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Insulin resistance-associated decreases in left ventricular diastolic function are strongly modified by the extent of concentric remodeling in a community sample

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ABSTRACT

Background: Whether excess adiposity, associated metabolic abnormalities or alternative risk factors for left ventricular (LV) diastolic function are modified rather than mediated by geometric LV remodeling, is uncertain.
Methods: Echocardiographic LV mass index (LVMI), relative wall thickness (RWT) and diastolic function (lateral and septal wall myocardial tissue lengthening at the level of the mitral annulus [e′] [n = 430], ratio of early-to-late transmitral blood flow velocity (E/A), and E/e′ [n = 430]) were determined in 737 randomly recruited participants of a community-based study (43% obese).
Results: Independent of LVMI and confounders, indexes of adiposity and the homeostasis model of insulin resistance (HOMA-IR) were independently associated with LV diastolic function ($p < 0.05$). In addition, RWT was independently associated with LV diastolic function ($p < 0.002$). Importantly, an independent interaction between HOMA-IR and RWT, but not between blood pressure or age and RWT, was related to LV diastolic function ($p < 0.05$). This translated into an independent relationship between HOMA-IR and lateral e′ (partial $r = -0.17$, $p < 0.02$), septal e′ (partial $r = -0.14$, $p = 0.05$), E/A (partial $r = -0.17$, $p < 0.005$) and E/e′ (partial $r = 0.19$, $p < 0.01$) in those with RWT above, but a lack of relationship between HOMA-IR and LV diastolic function ($p > 0.59$) in those with RWT below the median for the sample. Similarly, HOMA-IR was independently associated with LV diastolic dysfunction in those with RWT above ($p < 0.05$) but not below ($p > 0.19$) the median for the sample.
Conclusions: The relationship between insulin resistance, but not alternative risk factors and LV diastolic function is markedly modified by the presence of a more concentrically remodeled LV.

1. Introduction

Independent of conventional cardiovascular risk factors and myocardial infarction, obesity and associated insulin resistance predict the development of heart failure [1–3]. The impact of obesity or insulin resistance on the risk for heart failure may in-part be explained by abnormalities in left ventricular (LV) diastolic function. Indeed, LV diastolic abnormalities are correlated with obesity [4–7] independent of hemodynamic confounders [8]; improved by bariatric surgery-induced weight loss [9]; and predict the development of heart failure [10–12]. However, the relative importance of obesity, as opposed to alternative co-morbidities as a determinant of LV diastolic dysfunction has recently been questioned [13]. Hence identifying clinical features that characterize those in whom weight loss may be of benefit in preventing the progression to heart failure is of importance.

Well-recognized determinants of a reduced LV diastolic function are LV hypertrophy (LVH) and concentric LV remodeling (as indexed by relative wall thickness [RWT]) [14]. As obesity causes LVH and several studies have shown associations between obesity and an increased RWT (concentric LV remodeling) [9,15], the question arises as to whether LVH and/or RWT modify the impact of obesity or associated metabolic alterations on diastolic LV function. In this regard, although numerous studies have reported an association between metabolic

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Table 1
Characteristics of the study sample.

Sample number (% female)	737 (64.0)
Age (years)	44.8 ± 18.0
Body mass index (kg/m^2)	29.6 ± 7.8
% overweight/obese/morbidly obese	23.6/19.9/24.3
Waist circumference (cm)	91.3 ± 16.6
% abnormal waist circumference	45.8
Regular tobacco (% subjects)	14.5
Regular alcohol (% subjects)	19.5
% diabetes mellitus or an HbA_{1c} >6.1%	26.6
% hypertensive	45.9
% treated hypertension	25.1
HOMA-IR	3.30 ± 4.85
Brachial SBP/DBP (mm Hg)	130 ± 22/84 ± 12
E/A	1.27 ± 0.48
E/e′ (n = 455)	7.81 ± 4.38
Lateral e′ (cm/s) (n = 455)	10.9 ± 3.7
Septal e′ (cm/s) (n = 455)	9.6 ± 3.4
Left atrial volume index (ml/m^2) (n = 455)	19.7 ± 6.6
Left ventricular mass index (g/m$^{1.7}$)	68.3 ± 23.9
LV relative wall thickness	0.39 ± 0.08

HbA_{1c}, glycated hemoglobin; SBP, systolic blood pressure; DBP, diastolic BP; HOMA-IR, homeostasis model of insulin resistance; E/A, ratio of transmitral early-to-atrial (late) blood flow velocity; E/e′, E/velocity of the mean value of lateral and septal wall myocardial tissue lengthening in early diastole at the mitral annulus; LV, left ventricle.

disease and diastolic dysfunction independent of LVH [16–18]; to our knowledge no study has investigated the possible interactive (synergistic) effect of LV remodeling on the association between metabolic disease or alternative risk factors and diastolic dysfunction. Importantly, LV remodeling may not mediate the effect of a risk factor, but may have a pronounced modifying influence on the impact of a risk factor on LV diastolic function. Indeed, as strong correlations between change in RWT and diastolic function [19] and consistent decreases in RWT and increases in diastolic function [19–21] occur with bariatric surgery, it is possible that RWT if not mediating the impact of metabolic disease on diastolic function, may modify the impact of metabolic disease on diastolic function. This would suggest that targeting metabolic disease may only influence LV diastolic function in a more concentrically remodeled LV. However, whether obesity- or insulin resistance-associated LV diastolic abnormalities are influenced by LV geometric remodeling is unknown. Hence, in the present study conducted in a relatively large community-based sample with a high prevalence of obesity-associated LVH [22,23] and increases in RWT [22], we evaluated whether relations between adiposity indexes or associated-insulin resistance and LV diastolic function are modified by LV mass or RWT and if so whether these interactive effects with LVH or remodeling are also noted for alternative causes of LV diastolic abnormalities such as increases in blood pressure or age.

