDI radial strain[b] (%)	56.2 ± 11.9	59.1 ± 12.8†
LV diastolic function		
E peak (cm/s)	71.7 ± 14.9	80.3 ± 15.7‡
A peak (cm/s)	59.8 ± 16.0	67.3 ± 17.8‡
E/A ratio	1.30 ± 0.50	1.28 ± 0.44
TDI *e′* peak (cm/s)[a]	11.6 ± 3.65	11.8 ± 3.56
TDI *a′* peak (cm/s)[a]	10.3 ± 2.14	9.79 ± 1.97†
E/e′ ratio[a]	6.54 ± 1.75	7.35 ± 2.42‡

Values are mean (±SD) or number of participants (%). BSA, body surface area; EDV, end-diastolic volume; ESV, end-systolic volume; LV, left ventricle; MAP, mean arterial pressure; TDI, tissue doppler imaging.
[a]Average of septum, lateral, inferior and posterior mitral annulus sites.
[b]Measurements of longitudinal and radial strain were available for 504 and 502 individuals, respectively.
$^{\dagger}P \leq 0.01$.
$^{\ddagger}P \leq 0.001$.

treatment, but decreased with heart rate. Pf also increased with MAP, diabetes mellitus and antihypertensive treatment, but decreased with women. All covariables together, including age and age^2, explained 51.9, 47.7, 29.4 and 53.2% of the total variance in peripheral PP, cPP, Pf and Pb, respectively. Independent correlates of reflection magnitude included age, age^2, female sex, heart rate, BMI, MAP, history of diabetes mellitus and smoking, explaining 54.2% of the total variance in reflection magnitude.

The direct correlation between Pb and Pf was modified by age analysed as continuous variables ($P < 0.0001$ for interaction). To illustrate the age-dependency, we extrapolated the multivariable-adjusted relation between Pb and Pf at fixed levels of age (Fig. 3). In both men and women, the relationship between Pb and Pf steepened at higher age ($P_{int} < 0.0001$).

Association between left ventricular diastolic function and central haemodynamic load components

Multivariable-adjusted estimates (95% CI) associated with a 1-SD increase in cPP (+15 mmHg), Pf (+10 mmHg) and Pb (+8 mmHg) are presented in Table 5 for all participants. After full adjustment, crude as well as indexed left atrial volumes were directly related to cPP, Pf and Pb ($P \leq 0.013$ for all; Table 5; Supplemental Table S4, http://links.lww.com/HJH/A878). Furthermore, transmitral *E* and *A* peaks, TDI *e′* peak and *E/e′* ratio increased independently with higher cPP, Pf and Pb ($P \leq 0.037$ for all), whereas TDI *a′* peak independently decreased with higher central haemodynamic indexes ($P \leq 0.025$; Table 5). With exception of *E/A* ratio ($P = 0.015$), none of the echocardiographic indexes reflecting LV diastolic function were associated with reflection magnitude after full adjustment ($P \geq 0.072$; Table 5). Addition of cPP to the basic model (i.e. the multivariable-adjusted model without inclusion of any central haemodynamic index) provided higher chi-square statistics for its effect in relation to left atrial volume, transmitral *E* and *A* peaks and *E/e′* ratio as compared with models, which additionally included Pf or Pb (Supplemental Table S5, http://links.lww.com/HJH/A878).

We repeated the regression analyses separately in women and men (Table 6). We did not observe any significant interaction between sex and the central haemodynamic load components ($P_{int} > 0.069$) in relation to left atrial volume and LV Doppler transmitral or TDI velocities. On the other hand, we found a better correlation of *E/e′* ratio with cPP, Pf and Pb in women compared with men ($P_{int} \leq 0.020$, Table 6).

Association between left ventricular systolic function and central haemodynamic load components

In both men and women, LV ejection fraction as well as LV longitudinal and radial strains were not associated with cPP, Pf and Pb after full adjustment ($P \geq 0.13$). Dichotomized by

