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Independent of left ventricular mass, circulating inflammatory markers rather than pressure load are associated with concentric left ventricular remodelling☆

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ABSTRACT

Background: A reason for concentric left ventricular (LV) remodelling predicting cardiovascular outcomes independent of conventional risk factors and LV mass (LVM) has not been provided. We hypothesized that independent of LVM, concentric LV remodelling is associated with inflammatory changes rather than a pressure load on the LV.

Methods: In 764 randomly selected community participants, we assessed relations between several inflammatory markers (ELISA) and LV relative wall thickness (RWT) (echocardiography), LV mass index (LVMI), and indexes of diastolic function.

Results: No independent relations were noted between circulating concentrations of inflammatory markers and LVM index (LVMI) ($p > 0.13$ for all). However, independent of confounders including LVMI and blood pressure (BP), circulating tumour necrosis factor-α (TNF-α) (partial $r = 0.14$, $p < 0.0005$) and to a lesser degree interleukin-6 (partial $r = -0.09$, $p < 0.02$) were associated with RWT. The impact (standardized β-coefficient) of TNF-α on RWT (0.12 ± 0.03, $p < 0.0005$) was at least as strong as age (0.13 ± 0.05, $p < 0.005$), and second only to LVMI (0.27 ± 0.04, $p < 0.0001$), whilst neither office, 24-hour, central aortic BP, nor aortic stiffness were associated with RWT independent of LVMI. With adjustments, as compared to participants with a normal LVMI and geometry (12.7 ± 0.8), circulating TNF-α concentrations (pg/ml) were increased as much in participants with concentric LV remodelling (16.8 ± 1.5, $p < 0.05$) as in those with concentric LV hypertrophy (LVH) (17.0 ± 1.3, $p < 0.005$), whilst eccentric LVH (13.7 ± 0.9) was not. No independent relations between inflammatory markers and LV diastolic function (trans-mitral and tissue Doppler) were noted.

Conclusions: Independent of LVMI, a pro-inflammatory state rather than BP load is strongly associated with LV concentric remodelling.

1. Introduction

Independent of conventional risk factors and coronary artery disease left ventricular hypertrophy (LVH) is a well-recognised risk factor for cardiovascular events [1–3]. However, structural remodelling of the LV includes not only hypertrophy, but also geometric changes. In this regard, as compared to a normal LV geometry, concentric LV remodelling, as indexed by either an increased wall thickness-to-internal diameter (relative wall thickness-RWT) [4–6] or an increased LV mass (LVM)-to-volume [7,8] ratio, has been demonstrated to independently predict cardiovascular outcomes. Even in studies where concentric LV remodelling alone failed to predict outcomes, concentric LVH showed a stronger ability to independently predict outcomes than eccentric LVH [9–12]. Although the geometry of the LV appears to add to cardiovascular risk prediction

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beyond LV mass (LVM), an explanation for this observation is presently unclear.

According to the Law of La Place, concentric LV remodelling is traditionally viewed as a compensatory response to increased LV loading conditions (to reduce wall stress), and hence to reflect the impact of cumulative changes in LV loads over time. Importantly however, concentric LV remodelling is also a pathognomonic change in heart failure with a preserved ejection fraction (HFpEF). In this regard, HFpEF may occur as a consequence of inflammatory-induced coronary microvascular endothelial dysfunction which mediates several interstitial and cardiomyocyte alterations associated with HFpEF [13]. Therefore, in addition to indexing temporal changes in LV load, concentric LV remodelling may reflect a pro-inflammatory state associated with endothelial dysfunction. Nevertheless, large studies [14–16] have failed to show convincing blood pressure (BP) or LV mass-independent relations between circulating pro-inflammatory markers and LV geometry. However, in these studies [14–16], a high proportion of participants were receiving therapeutic agents that modify LV geometry or endothelial function. Consequently, in a large, well-characterized community-based sample of young-to-middle aged participants, few of whom were receiving therapeutic agents that modify LV geometry or endothelial function, we assessed the LVM and BP-independent relations between several circulating inflammatory markers and LV geometry.

