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ORIGINAL ARTICLE

Cardio-ankle vascular index and subclinical heart disease

Giuseppe Schillaci[1,2], Francesca Battista[1,2], Laura Settimi[1], Fabio Anastasio[1,2] and Giacomo Pucci[1,2]

The relationship between arterial stiffness, measured as pulse wave velocity (PWV), and the left ventricle is confounded by the effects of blood pressure. We evaluated the relationship between carotid–femoral PWV and cardio-ankle vascular index (CAVI), a less pressure-dependent measurement of the stiffness constant (β) of the aorta and the iliac, femoral and tibial arteries, and obtained prognostically relevant measurements of left ventricular structure and systolic function. CAVI, carotid–femoral PWV and echocardiographic left ventricular mass and systolic function were determined in 133 subjects with either hypertension or high–normal blood pressure (33% treated; 56 ± 16 years, blood pressure 145/89 ± 21/12 mm Hg). Carotid–femoral PWV exhibited a direct relationship with systolic and diastolic blood pressure ($r = 0.33/0.26$, $P < 0.001/0.014$), whereas CAVI demonstrated no such relationship ($r = 0.12/-0.05$, both $P > 0.1$). Both CAVI and PWV correlated significantly with left ventricular mass index ($r = 0.31$, $P < 0.001$; $r = 0.21$, $P = 0.014$). Subjects with inappropriately high left ventricular masses for a given cardiac workload ($n = 44$) had higher CAVI values (9.1 ± 2.0 *vs.* 7.9 ± 1.6, $P < 0.001$), but not higher PWV values (8.5 ± 2.5 *vs.* 8.7 ± 2.4, $P > 0.1$). In a multivariate regression model, CAVI was independently associated with inappropriate left ventricular mass ($\beta = 0.40$, $P < 0.001$), along with body mass index. CAVI also demonstrated a negative relationship with left ventricular midwall fractional shortening ($r = -0.41$, $P = 0.001$) that was independent of age, sex, blood pressure and left ventricular mass in a multivariate analysis. In conclusion, a high CAVI is associated with inappropriately high left ventricular mass and low midwall systolic function. As a marker of arterial diastolic-to-systolic stiffening, CAVI may have a relationship with left ventricular structure and function that is independent of blood pressure levels.
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Keywords: arterial stiffness; cardio-ankle vascular index; inappropriate left ventricular mass; midwall fractional shortening; pulse wave velocity

INTRODUCTION

Arterial stiffness is both a major contributor to systolic hypertension and an independent predictor of cardiovascular morbidity and mortality in the general population,[1–3] as well as in the settings of high-risk conditions such as hypertension[4] and type 2 diabetes.[5] Measurement of carotid–femoral pulse wave velocity (PWV), a direct measure of large-artery stiffness, improves model fit and reclassifies risk for future cardiovascular events in models that include standard risk factors.[6] Consequently, the assessment of aortic PWV has been recommended by the European Societies of Hypertension and Cardiology for cardiovascular risk stratification in hypertensive subjects.[7]

Arterial wall stiffness is a major determinant of left ventricular (LV) afterload. Carotid–femoral PWV, a direct measure of aortic stiffness, has a significant and direct relationship with LV mass.[8–10] However, PWV is intrinsically dependent on blood pressure (BP),[11,12] and the above relationships between PWV and LV mass are generally no longer significant when the effects of BP are taken into account.[8–10] Notably, PWV is measured using diastolic pressure, as transit time is calculated at the foot of the pulse wave. As arterial elastic behavior is pressure dependent,[13,14] aortic PWV, which is used to estimate diastolic stiffness, may be a less suitable means of determining effective cardiac afterload. Previous studies have suggested that increases in arterial stiffness, which may be observed during physical exercise[15] and throughout the cardiac cycle using diastolic and systolic BP levels,[16] may be more closely related to LV mass, although there is a need for simple, easy-to-use bedside markers of the pressure dependency of arterial stiffness.