Table 2
Multivariate adjusted relationships between indexes of adiposity or the homeostasis model of insulin resistance (HOMA-IR) and left ventricular diastolic function in a community sample.

	Adjustments	Partial r (95% CI)	p value
Waist circumference versus			
Log E/A (n = 737)	[a]	−0.10 (−0.17 to −0.02)	<0.05
	[a] + LVMI	−0.08 (−0.16 to −0.01)	<0.05
	[a] + RWT	−0.09 (−0.17 to −0.02)	<0.05
Log E/e′ (n = 430)	[a]	0.13 (0.03 to 0.23)	<0.01
	[a] + LVMI	0.12 (0.02 to 0.22)	<0.02
	[a] + RWT	0.12 (0.02 to 0.22)	<0.02
Log lateral e′ (n = 430)	[a]	−0.14 (−0.23 to −0.04)	<0.01
	[a] + LVMI	−0.12 (−0.22 to −0.03)	<0.02
	[a] + RWT	−0.13 (−0.23 to −0.03)	<0.02
Body mass index versus			
Log E/A (n = 737)	[a]	−0.07 (−0.15 to −0.001)	<0.05
	[a] + LVMI	−0.05 (−0.13 to 0.02)	=0.15
	[a] + RWT	−0.07 (−0.14 to 0.000)	=0.05
Log E/e′ (n = 430)	[a]	0.10 (0.003 to 0.19)	<0.05
	[a] + LVMI	0.08 (−0.01 to 0.18)	=0.09
	[a] + RWT	0.09 (−0.01 to 0.18)	=0.07
Log lateral e′ (n = 430)	[a]	−0.13 (−0.23 to −0.04)	<0.01
	[a] + LVMI	−0.11 (−0.21 to −0.02)	<0.02
	[a] + RWT	−0.12 (−0.21 to −0.03)	<0.02
Log HOMA-IR versus			
Log E/A (n = 737)	[a]	−0.11 (−0.18 to −0.04)	<0.005
	[a] + LVMI	−0.10 (−0.17 to −0.03)	<0.01
	[a] + RWT	−0.10 (−0.17 to −0.03)	<0.01
Log E/e′ (n = 430)	[a]	0.12 (0.02 to 0.21)	<0.02
	[a] + LVMI	0.11 (0.01 to 0.20)	<0.05
	[a] + RWT	0.11 (0.01 to 0.20)	<0.05
Log lateral e′ (n = 430)	[a]	−0.12 (−0.21 to −0.02)	<0.02
	[a] + LVMI	−0.11 (−0.20 to −0.01)	<0.05
	[a] + RWT	−0.10 (−0.20 to −0.01)	<0.05

E/A, ratio of transmitral early-to-atrial (late) blood flow velocity; E/e′, E/velocity of the mean value of lateral and septal wall myocardial tissue lengthening in early diastole at the mitral annulus; LVMI, left ventricular mass index; RWT, relative wall thickness.

[a] Adjustments are for age, sex, diastolic blood pressure (E/A) or systolic blood pressure (E/e′ and lateral e′), regular tobacco use, regular alcohol consumption, treatment for hypertension, diabetes mellitus or an abnormal blood glucose control (HbA_{1c} > 6.1%), pulse rate (E/A) and LVMI or RWT as indicated.

2. Methods

2.1. Study group

The present 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 and M12-04-108). Participants gave informed, written consent. The study design has previously been described [22–25]. 737 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. Tissue Doppler measures of myocardial function were obtained in a sub-study conducted in 430 participants.

2.2. Clinical, demographic, blood and anthropometric measurements

A standardized questionnaire was administered to obtain demographic and clinical data [22–25]. Height, weight, and waist circumference (WC) were measured using standard approaches and participants were identified as being overweight if their body mass index (BMI) was ≥25 kg/m^2, obese if their BMI was ≥30 kg/m^2 and morbidly obese of their BMI was ≥35 kg/m^2. Central obesity was defined as an enlarged WC (≥88 cm in women and ≥102 cm in men). Laboratory blood tests including percentage glycated hemoglobin (HbA_{1c}) were performed.

Table 3
Multivariate adjusted associations between indexes of adiposity or the homeostasis model of insulin resistance (HOMA-IR) and left ventricular (LV) diastolic dysfunction (DD) in the study group.

	Odds ratio[a] (95% CI)	Wald X^2	p value
Associations with E/A ≤ 0.80			
Waist circumference	1.014 (0.994 to 1.034)	1.920	=0.17
Body mass index	1.017 (0.977 to 1.058)	0.666	=0.41
Log HOMA-IR	1.967 (1.112 to 3.480)	1.054	=0.02
Associations with moderate-to-severe DD (Lateral e′ ≤ 10, Septal e′ ≤ 8, or LA volume ≥ 34, and E/e′ ≥ 13 and E/A ≥ 0.80)			
Waist circumference	1.014 (0.992 to 1.037)	1.54	=0.21
Body mass index	1.029 (0.983 to 1.077)	1.53	=0.22
Log HOMA-IR	1.462 (0.769 to 2.783)	1.34	=0.25

E/A, ratio of transmitral early-to-atrial (late) blood flow velocity; E/e′, E/velocity of the mean value of lateral and septal wall myocardial tissue lengthening in early diastole at the mitral annulus.

[a] Included in the models were age, sex, diastolic blood pressure (decreased E/A) or systolic blood pressure (moderate-to-severe DD), regular tobacco use, regular alcohol consumption, treatment for hypertension, diabetes mellitus or an abnormal blood glucose control (HbA_{1c} > 6.1%), pulse rate (for E/A) and left ventricular mass index.