2. Methods

2.1. Study group

The present study was conducted according to the principles outlined in the Helsinki declaration. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval number: M02-04-72 and renewed as M07-04-69, M12-04-108 and M17-04-01). Participants gave informed, written consent. The present study design has previously been described [17,18]. Briefly, of 1045 participants from randomly recruited (from the population census figures of 2001) families of black African descent (Nguni and Sotho chiefdoms) from the South West Township (SOWETO) of Johannesburg, South Africa, with siblings older than 16 years, in a sub-study 764 had LVM index (LVMI), RWT and LV function determined by echocardiography.

2.2. Clinical, demographic, anthropometric and hemodynamic measurements

A questionnaire was administered to obtain demographic and clinical data including a previous clinical diagnosis of heart failure requiring heart failure therapy [17,18]. Participants reporting shortness of breath to the study nurse were evaluated by a clinician (GRN) for signs of heart failure. Height and weight were measured using standard approaches and participants were considered to be overweight if their body mass index (BMI) was ≥25 kg/m^2 and obese if their BMI was ≥30 kg/m^2. Laboratory blood tests of renal function, liver function, blood glucose, hematological parameters, and percentage glycated hemoglobin (HbA_{1c}) were performed. Diabetes mellitus (DM) or an abnormal blood glucose control was defined as the use of insulin or oral hypoglycemic agents or an HbA_{1c} value >6.1%. High quality office brachial blood pressure (BP) measurements were obtained in the seated position and after 5 min of rest, by a trained nurse-technician using a standard mercury sphygmomanometer according to guidelines [17]. The mean of 5 measurements obtained at least 30 s apart was taken as office BP. 24-hour ambulatory BP monitoring was performed using oscillometric monitors (SpaceLabs, model 90207) as previously described [17]. The size of the cuff was the same as that used for conventional BP measurements. Monitors were programmed to measure 24-hour BP at 15-min intervals from 06:00 to 22:00 h and at 30-min intervals from 22:00 to 06:00 h. 256 participants had either incomplete recordings or did not consent to 24-hour BP measurements. Hypertension was defined as a mean office BP ≥ 140/90 mm Hg or the use of antihypertensive medication. Central aortic hemodynamics were estimated using pulse wave analysis as previously described (applanation tonometry and SphygmoCor version 9.0 software) [17,18]. Aortic pulse wave velocity (PWV) was determined from sequential waveform measurements at carotid and femoral sites. Aortic PWV could not be obtained in 97 participants who were too obese to acquire adequate femoral measurements.

2.3. Echocardiography

Echocardiographic measurements were recorded and analysed off-line by experienced investigators (CDL and AJW) who were unaware of the clinical data of the participants and whom had a low degree of inter- and intra-observer variability [17]. Left ventricular mass index (LVMI) was determined from transthoracic two-dimensional targeted M-mode echocardiography obtained in the long axis parasternal view. Variables were analysed according to the American Society of Echocardiography convention [19]. Left ventricular mass was determined using a standard formula [20] and indexed (LVMI) to height$^{1.7}$ [21]. Left ventricular hypertrophy (LVH) was identified as an LVMI-ht$^{1.7}$ >80 g/m$^{1.7}$ for men and >60 g/m$^{1.7}$ for women [21]. Concentric LV remodelling and concentric LVH were defined as a RWT ≥0.42 or ≥0.44 (upper 90 or 95% confidence interval of RWT in 306 normotensive, non-obese, non-diabetic participants). Left ventricular dilatation was identified as those with an LV end diastolic diameter of ≥5.5 cm.

Left ventricular ejection fraction was calculated using the biplane Simpson method. Left ventricular systolic function was further assessed from endocardial (FSend) and midwall (FSmid) fractional shortening using standard M-Mode approaches. Left ventricular diastolic function was assessed from a pulsed wave Doppler examination of the mitral inflow at rest and using tissue Doppler indices (TDI) as well as left atrial volumes as previously described [22] in 462 participants recruited from 2008 to-date when TDI became available for routine use. Left atrial volume indexed to body surface area, was calculated using the area-length method.

