Original Article

Limited contribution of left ventricular mass and remodelling to the impact of blood pressure on diastolic function in a community sample

Adamu J. Bamaiyi*, Gavin R. Norton*, Vernice Peterson, Carlos D. Libhaber, Pinhas Sareli, and Angela J. Woodiwiss*

Aims: Although the development of left ventricular (LV) dysfunction in hypertension has traditionally been viewed as a transition process from a phase of structural LV remodelling to dysfunction, the extent to which LV mass (LVM) and remodelling account for blood pressure (BP)-associated alterations in LV diastolic function is uncertain. In product of coefficient mediation analysis, we aimed to determine the extent to which LVM index (LVMI) or relative wall thickness (RWT) account for relations between BP and LV diastolic function.

Methods: In 709 randomly selected participants from a community sample with a high prevalence of hypertension (49.6%), we determined BP and LVMI, RWT and several indices of diastolic function from transmitral blood flow and myocardial tissue Doppler (*E*/*A*, *e*′/*a*′, *e*′ and *E*/*e*′) and left atrial volume using standard echocardiographic techniques.

Results: With adjustments for confounders, LVMI ($P < 0.001$–0.0001) and RWT ($P < 0.05$–0.001) were independently associated with *E*/*A*, *e*′/*a*′, *e*′ and *E*/*e*′. However, in product of coefficient mediation analysis, LVM and RWT failed to account for most BP-associated changes in diastolic function. Indeed, whilst a one SD increase in DBP or SBP (13 and 22 mmHg, respectively) translated into a 0.07, 0.13 and 0.53 decrease in *E*/*A*, *e*′/*a*′, *e*′ and a 0.73 increase in *E*/*e*′, respectively, in mediation analysis LVMI accounted for only 0.0005, 0.0017, 0.05 and 0.08 of the impact of a one SD effect of LVMI on *E*/*A*, *e*′/*a*′, *e*′ and *E*/*e*′, respectively. Similar contributions of RWT as for LVMI to BP-associated LV diastolic functional changes were noted and the contribution of LVMI or RWT to BP-related alterations in diastolic function was similar in those participants not receiving antihypertensive therapy.

Conclusion: Although structural LV remodelling is independently associated with changes in LV diastolic function, LVMI and RWT account for only a minor proportion of the impact of BP on diastolic function. Thus, most BP-associated decreases in LV diastolic function are likely to be a transition process independent of LV hypertrophy or concentric remodelling.

Keywords: hypertension, left ventricular diastolic function, left ventricular hypertrophy, left ventricular remodelling

Abbreviations: *a*′, myocardial tissue lengthening in late diastole at the mitral annulus; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; BP, blood pressure; *E*, trans-mitral velocity during the early period of left ventricular diastolic inflow; *E*/*A*, transmitral early/atrial blood flow velocity; *E*/*e*′, transmitral early blood flow velocity/velocity of the mean value of lateral and septal wall myocardial tissue lengthening in early diastole at the mitral annulus (an index of left ventricular filling pressure); *e*′, myocardial tissue lengthening in early diastole at the mitral annulus; HbA_{1c}, glycated haemoglobin; LAV, left atrial volume; LV, left ventricular; LVH, LV hypertrophy; LVM, LV mass; LVMI, LVM indexed to height1.7; RWT, relative wall thickness; TDI, tissue Doppler indices

INTRODUCTION

Heart failure with a preserved ejection fraction may contribute to close to half of all admissions for heart failure, and the outcomes may be equally as poor as heart failure with a reduced ejection fraction [1–4]. There is presently little evidence for proven treatment benefits for heart failure with a preserved ejection fraction [1,5,6]. Hence, a better understanding of the pathophysiological mechanisms involved, is essential. Decreases in left ventricular (LV) diastolic function are central to the pathophysiology and outcomes of heart failure with preserved ejection fraction [7–11] and preclinical LV diastolic dysfunction predicts the progression to heart failure with a preserved ejection fraction [12]. Although it is now well

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Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Correspondence to Angela J. Woodiwiss, Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, University of the Witwatersrand Medical School, 7 York Road, Parktown, 2193 Johannesburg, South Africa. Tel: +27 11 717 2363; e-mail: angela.woodiwiss@wits.ac.za

*Adamu J. Bamaiyi, Gavin R. Norton and Angela J. Woodiwiss contributed equally to the article.

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recognized that sustained hypertension is a major determinant of LV diastolic dysfunction and the development of heart failure with a preserved ejection fraction, the transition process from a compensated LV to LV diastolic dysfunction in hypertension is unclear.

Traditionally, the development of LV dysfunction and consequently heart failure in hypertension has been viewed as the evolution from a phase of structural LV remodelling (concentric remodelling and hypertrophy) to LV decompensation. Consequently, the presence of LV hypertrophy (LVH) is thought to be an essential prelude to LV dysfunction, including LV diastolic dysfunction [13–15]. Indeed, LV diastolic dysfunction may be seen in up to 84% of hypertensive individuals with LVH [15]. Conversely, it has been estimated that only 11–20% of hypertensive patients have LV diastolic dysfunction without exhibiting LVH [13,16]. However, these estimates were obtained at a time when more contemporary noninvasive approaches to determining LV diastolic function were not available. Importantly, it has been well recognized for several decades [17] with even more novel mechanisms continuing to emerge [17,18] of a role for several cellular changes induced by hypertension that are unrelated to the hypertrophic process and which determine LV diastolic function. In this regard, many patients with heart failure with a preserved ejection fraction do not have LVH [19] despite the fact that hypertension is the dominant risk factor for this form of heart failure. Moreover, LV diastolic dysfunction without LVH is an early manifestation of hypertensive heart disease [20]. Consequently, the value of measures of LVH or the remodelling process as effective indices that herald the presence of LV diastolic dysfunction is unclear. In the current study we therefore evaluated in a reasonably large community-based study with a high prevalence of untreated hypertension, using product of coefficient mediation analysis, the extent to which LV mass (LVM) or relative wall thickness (RWT) account for the impact of blood pressure (BP) on indices of LV diastolic function.

