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Predictors Affecting Left Ventricular Geometry in Non-Hypertensive, Healthy Subjects: Association of Concentric Remodelling With Early Diastolic Dysfunction

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Abstract

The geometric patterns of remodelling are related to hemodynamic and traditional cardiovascular risk factors; however, the clinical significance of left ventricular (LV) concentric remodelling (CR) with a normal LV mass and small LV cavity in a general population is not known well. This study assessed the prevalence, predictors and function of LV CR in healthy subjects without hypertension. For cross-sectional analysis, 1049 subjects were enrolled and examined using conventional and tissue Doppler echocardiography. Parameters measured included diastolic function (septal e', E/e'), LV mass index (LVMI) and relative wall thickness (RWT). All subjects were categorized into four LV geometric patterns by LVMI and RWT (Normal geometry (N), normal LVMI and RWT; CR, normal LVMI and high RWT; concentric hypertrophy (CH), increased LVMI and high RWT; eccentric hypertrophy (EH), increased LVMI and normal RWT). Logistic regression analysis (CR vs. normal) was adjusted for age, sex, and cardiovascular and metabolic risk factors. Subjects (mean age, 62.8 ± 12.8 years; 59% male) were distributed as follows: normal, 51%; CR, 27%; CH, 13%; and EH, 9%. The CR prevalence increased with age, and this group demonstrated a significantly lower e' and higher E/e' compared to the normal group. No sex differences were observed. Age, waist circumference and systolic blood pressure were independent predictors of CR. Concentric remodeling frequently exists in healthy subjects and is associated with impaired myocardial relaxation.

Keywords: Geometry; Concentric remodelling; Diastolic dysfunction; Aging; Waist circumference; Systolic pressure; Medical check-up

Introduction

The cardiac size in animals, including humans, is determined by gravitational forces and it is also dependent on body size [1,2]. Furthermore, the heart demonstrates plasticity in response to multiple stimuli from the environmental stimuli (e.g. age, activity, metabolism, etc.) [1,2]. Combinations of the left ventricular (LV) mass index (LVMI) and relative wall thickness (RWT) have been used to define four LV geometric patterns: normal geometry, concentric remodeling (CR), eccentric LV hypertrophy (EH), and concentric LV hypertrophy (CH). LV geometry is an important and independent predictor of increased cardiovascular risk, adverse cardiovascular events and mortality in hypertensive patients [3-8]. CR is defined as an increased RWT pattern with a normal LVMI [3]. In patients with hypertension, CR is the earliest change, and it is associated with potential abnormal cardiac function along with an increased rate of cardiovascular morbidity [9,10]. The pathophysiological significance of CR is not yet thoroughly understood. In two recent studies, the prevalence of CR increased with age and was estimated at about 20% among normotensive subjects [11,12]. Whether CR is associated with specific abnormalities of cardiac function in healthy subjects remains unknown. Herein, we evaluated subjects who attended their medical check-up to determine the impact of CR on cardiac function, especially LV relaxation and filling, compared to the other LV geometries.

Materials and Methods

Study design and sample

The present cross-sectional observational study evaluated 1,049 Japanese subjects who attended a medical check-up and 221 hypertensive patients in our department between January 2008 and January 2011. This investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by the Ethical Committee of Tokyo Women's Medical University. All the subjects provided informed consent to participate.

Medical check-up subjects who met the following criteria were excluded: LV ejection fraction <50%, complete left bundle branch block, known history of hypertension and diabetes mellitus, old myocardial infarction, significant primary valvular heart disease, congenital heart disease, severe pulmonary disease, atrial flutter and fibrillation, previous pacemaker implantation or a history of cardiovascular surgery. The remaining subjects were categorized into four groups according to the LV geometry. To assess the effects of age and blood pressure on the frequency of LV geometry, the subjects were divided into six age ranges (<40, 40-50, 50-60, 60-70 and ≥ 70 years) and six blood pressure ranges (<100, 100-110, 110-120, 120-130, 130-140 and ≥ 140 mm Hg). For each subject, blood was collected early in the morning in order to measure B-type natriuretic peptide (BNP) levels by using a chemiluminescent enzyme immunoassay.