2.4. Inflammatory markers

Blood samples were centrifuged and immediately stored at −80 °C. Plasma concentrations of TNF-α, interleukin 6 (IL-6) and serum high sensitivity C-reactive protein (hs-CRP) concentrations were measured using enzyme-linked immunosorbent assays (Quantikine, R&D Systems Inc., Minneapolis, MN, USA). The lower detection limits and intra-assay and inter-assay coefficients of variation for each of the assays were as follows: TNF-α: 1.6 pg/ml and 4.2 to 5.2% and 4.6 to 7.4% respectively; IL-6: 0.70 pg/ml and 1.6 to 4.2% and 3.3 to 6.4% respectively; hs-CRP assay (range 0.01 to 50 ng/ml): 0.010 ng/ml and 3.8 to 8.3% and 6.0 to 7.0% respectively.

2.5. Data analysis

For database management and statistical analysis, SAS software, version 9.4 (SAS Institute Inc., Cary, NC) was employed. Serum concentrations of inflammatory markers were non-normally distributed and hence were transformed to improve on the distribution (Table S1). Multiple linear regression analysis was performed to determine independent relations between continuous variables. Multivariate adjusted logistic regression analysis was performed to determine the independent relations with categories of LV remodelling and LVH (discrete data). Adjustments included in multivariate models were those correlated with LVMI, RWT or LV function. To determine probability values, further adjustments for non-independence of family members was performed using non-linear regression analysis (mixed procedure as defined in the SAS package). Regression coefficients were compared with z statistics. In order to ensure that the results were not influenced by the presence of antihypertensive therapy, sensitivity analysis was also conducted in participants not receiving antihypertensive therapy. Moreover, because females have a more concentric LV, sensitivity analysis was also conducted in females and males separately.

3. Results

The clinical and demographic characteristics of the participants included in the echocardiographic sub-study (Table S2) were no different from those participants not included in the sub-study (Table S3) except for a modestly lower age. A high proportion of participants were hypertensive, but not receiving antihypertensive therapy and no patients had a prior clinical diagnosis of heart failure or were noted to have clinical evidence of heart failure if shortness of breath was reported. Based on a RWT threshold of 0.42, in the whole sample 9.4% of participants had concentric remodelling, 14.9% concentric LVH and 32.5% eccentric LVH. In the participants not receiving antihypertensive therapy, 9.0% of participants had concentric remodelling, 12.5% concentric LVH and 29.9% eccentric LVH. Few participants had concentric, dilated LVH (3.5%). However, a significant proportion had eccentric, dilated LVH (16.5%).

In unadjusted models, circulating concentrations of inflammatory markers were correlated with several indexes of LV remodelling (Table S5). In multivariate adjusted models, serum concentrations of TNF-α, and IL-6, but not hs-CRP concentrations were associated with RWT and mean wall thickness (septal + posterior), but not LVMI, or end diastolic diameter (Table 1). These independent relations between TNF-α or IL-6 concentrations and RWT (Table 2) or mean wall thickness (data not shown) remained with further adjustments for several BP variables or PWV (Table S6). Similar relations were noted in women as in men (Table S7). These relationships translated into stepwise increases in RWT and mean wall thickness across quintiles of TNF-α and higher RWT and mean wall thickness values in the higher quintiles of IL-6 concentrations (Fig. 1). Moreover, these independent relations between TNF-α (partial $r = 0.14$, $p < 0.0005$) or IL-6 (partial $r =$

Table 1
Multivariate adjusted relations between circulating inflammatory markers and indexes of left ventricular (LV) remodelling or mass (LVM) in a community sample.