METHODS

Study sample

The current study was approved by the University of the Witwatersrand Committee for Research in Human Subjects (approval number M02-04-72 renewed as M07-04-69, M12-04-108 and M17-04-01). Participants gave informed, written consent. The study design has previously been described [21–25]. A total of 1044 participants of nuclear families of black African descent with siblings older than 16 years were randomly recruited from the South West Township of Johannesburg, South Africa for echocardiographic studies. Random recruitment of families living in formal dwellings (but not institutions) was performed based on the national census figures of 2001 (Department of Home Affairs) and a participation rate of 72% was obtained [21–25]. No individuals of mixed, Asian or European ancestry and no Khoi-San individuals were recruited. Tissue Doppler measures of myocardial function were obtained in a sub-study conducted in 709 participants from the time that these measures became routinely available.

Demographic and clinical information

A standardized questionnaire was administered to obtain demographic and clinical data [21–25]. Height, weight and waist circumference were measured using standard approaches and participants were identified as being overweight if their BMI was at least 25 kg/m^2, and obese if their BMI was at least 30 kg/m^2. Central obesity was defined as an enlarged waist circumference ($\geq$88 cm in women and $\geq$102 cm in men). Laboratory blood tests including percentage glycated haemoglobin (HbA_{1c}) were performed. Diabetes mellitus was defined as the use of insulin or oral hypoglycaemic agents or a HbA_{1c} (Roche Diagnostics, Mannheim, Germany) value greater than 6.5%.

Nurse-derived conventional BP was measured according to guidelines using a mercury sphygmomanometer after 5 min of rest in the seated position as previously described [23]. Five consecutive BP readings were obtained using an appropriately sized cuff, 30–60 s apart. The average of the five readings was taken as the BP. None of the visits had fewer than the planned BP recordings. Hypertension was defined as the use of antihypertensive medication or if the mean of the five conventional BP measurements was more than 140 (SBP) or 90 (DBP) mmHg in those not receiving medication.

Echocardiography

Echocardiographic measurements were performed as previously described [21,22,24] by two experienced observers (A.J.W. and C.D.L.) with the participants in the partial left decubitus position. Details of the measurements are described in the on-line supplement. LV dimensions were determined using two-dimensional directed M-mode echocardiography in the short axis view and these recordings were analysed according to the American Society of Echocardiography convention [26]. LV mass was determined using a standard formula [27] and due to the high prevalence of obesity and hypertension in the community studied, indexed (LVMI) to both height$^{1.7}$ as well as BSA. LV RWT was assessed using standard M-mode approaches. LV ejection fraction was calculated using the biplane Simpson method. LV diastolic function was determined from a pulsed wave Doppler examination of the mitral inflow at rest [early (E) and late (atrial contraction-A) velocity] and using tissue Doppler indices (TDI) [early (e') and late (atrial contraction a') velocity] as well as left atrial volumes (LAVs) [24]. Data were expressed as E/A, e'/a' and the E/e' ratio (an index of LV filling pressures). Left atrial volume was indexed to BSA. Intra and interobserver variability for echocardiographic parameters has either previously been reported on [28,29] or further provided in the on-line supplement.

As several approaches to identifying diastolic dysfunction have been advocated and not all of those individuals identified as having diastolic dysfunction according to one method have diastolic dysfunction using an alternative method, we employed two approaches to diagnosing diastolic dysfunction. In this regard, at the time of initiating our study, pulmonary artery pressures were not advocated, and we were unable to obtain consistent E and A data during the Valsalva manoeuvre. Hence, we employed modified

approaches to that advocated by guidelines [30] and to that originally suggested [31]. Based on current guidelines, in those participants with an ejection fraction more than 50%, diastolic dysfunction was therefore identified by the presence of at least two of the following: a lateral e' less than 10 cm/s or a septal e' less than 8 cm/s, E/e' more than 14 or LAV at least 34 ml/m^2 [30]. For those participants with an ejection fraction less than 50%, we identified diastolic dysfunction if participants had an E/A more than 2.0 (restrictive filling pattern) or an E/A 0.8–2.0 with both E/e' more than 14 and LAV at least 34 ml/m^2 [30]. We further identified the presence of either mild, moderate or severe diastolic dysfunction using previous criteria if E/A was less than 0.75 (mild diastolic dysfunction), E/A was between 0.75 and 1.5 and E/e' was more than 10 (moderate diastolic dysfunction), or if E/A was more than 1.5 and E/e' was more than 10 (severe restrictive filling pattern) [31].

