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Abstract—Aging of the vasculature results in arterial stiffening and an increase in systolic and pulse pressures. Although pressure load is a stimulus for left ventricular hypertrophy, the extent to which vascular stiffening per se, independent of blood pressure, influences left ventricular structure is uncertain. Two hundred seventy-six subjects (79 normotensive and 197 otherwise healthy hypertensive individuals) underwent echocardiography to assess left ventricular structure. Arterial stiffness was estimated by the pressure-independent stiffness index, β, and the pressure-dependent elastic modulus derived from simultaneous carotid ultrasound and applanation tonometry. Systemic arterial compliance (the inverse of stiffness) was estimated by the arterial compliance index. In multivariate analysis, β was related to age ($P<0.001$) and smoking history ($P<0.01$) but not mean pressure, whereas elastic modulus was related to age and mean pressure (both $P<0.001$). The arterial compliance index was only related to age. Whereas systolic and diastolic pressures and the elastic modulus were positively associated with left ventricular mass (all $P<0.001$), primarily because of increases in wall thicknesses, β and the arterial compliance index bore no relation to left ventricular mass. β was inversely related to chamber diameter and directly related to left ventricular relative wall thickness, the ratio of wall thickness to chamber radius. Younger and older hypertensive subjects had comparable left ventricular mass, despite higher systolic and pulse pressures in the older group, whereas older hypertensives had higher mean relative wall thickness, associated with a significant increase in arterial stiffness (β, 7.06 versus 5.17; elastic modulus, 595 versus 437 dyne/cm^2 $\times 10^{-6}$) and reduction in the arterial compliance index (0.87 versus 1.05 mL/mm Hg per square meter) (all $P<0.001$). Thus, the extent to which arterial stiffness relates to left ventricular hypertrophy is dependent on the method by which arterial stiffness is estimated. Pressure-dependent methods show an association with left ventricular hypertrophy, whereas the pressure-independent stiffness index, β, and the arterial compliance index are most strongly associated with aging and left ventricular concentric remodeling but not hypertrophy. (**Hypertension**. 2000;36:489-494.)

Key Words: arteriosclerosis ■ arteries ■ hypertrophy ■ blood pressure

An increase in arterial stiffness is a common feature of both the aging process[1,2] and hypertension.[3,4] Aging is associated with structural changes (both hypertrophy and atherosclerosis) within the capacitance arteries that result in an increase in pulse wave velocity and consequent alterations in the pressure waveform and increases in systolic and pulse pressures.[1,5] Arterial stiffening associated with hypertension may primarily reflect the obligatory increase in distending pressure, a phenomenon that becomes manifest when vascular stiffness is assessed by isobaric or pressure-independent methods.[3,6–9] Alternatively, arterial stiffening may additionally result from disease-related structural adaptation,[10] although the extent to which vascular function is altered may depend on the vascular bed under examination.[11,12] Thus, uncertainty exists regarding the temporal relation between hypertension and arterial stiffening, although recent population-based prospective data suggest that decreased elasticity may precede the development of hypertension.[13]

Left ventricular (LV) structure is likewise influenced by both aging and hypertension. In otherwise healthy, aging individuals, LV structure appears to remodel primarily with an increase in relative wall thickness (ratio of wall thickness to chamber radius) and little or no increase in overall LV mass.[14] In contrast, hypertension commonly results in LV hypertrophy, with the specific geometric pattern (concentric versus eccentric) depending on the interaction of volume and pressure components of systemic hemodynamics.[15] Superimposition of the aging process on hypertension does not increase overall LV mass in the absence of concurrent disease[16] but may result in further geometric remodeling.[17] Thus, there may be differential impacts on LV structure of arterial stiffness related to vascular sclerosis and atherosis as opposed to that due to increased distending pressure. Therefore, the present study was designed to examine the relative impacts of elevated blood pressure (BP) and arterial stiffness, estimated by both pressure-independent and pressure-

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dependent methods, on LV structure and geometry in normotensive and healthy, untreated hypertensive subjects over a wide age range.