	All ($n = 764$)		Untreated ($n = 569$)	
	Partial r (95% CI)	p-Value	Partial r (95% CI)	p-Value
LV relative wall thickness (RWT) versus				
CRP[a]	0.01 (−0.06 to 0.08)	=0.80	0.02 (−0.07 to 0.10)	=0.73
IL-6[a]	−0.09 (−0.16 to −0.02)	<0.02	−0.09 (−0.17 to −0.01)	<0.05
TNF-α[a]	0.14 (0.07 to 0.20)	<0.0005	0.11 (0.02 to 0.19)	<0.02
LVMI versus				
CRP[a]	−0.003 (−0.07 to 0.07)	=0.94	0.05 (−0.08 to 0.09)	=0.91
IL-6[a]	−0.01 (−0.08 to 0.06)	=0.71	−0.03 (−0.11 to 0.05)	=0.49
TNF-α[a]	0.05 (−0.02 to 0.12)	=0.13	0.06 (−0.02 to 0.14)	=0.15
LV mean wall thickness (MWT) versus				
CRP[a]	−0.002 (−0.07 to 0.07)	=0.94	0.01 (−0.07 to 0.09)	=0.81
IL-6[a]	−0.13 (−0.19 to −0.06)	=0.0005	−0.16 (−0.24 to −0.07)	<0.0005
TNF-α[a]	0.16 (0.09 to 0.23)	<0.0001	0.16 (0.08 to 0.24)	<0.0005
LV end diastolic diameter (EDD) versus				
CRP[a]	−0.01 (−0.08 to 0.07)	=0.91	0.001 (−0.08 to 0.08)	=0.97
IL-6[a]	0.06 (−0.01 to 0.14)	=0.08	0.07 (−0.01 to 0.15)	=0.09
TNF-α[a]	−0.07 (−0.14 to −0.01)	<0.05	−0.04 (−0.13 to 0.04)	=0.33

CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumour necrosis factor-α.
[a] Adjustors are age, sex, body weight, body height (except for LVMI), regular smoking, regular alcohol intake, diabetes mellitus or an $HbA_{1c} > 6.1\%$, and LVMI for RWT.

−0.09, $p < 0.02$) concentrations and RWT were independent of each other. Importantly, the magnitude of the size effect (standardized β-coefficient) of TNF-α on RWT was similar to that of age and second only to that of LVMI (Table 2).

In unadjusted (data not shown) and multivariate adjusted (Fig. 2 and Table S8) models, TNF-α, but not IL-6 or hs-CRP concentrations were increased in those with both concentric LV remodelling and concentric LVH, but not with eccentric LVH. The increase in TNF-α concentrations in those with concentric LV remodelling was similar in magnitude to that in those with concentric LVH. These relationships persisted with further adjustments for several BP variables or PWV (Table S9).

Neither TNF-α, IL-6, nor hs-CRP concentrations were independently associated with E/A, E/e, e′, left atrial volume, LV EF, FSend or FSmid (Table S10).

4. Discussion

The main findings of the present study are that in a large community-based sample, circulating concentrations of the inflammatory marker TNF-α, and to a lesser extent, IL-6, were independently associated with LV wall thickness and concentric LV remodelling, but not LVMI or LVH. Importantly, the relations between inflammatory markers and a concentric LV geometry were independent of confounders, LVMI, and several hemodynamic factors including office, 24-hour ambulatory and central aortic BP as well as aortic PWV. These relations translated into increases in TNF-α concentrations in those with a concentric LV geometry, irrespective of LVH. In addition, independent of LVMI and confounders, TNF-α concentrations were associated with a similar size effect on RWT as age and a greater effect than any other risk factor including 24-hour and aortic BP, or aortic PWV. In contrast, hs-CRP concentrations were not independently associated with LV RWT. Whilst circulating concentrations of inflammatory markers were independently associated with mean wall thickness and RWT, no independent relations between inflammatory markers and indexes of LV diastolic dysfunction were noted.

