Correlation of pulse wave velocity with left ventricular mass in patients with hypertension once blood pressure has been normalized

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Abstract

Vascular stiffness has been proposed as a simple method to assess arterial loading conditions of the heart which induce left ventricular hypertrophy (LVH). There is some controversy as to whether the relationship of vascular stiffness to LVH is independent of blood pressure, and which measurement of arterial stiffness, augmentation index (AI) or pulse wave velocity (PWV) is best. Carotid pulse wave contor and pulse wave velocity of patients (n=20) with hypertension whose blood pressure (BP) was under control (<140/90 mmHg) with antihypertensive drug treatment medications, and without valvular heart disease, were measured. Left ventricular mass, calculated from 2D echocardiogram, was adjusted for body size using two different methods: body surface area and height. There was a significant (P<0.05) linear correlation between LV mass index and pulse wave velocity. This was not explained by BP level or lower LV mass in women, as there was no significant difference in PWV according to gender (1140.1+67.8 *vs* 1110.6+57.7 cm/s). In contrast to PWV, there was no significant correlation between LV mass and AI. In summary, these data suggest that aortic vascular stiffness is an indicator of LV mass even when blood pressure is controlled to less than 140/90 mmHg in hypertensive patients. The data further suggest that PWV is a better proxy or surrogate marker for LV mass than AI and the measurement of PWV may be useful as a rapid and less expensive assessment of the presence of LVH in this patient population.

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Key words: left ventricular mass, hypertension, pulse wave velocity, arterial stiffness.

Conflict of interest: the authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Contributions: SWR designed the study, analyzed the data and co-wrote the paper; SHC collected and analyzed the data and co-wrote the paper.

Received for publication: 9 May 2011.
Accepted for publication: 19 September 2011.

Heart International 2012; 7:e5
doi:10.4081/hi.2012.e5

Introduction

Increased left ventricular mass (LVH) in patients with hypertension is a significant predictor of subsequent morbidity and mortality.[1,2] The mechanisms by which hypertension produces LVH are complex but are believed to involve an increased (after)load on the heart along with neurohumeral factors found in hypertension, to initiate a signal transduction cascade leading to myocardial cell hypertrophy.[3,4] The load on the left ventricle is a composite of load inertia (overcoming the inertia and viscous elements of the blood), dynamic loading (aortic arterial pressure), and resistance loading (the properties of the aorta into which the ventricle is ejecting blood).[5] The aortic component of the resistance load can be considered as aortic compliance, which in turn is a function of the physical properties of the artery (viscoelasticity, dimensions, etc.) and the reflected pressure waves generated in the more distal parts of the arterial tree.[6] While arterial viscoelasticity and reflected waves are inter-related properties of the large arteries, viscoelastic properties may be more readily measured by pulse wave velocity (PWV), the speed of travel of the pulse wave in the aorta. Reflected waves are indicated by augmentation index (AI) or the amount of increase or decrease in the second part of the aortic pulse contour as a percentage of the peak.

The relationship of arterial stiffness and left ventricular mass in individuals without kidney disease is controversial. Several studies reported a significant relationship between PWV and LV mass but only if the level of systolic BP is not considered in the analysis.[7-9] Once blood pressure was considered, or the data were adjusted for the blood pressure level, no relationship was evident.[9] PWV did not correlate with LV mass in two studies with untreated hypertensive patients.[10,11] While arterial compliance did not correlate with left ventricular hypertrophy, in some studies, it did correlate with left ventricular concentric remodeling.[12] A relationship between PWV and LV mass was found in patients with concentric cardiac hypertrophy but not after correction for blood pressure in some[9] but not all[13] studies. Differences in the relationship between PWV and LV mass have been attributed to gender with a significant relationship reported in women but not in men. This, however, has not been consistent.[14] A significant correlation between reflected waves, as measured by augmentation index, and LV mass has been reported in normotensive subjects[15] and patients with hypertension.[10,16]