Cardio-ankle vascular index (CAVI) is a noninvasive indirect estimate of the arterial stiffness index, β, of the aorta and the iliac, femoral and tibial arteries based on the formula of Bramwell–Hill.[17] The stiffness parameter β is based on changes in vascular diameter corresponding to changes in arterial pressure, and its value does not depend on BP at the time of measurement.[13,18] As a measure of the increase in arterial stiffness occurring between diastolic and systolic BP values, β incorporates information on arterial properties during the entirety of systole (diastolic-to-systolic 'stiffening').[17] CAVI is less pressure dependent than PWV that samples arterial stiffness at a given

[1]Dipartimento di Medicina, Università di Perugia, Perugia, Italy and [2]Struttura Complessa di Medicina Interna, Azienda Ospedaliero-Universitaria di Terni, Terni, Italy
Correspondence: Professor G Schillaci, Unità di Medicina Interna, Azienda Ospedaliero-Universitaria di Terni, Piazzale Tristano di Joannuccio, 1, IT-05100 Terni, Italy.
E-mail: giuseppe.schillaci@unipg.it
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point of the cardiac cycle—usually end-diastole—and is therefore strongly dependent on BP.[17]

To the best of our knowledge, the impacts of CAVI and carotid-femoral PWV on cardiac structure and function have never been compared directly. As pressure-dependent changes in arterial stiffness affect arterial compliance and LV afterload, we hypothesized that CAVI, an indirect marker of diastolic-to-systolic 'stiffening', may be related to LV mass and systolic function. Therefore, we undertook the present study with the aim of investigating the links between CAVI and carotid–femoral PWV with LV mass and systolic function in subjects with either high–normal or high BP. We focused particularly on the impact of arterial stiffness indices on two prognostically relevant markers of subclinical cardiac organ damage, namely inappropriately high LV mass, or values of LV mass exceeding levels needed to compensate for a given hemodynamic load,[19,20] and LV systolic dysfunction, defined as low afterload-corrected midwall fractional shortening.[21–23]

METHODS

Subjects

We analyzed data from 161 consecutive subjects with either high–normal or high BP who were referred to our hypertension outpatient clinic by their general practitioners. Subjects with either high–normal BP (office BP between 130/85 and 139/89 mm Hg on $\geqslant 3$ visits at 1-week intervals) or essential hypertension (office BP $\geqslant 140/90$ mm Hg on $\geqslant 3$ visits at 1-week intervals or receiving BP-lowering drug treatment) were enrolled. Hypertensive subjects were included if they were either untreated or receiving stable drug treatment: subjects who had started or changed their antihypertensive treatment within a year of the study were excluded. We also excluded subjects with an LV ejection fraction $<50\%$, clinical or laboratory evidence of heart failure, coronary heart disease, previous stroke, valvular defects or secondary causes of hypertension, atrial fibrillation or important concomitant disease. A total of 18 individuals (11%) were excluded because of poor-quality echocardiograms. As lower-extremity arterial disease artificially decreases lower-extremity arterial stiffness,[24] we excluded 10 subjects with an ankle-brachial BP index of <1, leaving 133 patients for analysis. All subjects provided informed consent to participate in the study that was approved by the institutional ethics committee.

Clinical and vascular assessment

All measurements were conducted in a quiet room kept at a constant temperature. Office BPs were measured by a physician in the hospital outpatient clinic with a mercury sphygmomanometer, with the subject sitting for $\geqslant 10$ min. The average of six measurements from $\geqslant 2$ sessions was used for analysis.

CAVI was recorded using a Vasera VS-1500 vascular screening system (Fukuda Denshi, Tokyo, Japan) immediately following the echocardiographic examination, with the patient resting in a supine position. CAVI is used to measure arterial stiffness from the aortic valve to the ankle.[17] Briefly, CAVI is an indirect estimate of the arterial stiffness index, β, as described by Hayashi *et al.*,[13] with PWV replacing arterial distension according to the equation of Bramwell–Hill. CAVI was determined using the following equation:

$$\mathrm{CAVI} = a\left[\left(\frac{2\rho}{\mathrm{SBP}-\mathrm{DBP}}\right)\times \ln\left(\frac{\mathrm{SBP}}{\mathrm{DBP}}\right)\times \mathrm{PWV}^2\right] + b,$$

where SBP and DBP are systolic and diastolic blood pressure, ρ is blood density, PWV is calculated from the aortic valve to the ankle, and a and b are constants. ECG electrodes were placed on both wrists: a microphone to detect heart sounds was placed on the sternum, and cuffs were wrapped around both arms and both ankles. Following automatic measurements, data were analyzed using VSS-10 software (Fukuda Denshi), and right and left CAVI values were calculated. The higher of the two CAVI values was used for analysis. In our laboratory, the intraobserver coefficient of variation of CAVI was 5.7% in 40 healthy young volunteers.