Although a number of studies indicate that concentric LV remodelling either independently predicts cardiovascular outcomes [4–8] or determines the extent to which LVH predicts outcomes [9–12], an explanation for these findings has not been forthcoming. Despite several large studies evaluating relations between LVMI or geometry and inflammatory markers [14–16], these studies have produced equivocal results and any relations reported on have been unconvincing. In this regard, in 3939 patients with chronic renal insufficiency, 60–70% of whom were receiving renin-angiotensin system blockers, neither TNF-α, IL-6, nor CRP concentrations were independently associated with LV remodelling [14]. However, in that study [14] TNF-α concentrations were marginally associated with a concentric, but not eccentric LVH ($p = 0.04$). Furthermore, in 1370 elderly participants in whom antihypertensive therapy was unspecified, circulating concentrations of TNF-α receptor, CRP, and IL-6 concentrations failed to show independent relations with LVMI [16]. However, in that study [16], TNF-α

Table 2
Relative impact (standardized β-coefficient) of circulating tumour necrosis factor-α (TNF-α) concentrations versus other risk factors on left ventricular (LV) geometric remodelling (relative wall thickness [RWT]) in a community sample.

Models with→	Brachial SBP		24-hour SBP		Aortic PP		Aortic PWV	
	$n = 764$		$n = 508$		$n = 764$		$n = 667$	
RWT vs	β-Coeff ± SEM[a]	p-Value	β-Coeff ± SEM[a]	p-Value	β-Coeff ± SEM[a]	p-Value	β-Coeff ± SEM[a]	p-Value
LVMI	0.271 ± 0.038	<0.0001	0.240 ± 0.049	<0.0001	0.273 ± 0.038	<0.0001	0.271 ± 0.040	<0.0001
TNF-α	0.124 ± 0.034	<0.0005	0.157 ± 0.049	<0.0005	0.124 ± 0.034	<0.0005	0.126 ± 0.035	<0.0005
Age	0.133 ± 0.046	<0.005	0.128 ± 0.056	<0.05	0.132 ± 0.047	<0.01	0.090 ± 0.052	=0.08
Female gender	0.054 ± 0.041	=0.19	0.005 ± 0.050	=0.93	0.048 ± 0.041	=0.24	0.057 ± 0.043	=0.19
DM or $HbA_{1c} > 6.1\%$	−0.015 ± 0.038	=0.68	0.008 ± 0.048	=0.87	−0.021 ± 0.038	=0.59	−0.010 ± 0.04	=0.81
Body mass index	−0.024 ± 0.043	=0.57	0.039 ± 0.057	=0.49	−0.027 ± 0.044	=0.19	−0.064 ± 0.048	=0.19
Office SBP	0.058 ± 0.039	=0.14	–	–	–	–	–	
24-hour SBP	–	–	0.048 ± 0.049	=0.31	–	–	–	–
Aortic SBP	–	–	–	–	0.050 ± 0.040	=0.22	–	–
Aortic PWV	–	–	–	–	–	–	0.099 ± 0.046	<0.05

[a] β-Coeff, standardized β-coefficient (slope) of the relationship with RWT; LVMI, left ventricular mass index; DM, diabetes mellitus; SBP, systolic blood pressure; PWV, aortic pulse wave velocity. Also included in the models are regular smoking, regular alcohol intake and treatment for hypertension.