Methods

Study Population

The study population consisted of 276 subjects who were studied in ongoing, long-standing protocols to assess the impact of hypertension on cardiovascular structure and function.[10,16,18] Subjects were selected who had undergone both echocardiography and carotid ultrasonography with simultaneous acquisition of central arterial pressure waveforms (see below). Seventy-nine healthy, unmedicated normotensive (mean age, 50±17 years; 71% men; mean BP, 123/72 mm Hg) and 197 otherwise healthy, untreated hypertensive (mean age, 55±12 years; 62% men; mean BP, 157/93 mm Hg) individuals were available for study. Hypertension was defined as the sustained elevation of BP (≥140 mm Hg systolic and/or ≥90 mm Hg diastolic) on at least 3 separate determinations obtained on different days. Sixty-five percent of the hypertensive subjects had previously received antihypertensive therapy, which was discontinued at least 3 weeks before the day of study. None of the subjects had diabetes, significant hyperlipidemia, valvular heart disease, or clinically apparent cardiovascular disease; none of the hypertensive subjects had evidence of secondary forms of hypertension. Study protocols were approved by the Committee on Human Rights in Research.

Echocardiography

M-mode, 2-dimensional, and Doppler echocardiograms were performed in all subjects by a highly skilled research technician. M-mode strip chart recordings were coded by the technician and read blindly by a single experienced cardiologist. Measurements were marked on up to 6 cycles and processed on a digitizing tablet with the use of custom-written software. LV mass was calculated according to the Penn Convention[19,20] and adjusted for differences in body size by use of both body surface area and height.[2,7,21] Diastolic relative wall thickness, which increases with concentric remodeling and concentric hypertrophy, was calculated as 2×posterior wall thickness/chamber diameter. Stroke volume was calculated by the Teichholz correction of the cube method.[22] Aortic diameter was measured at the sinuses of Valsalva. Whenever M-mode measurements were considered technically inadequate, 2-dimensional measurements were performed with the use of American Society of Echocardiography criteria.[23] BP was obtained in triplicate and averaged at the completion of the study with the patient in the supine position with a cuff and mercury sphygmomanometer.

Carotid Ultrasonography and Applanation Tonometry

Carotid ultrasonography was performed by the research technician after completion of the echocardiogram, using previously described techniques.[10] M-mode recordings of the distal common carotid artery (CCA) were obtained. Intimal-medial thickness (IMT) of the far wall of the CCA was measured at end-diastole. End-diastolic and peak-systolic (minimum and maximum) CCA diameters were obtained by continuous tracing of the lumen-intima interfaces of the near and far walls. High reproducibility of IMT and diameter measurements has been demonstrated in our laboratory.[10] The presence of discrete plaque was defined as focal intimal-medial thickening ≥50% greater than the surrounding wall.[24] Applanation tonometry of the contralateral CCA was performed by a physician-investigator highly experienced in the technique using the external Millar transducer (Millar Instruments) with superimposition of the acquired arterial pressure waveform on the simultaneous M-mode tracing of the pulsating vessel. Applanation tonometry has been validated to yield accurate estimates of intra-arterial pulse pressure.[25]

Estimation of Arterial Stiffness and Compliance

The arterial pressure waveform was calibrated with the calculated mean brachial BP based on the assumption that mean BP is comparable within the conduit vessels despite variability of systolic and diastolic BP.[26] Carotid pressures and diameters were used to calculate 2 estimates of arterial stiffness, the arterial stiffness index, β[27,28]:

$$\beta = [\ln(P_s/P_d)]/[(D_s - D_d)/D_d]$$

where P_s and P_d are carotid systolic and diastolic pressures, respectively, and D_s and D_d are carotid systolic and diastolic diameters, respectively, and the elastic modulus (EM)[29]:

$$EM = [(P_s - P_d)/(D_s - D_d)] \times D_d$$

The stiffness index, β, has been shown to be unaltered by an acute 40 mm Hg change in systolic BP, whereas a linear reduction in the EM was seen with nitroprusside-induced reduction in BP.[28] Thus, the stiffness index may be considered relatively independent of current distending pressure, whereas the EM is clearly pressure dependent. Systemic arterial compliance, the inverse of stiffness, was estimated by the arterial compliance index (ACI): diastolic area of the pressure waveform divided by total vasomotor resistance normalized for body size.[7]

Statistical Methods

Data were stored and analyzed with SPSS 9.0 software. Group means were compared with the independent sample *t* test. ANOVA was used for comparison between tertiles of arterial stiffness. ANCOVA was performed to adjust for significant group differences. Linear regression analysis was used to assess univariate relations of continuous variables. Multiple linear regression was performed to determine the independence of association with continuous variables.