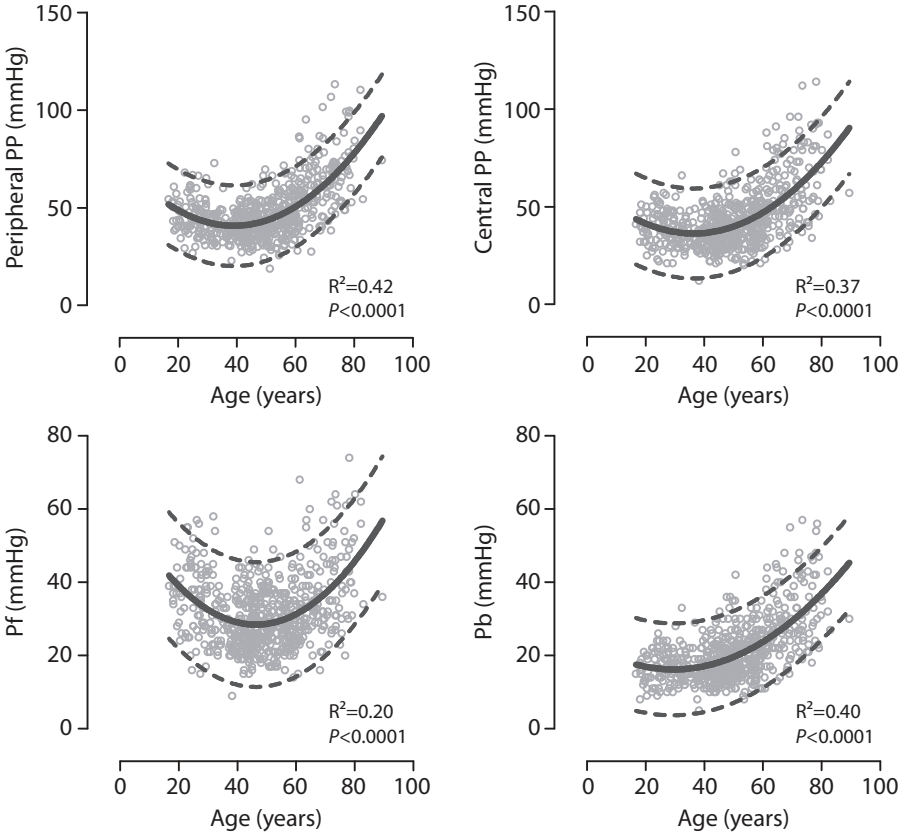

FIGURE 2 Univariate relationship of haemodynamic indexes with age. Each panel shows the second order polynomial, its 95% prediction band, the coefficient of determination (R^2) and associated *P* value resulting from a best-fit (least squares) procedure. Pb, backward wave amplitude; Pf, forward wave amplitude; PP, pulse pressure.

age quartiles, however, fully adjusted LV radial strain increased significantly with cPP, Pf and Pb in middle-aged participants (40–50 years) only (Supplemental Table S6, http://links.lww.com/HJH/A878). Figure 4 shows adjusted radial strain in relation to the central haemodynamic loads at fixed levels of age and limited to 466 study participants older than 40 years. In both sexes, the slopes of the relationship between radial strain and the central haemodynamic loads shifted from positive at 50 years of age towards negative at 80 years of age, supporting an age-dependent relationship between LV radial strain and any of the central haemodynamic indexes ($P_{int} = 0.012$, 0.073 and 0.040 for cPP, Pf and Pb, respectively).

Association between left ventricular geometry and central haemodynamic load components

In contrast to LV septal and posterior wall thickness ($P \geq 0.10$), LV internal diameter was independently and directly related to cPP, Pf and Pb ($P \leq 0.031$; Supplemental Table S7, http://links.lww.com/HJH/A878). Furthermore, crude and body surface area (BSA)-indexed LV mass were correlated independently with cPP and Pb ($P \leq 0.026$; Supplemental Table S4, http://links.lww.com/HJH/A878). In both men and women, however, LV mass indexed for body height$^{2.7}$ as well as relative wall thickness was not related to any of the central hemodynamic load components after full adjustment ($P \geq 0.12$ for all; Table 6). In men only, we

TABLE 3. Haemodynamic characteristics of 616 participants by age quartiles

Characteristic	Age quartile (years)				
	Less than 40 ($n = 150$)	40–50 ($n = 172$)	50–60 ($n = 152$)	More than 60 ($n = 142$)	$P_{quartile}$
Peripheral PP (mmHg)	43.8 ± 9.03	41.8 ± 7.58*	45.2 ± 9.63†	62.9 ± 16.7*,†,‡	<0.0001
Central PP (mmHg)	38.2 ± 8.92	37.7 ± 9.01	41.7 ± 10.5*,†	58.9 ± 18.3*,†,‡	<0.0001
Wave separation analysis					
Pf (mmHg)	33.4 ± 9.72	28.7 ± 7.21*	29.3 ± 7.35*	37.4 ± 11.7*,†,‡	<0.0001
Pb (mmHg)	16.8 ± 4.51	18.2 ± 5.22*	20.6 ± 5.94*,†	30.0 ± 9.68*,†,‡	<0.0001
Reflection magnitude (%)	51.7 ± 13.3	63.9 ± 14.5*	71.0 ± 16.7*,†	80.5 ± 13.2*,†,‡	<0.0001

Values are means (±SD). Pb, backward wave amplitude; Pf, forward wave amplitude; PP, pulse pressure; $P_{quartile}$ indicates the *P* value for overall interquartile differences.
*$P < 0.05$ versus less than 40 years.
†$P < 0.05$ versus 40–50 years.
‡$P < 0.05$ versus 50–60 years.