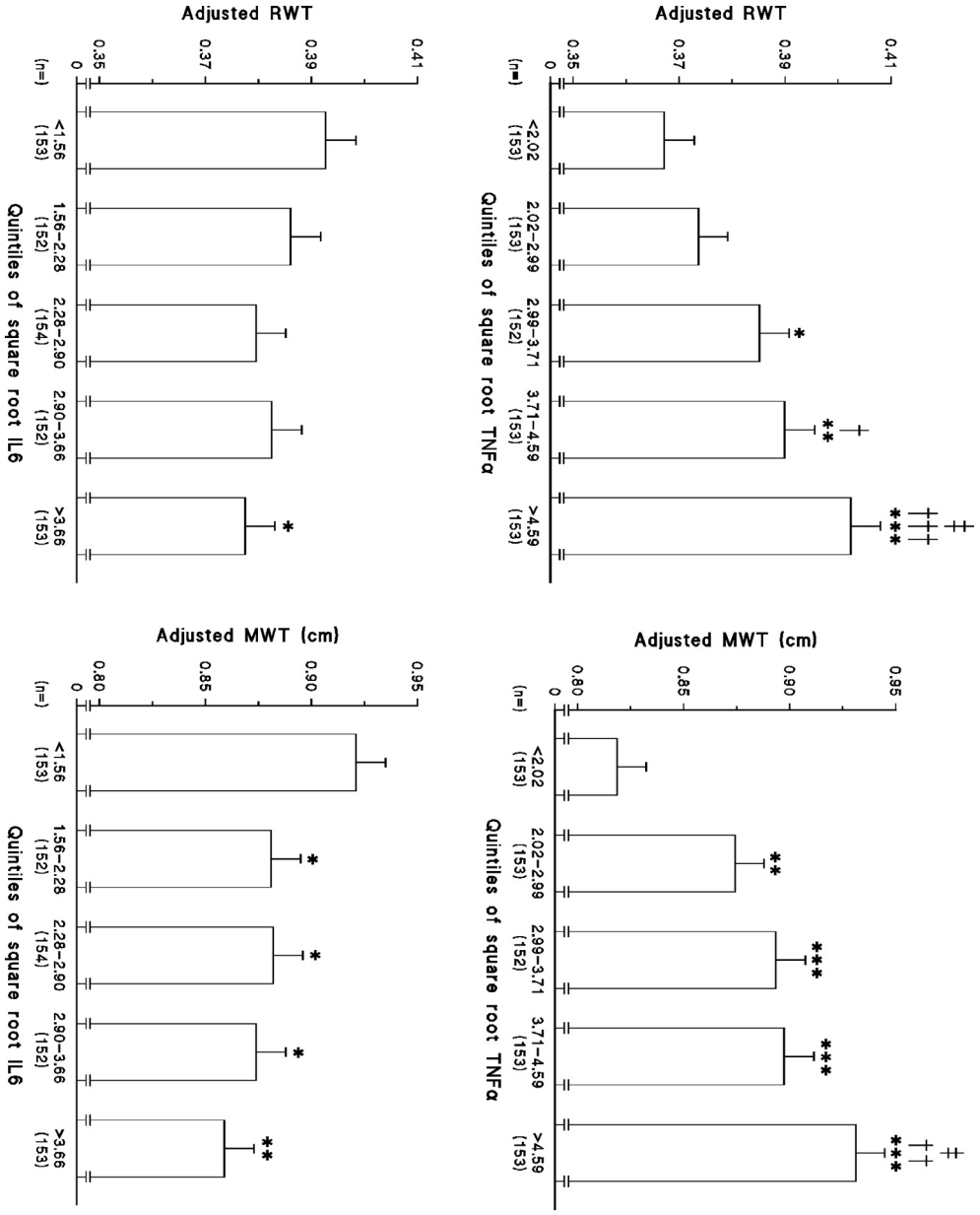
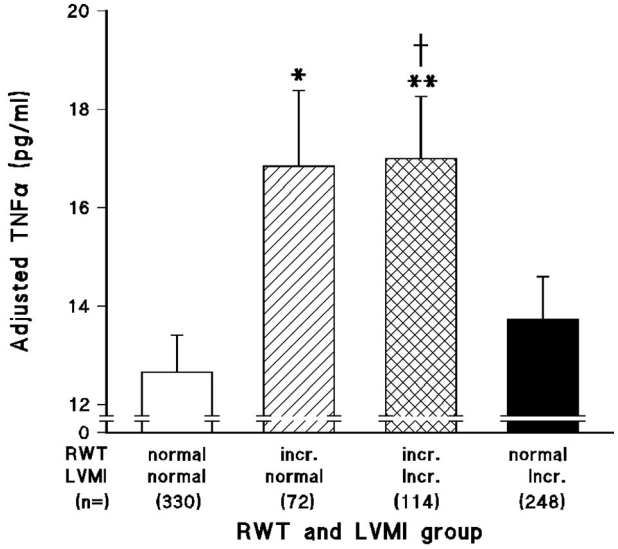
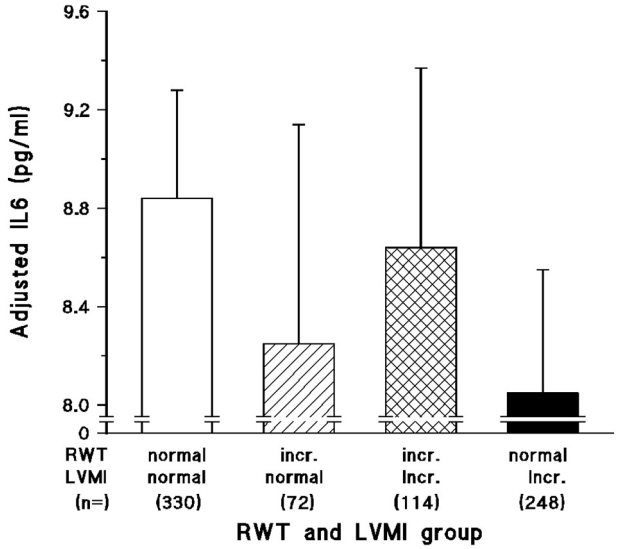