The non-linear pressure-volume relationship in the vasculature means that arterial stiffness is positively related to distending pressure.[17] The higher the blood pressure at the time of the measurement, the higher the measured arterial stiffness without any change in the structure of the vessel. Thus *functional* as distinct from *structural* modification of arterial stiffness[17] may explain the variable and at times discordant relationship between LV mass and reflected waves in patients with hypertension and elevated arterial pressure. One way to overcome this issue is to assess arterial stiffness in individuals with hypertension whose blood pressure has been normalized. We examined the hypothesis that, in patients with hypertension whose blood pressure had been controlled with antihypertensive drug therapy, arterial stiffness

will correlate with left ventricular mass, and that one of the two indices of arterial stiffness will be better than the other.

Materials and Methods

Study subjects

Patients from a cardiology clinic at a University teaching hospital were studied. Inclusion criteria were: men or women, aged 50 to 85 years, who had had hypertension requiring antihypertensive drug therapy for at least one year and whose blood pressure had been reduced to less than 140/90mmHg. Patients were excluded if they had secondary hypertension and/or had significant renal disease (eGFR <60 mL/min/1.73 m^2).

Study procedures

PWV and augmentation index were measured on an Omron Colin VP1000/2000 (Ill, USA). Briefly, the subject was examined while resting in a supine position, with electrocardiogram electrodes placed on both wrists with a microphone for detecting heart sounds placed on the left edge of the sternum. After the participants had rested in the supine position, the right carotid pulse wave and femoral artery contours were recorded simultaneously by placement of a transducer over these arteries. Using the carotid pressure waveform, the augmentation index (AI) was calculated as the difference between the second and the first systolic shoulder, and expressed as a percentage of the carotid pulse contour. PWV was calculated as the ratio of the distance in meters from the heart to the femoral artery (based on patient height), to the transit time in seconds from the heart to the beginning of the upstroke of the carotid pulse, to the beginning of the upstroke of the arterial pressure waveform at the femoral artery, plus an estimate of transit time from heart to carotid artery (onset of S2 to carotid dicrotic notch) (Omron Colin VP1000/2000 Ill, USA).

Two-dimensional echocardiograms were performed. Parasternal long- and short-axis views were used to determine LV end-diastolic and end-systolic measurements and wall thickness dimensions according to the recommendations of the American Society of Echocardiography.[18] All measurements were recorded by an ultrasonographer who had not been informed of the patient's clinical condition. Left ventricular mass was calculated according to the formula:

$1.04\,([LVIDd+IVSTd+PWTd]^3–LVIDd^3)–14$ g

where: LVIDd is the left ventricular internal dimension at end-diastole; IVSTd is the interventricular septal thickness at end-diastole; PWTd is the posterior wall thickness at end-diastole.

Two methods were used to adjust for body size. LVM was divided by body surface

$$([(weight^{0.425}\times height^{0.725})/139.2])$$

or divided by height.$^{2.7}$ The latter is considered a more precise adjustment of body size because it avoids errors in estimating the impact of being overweight.[19]

Statistical analysis

To assess the relationship between two variables, linear least squares regression analysis was performed. Comparison of between group means used analysis of variance. The null hypothesis was rejected at the 5% level ($P<0.05$). Sample size calculations were not performed because there were no prior data on which to base them.

Results

Patients' demographics show that the group had a mean age of 67.8 years (range 54-83 years) with 75% being 60 years of age or older. Sixty percent were men and the group had an average blood pressure of 129/75 mmHg (Table 1). Thirty percent had concomitant diabetes mellitus. All patients had been suffering from hypertension for at least two years. All were receiving antihypertensive drugs with all major classes of drugs being represented. Fifty-five percent were taking combinations of more than one antihypertensive medication. The echocardiographic data indicate normal left ventricular size and systolic function (Table 2). Left ventricular mass was normalized for body size using two different methods: body surface area and height to the power of 2.7.