Results

Determinants of Arterial Stiffness

Univariate relations of the stiffness index (β), the EM, and the ACI to age, BP, and several other potential determinants are listed in Table 1. Because systolic and diastolic BP enter into the calculation of arterial stiffness, mean BP was used in subsequent analyses to lessen autocorrelation. Likewise, carotid artery IMT and relative wall thickness were analyzed but not lumen diameter. Both measures of arterial stiffness and the ACI were related to age and carotid IMT. The stiffness index and the ACI were significantly, albeit weakly, related to mean BP in the entire population, primarily as a consequence of increased sample size, whereas the strengths of association between mean BP and EM were greater and were significant in both the normotensive and hypertensive subgroups. Arterial stiffness was greater and ACI was lower in individuals with plaque than in those without (β, 6.90 versus 5.40; EM, 564 versus 439 dyne/cm^2 ×10^{-6}, both $P=0.001$; ACI, 0.88 versus 1.10 mL/mm Hg per square meter, $P=0.012$); however, these differences were eliminated after adjustment for age (6.01 versus 5.70, 493 versus 463 dyne/cm^2 ×10^{-6}, and 1.02 versus 1.05 mL/mm Hg per square meter). Former (n=78) or current (n=24) smokers had significantly higher values of β, even after adjustment for age differences (6.42 versus 5.40, $P=0.005$) than individuals who had never smoked, whereas differences in EM and ACI were eliminated by age adjustment. Both measures of arterial stiffness and ACI were unrelated to total cholesterol.

In multivariate analysis involving the entire population, with either hypertension status (no, yes) used as a categorical

TABLE 1. Univariate Relations of Arterial Stiffness and Arterial Compliance to Potential Determinants

Variable	Normotensive			Hypertensive			Entire Population		
	β	EM	ACI	β	EM	ACI	β	EM	ACI
Age	0.50*	0.51*	−0.38‡	0.40*	0.43*	−0.22‡	0.43*	0.45*	−0.33*
Height	−0.23†	−0.15	0.26†	−0.17†	−0.12	0.00	−0.18‡	−0.12	0.09
Systolic pressure	0.21	0.35‡	−0.18	0.23‡	0.42*	−0.07	0.27*	0.49*	−0.20‡
Diastolic presssure	0.00	0.14	0.09	−0.05	0.10	0.11	0.08	0.28*	−0.08
Mean pressure	0.10	0.26†	−0.02	0.15	0.30*	0.00	0.18‡	0.41*	−0.16†
Total cholesterol	−0.05	0.00	−0.01	0.06	0.07	−0.10	0.03	0.05	−0.07
IMT	0.24†	0.37*	−0.21	0.17†	0.20†	−0.01	0.22*	0.30*	−0.14†
Arterial relative wall thickness	0.17	0.24†	−0.25†	0.02	−0.03	0.00	0.08	0.09	−0.15†

*$P<0.001$, †$P<0.05$, ‡$P<0.005$.

variable or mean BP, the arterial stiffness index was found to be independently related to age ($\beta=0.355$, $P<0.001$) and smoking history ($\beta=0.151$, $P<0.01$) but not to height, hypertension status (or mean pressure), carotid IMT, or presence of plaque. In contrast, the EM was independently related to age ($\beta=0.360$, $P<0.001$) and mean BP ($\beta=0.320$, $P<0.001$). The ACI was independently related to age ($\beta=0.314$, $P<0.001$) but not to mean pressure.

Relation of BP and Arterial Stiffness to LV Structure

Both systolic and diastolic BPs were significantly related to LV mass in the entire population ($r=0.41$ for systolic and $r=0.51$ for diastolic, both $P<0.001$) as well as in the normotensive and hypertensive groups. In contrast, the stiffness index (β) bore no relation to unindexed or indexed LV mass (Table 2). The stiffness index was additionally unrelated to absolute LV wall thicknesses but was inversely related to chamber diameter and hence was positively related to relative wall thickness. However, when arterial stiffness was estimated by use of the EM, significant relations were found between arterial stiffness and LV mass, primarily because of a direct relation between EM and LV wall thicknesses. Like β, the ACI was unrelated to LV mass but was related (inversely) to LV relative wall thickness.