Carotid–femoral PWV was determined with the SphygmoCor system (SphygmoCor Vx, AtCor Medical, Sydney, Australia) that uses a high-fidelity applanation tonometer to sequentially measure pressure pulse waveforms in two peripheral artery sites. PWV was obtained using measurements of common carotid and femoral artery waveforms as described previously.[25] Transit time was calculated using the R-wave of the surface ECG as a common reference. PWV was automatically calculated using measurements of pulse transit time and the distance between the two sites according to the following formula: PWV ($\mathrm{m\,s^{-1}}$) = distance (m)/transit time (s). Path length was calculated by subtracting the distance between the carotid artery measurement site and the suprasternal notch from the distance between the femoral artery site and the suprasternal notch, all of which were measured directly using a caliper. The intraobserver coefficient of variation of carotid–femoral PWV in our laboratory was 5.1%.[26]

Echocardiography

M-mode echocardiographic studies of the left ventricle were performed under two-dimensional control as reported previously[27] by two investigators (GS and GP) who were unaware of patients' clinical data. LV mass was indexed by height$^{2.7}$ to correct for weight.[28] LV hypertrophy was defined as an LV mass index $\geqslant 51\,\mathrm{g\times m^{-2.7}}$ in both sexes. Relative wall thickness was calculated as follows: (2 × posterior wall thickness/LV internal diameter). LV end-diastolic and end-systolic volumes and stroke volume were calculated using the formula of Teichholz *et al.*[29] In our laboratory, the intraobserver test–retest 90% interval of agreement for LV mass measurements was −16 to +14 g.[30] The interobserver test–retest 90% interval of agreement was −20 to +18 g.

Excess LV mass, determined relative to the mass needed to sustain cardiac load, a well-known physiologic concept referred to as inappropriately high LV mass,[31] was estimated on the basis of the following equation developed using a reference population of 121 normotensive, normal-weight adults, aged 18 to 84 years ($R^2 = 0.53$, standard error of the estimate 27.3 g, $P<0.001$): predicted LV mass (g) = −11.4+(0.44 × stroke work)+(17.9 × height$^{2.7}$)+(18.2 × sex), where sex = 2 for men and 1 for women.[30] Stroke work was estimated as systolic BP multiplied by stroke volume and converted to g × m by multiplying by 0.0144.[32] Total external myocardial work may be dimensionally represented by the force (maximal systolic pressure) needed to eject a certain amount of blood into the aorta. Maximal systolic pressure may be surrogated using cuff systolic pressure under the assumption that kinetic energy is negligible in resting conditions.[33] This allows for an efficient determination of stroke work and an individual assessment of compensatory and noncompensatory LV modifications using fully noninvasive methods. An observed/predicted LV mass ratio of 133% identified the 95th percentile of its distribution in the reference population. The subjects with observed/predicted LV mass ratios of $>133\%$ were classified as having inappropriately high LV masses.[30]

LV mechanics was assessed at the chamber level as endocardial fractional shortening, and at the midwall level using a geometric model that takes into account the nonuniform systolic thickening of the LV wall.[21,22] Fractional shortening was considered both in absolute terms and after correcting for afterload, as a percentage of the value predicted from end-systolic circumferential wall stress with regression equations from previously studied normotensive subjects.[23] A midwall fractional shortening value below the 5th percentile of afterload-corrected midwall fractional shortening for normotensive subjects was defined as midwall systolic dysfunction, and a midwall fractional shortening value of >5th percentile was defined as normal midwall systolic function.

Statistical analysis

Descriptive statistics are provided as means and s.d. or as frequencies and percentages. Pearson's correlation coefficients were used when appropriate and compared using the z-test. The associations of continuous parameters in univariate analyses were evaluated using Pearson's correlation. Characteristics of participants with appropriate and inappropriate LV masses were compared using the unpaired-sample t-test. Before performing the linear regression analysis, we assessed whether the relationship between CAVI and LV parameters was any different between treated and untreated subjects using linear regression models for CAVI with terms for LV mass, treatment status

and an LV mass × treatment status interaction term. As the interaction terms were not significant, the study population as a whole was used to assess the independent predictors of appropriate LV mass and midwall fractional shortening using stepwise multivariate linear regression. Variables were included in the model if they were established or putative determinants, or if they achieved a significance value of <0.30 in an initial regression analysis with an 'entry' model. The final models were evaluated for other linear relationships among variables (multicollinearity) that have the potential to render significance testing unreliable. A variance inflation factor of <5 was assumed to exclude significant collinearity among the covariates in the models.[34]

RESULTS

We examined 33 individuals with high–normal BP and 100 patients with essential hypertension. Fifty-six hypertensive subjects were untreated, and 44 had been receiving stable BP-lowering drug treatment for $\geqslant 1$ year. Primary characteristics of the study population are reported in Table 1.