Data analysis

Database management and statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). Data from individuals were averaged and expressed as mean ± SD or SEM. To improve on the distribution of data lateral e', septal e', E/e', E/A, e'/a' and LAV were logarithmically transformed. To determine independent relations, multivariate adjusted linear (continuous data) or logistic (discrete data) regression analysis was performed. Adjustments were performed for all factors correlated with BP, indices of LV remodelling, or indices of LV diastolic function. As we have previously demonstrated differential relations between SBP and DBP and various indices of LV diastolic function [22], in relations with e' or E/e', SBP was employed and in relations with E/A and e'/a', DBP was employed as the BP index. To determine the relative contribution of factors toward LV diastolic function, multivariate stepwise regression analysis was performed and factors not independently associated with LV diastolic function were forced into the model. To determine the contribution of LVMI or RWT to the impact of BP on LV diastolic function, multivariate adjusted product of coefficient mediation analysis, which accounts for hierarchical causal structures, was performed. This analysis was conducted as described using the example given in the online supplement. For the derivation of probability values, further adjustments were made for nonindependence of family members using the mixed procedure as outlined in the SAS package. Sensitivity analysis was conducted in those not receiving antihypertensive therapy and in sex-specific and obese and nonobese subgroups.

RESULTS

Characteristics of study sample

Table 1 gives the demographic and clinical characteristics of the participants. More women than men participated in the study and a high proportion of participants were overweight, or obese and had central obesity. A high proportion of participants were hypertensive and were not receiving antihypertensive therapy and hence the proportion of participants with uncontrolled hypertension was high. As compared with participants recruited prior to TDI becoming available, participants in whom echocardiography was performed once routine TDI became available, were modestly older with more abdominal obesity (Table S1, http://links.lww.com/HJH/B61). Based on current guidelines, 15.4% of the participants had diastolic dysfunction and this was largely determined by a combination of either reductions in lateral or septal e' and increases in E/e' (11.6%). Based on previous criteria, 28.1% of the participants had diastolic dysfunction and this was largely determined by mild (12.8%) or moderate (11.3%) diastolic dysfunction. No participants had an ejection fraction less than 40 and 4.1% had an ejection fraction less than 50%. Of the sample 39.6% had LVH (LVMI > 80 g/m$^{1.7}$ for men and >60 g/m$^{1.7}$ for women) and 18.1% had concentric LV remodelling (RWT > 0.42). A greater proportion of hypertensive patients than normotensive patients had LVH and concentric LV remodelling.

Factors related to left ventricular mass index or relative wall thickness

Independent of age, sex, regular smoking or alcohol intake, or the presence of diabetes mellitus, SBP and indices of adiposity (waist circumference or BMI) were associated with LVMI ($P < 0.0001$). In addition, independent of confounders SBP ($P = 0.05$) and BMI ($P < 0.01$) were associated with RWT.

Independent relations with left ventricular diastolic function

With adjustments for confounders, SBP (Table 2 and Table S2, http://links.lww.com/HJH/B61), and either waist circumference (Table 2 and Table S2, http://links.lww.com/HJH/B61) or BMI (data not shown) were independently associated with lateral wall e' and E/e'. Moreover, with adjustments for confounders, DBP (Table 3 and Table S2,

TABLE 1. Characteristics of the study sample

Sample number (% female)	709 (67.6)
Age (years)	47.2 ± 18.1
BMI (kg/m^2)	30.0 ± 7.9
% Overweight/obese	22.9/46.5
Waist circumference (WC) (cm)	94.4 ± 18.0
% Abnormal waist circumference	53.7
Regular tobacco (% individuals)	16.2
Regular alcohol (% individuals)	19.5
% Diabetes mellitus or an $HbA_{1c} > 6.5\%$	13.1
% Hypertensive	49.6
% Treated for hypertension	29.3
% Uncontrolled blood pressure	35.0
Brachial SBP/DBP (mmHg)	128 ± 22/83 ± 13
Lateral e' (cm/s)	11.3 ± 4.1
E/A	1.26 ± 0.51
e'/a'	1.40 ± 0.70
E/e'	7.5 ± 4.2
Left atrial (LA) volume index (ml/m^2)	19.7 ± 7.5
LVM indexed to height (LVMI-ht$^{1.7}$)(g/m$^{1.7}$)	62.7 ± 23.1
LVM indexed to BSA (LVMI-BSA) (g/m^2)	68.9 ± 27.6
LV relative wall thickness (RWT)	0.36 ± 0.08

a', myocardial tissue lengthening in late diastole at the mitral annulus; E/A, transmitral early/atrial blood flow velocity; E/e', transmitral early blood flow velocity/velocity of the mean value of lateral and septal wall myocardial tissue lengthening in early diastole at the mitral annulus; e', myocardial tissue lengthening in early diastole at the mitral annulus; HbA_{1c}, glycated haemoglobin; LVM, left ventricular mass.