We constructed a multivariate model to explain LV mass on the basis of those variables most strongly related to LV mass in univariate analyses, taking care to utilize the strongest correlate within a given group of interrelated variables, eg, using only the strongest measure of body size or primary

LV measurement. Five variables were able to explain 71% of the variability of LV mass in the current population (Table 3). Age, gender, arterial stiffness (by either measure), and ACI did not enter the model. When EM was substituted for mean BP, it entered the model ($P=0.012$), which was slightly weakened in comparison to use of mean BP (adjusted R^2 of 0.65). However, when either the arterial stiffness index (β) or the ACI was substituted for mean BP, neither entered the model to predict LV mass. Results were comparable when systolic BP was substituted for mean BP in the model and when stroke volume was measured by an invasively validated Doppler method rather than from LV dimensions.

The strongest univariate correlates of LV relative wall thickness were mean or systolic BP, age, carotid IMT, both measures of arterial stiffness, ACI (all $P<0.001$), and body mass index ($P<0.005$). Multivariate models of the determinants of relative wall thickness were much weaker than those for LV mass (all $R^2<0.25$). In a model including age and mean (or systolic) pressure, BP was the strongest independent determinant of relative wall thickness, with no significant contribution of either measure of arterial stiffness, whereas when age was excluded from the model, both measures of arterial stiffness were independently related to relative wall thickness in addition to mean (or systolic) BP. In contrast, ACI was independently related to relative wall thickness even when mean pressure was included in the model (mean BP: $\beta=3.36$, $P<0.001$; ACI: $\beta=−3.19$, $P=0.002$; age: $\beta=2.78$, $P=0.006$). The stiffness index bore an inverse relation to LV end-diastolic diameter, independent of age and BP. To further

**TABLE 2. Univariate Relations of Stiffness Index and EM to LV Structure**

Variable	β	EM	ACI
Septal thickness	0.08	0.21†	−0.12
Posterior wall thickness	0.11	0.26†	−0.15‡
End-diastolic diameter	−0.17*	−0.05	0.19*
Relative wall thickness	0.21†	0.28†	−0.28†
Mass	−0.02	0.13‡	0.02
Mass/body surface area	0.05	0.22†	−0.02
Mass/height$^{2.7}$	0.08	0.22†	−0.03

*$P<0.01$, †$P<0.001$, ‡$P<0.05$.

TABLE 3. Multivariate Analysis of Determinants of LV Mass

Variable	β	Adjusted R^2	P
Stroke volume	0.468	0.423	<0.001
Mean pressure	0.301	0.544	<0.001
Body surface area	0.218	0.653	<0.001
Fractional shortening	−0.255	0.699	<0.001
Aortic diameter	0.086	0.713	0.045
Age	Did not enter		
Gender	Did not enter		
Arterial stiffness	Did not enter		
Arterial compliance	Did not enter		
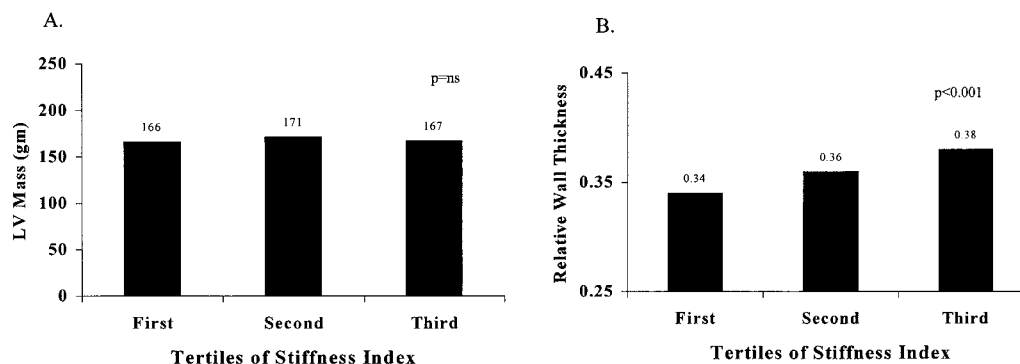
Comparison of LV mass (A) and relative wall thickness (B) in the population subdivided by tertile of arterial stiffness index (β).

examine the impact of arterial stiffness on LV structure, the study population was divided into 3 groups on the basis of tertiles of the arterial stiffness index (β). LV mass was similar in the 3 groups, whereas relative wall thickness progressively rose from the first to the third tertile ($P<0.001$) (Figure).