As expected, carotid–femoral PWV significantly and directly correlated with both systolic BP ($r=0.33$, $P<0.001$) and diastolic BP ($r=0.25$, $P<0.01$). CAVI had no significant relationships with either systolic BP ($r=0.15$, $P=0.11$; Figure 1, left panel) or diastolic BP ($r=-0.02$, $P=0.76$). The relationship between systolic BP and PWV was significantly stronger than that between systolic BP and CAVI ($P=0.014$, *z*-test for comparison between *r* values). CAVI and carotid–femoral PWV correlated significantly with each other, although the strength of the correlation was only moderate ($r=0.46$, $P<0.001$; Figure 1, right panel).

As the analysis of the interaction term 'treatment status × inappropriate LV mass' revealed no significant effects of treatment status on the relationship between CAVI and inappropriate LV mass ($P=0.45$), the study population as a whole was used to assess the relationships between CAVI and inappropriate LV mass. CAVI significantly and directly correlated with LV mass when indexed by body surface area ($r=0.33$, $P<0.001$) and height$^{2.7}$ ($r=0.31$, $P<0.001$; Figure 2, left panel). Carotid–femoral PWV also correlated with LV mass index among the entire population ($r=0.20$, $P=0.033$ and $r=0.21$, $P=0.014$, respectively), as well as within the subgroup with appropriate LV masses ($r=0.26$, $P=0.017$ and $r=0.29$, $P=0.008$, respectively). Participants with inappropriate LV masses ($n=44$) did not differ in age from the subjects whose LV masses were appropriate for their cardiac workloads ($n=89$; 58.5 ± 15 years *vs.* 54.1 ± 16 years, $P=0.13$). As shown in Figure 3, individuals with inappropriate LV masses had significantly higher CAVIs, although the two groups did not differ in terms of carotid–femoral PWV. In a multivariate linear regression model (multiple $R^2=0.20$), inappropriately high LV mass was independently predicted by CAVI ($\beta=0.40$, $P<0.001$) and body mass index ($\beta=0.19$, $P=0.022$). Systolic BP, age, sex, body height, serum lipids and glucose, antihypertensive drug treatment and smoking habits failed to enter the model. When the analysis was limited to only untreated subjects ($n=89$), CAVI remained an independent predictor of inappropriate LV mass ($\beta=0.57$, $P<0.001$).

An inverse relationship was observed between CAVI and LV fractional shortening, the latter of which was assessed at both endocardial ($r=-0.33$, $P<0.001$) and midwall levels ($r=-0.41$, $P<0.001$; Figure 2, right panel). Carotid–femoral PWV was not significantly related to measurements of LV systolic function (endocardial fractional shortening, $r=-0.04$, $P=0.66$; midwall fractional shortening, $r=-0.14$, $P=0.14$). Participants with low LV midwall systolic function ($n=24$) were older (62.7 ± 17 *vs.* 53.9 ± 16 years) and had a higher systolic BP ($149/89\pm21/13$ *vs.* $144/89\pm20/11$ mm Hg) than subjects with normal systolic function ($n=109$), although the difference in BP was not significant. As shown in Figure 4, individuals with low LV midwall systolic function had a significantly higher CAVI than subjects with normal systolic function, although the two groups did not differ in terms of carotid–femoral PWV. In a multivariate linear regression model (multiple $R^2=0.29$), midwall fractional shortening was independently predicted by and inversely related to LV mass ($\beta=-0.37$, $P<0.001$) and CAVI ($\beta=-0.31$, $P<0.001$). Body mass index, systolic BP, age, sex, body height, serum lipids and glucose, antihypertensive drug treatment and smoking habits failed to enter the model. The independent relationship between CAVI with LV midwall fractional shortening was also confirmed in untreated subjects ($\beta=0.27$, $P<0.01$).