The vascular segment from the heart to the femoral artery (hfPWV) was considered the major load on the heart and was 1375±61.0 cm/s for the patient group. There was a significant correlation between hfPWV and LV mass. The correlation was significant after left ventricular mass was adjusted for body size by either body surface area or height^{2,7} (Figure 1). Because women have lower LV mass than men, we tried to determine whether the relationship between PWV and LV mass could be due to difference in gender, *i.e.* a lower PWV in women with lower LV mass and higher PWV in men with higher LV mass. This was not the case. There was no significant difference between cfPWV in women and men which was 1140.1±67.8 *vs* 1110.6±57.7 cm/s, respectively. In the group of patients whose blood pressure was controlled, there was no relationship between blood pressure and LV mass as there was no significant correlation between systolic blood pressure or mean blood pressure and LV mass adjusted for body surface area ($r^2=0.010$) or height$^{2.7}$ ($r^2=0.021$).

The group had an augmentation index of 19.0±3.3%. There was no correlation between augmentation index and left ventricular mass (Figure 2). Because AI can be related to heart rate, we examined the relationship of heart rate to LV mass. There was no correlation between heart rate and LV mass adjusted for body surface area ($r^2=0.048$) or height$^{2.7}$ ($r^2=0.030$). The absence of a correlation between augmentation index and hfPWV indicated that these variables are unrelated (Figure 3).

Discussion

This study examined a unique group of hypertensive patients whose blood pressure had been reduced to less than 140/90 mmHg by antihypertensive drug therapy, and found a

Table 1. Patients' clinical characteristics.

Characteristics	Total
N. patients	20
Age (years)	67.8±9.3*
Male (%)	60
Systolic blood pressure (mmHg)	129.0±7.2
Diastolic blood pressure (mmHg)	75.4±9.8
Heart rate (bpm)	65.4±10.4
BMI (Kg/m^2)	24.9.1±3.9
Type 2 diabetes mellitus (%)	30.0%
Antihypertensive medications°	
CCB	30%
ACEi/ARB	75%
Beta blocker	40%
Diuretic	55%

*Mean+SD; °55% of patients were on 2 or more medications from different classes.

Table 2. Echocardiographic data.

Echocardiographic data	Mean±SD
LVDD (mm)	45.4±4.6
LVSD (mm)	29.6±4.8
IVS (mm)	10.4±1.3
PW (mm)	10.2±1.0
LA size (mm)	40.2±6.3
LA volume (ml)	39.3±3.6
LV mass (male) (g)	160.4±25.1
LV mass index (male) (g/m^2)	80.8±13.6
LV mass index (male) (g/$Ht^{2.7}$)	36.0±6.9
LV mass (female) (g)	122.9±11.5
LV mass index (female) (g/m^2)	73.5±11.7
LV mass index (female) (g/ $Ht^{2.7}$)	33.7±4.7
Ejection fraction (%)	60.9±6.7

significant relationship between LV mass and PWV. In contrast, there was no significant relationship between AI index and LV mass. These data suggest that PWV detects vascular abnormalities that are not recognized by AI, and PWV correlates better with a target organ effect of hypertension, even once blood pressure has fallen to within a normal or acceptable target range after treatment.

A complex interplay between aortic PWV and left ventricle hypertrophy in hypertensive subjects has been proposed by Schillaci *et al.* They found that, in middle-aged and older subjects, PWV is overwhelmingly determined by aortic stiffness, while in young individuals (<40 years of age) aortic PWV is determined to a significant extent by the velocity of LV contraction.[11] As our patient group was mainly 54 years of age or over, PWV was determined by aortic stiffness and not the velocity of LV contraction. We did not adjust for age, because we used left ventricular mass rather than LV wall thickness. In healthy adults, relative wall thickness increases with age whereas left ventricular mass does not change.[20] The relationship of PWV to LV mass has been suggested to vary in men and women[14] but we found no gender differences in LV mass.

We found a significant relationship between PWV and LV mass. Most of the studies that did not show a correlation between PWV and LV mass studied either untreated hypertensive patients[10,11] or non-hypertensive individuals.[12] In addition to differences in the patient population, our study used the heart to femoral vascular segment to assess PWV rather than the shorter carotid to femoral PWV used by others. The longer segment, which includes the proximal aorta, should be more representative of the load on the left ventricle. Also, the heart to femoral segment is a more powerful indicator of arterial disease than other arterial segments.