TABLE 4. Correlates of central haemodynamic indexes

Variables	Peripheral PP (mmHg)	Central PP (mmHg)	Pf (mmHg)	Pb (mmHg)	Reflection magnitude
Mean ± SD	48.0 ± 13.8	43.7 ± 14.7	31.9 ± 9.68	21.1 ± 8.25	66.5 ± 17.8
Adjusted R^2					
Explained by age and age^2‡	41.9%	36.9%	18.6%	41.5%	36.7%
Explained by all covariables	51.9%	47.7%	29.4%	53.2%	54.2%
Partial regression coefficients (additional percentage of variance explained)					
Female sex	2.86 ± 0.83 (0.86%)†	2.04 ± 0.93 (0.37%)*	−2.62 ± 0.68 (1.47%)‡	2.08 ± 0.51 (1.93%)‡	11.9 ± 1.04 (7.34%)‡
Heart rate, +10 bpm	−1.74 ± 0.42 (0.75%)†	−3.29 ± 0.48 (4.10%)‡	–	−2.43 ± 0.25 (3.74%)‡	−6.17 ± 0.53 (6.45%)‡
Body mass index, +4 kg/m^2	–	–	–	−0.75 ± 0.24 (0.44%)*	−1.35 ± 0.50 (0.65%)†
MAP, +10 mmHg	4.81 ± 0.44 (7.85%)‡	4.47 ± 0.51 (5.12%)‡	2.09 ± 0.36 (7.33%)‡	2.67 ± 0.27 (5.10%)‡	3.65 ± 0.57 (2.20%)‡
Antihypertensive treatment	–	3.60 ± 1.20 (0.90%)†	1.81 ± 0.89 (0.47%)*	1.47 ± 0.63 (0.52%)†	–
History of diabetes mellitus	6.04 ± 2.00 (0.68%)†	6.62 ± 2.42 (0.65%)†	5.90 ± 1.70 (2.08%)‡	2.70 ± 1.19 (0.43%)*	−5.23 ± 2.52 (0.32%)*
Smoking	–	–	–	–	4.01 ± 1.23 (1.08%)‡

We performed stepwise multiple regression with age and age^2 forced into the models to assess the independent correlations between haemodynamic indexes and risk factors such as sex, body mass index, heart rate, mean arterial pressure (MAP), history of diabetes mellitus, smoking and drinking status, and antihypertensive drug treatment. The partial regression coefficients are adjusted for age, age^2 and all other covariables entered in the model. *P* values for covariables to enter and stay in the regression models was set at 0.10 and 0.05, respectively. MAP, mean arterial pressure; Pb, backward wave amplitude; Pf, forward wave amplitude; PP, pulse pressure.
*$P < 0.05$.
†$P < 0.01$.
‡$P < 0.001$.

found borderline significant associations between end-diastolic volume index and cPP ($P = 0.035$) and between both end-diastolic and end-systolic volume index and Pf ($P \leq 0.049$; Supplemental Table S7, http://links.lww.com/HJH/A878). With exception of LV posterior wall thickness in women ($P = 0.038$), none of the LV structural and volumetric indexes were associated with reflection magnitude ($P \geq 0.067$ for all; Table 6; Supplemental Table S7, http://links.lww.com/HJH/A878).

DISCUSSION

The key findings of this study can be summarized as follows: an automated, commercial WSA algorithm often failed to separate Pf and Pb pulsatile load components from central aortic pressure waveform particularly in older women with unfavourable haemodynamic status; age significantly modified the relationship between forward and backward wave amplitudes; echocardiographic indexes reflecting LV diastolic function including left atrial volume were associated with both forward and backward haemodynamic load components similarly to the associations of LV indexes with cPP; the relationship between LV radial strain and any of the central hemodynamic load components was age-dependent, shifting from a positive to a negative relation from middle to older age.

Triangular-flow pressure-based WSA is proposed as a method that does not require measurement of aortic blood flow to derive forward and backward haemodynamic load components from central pressure waveforms [17]. Using a custom-designed program of pressure-based WSA method, Zamani *et al.* [14] was able to derive pulsatile load components from central pressure waveforms in 94.5% of 6336 participants recruited from a general population. On the other hand, previous study by Kips *et al.* [23] demonstrated that values of derived haemodynamic load components or aortic pulse transit time by pressure-based WSA algorithm differed substantially from the values obtained whenever using both measured aortic pressure and flow information.