Impact of Age on Hypertensive LV Hypertrophy

The hypertensive population was subdivided into 2 groups on the basis of median age (55 years). As expected, systolic and pulse pressures and both measures of arterial stiffness were higher and diastolic BP lower in the older group, with no difference in mean BP (Table 4). However, the younger and older groups had comparable LV masses. Relative wall thickness was significantly higher in the older group because of a tendency for posterior wall thickness to be higher and LV internal diameter to be smaller in comparison to the younger group.

Discussion

The present study represents the first systematic examination of the impact of arterial stiffening, using both pressure-dependent and pressure-independent approaches, on LV structure and geometry. The study confirms the well-

established association of BP elevation with LV hypertrophy. However, arterial stiffness, another potential measure of afterload imposed on LV structure, bore no relation to LV mass when relatively pressure-independent estimates, β and ACI, were used. Higher values of the stiffness index and lower values of the compliance index were most strongly related to age and appear to result in remodeling rather than hypertrophy of the LV, ie, an increase in LV relative wall thickness but not absolute wall thicknesses. In contrast, when a pressure-dependent estimate of arterial stiffness (EM) was examined, arterial stiffness was related to LV mass because of its strong association with pressure, as demonstrated in multivariate analyses. These novel observations help to clarify aspects of ventricular-vascular interaction and of methodological approaches in the assessment of LV afterload.

Previous studies of the impact of arterial stiffness on LV structure have used invasive determination of aortic input impedance or effective arterial elastance in relatively small series to demonstrate a reduction in cardiac output and increase in ventricular stiffness associated with aging and vascular stiffening.[30,31] Recent advances in the quality of ultrasound imaging and the availability of high-fidelity external transducers have allowed more systematic evaluation of larger numbers of unselected individuals. Aortic input impedance and effective arterial elastance may now be estimated noninvasively,[32] and we have recently confirmed a reduction in cardiac output and myocardial efficiency as well as demonstrated a reduction in endocardial shortening and myocardial contractility associated with an increase in arterial stiffness measured as effective arterial elastance.[33]

The impact of arterial stiffening on LV structure, particularly independent of distending pressure, has been less commonly examined. We have previously reported no difference in arterial stiffness (β) in hypertensive compared with normotensive individuals, despite significant increases in LV mass in the former group,[7,10] or among groups of hypertensive subjects classified according to LV geometric pattern.[18] Bouthier et al[34] found a direct relation between pulse wave velocity and LV mass/volume ratio, a measure somewhat comparable to relative wall thickness, in a group of 20 normotensive and 20 hypertensive subjects; however, pulse wave velocity was strongly related to systolic pressure ($r=0.73$). Among 20 subjects in whom brachial artery compliance was measured, an inverse relation was seen between compliance and the LV mass/volume ratio.[34]

TABLE 4.   Comparison of BP, Arterial Stiffness, and LV Structure in Younger and Older Hypertensive Subjects

Variable	Younger	P	Older
Age, y	46±7		65±6
Systolic pressure, mm Hg	152±18	<0.001	162±23
Diastolic pressure, mm Hg	96±11	<0.001	91±10
Pulse pressure, mm Hg	56±14	<0.001	72±19
Mean pressure, mm Hg	114±12	NS	115±13
Stiffness index (β)	5.17±2.41	<0.001	7.06±3.79
EM, dyne/cm^2×10^{-6}	473±176	<0.001	595±287
ACI, mL/(mm Hg · m^2)	1.05±0.50	0.008	0.87±0.41
Septum, cm	1.01±0.15	NS	0.98±0.13
Posterior wall, cm	0.93±0.14	NS	0.95±0.11
Internal diameter, cm	5.01±0.50	NS	4.99±0.51
Mass, g	182±54	NS	174±42
Mass index, g/m^2	94±22	NS	94±19
Mass/height$^{2.7}$, g/m$^{2.7}$	41.6±10.3	NS	42.1±8.7
Relative wall thickness	0.37±0.05	0.03	0.39±0.06