TABLE 2. Relative contribution (standardized β-coefficient) of risk factors toward indices of left ventricular diastolic function in a community sample ($n = 709$)

	Log lateral wall e'						Log E/e'					
	β-coef ± SEM	*P* value	β-coef ± SEM	*P* value	β-coef ± SEM	*P* value	β-coef ± SEM	*P* value	β-coef ± SEM	*P* value	β-coef ± SEM	*P* value
LVMI-ht$^{1.7}$	–	–	−0.100 ± 0.032	(<0.005)	–	–	–	–	0.112 ± 0.039	(<0.005)	–	–
RWT	–	–	–	–	−0.067 ± 0.030	(<0.05)	–	–	–	–	0.099 ± 0.036	(<0.01)
SBP	−0.147 ± 0.032	(<0.0001)	−0.131 ± 0.032	(<0.0001)	−0.142 ± 0.032	(<0.0001)	0.189 ± 0.039	(<0.0001)	0.171 ± 0.040	(<0.0001)	0.181 ± 0.039	(<0.0001)
WC	−0.159 ± 0.034	(<0.0001)	−0.127 ± 0.036	(<0.0005)	−0.156 ± 0.034	(<0.0001)	0.130 ± 0.042	(<0.005)	0.095 ± 0.044	(<0.05)	0.126 ± 0.042	(<0.005)
Age	−0.401 ± 0.039	(<0.0001)	−0.387 ± 0.039	(<0.0001)	−0.386 ± 0.039	(<0.0001)	0.169 ± 0.047	(<0.0005)	0.153 ± 0.047	(<0.002)	0.147 ± 0.048	(<0.005)

β-coef, standardized β-coefficient (slope). See Table 1 for other abbreviations. Also included in the models are sex, regular tobacco use and regular alcohol consumption, treatment for hypertension, diabetes mellitus and pulse rate. For models with LVMI-BSA see Table S4, http://links.lww.com/HJH/B61.

http://links.lww.com/HJH/B61), and either waist circumference (Table 2 and Table S3, http://links.lww.com/HJH/B61) or BMI (data not shown) were independently associated with E/A and lateral wall e'/a'. With the inclusion of LVMI-ht$^{1.7}$ or RWT in the regression models, although both LVMI or RWT were independently associated with lateral wall e' or E/e' (Table 2 and Table S2, http://links.lww.com/HJH/B61), or E/A or e'/a' (Table 3 and Table S3, http://links.lww.com/HJH/B61), the impact of alternative risk factors on these indices of diastolic function was hardly modified. The use of LVMI-BSA rather than LVMI-ht$^{1.7}$ produced essentially the same results (Table S4, http://links.lww.com/HJH/B61). The lack of impact of adjustments for LVMI or RWT on relations between BP and indices of LV diastolic function was reproduced in men and women (refer to Table S5, http://links.lww.com/HJH/B61 for LVMI in the model with RWT showing similar data) and in obese versus nonobese (refer to Table S6, http://links.lww.com/HJH/B61 for LVMI in the model with RWT showing similar data) participants. SBP was modestly and independently associated with LAV index in the whole group (Table 4), but not in the group having never received antihypertensive therapy (Table S7, http://links.lww.com/HJH/B61). Neither waist circumference (Table 4 and Table S7, http://links.lww.com/HJH/B61) nor BMI (data not shown) were independently associated with LAV index. LVMI, but not RWT was independently associated with LAV index. With the inclusion of LVMI, but not RWT in the regression models, SBP was no longer independently associated with LAV index (Table 4).

Product of coefficient mediation analysis

Adjustments for LVMI-ht$^{1.7}$ or LVMI-BSA failed to modify the impact of a one SD effect of BP on e', E/e', E/A or e'/a' (Fig. 1 and Fig. S1, http://links.lww.com/HJH/B61) and in mediation analysis, LVMI-ht$^{1.7}$ or LVMI-BSA failed to account for a significant proportion of the impact of a one SD effect of BP on either e', E'/e, E/A or e'/a' (Fig. 1 and Fig. S1, http://links.lww.com/HJH/B61). Similarly, adjustments for RWT failed to modify the impact of a one SD effect of BP on e', E/e', E/A or e'/a' (Fig. 1 and Fig. S1, http://links.lww.com/HJH/B61) and in mediation analysis, RWT failed to account for a significant proportion of the impact of a one SD effect of BP on either e', E'/e, E/A or e'/a' (Fig. 1 and Fig. S1, http://links.lww.com/HJH/B61).

Relations with left ventricular diastolic dysfunction

Irrespective of the criteria employed to diagnose diastolic dysfunction, SBP ($P = 0.005$), LVMI ($P < 0.0005$) and RWT ($P < 0.001$), were independently associated with LV dia-

TABLE 3. Relative contribution (standardized β-coefficient) of risk factors toward indices of left ventricular diastolic function in a community sample ($n = 709$)

	Log lateral wall e'/a'						Log E/A					
	β-coef ± SEM	*P* value	β-coef ± SEM	*P* value	β-coef ± SEM	*P* value	β-coef ± SEM	*P* value	β-coef ± SEM	*P* value	β-coef ± SEM	*P* value
LVMI-ht$^{1.7}$	–	–	−0.070 ± 0.027	(<0.01)	–	–	–	–	−0.024 ± 0.030	(=0.44)	–	–
RWT	–	–	–	–	−0.042 ± 0.025	(=0.10)	–	–	–	–	−0.035 ± 0.029	(=0.22)
DBP	−0.137 ± 0.025	(<0.0001)	−0.134 ± 0.025	(<0.0001)	−0.135 ± 0.025	(<0.0001)	−0.124 ± 0.029	(<0.0001)	−0.123 ± 0.029	(<0.0001)	−0.122 ± 0.029	(<0.0001)
WC	−0.185 ± 0.029	(<0.0001)	−0.162 ± 0.031	(<0.0005)	−0.183 ± 0.029	(<0.0001)	−0.099 ± 0.033	(<0.005)	−0.091 ± 0.035	(<0.01)	−0.097 ± 0.033	(<0.005)
Age	−0.551 ± 0.031	(<0.0001)	−0.537 ± 0.031	(<0.0001)	−0.541 ± 0.032	(<0.0001)	−0.563 ± 0.035	(<0.0001)	−0.558 ± 0.036	(<0.0001)	−0.554 ± 0.036	(<0.0001)

β-coef, standardized β-coefficient (slope). See Table 1 for other abbreviations. Also included in the models are sex, regular tobacco use and regular alcohol consumption, treatment for hypertension, diabetes mellitus and pulse rate. For models with LVMI-BSA see Table S4, http://links.lww.com/HJH/B61.