Echocardiography

Echocardiographic studies were performed using the Vivid 7 system (GE Medical System). We collected a large set of echocardiographic data, including the left atrial diameter (LA), interventricular septal thickness, posterior wall thickness, LV end-diastolic diameter, LV

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end-systolic diameter, LV fractional shortening and ejection fraction, LVMI, RWT and systolic pulmonary arterial pressure (derived from the maximum velocity of tricuspid regurgitant flow using the modified Bernoulli's equation). Peak velocities of early (E) and late (A) diastolic filling and deceleration time were derived from the transmitral Doppler profile. Doppler tissue imaging was recorded from the septal mitral annulus, and it revealed early diastolic peak velocities (e') from which the mitral E/e' ratio was subsequently calculated. Moreover, the LV mass index (LVMI) was calculated using the formula of Devereux and was normalized to height [4]. A normal LVMI was defined as a mass of <51 g/m^2. RWT was the ratio of the average of ventricular septal and posterior free wall thicknesses to the cavity radius; a normal RWT was defined as a ratio of <0.41. Normal geometry was considered present when the LVMI and RWT were normal. An increased RWT and normal LVMI were classified as CR, increased LVMI and normal RWT were classified as EH and increased RWT and LVMI were classified as CH.

Statistical Analysis

Clinical continuous variables were expressed as a median (interquartile range), unless stated otherwise, and were assessed using the Kolmogorov-Smirnov test for goodness of fit between a sample distribution (the normal distribution). A comparison of the continuous variables was performed using a nonparametric Kruskal-Wallis test. Categorical data were expressed as the frequency of occurrences. The Cramer's V was used to analyse differences between groups based on categorical variables. Correlations between continuous variables were assessed using the Spearman's correlation coefficient. The independent diagnostic value of CR was assessed using a multivariate logistic regression model containing all the variables that proved to be significant in the univariate analysis of subjects within the normal and CR groups. Differences with P values<0.05 were considered statistically significant. All analyses were performed using IBM SPSS Statistics, version 21.0.0 (IBM, Corp.).

Results

The clinical characteristics of the medical check-up subjects who were grouped according to the LV geometric pattern are listed in Table 1. The mean age of all the subjects was 62.8 ± 12.8 years (male, 59%). Among all the subjects, 538 (51%) were categorized as normal, 287 (27%) as CR, 132 (13%) as CH and 91 (9%) as EH. CR was the most frequently observed abnormal LV geometric pattern. Subjects with an abnormal geometry tended to be older and demonstrated a higher body mass index and waist circumference compared to those with a normal geometry. The hypertensive patients (male, 68%; mean age, 69.4 ± 10.6 years) were receiving appropriate therapy for hypertension (angiotensin receptor blockers in 46%, angiotensin converting enzyme inhibitors in 29%, calcium antagonists in 57% and beta-blockers in 28%). The hypertensive patients had a higher LVMI and RWT compared to those in the medical check-up subjects. The proportion of CR, CH and EH in all the subjects progressively increased across the five age stratifications (Figure 1). CR had a prevalence of 20-30% in all the blood pressure ranges. The proportion of CH and EH in all the subjects progressively increased with systolic blood pressure, whereas the CR proportion was not dependent on blood pressure within the limit of systolic pressure ≥110 mm Hg (Figure 2). The proportion of CR decreased in hypertensive patients. No significant difference in

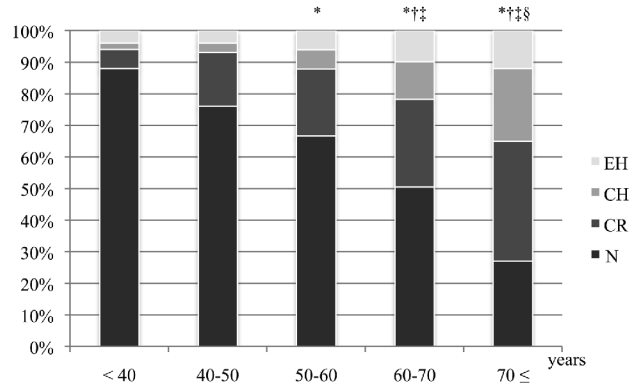

Figure 1: The proportion of eccentric hypertrophy (EH, upper column), concentric hypertrophy (CH, second column), concentric remodelling (CR, third column) and normal (N, lowest column) subjects in each of the five age groups.