Table 1 Clinical characteristics of 133 study subjects with high–normal or high blood pressure

Variable	*Mean (s.d.) or %*
Age, years	56 (16)
Men, %	62
Body mass index, kg m^{-2}	26.7 (5)
Smokers, %	17
Diabetes, %	11
Systolic/diastolic BP, mm Hg	145/89 (21/12)
Heart rate, b.p.m.	68 (12)
LV mass index, g m$^{-2.7}$	45.6 (12)
LV relative wall thickness	0.44 (0.07)
Cardio-ankle vascular index	8.4 (1.9)
Carotid–femoral PWV, m s^{-1}	8.7 (2.4)

Abbreviations: BP, blood pressure; LV, left ventricular; PWV, pulse wave velocity.

DISCUSSION

The primary novel finding of the present paper is that the CAVI parameter of arterial stiffness is higher in patients with subclinical heart disease, defined as inappropriately high LV mass or LV systolic dysfunction among subjects with hypertension or with high–normal BP. CAVI was independently associated with important, prognostically adverse markers of LV structure and function, such as inappropriate LV mass and low LV midwall fractional shortening, relationships independent of BP. We also confirmed that CAVI is a less pressure-dependent measurement than aortic PWV.

Arterial stiffness determines the premature return of reflected waves in systole that increases central pulse pressure and left ventricular afterload. The heart adapts to face the arterial stiffness-related increase in LV afterload by developing ventricular hypertrophy that eventually leads to systolic dysfunction. Although aortic stiffness, which is assessed by carotid–femoral PWV, has been linked to LV remodeling and dysfunction in cross-sectional studies,[8–10] the relationship between PWV and the left ventricle is confounded by the effects of BP that is both a major determinant of LV mass[35,36] and a strong correlate of arterial PWV.[11,12] Previous studies have generally shown that aortic PWV does not significantly correlate with LV mass when the effects of BP are taken into account.[8–10] The present study confirms that carotid–femoral PWV does not have a significant BP-independent relationship with LV mass. Moreover, we found that PWV has an inverse relationship with LV midwall systolic function, although the above relationship was not insignificant and was not independent of BP values. Taken together, our findings and previous data[16] suggest that diastolic arterial stiffness may not have a major impact on LV mass and function once the role of BP is taken into account.

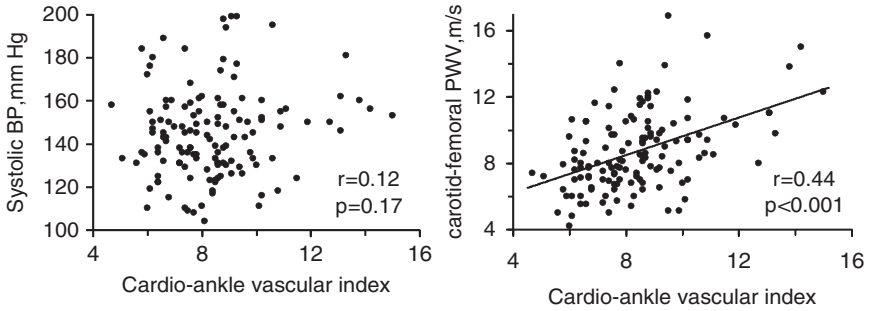

Figure 1 Scatter plots illustrating the bivariate correlations of cardio-ankle vascular index (CAVI) with systolic blood pressure (BP; left panel) and with carotid–femoral pulse wave velocity (PWV; right panel) in 133 subjects with either hypertension or high–normal blood pressure.

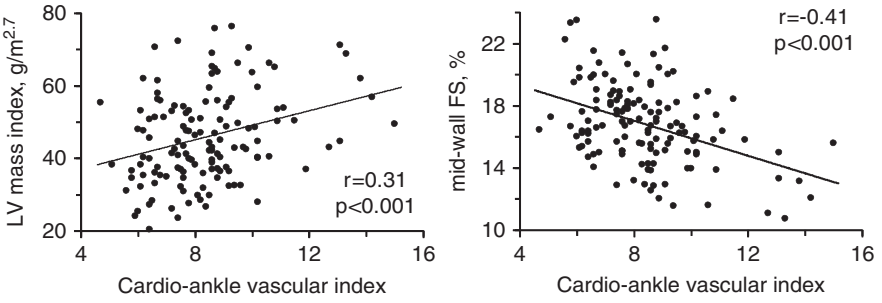

Figure 2 Scatter plots illustrating the bivariate correlations of cardio-ankle vascular index (CAVI) with left ventricular (LV) mass index (left panel) and with left ventricular midwall fractional shortening (FS; right panel) in 133 subjects with either hypertension or high–normal blood pressure.