Blood pressure (systolic or diastolic) was not a factor in the present study as hypertension had been controlled, and there was no correlation between blood pressure and LV mass.

The relationship of PWV to LV mass has been reported to disappear after adjustment for elevated blood pressure.[7-9] This has led to conflicting suggestions that blood pressure load on the ventricle, regardless of the cause, is the most important factor producing LVH, or that decreases in aortic compliance/distensibility produce cardiac hypertrophy mainly through the increase in systolic pressure.[9] Whether this increase in aortic stiffness is the cause or effect of the elevated systolic blood pressure, however, remains unresolved.[21] In contrast, our study suggests that the relationship of PWV to LV mass was independent of blood pressure.

There was no relationship between AI and LV mass in this patient group, in contrast to Hashimoto *et al.*[10] However, they reported on untreated hypertensive patients and assessed carotid femoral PWV and this may account for the differences between the two studies. The very small r value makes it highly unlikely that a relationship would have been seen with a much larger study group. The significant relationship between PWV but not AI and LV mass may have several explanations. The main reason could be that the vasculature component, related to arterial stiffness whose link to LV mass is stronger and lasts longer,[6] is measured by PWV and not AI. Our study is consistent with the concept that PWV and AI measure different components of the vasculature. Aortic compliance is a function of the physical properties of the artery (viscoelasticity, dimensions, etc.) and the reflected pressure waves generated in the more distal parts of the arterial tree.[6] The hypothesis that PWV reflects the viscoelastic properties of the aorta and AI is an indicator of the reflected waves seems to be a reasonable way to differentiate between PWV and AI. These two factors are interrelated as increased arterial stiffness can be measured by both PWV and AI. However, our data have shown differences in relationship to a target organ effect of hypertension. PWV, but not AI, has been found to be associated with diabetic retinopathy in patients with diabetes.[22] Another possibility expressed by some investigators is that increased AI is not a reliable surrogate for increased aortic stiffness.[23] Regardless of this, our study found differences between PWV and AI with respect to linking the vasculature to the process of LVH.

Consistent with the different relationships between LV mass and PWV compared to AI, we did not find any correlation between PWV and AI in this patient population. The absence of a correlation between PWV and AI is supported by the work of others.[24] The differences between PWV and AI can be due not only to measurement of different properties of the vasculature but other differences reflect that AI is also more influenced than PWV by heart rate and blood pressure.[25,26] Another potential explanation for our finding is that antihypertensive drugs may more readily reverse the reflected wave component of arterial resistance than hypertension-induced changes in the viscoelastic properties of the aorta. The majority of the patients in this study were receiving angiotensin converting-enzyme inhibitors (ACEs), angiotensin receptor blockers or calcium channel blockers. These agents have been shown to reduce AI.[27-30] The next most common agent, diuretics, appears not to change AI, while beta blockers may increase AI.[31,32] The patients in our study also used combination drug therapy that would be expected to reduce AI.[33] Peripheral muscular arteries, from which reflected waves arise,

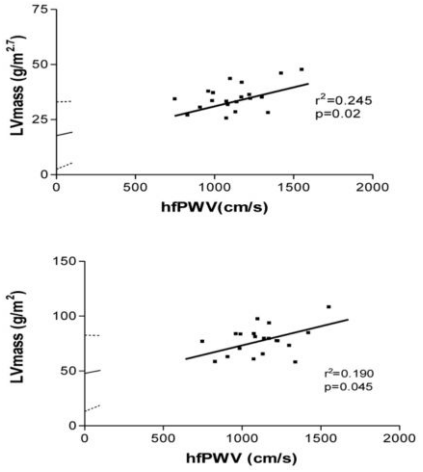

Figure 1. The relationship of pulse wave velocity: heart to femoral (hfPWV) to left ventricular mass adjusted for height (upper panel) or body surface area (lower panel).