TABLE 4. Relative contribution (standardized β-coefficient) of risk factors toward left atrial volume index in a community sample ($n = 709$)

	β-coef ± SEM	*P* value	β-coef ± SEM	*P* value	β-coef ± SEM	*P* value
LVMI-ht$^{1.7}$	–	–	0.265 ± 0.041	(<0.0001)	–	–
RWT	–	–	–	–	0.058 ± 0.041	(=0.15)
SBP	0.089 ± 0.043	(<0.05)	0.045 ± 0.042	(=0.29)	0.085 ± 0.043	(<0.05)
WC	0.053 ± 0.046	(=0.25)	−0.026 ± 0.047	(=0.57)	0.050 ± 0.046	(=0.28)
Age	0.170 ± 0.052	(<0.002)	0.129 ± 0.051	(<0.02)	0.159 ± 0.053	(<0.005)

β-coef, standardized β-coefficient (slope). See Table 1 for other abbreviations. Also included in the models are sex, regular tobacco use and regular alcohol consumption, treatment for hypertension, diabetes mellitus and pulse rate.

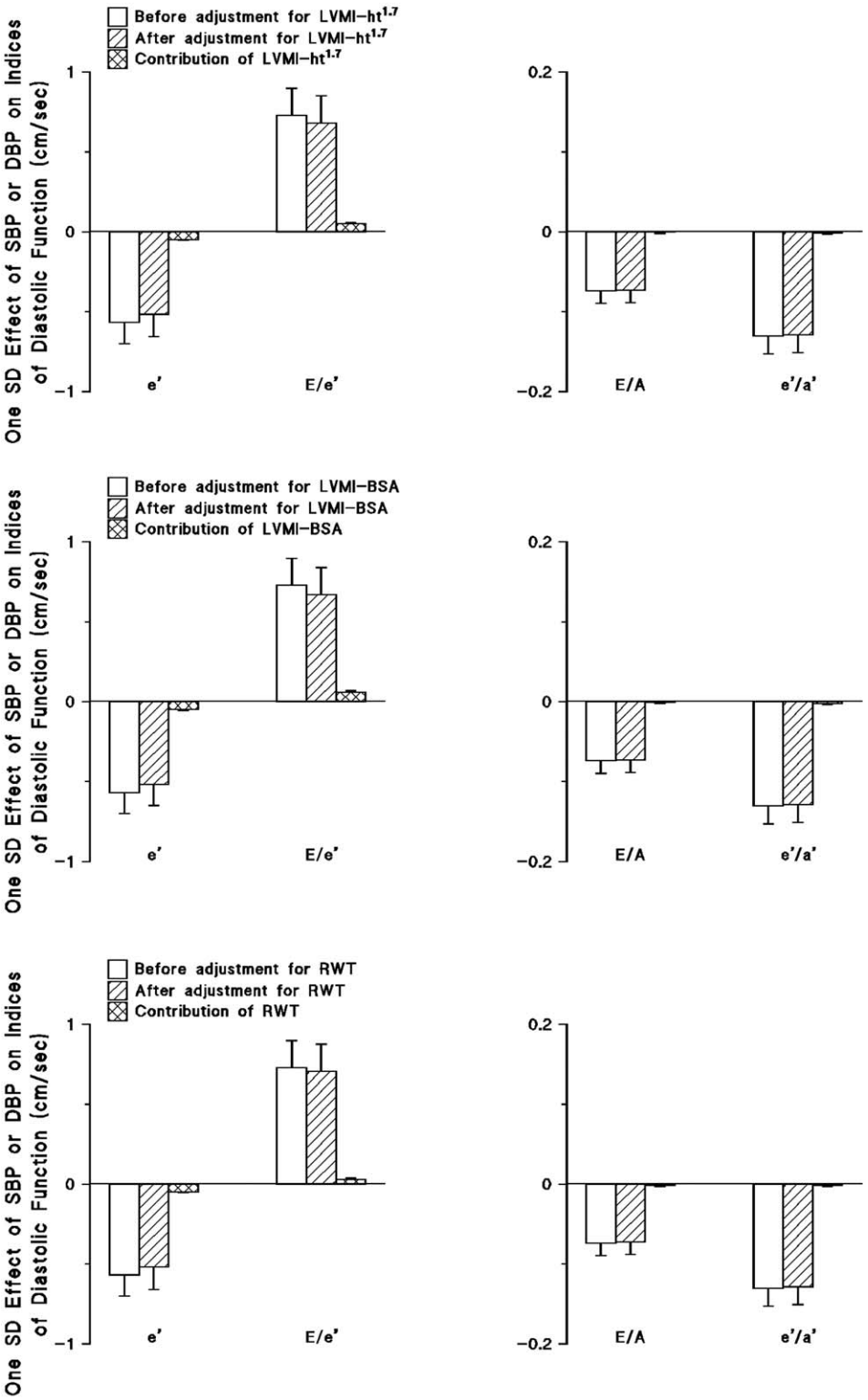
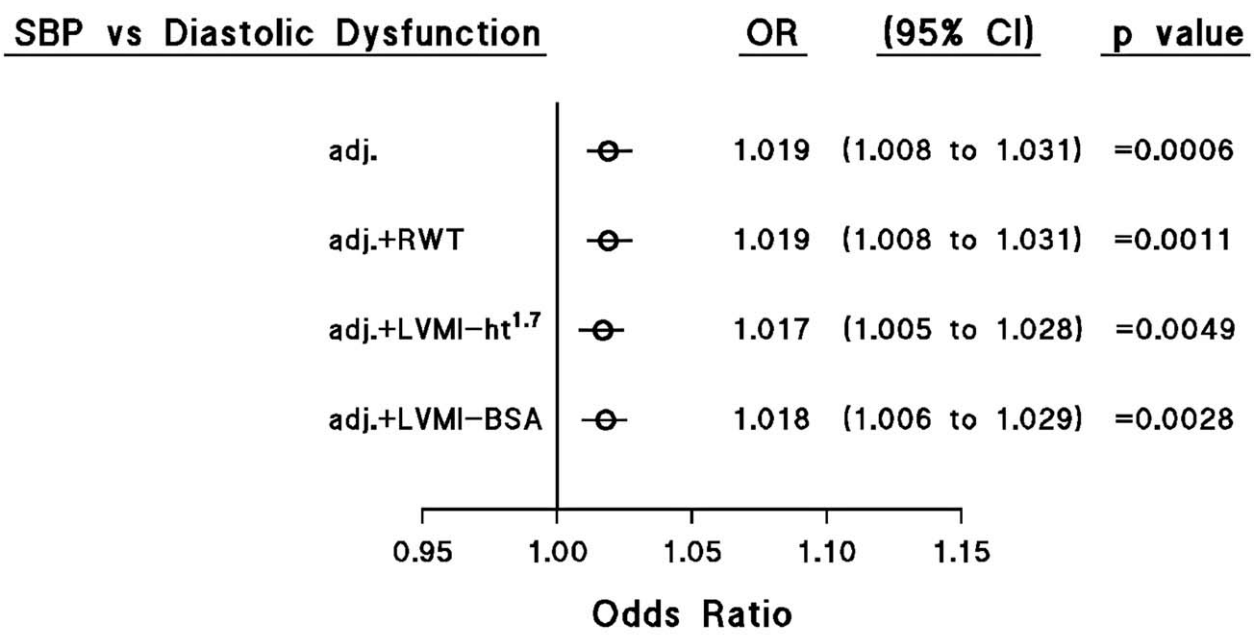