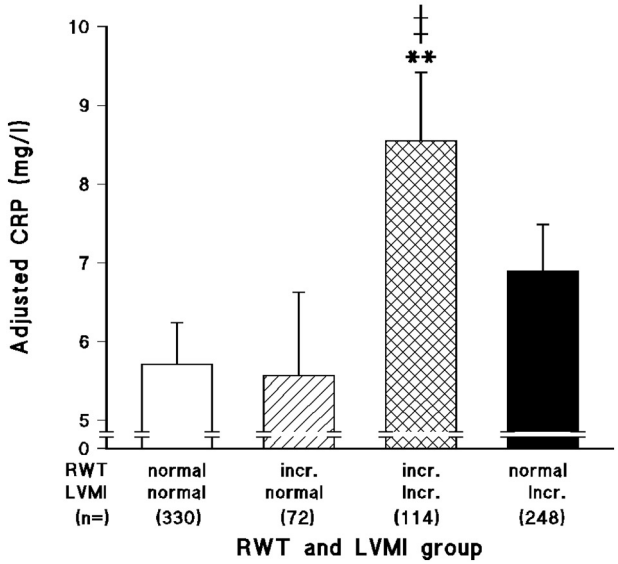
Fig. 1. Multivariate adjusted left ventricular relative (RWT) and mean (MWT) wall thickness across quintiles of concentrations of inflammatory markers in a community sample. $^{*}p < 0.05$, $^{**}p < 0.005$, $^{***}p < 0.0001$ versus quintile 1; $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.005$, $^{\dagger\dagger\dagger}p < 0.0005$ versus quintile 2; $^{\ddagger}p < 0.05$ versus quintile 3. Adjustments are for office systolic blood pressure, age, sex, height, body weight, regular smoking, regular alcohol intake, diabetes mellitus or an $HbA_{1c} > 6.1\%$, and treatment for hypertension. For relations with RWT, additional adjustments are for LVMI. See Table 1 for abbreviations.

receptor concentrations were marginally ($p < 0.02$) and independently associated with an increased RWT. A further large study ($n = 1016$), nevertheless, failed to show even modest relations between circulating concentrations of inflammatory markers (including TNF-α) and either LV remodelling or the type of LVH [15]. However, most participants in that study [15] were receiving antihypertensive therapy. Importantly, in all of these large studies [14–16], because of the confounding influence of antihypertensive therapy on both endothelial function and the extent of LV remodelling, relationships between TNF-α or TNF-α receptor concentrations and LV remodelling, may have been masked. In contrast, in a sample in which only 25.5% were receiving antihypertensive therapy, and where the findings were confirmed in sensitivity analysis conducted in untreated participants only, robust relationships between TNF-α, and to some extent IL-6 concentrations and LV geometric remodelling independent of confounders as well as LVMI and several hemodynamic factors associated with LV remodelling were noted. These relations between LV geometric remodelling and circulating inflammatory markers translated into striking increases in circulating concentrations of these inflammatory substances in those with a more concentric LV irrespective of LVMI.