Recently, an automated pressure-based WSA algorithm was implemented in the commercially available SphygmoCor software. Two recently published studies applied this automated WSA algorithm to derive Pf and Pb in a cohort of 879 outpatients across a wide age range and in 524 young-to-middle aged participants recruited from a general

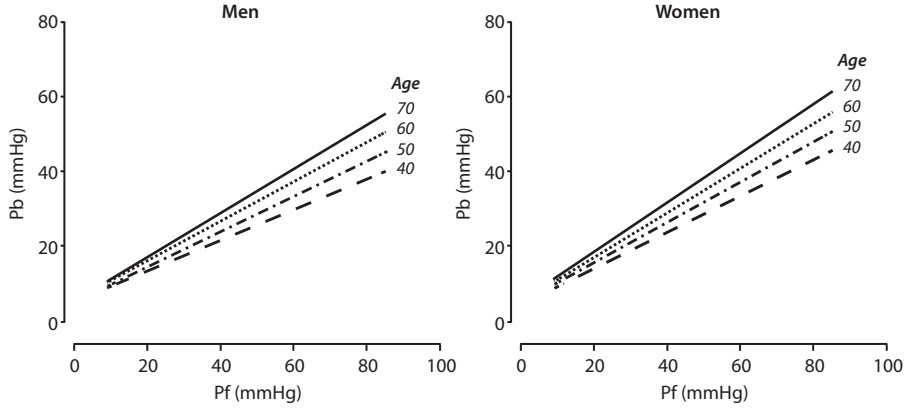

FIGURE 3 Extrapolation from the multivariable-adjusted relation between forward and backward wave amplitude at fixed levels of age and by sex. Backward (Pb) and forward (Pf) wave amplitude were adjusted for body mass index, heart rate, mean arterial pressure and treatment for hypertension. The number at the extrapolation line indicates the fixed level of age.

TABLE 5. Multivariable-adjusted associations of LV diastolic function and structure with central haemodynamics

	Central PP (+15 mmHg)		Pf (+10 mmHg)		Pb (+8 mmHg)		Reflection magnitude (+18%)	
Component	Parameter estimate (95% CI)	*P* value	Parameter estimate (95% CI)	*P* value	Parameter estimate (95% CI)	*P* value	Parameter estimate (95% CI)	*P* value
LV diastolic function								
LAV/height$^{2.0}$ (ml/m^2)	0.59 (0.21, 0.98)	0.0026	0.42 (0.088, 0.76)	0.013	0.50 (0.11, 0.90)	0.013	−0.099 (−0.54, 0.35)	0.66
E peak (cm/s)	3.56 (2.22, 4.89)	<0.0001	2.76 (1.60, 3.92)	<0.0001	2.86 (1.45, 4.27)	<0.0001	−0.81 (−2.43, 0.79)	0.32
A peak (cm/s)	2.91 (1.80, 4.02)	<0.0001	2.11 (0.11, 3.08)	<0.0001	2.52 (1.35, 3.69)	<0.0001	0.094 (−1.24, 1.43)	0.89
E/A ratio	0.033 (0.003, 0.062)	0.029	0.038 (0.012, 0.063)	0.0036	0.020 (−0.011, 0.051)	0.20	−0.043 (−0.078, −0.009)	0.015
TDI *e*′ peak (cm/s)	0.27 (0.085, 0.46)	0.0046	0.29 (0.13, 0.46)	0.0005	0.21 (0.013, 0.41)	0.037	−0.21 (−0.43, 0.018)	0.072
TDI *a*′ peak (cm/s)	−0.22 (−0.37, −0.060)	0.0066	−0.15 (−0.29, −0.019)	0.025	−0.23 (−0.40, 0.070)	0.0052	−0.028 (−0.21, 0.16)	0.76
E/e′ ratio	0.44 (0.29, 0.60)	<0.0001	0.32 (0.18, 0.45)	<0.0001	0.37 (0.21, 0.54)	<0.0001	−0.061 (−0.25, 0.13)	0.52
LV structure								
RWT	−0.003 (−0.008, 0.003)	0.34	−0.003 (−0.008, 0.002)	0.21	−0.001 (−0.007, 0.005)	0.68	0.006 (0.001, 0.012)	0.069
LVM/height$^{2.7}$ (g/m$^{2.7}$)	0.60 (−0.32, 1.52)	0.20	0.28 (−0.52, 1.08)	0.49	0.59 (−0.36, 1.55)	0.22	0.27 (−0.79, 1.33)	0.62

Parameter estimates (95% confidence interval) indicate absolute changes in left ventricular index associated with a 1 SD increase in central haemodynamic index. All parameter estimates were adjusted for age, sex, body height, body weight, heart rate, mean arterial pressure and class of antihypertensive treatment [β-blocker, calcium channel blocker and renin–angiotensin–aldosterone system (RAAS) inhibitors]. Adjustments for indexed left atrial volume and LV mass did not include body height and body weight. CI, confidence intervals; LAV, left atrial volume; LVM, left ventricular mass; Pb, backward wave amplitude; Pf, forward wave amplitude; PP, pulse pressure.

population [15,24]. Both studies did not report details on the software's feasibility in their cohorts [15,24]. In our community-based cohort, this automated WSA algorithm often failed to derive the haemodynamic load components particularly in older women with an unfavourable haemodynamic status. It should be noted that older women are more vulnerable to the detrimental effects of increased aortic pulsatility on LV function [9,11–13]. Thus, the low feasibility of applying the automated WSA algorithm in these patients might hamper its clinical applicability.