FIGURE 1 Contribution of left ventricular mass index or geometric remodelling (relative wall thickness left ventricular mass index) to the relationship between SBP or DBP and indices of left ventricular diastolic function in a community sample ($n = 709$). Figures show one SD effect of blood pressure before and after adjustments for left ventricular mass index or relative wall thickness on left ventricular diastolic function and the contribution of left ventricular mass index or relative wall thickness to the one SD effect of blood pressure on left ventricular diastolic function (product of coefficient mediation analysis). See Table 1 for abbreviations. Adjustments are for left ventricular mass index or relative wall thickness as indicated and age, sex, waist circumference, the presence of diabetes mellitus, treatment for hypertension, regular tobacco use, regular alcohol consumption and pulse rate.



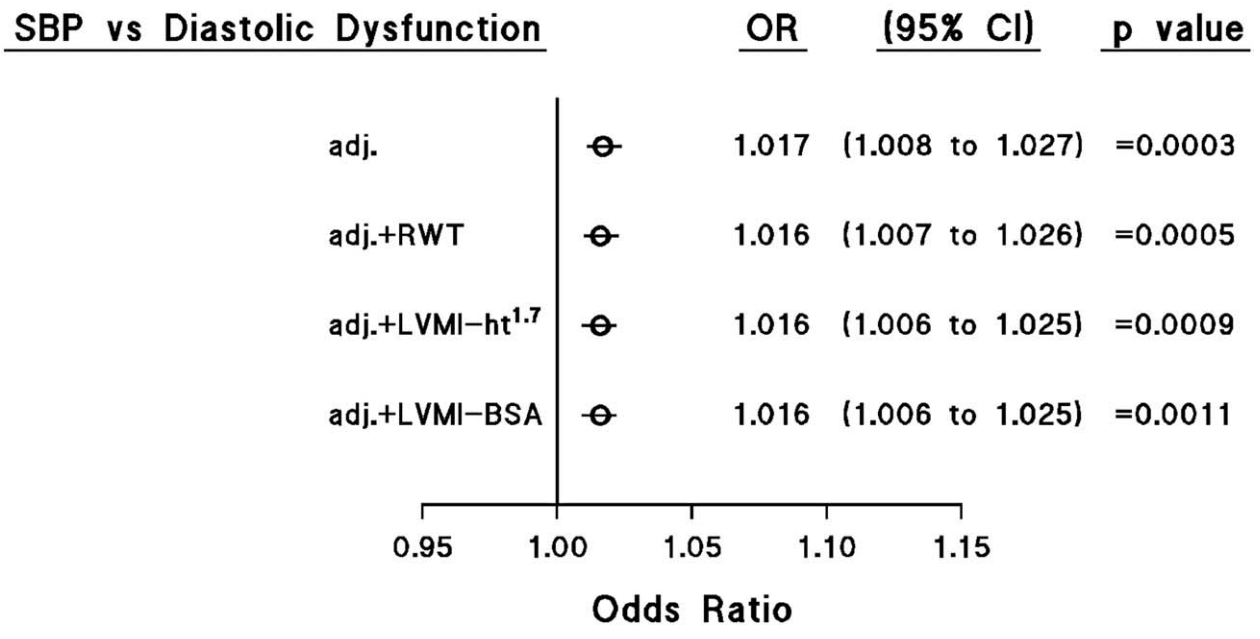


FIGURE 2 Impact of adjustments for left ventricular mass index or relative wall thickness on the independent associations between SBP and the presence of left ventricular diastolic dysfunction in a community sample ($n = 709$). Adjustments are for left ventricular mass index or relative wall thickness as indicated and age, sex, waist circumference, the presence of diabetes mellitus, treatment for hypertension, regular tobacco use, regular alcohol consumption and pulse rate. Upper panel shows relations with diastolic dysfunction determined using criteria from current guidelines [31] and the lower panel shows relations with diastolic dysfunction determined using previously described criteria [32].

stolic dysfunction. However, with adjustments for LVMI-ht$^{1.7}$, LVMI-BSA or RWT, the independent relations between SBP and diastolic dysfunction were unchanged (Fig. 2 and Fig. S2, http://links.lww.com/HJH/B61).

DISCUSSION

The main findings of the current study are as follows; in a reasonably large community-based study with a high prevalence of untreated and uncontrolled hypertension we show that although both LVMI and RWT are independently associated with several characteristic changes in LV diastolic function, they account for little of the relationship between BP and LV diastolic function. Indeed, in product of coefficient mediation analysis, the contribution of either LVMI or RWT to relationships between BP and lateral wall e', E/e', E/A and e'/a' was minor at best and adjustments for LVMI or RWT failed to significantly modify relationships

between BP and either indices of LV diastolic function or the presence of diastolic dysfunction. These effects were noted irrespective of whether all participants were considered or only those having never received antihypertensive agents.

LV hypertrophy and remodelling have traditionally been viewed as an almost necessary prelude to LV dysfunction and heart failure in hypertension. In this regard, concentric LV remodelling and hypertrophy are thought to progress to LV diastolic dysfunction and eccentric hypertrophy to LV systolic dysfunction. Using less contemporary approaches to identifying LV diastolic dysfunction, 84% of hypertensive patients with LVH have previously been noted to have LV diastolic dysfunction [15], and it is estimated that only 11–20% of hypertensive patients have LV diastolic dysfunction without exhibiting LVH [13,16]. However, these estimates were obtained at a time when more recent noninvasive approaches to determining LV diastolic function were not available. In contrast however, it is also well recognized that many patients