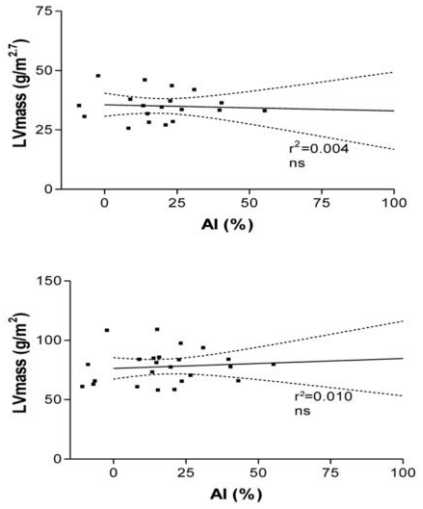

Figure 2. The relationship of augmentation index to left ventricular mass adjusted for height (upper panel) or body surface area (lower panel).

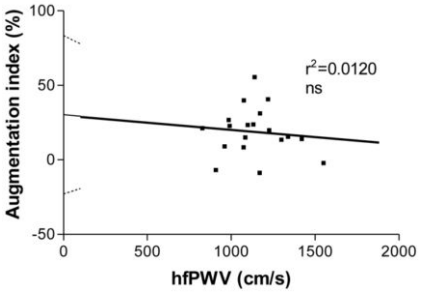

Figure 3. The relationship of augmentation index to pulse wave velocity (hfPWV)

may be more amenable to antihypertensive drugs than central arterial stiffness. This latter proposal would be consistent with those investigators who believe that LVH is mediated primarily through increases in blood pressure and that there should be no LVH once blood pressure is normalized. While our study might raise the question as to how increased PWV could lead to LVH in the absence of a relationship between blood pressure and LVH, it is more likely that our results are consistent with the concept that differences in vascular stiffness and LVH can still be observed in patients whose blood pressure is lowered or even normalized with antihypertensive drugs.

This study has several limitations which need to be considered: i) the small sample size is of concern. However, a statistically significant relationship between PWV and LVH was identified even with this small number of participants. Furthermore, the correlation coefficient between AI and LVH was extremely small so that it would have been unlikely that even a much larger sample size would have shown a significant relationship; ii) PWV is usually measured between two points; the use of heart to femoral PWV partially relied on the use of a heart sound as a reference point for PWV that may have influenced the findings. However, measurement of the segment from heart to carotid upstroke usually relies on this as an indicator of onset of left ventricular ejection; iii) there may have been an underlying relationship between heart rate and/or blood pressure and PWV or AI that was not taken into account in the univariate analysis relating PWV or AI to LVH. While this possibility cannot be excluded, there was no statistically significant relationship between LVH and either heart rate or blood pressure suggesting that it is unlikely that the association of PWV with LVH was mediated through blood pressure or heart rate; iv) AI was lower than anticipated in this study group of whom the majority were older than 60 years; v) there might be a concern that it is difficult to differentiate the (true) relationship between LVH and PWV or AI, from different effects of antihypertensive drugs on AI or PWV in this study. However, it is not possible to obtain a patient group with hypertension that is significant enough to induce cardiovascular alterations and have blood pressure normalized unless antihypertensive drugs are used. Specific drug effects are an unlikely explanation for the findings of the study because the majority of patients were being treated by the same class of agents, *i.e.* rennin angiotensin system inhibitors. We did not include a normotensive group to compare with the controlled hypertension group in order to eliminate drug effect because the normotensive group would be expected to show a relationship between vascular stiffness and LV mass.

In summary, PWV but not AI correlates significantly with LV mass in hypertensive individuals whose blood pressures have been reduced to less than 140/90 mmHg. These findings suggest that the component of arterial compliance measured by PWV is a more important determinant of LV mass or that antihypertensive drugs can not as readily correct the changes in the vasculature that alter PWV as they can reduce the increase in reflected waves that generate AI. The data further suggest that PWV is a better proxy or surrogate marker for LV mass than AI and the measurement of PWV may be useful as a rapid and less expensive assessment of the presence of LVH in this patient population.

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