TABLE 6. Multivariable-adjusted associations of LV diastolic function and structure with central haemodynamic loads by sex

	Central PP (+15 mmHg)		Pf (+10 mmHg)		Pb (+8 mmHg)		Reflection magnitude (+18%)	
LV index	PE (95% CI)	*P* value	Parameter estimate; (95% CI)	*P* value	Parameter estimate; (95% CI)	*P* value	Parameter estimate; (95% CI)	*P* value
LV diastolic index								
LAV/height^2 (ml/m^2)								
Men	0.77 (0.22, 1.33)	0.0062	0.54 (0.067, 1.01)	0.025	0.68 (0.10, 1.26)	0.021	0.027 (−0.60, 0.66)	0.93
Women	0.58 (0.057, 1.09)	0.030	0.42 (−0.043, 0.88)	0.075	0.47 (−0.067, 1.00)	0.086	−0.22 (−0.83, 0.38)	0.47
E peak (cm/s)								
Men	3.00 (1.23, 5.73)	0.0010	2.37 (0.87, 3.87)	0.0021	1.88 (−0.016, 3.78)	0.052	−1.22 (−3.24, 0.80)	0.23
Women	4.01 (1.99, 6.02)	0.0001	3.18 (1.38, 4.97)	0.0006	3.67 (1.58, 5.77)	0.0007	−0.25 (−2.77, 2.26)	0.84
A peak (cm/s)								
Men	2.99 (1.57, 4.41)	<0.0001	2.19 (0.98, 3.40)	0.0004	2.28 (0.76, 3.80)	0.0034	−0.40 (−2.03, 1.24)	0.64
Women	2.75 (1.02, 4.48)	0.0019	1.99 (0.045, 3.54)	0.012	2.67 (0.87, 4.47)	0.0038	0.82 (−1.33, 2.96)	0.46
E/A ratio								
Men	0.021 (−0.022, 0.064)	0.33	0.035 (−0.001, 0.071)	0.059	0.001 (−0.045, 0.046)	0.98	−0.055 (−0.10, −0.007)	0.025
Women	0.038 (−0.002, 0.078)	0.060	0.037 (0.001, 0.072)	0.042	0.032 (−0.009, 0.074)	0.13	−0.035 (−0.084, 0.013)	0.15
TDI *e*′ (cm/s)								
Men	0.32 (0.053, 0.60)	0.020	0.33 (0.098, 0.56)	0.0053	0.22 (−0.071, 0.51)	0.14	−0.19 (−0.50, 0.12)	0.24
Women	0.16 (−0.10, 0.42)	0.23	0.24 (0.005, 0.47)	0.045	0.12 (−0.15, 0.39)	0.40	−0.34 (−0.65, −0.022)	0.036
TDI *a*′ (cm/s)								
Men	−0.16 (−0.38, 0.070)	0.18	−0.10 (−0.29, 0.087)	0.29	−0.18 (−0.42, 0.056)	0.13	−0.032 (−0.29, 0.22)	0.80
Women	−0.27 (−0.48, −0.051)	0.016	−0.18 (−0.37, 0.017)	0.074	−0.29 (−0.51, −0.063)	0.012	−0.090 (−0.35, 0.18)	0.51
E/e′ ratio								
Men	0.29 (0.11, 0.48)	0.0017	0.20 (0.054, 0.37)	0.0087	0.22 (0.021, 0.41)	0.030	−0.088 (−0.30, 0.12)	0.41
Women	0.59 (0.34, 0.85)	<0.0001	0.42 (0.19, 0.65)	0.0004	0.56 (0.29, 0.82)	<0.0001	0.047 (−0.27, 0.37)	0.78
LV structure								
RWT								
Men	−0.004 (−0.012, 0.004)	0.28	−0.004 (−0.011, 0.003)	0.27	−0.003 (−0.012, 0.005)	0.46	0.004 (−0.005, 0.012)	0.40
Women	−0.001 (−0.009, 0.007)	0.73	−0.002 (−0.009, 0.005)	0.54	0.0002 (−0.008, 0.008)	0.96	0.007 (−0.002, 0.017)	0.12
LVM/height$^{2.7}$ (g/m$^{2.7}$)								
Men	0.98 (−0.28, 2.24)	0.13	0.67 (−0.41, 1.75)	0.22	0.82 (−0.51, 2.16)	0.23	−0.35 (−1.77, 1.07)	0.63
Women	0.63 (−0.68, 1.95)	0.34	0.24 (−0.93, 1.41)	0.68	0.74 (−0.60, 2.09)	0.28	0.98 (−0.57, 2.53)	0.22