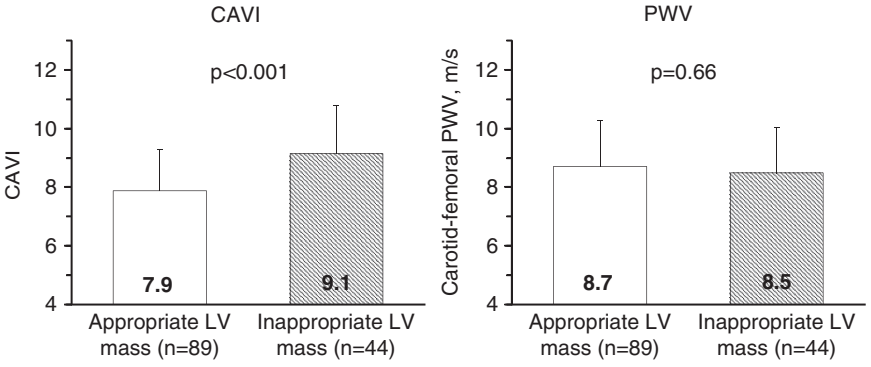

Figure 3 Cardio-ankle vascular index (CAVI; left panel) and carotid–femoral pulse wave velocity (PWV; right panel) in study participants with appropriate and inappropriate left ventricular (LV) masses. See text for explanations.

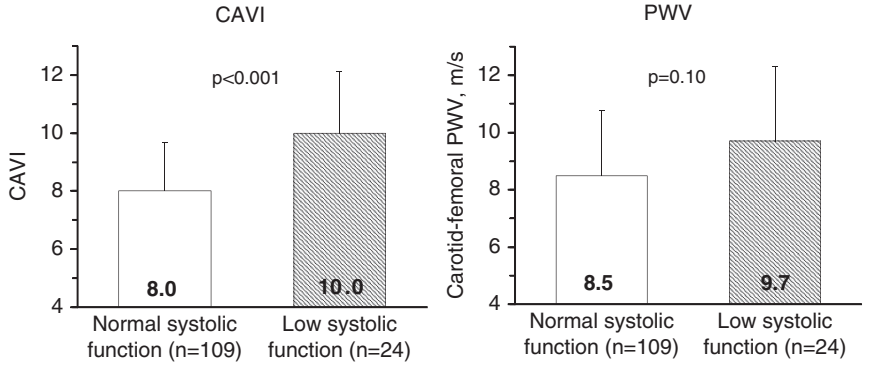

Figure 4 Cardio-ankle vascular index (CAVI; left panel) and carotid–femoral pulse wave velocity (PWV; right panel) in study participants with left ventricular midwall systolic dysfunction *vs.* study participants without left ventricular (LV) midwall systolic dysfunction. See text for explanations.

Among the various noninvasive markers of arterial stiffness, CAVI has been theoretically proposed as an indirect estimate of the stiffness parameter, β, that is obtained by the logarithmic expression of the change in internal pressure of the vessel wall and changes in vascular diameter and is independent of BP.[13] It should be noted that although systolic and diastolic BP are included in the equation, CAVI itself may not be pressure dependent, as it expresses the theoretically pressure-independent stiffness parameter, β. Previous studies have demonstrated that the contribution of BP to CAVI was weaker than its contribution to carotid–femoral PWV.[17] Our findings also support the weak correlation between CAVI and systolic and diastolic BP.