with heart failure with a preserved ejection fraction do not have LVH [19] despite the fact that hypertension is the dominant risk factor for this form of heart failure. Moreover, LV diastolic dysfunction without LVH is an early manifestation of hypertensive heart disease [20]. Indeed, the cellular changes responsible for LV diastolic dysfunction in hypertension are often independent of the hypertrophic process [17,18]. In this regard, myocardial fibrosis is correlated with diastolic dysfunction determined using tissue Doppler imaging in hypertensive patients irrespective of LVM, and myocardial fibrosis may precede LVH in the evolution of hypertensive heart disease [32]. In support of the notion that neither LVMI nor RWT explain BP-related decreases in LV diastolic function, little of the impact of BP on several aspects of LV diastolic function noted in the current study could be accounted for by LVMI or RWT. Importantly, these findings were noted when assessing relations between BP and diastolic function or dysfunction with as compared with without adjustments for LVMI or RWT and in product of coefficient mediation analysis. These data are in-part consistent with a dissociation noted between ethnicity and LVM versus diastolic dysfunction in a recent large echocardiographic study [33], and the limited contribution of concentric LVH to diastolic dysfunction in hypertensive patients recently described [34]. In this regard, the current study suggests that neither LVH nor the LV remodelling process contribute to any significant degree to BP-associated changes in LV diastolic function.

Although the results of the current study suggest that LVMI and RWT are not necessary preludes to LV diastolic dysfunction in hypertension, they do not suggest that those with LVH or concentric LV remodelling are not at risk of LV diastolic dysfunction or the development of heart failure with a reduced ejection fraction. Indeed, diastolic dysfunction may be worse in patients with LVH as compared with those without LVH [35], and in the current study LVH and RWT were independently associated with diastolic dysfunction. Moreover, LVH is well recognized as progressing to both diastolic dysfunction and heart failure and concentric LVH is thought to progress to heart failure with a preserved ejection fraction [36,37]. The current study nevertheless raises the question of whether diastolic dysfunction in LVH or the progression to diastolic dysfunction in those with LVH is attributed to the impact of structural remodelling of the LV or rather separately to BP effects. Indeed, it is mainly those with LVH who, in addition to a structural change in the LV, have biomarker evidence of increased loading conditions or myocardial damage produced presumably by increased loads, that progress to heart failure [38]. Moreover, assigning those with LVH to concentric versus eccentric subtypes only moderately differentiates participants at increased risk of heart failure with a preserved versus reduced ejection fraction [39]. Consequently, LVH and RWT alone may not be strong phenotypes for detecting the risk for heart failure or heart failure subtypes in hypertension. In this regard, the current study adds to this notion by suggesting the neither LVMI nor RWT are strong phenotypes for identifying the presence of BP-associated decreases in LV diastolic function. Nevertheless, whether as recently suggested, the combination of LVH and diastolic dysfunction is a worse cardiac phenotype in hypertensive heart disease than either considered separately [20] requires further study.