Parameter estimates (95% confidence interval) indicate absolute changes in left ventricular index associated with a 1 SD increase in central haemodynamic index. All parameter estimates were adjusted for age, body height, body weight, heart rate, mean arterial pressure and antihypertensive treatment. Adjustments for indexed left atrial volume and LV mass index did not include body height and body weight. LAV indicates left atrial volume; LVM, left ventricular mass; Pb, backward wave amplitude; Pf, forward wave amplitude; PP, pulse pressure; RWT, relative wall thickness.

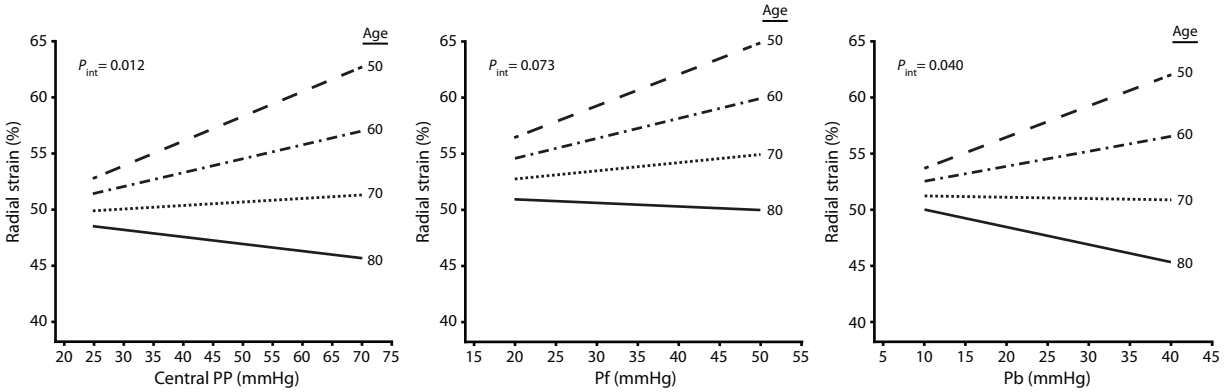

FIGURE 4 Extrapolation from the multivariable-adjusted relation of radial strain in relation to central haemodynamic load components at fixed levels of age. The number at the extrapolation line indicates the fixed level of age.

In our study, all derived pulsatile load components increased curvilinearly with age. Moreover, age significantly modulated the direct relationship between pulsatile load components (Pf and Pb). Aortic stiffening because of ageing or other cardiovascular risk factors results in greater changes in aortic pressure during LV ejection. Aortic (central) PP, thus, reflects pulsatile stress and aortic rigidity [25]. The central BP augmentation following arterial stiffening might be explained by decreased proximal aortic reservoir function [3–5] and increased forward wave propagation and reflection [1,2]. Numerous studies already showed that cPP plays an important role in the development of clinically overt heart failure [26,27]. In contrast, large-scale outcome studies investigating the prognostic value of the forward and backward pulsatile loads for incidence of cardiovascular morbidity [16], mortality [28] and heart failure [14] came to discrepant conclusions.

LV diastolic function tends to worsen over the adult life course and in the presence of cardiovascular risk factors such as hypertension and diabetes mellitus [29]. Conventional echocardiography and TDI allow the detection of subclinical deterioration of LV diastolic function [30]. Impaired LV myocardial relaxation is characterized by decreased transmitral early (*E*) and enhanced late (*A*) diastolic blood velocities. Furthermore, combining early transmitral flow velocity with early mitral annular TDI velocity (E/e' ratio) allows evaluation of LV-filling pressure.

Community-based studies reported an independent association between subclinical LV diastolic dysfunction and decreased aortic compliance as reflected by increased cPP [10–13]. For instance, in a recent longitudinal study in 607 random participants, we showed that women are more vulnerable to the detrimental effects of increased cPP on LV diastolic function over time than men [9]. In fact, the greater values of aortic stiffness and central pulsatility observed in women as compared with men might explain the higher likelihood of women to develop heart failure with preserved ejection fraction [10,12].