The reasons why CAVI may have a stronger impact on LV mass and function than carotid–femoral PWV may be twofold. First, CAVI is based on the pressure-independent stiffness constant (β), a marker of arterial diastolic-to-systolic stiffening, whereas PWV is a marker of diastolic arterial stiffness, as it accounts for foot-to-foot transit time that inherently involves measurements of diastolic BP. Diastolic-to-systolic stiffening, obtained from combined carotid ultrasound and tonometry recordings, may be more closely related to LV mass than to diastolic arterial stiffness,[16] and indices of hemodynamic load provoked by isometric exercise predict LV mass in hypertension better than carotid–femoral PWV measured at rest.[15] Taken together, these findings support our hypothesis that the pressure dependency of arterial stiffness, a marker of effective LV afterload,[37] may be a strong determinant of LV mass. Second, CAVI and carotid–femoral PWV explore different arterial pathways. Specifically, CAVI measurements include the proximal ascending aortic segment, as well as the femoral, popliteal and tibial arteries. Wall stiffness of the ascending aorta assessed by tissue-Doppler imaging is independently related to LV mass index,[38] and age-related elongation and stiffening of the ascending aorta assessed by magnetic resonance imaging are both related to LV mass and concentric remodeling.[39] The inclusion of lower-limb arterial segments may also play a role. Previous studies have shown that measures of regional stiffness, which also include peripheral arterial studies such as cardio-ankle PWV, were more strongly associated with electrocardiographic LV hypertrophy than carotid–femoral PWV.[40] Moreover, brachial-ankle PWV was more strongly related to echocardiographic LV mass than carotid–femoral PWV.[41] These data raise the possibility that peripheral muscular arteries may contribute to the ventricular–arterial interaction in a manner independent of the central arteries.

The findings of the present study have several clinical implications. Although LV hypertrophy in hypertension is a physiological response to hemodynamic overload, 'inappropriate' LV mass, or an increase in LV mass that exceeds levels needed to compensate for hemodynamic load,[28] independently predicts subsequent cardiovascular morbidity and mortality, with a predictive power similar to LV hypertrophy.[5] Our study suggests that the ratio of observed/predicted LV mass may be particularly sensitive to the hemodynamic impact of increased CAVI as a measure of LV afterload, perhaps more than the effects of BP would be. In addition, the inverse relationship between CAVI and systolic LV midwall function is of interest because systolic dysfunction of the left ventricle assessed at the midwall level, which is observed in approximately one-fifth of hypertensive individuals,[23] independently predicts myocardial infarction and heart failure in treated hypertension.[22,42] In a group of 102 treated hypertensive subjects, Masugata *et al.*[43] demonstrated an inverse relationship between CAVI and LV ejection fraction, although the relationship was no longer significant when examined with multivariate analysis. In a retrospective analysis of 30 subjects with acute heart failure, CAVI correlated inversely with LV ejection fraction.[44] Our findings confirm the inverse relationship between CAVI and LV ejection fraction in a population without clinically overt heart disease, a relationship that was previously reported in patients with ischemic heart disease[45] and reduced ejection fractions.[44,46] Our findings of an independent relationship between CAVI and prognostically relevant measures of subclinical heart disease may partly explain the previously described relationship with the prevalence[47] and incidence[48] of cardiovascular disease.

The present study has limitations. First, the results of this relatively small study need to be confirmed in a larger population. Second, cross-sectional studies cannot establish causality in a potentially bidirectional relationship between CAVI and subclinical cardiac changes. In particular, we cannot exclude that low LV systolic function may play a role in increasing CAVI. As the velocity of the pulse wave is estimated using pulse transmission time between the aortic valve and the ankle, and the timing of cardiac sounds may be influenced by systolic function, the latter may also theoretically influence CAVI. Third, several unproven assumptions are involved in the CAVI definition. Arterial distensibility is not measured directly but is estimated on the basis of the Bramwell–Hill equation, and heart–ankle distance and travel time are also estimated indirectly. As an effect of the approximations contained in these assumptions, the relationship between CAVI and the stiffness index β is only moderate.[49]

Our study shows that in asymptomatic individuals with either high–normal BP or essential hypertension and no obvious LV systolic dysfunction (LV ejection fraction $\geqslant 50\%$), CAVI is more strongly associated with prognostically relevant measures of preclinical heart disease, such as inappropriate LV mass and low midwall LV systolic function, than with carotid–femoral PWV. Although carotid–femoral PWV remains a mainstay in functional evaluations of the large arteries as a strong, independent predictor of all-cause and cardiovascular mortality,[1–6] parameters such as CAVI that assess changes in arterial stiffness during the entirety of the cardiac cycle also deserve consideration in cardiovascular risk assessments.

CONFLICT OF INTEREST

GS received grants from AtCor Medical as well as public speaking grants from Fukuda-Denshi. The other authors declare no conflict of interest.

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