A further question of importance that arises from the current study is whether in the treatment of hypertension, LV diastolic functional parameters improve in close association with on-treatment reductions in LVMI. Although several studies, including major clinical trials [40] have demonstrated improvements in contemporary measures of LV diastolic function following antihypertensive therapy, to the best of our knowledge we can find no reported data to suggest the extent to which regression of LVH explains the benefits of antihypertensive therapy on LV diastolic function. However, in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the marked differences in treatment groups in improvements in LV diastolic function were unaffected by adjustments for LVMI [40]. Hence, in-keeping with the current study, on-treatment reductions in LVMI in the ASCOT study [40] are unlikely to have contributed significantly to improvements in LV diastolic function. Although in the ASCOT study little difference in brachial BP was noted between treatment groups [40], marked differences in central aortic BP did occur between the treatment groups. Thus, on-treatment differences in the improvement of LV diastolic function in the ASCOT study [40] are likely to have been attributed to differences in the impact of treatment on pulsatile loads.

The criteria for the diagnosis of LV diastolic dysfunction have been debated over several decades. As recently highlighted [30], TDI of diastolic dysfunction (e' and E/e'), LAV and pulmonary artery pressures, are recommended for the diagnosis of diastolic dysfunction in the presence of a normal ejection fraction. Although we determined three of the four recommended measures of diastolic dysfunction (lateral and septal wall e', E/e' and LAVs), at the time of initiating the current study, we did not determine pulmonary artery pressures. As the diagnosis of diastolic dysfunction in those with a normal ejection fraction requires more than two of the four criteria to be present [30], we may have included indeterminate participants as having diastolic dysfunction. We nevertheless also showed similar relations with diastolic dysfunction when employing the original criteria proposed several years prior to the recent guidelines

[31]. However, using the previously described criteria for identifying diastolic dysfunction [31], pseudo-normalization of *E/A* may be determined from changes noted with the Valsalva manoeuvre, an approach which we were unable to reproducibly perform. Nevertheless, according to these original criteria [31] moderate diastolic dysfunction may also be identified from E/e' more than 10 [31], an approach employed in the current study for the diagnosis of diastolic dysfunction.

There are several additional limitations to the current study. This is a cross-sectional study and hence we cannot draw conclusions regarding causality. However, the causal relationship between BP and indices of LV diastolic function has been well described. In addition, concentric LV remodelling is more prevalent in groups of African descent than other origins, and female sex and obesity are well recognized risk factors for diastolic dysfunction. In this regard, the present findings were noted in a community sample of black African ancestry with a high prevalence of obesity and where more women than men volunteered to participate. Hence, it is important to consider the possibility that the findings are specific to groups of African ancestry and to obese females. Nevertheless, although we were not statistically powered to perform analysis on relations with a diagnosis of diastolic dysfunction in subgroups, the lack of contribution of LVMI or RWT to BP-associated changes in the individual criteria for diastolic dysfunction were reproduced in men and women and in obese versus nonobese participants of the current study. Further, the lack of impact of adjustments for LVM on the ability of decreases in BP to modify TDI of diastolic function previously described [40] was observed in a clinical trial conducted largely in patients of European ancestry with an equivalent male as compared with female distribution and whom had a low prevalence of obesity. Moreover, relations between circulating concentrations of procollagen type I and indices of diastolic function beyond LVM [32] were previously described in largely male whites with a low prevalence of obesity. Thus, the ability of BP and BP-associated changes in myocardial properties to associate with diastolic function beyond LVM is likely to be consistent across ethnic groups, sexes and levels of body size.

Although in the current study we show a limited contribution of LVM to BP effects on LV diastolic function, we failed to provide evidence for a mechanism that may explain these effects. In this regard, as indicated in the aforementioned paragraph, circulating concentrations of procollagen type I are correlated with TDI of diastolic function [32]. Importantly however, it is now well recognized that several mechanisms explain relationships between hypertension and diastolic dysfunction including alterations in myocardial calcium cycling, titin expression, collagen cross-linking (mediated by oxidative stress) and coronary microvascular alterations [17,18,41]. Indeed, unequivocal preclinical evidence challenges the role of both myocardial fibrosis and LVH independently mediating diastolic dysfunction in hypertension [41]. Hence, only biopsy studies will comprehensively identify the mechanisms of BP-mediated myocardial diastolic dysfunction.

In conclusion, in a relatively large community-based sample with a high prevalence of untreated hypertension, we show in product of coefficient mediation analysis, that independent of confounders, LVM and the extent of concentric LV remodelling account for little of the adverse effects of BP on LV diastolic function. Thus, most BP-associated decreases in LV diastolic function should be viewed as a transition process to LV dysfunction independent of LVH or concentric remodelling and hence that measures of LVM or LV remodelling offer little insight into the adverse effects of BP on LV diastolic function.

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Conflicts of interest

There are no conflict of interest.

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