Previous studies suggested that the detrimental effects of increased central haemodynamics on LV diastolic dysfunction and left atrial volume might be mediated by the haemodynamic loads of both the Pf and Pb waves. For instance, in 524 young-to-middle aged participants [15], E/e' ratio reflected LV-filling pressure was independently associated with both haemodynamic load components. These observations are in line with our findings. In addition, we showed greater association size and statistical significance of the association of E/e' ratio with both Pf and Pb components in women compared with men. On the other hand, we could not gain any additional information from the association of LV diastolic function with Pf or Pb over and beyond the association we already observed with cPP. Indeed, E/e' ratio was more strongly associated with the composite cPP compared with haemodynamic load components in all participants as well as in both sexes (Supplemental Table S4, http://links.lww.com/HJH/A878). Moreover, in our cross-sectional study, reflection magnitude was not significantly related to the most clinically useful parameters reflecting LV diastolic relaxation and filling pressure.

As we reported previously, our study also demonstrated the age-dependent relationship between radial systolic function and cPP [10]. Similarly, LV radial strain increased significantly with higher Pf and Pb only in middle-aged participants. Once again, no additional information was retrieved from the association between LV radial strain and Pf or Pb over and beyond the association we reported with cPP.

The present study must be interpreted within the context of its potential limitations and strengths. First, echocardiographic measurements are susceptible to measurement errors by cause of signal noise, acoustic artefacts and angle dependency. All echocardiographic images, however, were recorded and postprocessed by one experienced observer (T.K.) using a highly standardized protocol. Second, because of the failure of the commercial WSA algorithm to derive Pf and Pb, we excluded from the statistical analysis a substantial number of participants (18%), particularly elderly women with worse haemodynamic profile. Third, our study population included white Europeans only, limiting the extrapolation of our findings to other ethnicities.

In conclusion, our findings underscored the importance of central haemodynamics for prediction of LV dysfunction. We also questioned the clinical usefulness of an automated, commercial WSA algorithm because of its low feasibility in participants with unfavourable haemodynamic status.