As TNF-α is well-recognised as mediating endothelial dysfunction [23–25], and endothelial dysfunction is a key mechanism involved in mediating arterial disease and hence stroke and myocardial infarction, it is possible that RWT contributes to risk prediction by virtue of the relationship with TNF-α. In this regard, concentric LV remodelling may reflect inflammatory-induced coronary microvascular endothelial dysfunction with consequent LV structural changes (such as concentric LV remodelling) which ultimately result in diastolic dysfunction and HFpEF [13]. Although we were unable to show relations between inflammatory changes and LV diastolic function, beyond LVMI a more concentric LV reflects the interstitial changes responsible for LV diastolic dysfunction [26] and a concentric LV may therefore be a change that







antedates functional changes in the LV in the diastolic period. Alternatively, concentric LVH may progress to eccentric LVH and this change may be associated with a greater risk of cardiovascular events [27]. In this regard, the transition to a more dilated LV could be associated with a higher RWT at baseline and this transition and the subsequent development of events may be explained by associated pro-inflammatory changes.

TNF-α may be an important cause of increases in aortic stiffness [28]. Moreover, increases in aortic stiffness are independently related to concentric LV remodelling [29]. However, in the present study TNF-α concentrations were not correlated with aortic PWV. In addition, aortic PWV, although correlated with RWT, was not independently associated with RWT. Moreover, adjustments for aortic PWV failed to modify relations between circulating concentrations of inflammatory markers and RWT. Hence, the relations between circulating concentrations of inflammatory markers and RWT could not be explained by increases in aortic stiffness.

There are several limitations to the present study. First, this was a cross-sectional study and hence whether inflammatory changes cause alterations in RWT is uncertain. Intervention studies assessing the impact of TNF-α blockers on RWT are required to address this question. Second, although we adjusted for several factors related to geometric LV remodelling, including 24-hour and aortic BP and aortic PWV, we cannot exclude the possibility of residual confounding effects. Third, the present study was conducted in a group of black African ancestry. The present results may therefore be ethnic-specific and hence require validation in alternative ethnic groups. Fourth, although similar relations were noted between inflammatory markers and LV remodelling in women as in men, the study sample of men was too small to show consistent independent relations between TNF-α and RWT in men. Hence, the relations noted between inflammatory markers and LV remodelling may to some degree, be sex-specific.

In conclusion, the present study conducted in a community sample with a low prevalence of antihypertensive agent use (thus not confounding relations between inflammatory markers and LV remodelling) shows that beyond LVM, the circulating inflammatory marker TNF-α is associated with concentric LV remodelling independent of several hemodynamic measures that influence LV load as well as additional confounders. The association between inflammatory changes and a more concentric LV provides an alternative possible explanation to that traditionally posed (compensatory response to LV loading conditions) for the ability of concentric LV remodelling to add to the ability of LVH to risk predict or for concentric LVH to progress to a more dilated LV [27].

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Conflict of interest/disclosures

None of the authors have any conflict of interest to declare.

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Fig. 2. Multivariate adjusted concentrations of inflammatory markers in participants of a community sample across categories of left ventricular (LV) remodelling in a community sample. Concentric LV = relative wall thickness ≥ 0.42. $^{*}p < 0.05$, $^{**}p < 0.005$ versus normal LV structure; $^{\dagger}p < 0.05$ versus LVH; $^{\ddagger}p < 0.05$ versus concentric remodelling. Adjustments are for office systolic blood pressure, age, sex, body mass index, regular smoking, regular alcohol intake, diabetes mellitus or an $HbA_{1c} > 6.1\%$, and treatment for hypertension. See Table 1 for abbreviations, LVH, LV hypertrophy.

Mthuthuzeli Kiviet, Nomonde Molebatsi, Delene Nciweni and Nkele Maseko.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.059.

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