In a large series of normotensive and untreated hypertensive Chinese subjects, Chen et al[35] found echocardiographic LV mass to be directly related to arterial compliance (calculated as the LV stroke volume/brachial pulse pressure ratio; $r=0.25$, $P<0.001$) and EM and inversely related to arterial elastance. These results are comparable to findings in our previous study[33] and in the present population (LV stroke volume/pulse pressure ratio versus LV mass, $r=0.31$, $P<0.001$). Furthermore, these authors reported that arterial stiffness was independently related to LV mass only when BP was eliminated from the model.[35] The present study confirms this result with regard to use of the EM and further refines our understanding by use of the relatively pressure-independent estimate of arterial stiffness, β, and by more detailed assessment of LV structure and geometry. Interestingly, approximately 70% of the variability in LV mass was explained by 5 comparable variables in both studies.

Although arterial stiffening was related to concentric remodeling of the LV in the present study, a definite causal relation cannot be established in a cross-sectional study. Arterial stiffening may simply be an epiphenomenon for aging or some other more directly causative process. If a direct relation were to be present, the mechanism might involve ventricular stiffening in response to arterial stiffening[31,33] with resultant reduction in LV filling and consequent remodeling. LV stiffening has been shown to be associated with enhanced sensitivity to preload reduction.[31] Unfortunately, we do not have systematic Doppler assessment of LV filling in this population. Support of a direct relation between arterial and LV remodeling is found in an experimental model wherein Wistar rats underwent either proximal (aortic arch) or distal (suprarenal) aortic banding.[36] Although both groups had similar increases in peak systolic pressure and systemic resistance, the group with distal banding had a significantly greater reduction in the ratio of LV cavity volume to wall volume (ie, an increase in relative wall thickness) than sham-operated rats or rats with proximal banding. This finding appeared to be due to late-systolic augmentation of the central pressure waveform causing peak pressure to occur late in systole, comparable to the impact of late-peaking central arterial pressure waveform on LV wall thickness in normotensive humans.[37] In the present study population, individuals with a positive as opposed to a negative augmentation index had higher LV mass even after adjustment for age (169 versus 141 g, $P=0.004$), and the augmentation index was strongly related to both systolic BP ($r=0.45$, $P<0.001$) and LV mass ($r=0.20$, $P=0.001$). Thus, although arterial stiffness may not be independently related to LV mass, it may indirectly promote ventricular hypertrophy through its impact on pulse wave velocity and the augmentation of systolic pressure by early reflected waves.

Potential limitations of the present study include its cross-sectional nature such that the aging process is assessed by examination of individuals over a broad age range rather than serial study of aging individuals, an undertaking that might require decades given the gradual development of arterial stiffening. The extent to which the arterial stiffness index (β) is truly pressure independent constitutes another potential drawback in the ability to separate the independent effects of intrinsic arterial stiffening and distending arterial pressure on LV geometry. In the present study the arterial stiffness index was unrelated to BP or hypertension status in multivariate analyses. In addition, it should be noted that the arterial stiffness index, β, and the EM are, of necessity, derived from the same measures of central arterial pressure and carotid artery dimensions, leading to an inescapable correlation between these variables despite the differences in the treatment of both arterial pressure (natural log of systolic/diastolic pressure versus the pulse pressure) and arterial measurements (dividing as opposed to multiplying by diastolic diameter). However, the similarity between results obtained using β and ACI, calculated from different measurements, supports the interpretation that β and EM assess different aspects of arterial function despite their derivation from the same variables. Finally, the study subjects were largely healthy, and it is possible that results might differ in a population with more severe hypertension or that the results are subject to survivor bias. However, an advantage of studying a relatively healthy population is the minimization of factors other than BP, arterial stiffening, and aging that might influence LV structure, such as ischemic or valvular heart disease and diabetes mellitus.

In conclusion, the present study indicates that arterial stiffening, when assessed by a method that is relatively independent of distending pressure, is associated with concentric remodeling but not further hypertrophy of the LV structure. Arterial stiffness increases in hypertension because of increased distending pressure, associated structural changes in the conduit vessels, or both and, depending on the interplay of hemodynamic parameters, may result in increased LV mass and/or relative wall thickness. Aging, associated with vascular hypertrophy, stiffening, and atherosclerosis, results in concentric LV remodeling in both normotensive and hypertensive individuals, as manifested by an increase in relative wall thickness.

Acknowledgment

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