ACKNOWLEDGEMENTS

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Kass DA. Ventricular arterial stiffening: integrating the pathophysiology. *Hypertension* 2005; 46:185–193.
2. Nichols WW, Singh BM. Augmentation index as a measure of peripheral vascular disease state. *Curr Opin Cardiol* 2002; 17:543–551.
3. Wang JJ, O'Brien AB, Shrive NG, Parker KH, Tyberg JV. Time-domain representation of ventricular-arterial coupling as a windkessel and wave system. *Am J Physiol Heart Circ Physiol* 2003; 284:H1358–H1368.
4. Davies JE, Baksi J, Francis DP, Hadjiloizou N, Whinnett ZI, Manisty CH, *et al*. The arterial reservoir pressure increases with aging and is the major determinant of the aortic augmentation index. *Am J Physiol Heart Circ Physiol* 2010; 298:H580–H586.
5. Schultz MG, Davies JE, Hardikar A, Pitt S, Moraldo M, Dhutia N, *et al*. Aortic reservoir pressure corresponds to cyclic changes in aortic volume: physiological validation in humans. *Arterioscler Thromb Vasc Biol* 2014; 34:1597–1603.
6. Chen CH, Nakayama M, Nevo E, Fetics BJ, Lowell Maughan W, Kass DA. Coupled systolic-ventricular and vascular stiffening with age: implications for pressure regulation and cardiac reserve in the elderly. *J Am Coll Cardiol* 1998; 32:1221–1227.
7. Saba PS, Ganau A, Devereux RB, Pini R, Pickering TG, Roman MJ. Impact of arterial elastance as a measure of vascular load on left ventricular geometry in hypertension. *J Hypertens* 1999; 17:1007–1015.
8. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: Implications for systolic and diastolic reserve limitations. *Circulation* 2003; 107:714–720.
9. Cauwenberghs N, Knez J, D'hooge J, Thijs L, Yang WY, Wei FF, *et al*. Longitudinal changes in LV structure and diastolic function in relation to arterial properties in general population. *JACC Cardiovasc Imaging* 2017; Mar 10. pii: S1936-878X(17)30135-3. [Epub ahead of print].
10. Cauwenberghs N, Knez J, Tikhonoff V, D'hooge J, Kloch-Badelek M, Thijs L, *et al*. Doppler indexes of left ventricular systolic and diastolic function in relation to the arterial stiffness in a general population. *J Hypertens* 2016; 34:762–771.
11. Russo C, Jin Z, Palmieri V, Homma S, Rundek T, Elkind MS, *et al*. Arterial stiffness and wave reflection: sex differences and relationship with left ventricular diastolic function. *Hypertension* 2012; 60:362–368.
12. Coutinho T, Borlaug BA, Pellikka PA, Turner ST, Kullo IJ. Sex differences in arterial stiffness and ventricular-arterial interactions. *J Am Coll Cardiol* 2013; 61:96–103.
13. Shim CY, Park S, Choi D, Yang WI, Cho IJ, Choi EY, *et al*. Sex differences in central hemodynamics and their relationship to left ventricular diastolic function. *J Am Coll Cardiol* 2011; 57:1226–1233.
14. Zamani P, Bluemke DA, Jacobs DRJ, Duprez DA, Kronmal R, Lilly SM, *et al*. Resistive and pulsatile arterial load as predictors of left ventricular mass and geometry: the Multi-Ethnic Study of Atherosclerosis. *Hypertension* 2015; 65:85–92.
15. Peterson VR, Woodiwiss AJ, Libhaber CD, Raymond A, Sareli P, Norton GR. Cardiac diastolic dysfunction is associated with aortic wave reflection, but not stiffness in a predominantly young-to-middle-aged community sample. *Am J Hypertens* 2016; 29:1148–1157.
16. Cooper LL, Rong J, Benjamin EJ, Larson MG, Levy D, Vita JA, *et al*. Components of hemodynamic load and cardiovascular events: the Framingham Heart Study. *Circulation* 2015; 131:354–361.
17. Westerhof BE, Guelen I, Westerhof N, Karemaker JM, Avolio A. Quantification of wave reflection in the human aorta from pressure alone: a proof of principle. *Hypertension* 2006; 48:595–601.
18. Salvi E, Kuznetsova T, Thijs L, Lupoli S, Stolarz-Skrzypek K, D'Avila F, *et al*. Target sequencing, cell experiments, and a population study establish endothelial nitric oxide synthase (eNOS) gene as hypertension susceptibility gene. *Hypertension* 2013; 62:844–852.
19. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, *et al*. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; 28:1–39.e14.
20. Kuznetsova T, Herbots L, Lopez B, Jin Y, Richart T, Thijs L, *et al*. Prevalence of left ventricular diastolic dysfunction in a general population. *Circ Heart Fail* 2009; 2:105–112.
21. Kuznetsova T, Herbots L, Richart T, D'hooge J, Thijs L, Fagard RH, *et al*. Left ventricular strain and strain rate in a general population. *Eur Heart J* 2008; 29:2014–2023.
22. Bos WJW, Verrij E, Vincent HH, Westerhof BE, Parati G, van Montfrans GA. How to assess mean blood pressure properly at the brachial artery level. *J Hypertens* 2007; 25:751–755.
23. Kips JG, Rietzschel ER, De Buyzere ML, Westerhof BE, Gillebert TC, Van Bortel LM, *et al*. Evaluation of noninvasive methods to assess wave reflection and pulse transit time from the pressure waveform alone. *Hypertension* 2009; 53:142–149.
24. Namasivayam M, Adji A, O'Rourke MF. Evaluating the hemodynamic basis of age-related central blood pressure change using aortic flow triangulation. *Am J Hypertens* 2016; 29:178–184.
25. Safar ME. New problems raised by increased pulse pressure. *Eur Hear J* 2005; 26:2081–2082.
26. Curtis SL, Zambanini A, Mayet J, McG Thom SA, Foale R, Parker KH, *et al*. Reduced systolic wave generation and increased peripheral wave reflection in chronic heart failure. *Am J Physiol Heart Circ Physiol* 2007; 293:H557–H562.
27. Mitchell GF, Tardif JC, Arnold JM, Marchiori G, O'Brien TX, Dunlap ME, *et al*. Pulsatile hemodynamics in congestive heart failure. *Hypertension* 2001; 38:1433–1439.
28. Cheng HM, Chuang SY, Wang JJ, Shih YT, Wang HN, Huang CJ, *et al*. Prognostic significance of mechanical biomarkers derived from pulse wave analysis for predicting long-term cardiovascular mortality in two population-based cohorts. *Int J Cardiol* 2016; 215: 388–395.
29. Kuznetsova T, Thijs L, Knez J, Cauwenberghs N, Petit T, Gu YM, *et al*. Longitudinal changes in left ventricular diastolic function in a general population. *Circ Cardiovasc Imaging* 2015; 33 (Suppl 1):e66.
30. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, *et al*. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009; 22: 107–133.

Reviewer's Summary Evaluation

Reviewer 2

A central blood pressure (BP) approach may be more sensitive than a conventional brachial BP approach in estimating the impact of hemodynamic load on cardiovascular structure and function. Emerging evidence supports the view that the adverse effects of increased central hemodynamics on left ventricular diastolic properties might be dependent on the hemodynamic loads of both the forward and backward waves. The study by Cauwenberghs *et al*. adds a new piece of information on this issue by showing that the association between both the hemodynamic components and a validated Tissue Doppler index of LV filling pressure (E/e′ ratio) is greater in women than in men.