*, vs. <40 years; †, vs. 40-50 years; ‡, vs. 50-60 years; §, vs. 60-70 years; P<0.05 (chi-square test)

	Normal (Range)	CR (Range)	CH (Range)	EH (Range)	p-value
n	539	285	133	92	
Age (years)	59 (49-67)	68 (60-75)	71.5 (64-78)	68.5 (60-72)	<0.0001
Sex (male, %)	50	63	76	68	<0.0001
BMI (kg/m^2)	21.8 (19.7-23.9)	22.7 (21.0-24.8)	25.1 (23.1-26.6)	23.7 (22.1-26.0)	<0.0001
WC (cm)	82 (75-88)	86 (80-91)	90 (85.5-98.9)	88 (82-94.8)	<0.0001
SBP (mm Hg)	114 (104-126)	122 (112-134)	130 (120-142)	121 (114.3-135.3)	<0.0001
DBP (mm Hg)	70 (64-80)	72 (66-80)	74 (68-80)	72 (64-80)	0.05
LDL (mg/dL)	124 (105-143)	116 (101-140)	115.5 (100-134)	116.5 (101.8-139.3)	0.008
HDL (mg/dL)	63 (52-76)	61-72 (21)	52-68 (17)	58 (50-67)	<0.0001
TG (mg/dL)	83 (59-121.8)	94 (71-138)	116.5 (83-150)	101.5 (72.8-139.5)	<0.0001
FBS (mg/dL)	98 (91-105)	99.5 (94-106)	104 (97-111)	100 (94-109)	<0.0001
HbA1c (%)	5.1 (4.9-5.3)	5.2 (5.0-5.4)	5.3 (5.1-5.5)	5.1 (4.98-5.33)	<0.0001
Serum Cr (mg/dL)	0.7 (0.59-0.82)	0.8 (0.62-0.93)	0.8 (0.67-0.95)	0.7 (0.67-0.85)	<0.0001
CCR (mL/min/1.73 m^2)	87.0 (70.3-106.8)	75.2 (61.6-94.4)	77.4 (59.5-97.3)	84.7 (66.95-103.2)	<0.0001
BNP (pg/mL)	18.5 (10.2-29.6)	14.9 (9.7-24.5)	20.7 (13.5-50.2)	32.5 (19.2-57.7)	0.009

Table 1 Characteristics of subjects grouped by the left ventricular geometric pattern.

CR: Concentric Remodelling; CH: Concentric Hypertrophy; EH: Eccentric Hypertrophy; BMI: Body Mass Index; WC: Waist Circumference; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; TG: Triglycerides; FBS: Fasting Blood Sugar; HbA1c: Haemoglobin A1c; Cr: Creatinine; CCR: Creatinine clearance (Cockcroft and Gault); BNP: B-Type Natriuretic Peptide

the BNP level was observed across the four geometric patterns. Table 2 presents the echocardiographic characteristics of the medical check-up subjects who grouped according to the LV geometry. Subjects with CR demonstrated a higher LVMI compared to normal subjects and a lower RWT compared to subjects with CH. In addition, subjects with CR demonstrated an enlarged LA and greater wall thickness compared to normal subjects. Among subjects with CR, the LV dimension was significantly smaller compared to subjects with a normal geometry, and it was larger compared to subjects with CH. Subjects with CR also demonstrated a greater LV ejection fraction compared to those with a normal geometry. In contrast, fractional shortening appeared similar across the four LV geometric patterns.

LV e' decreased from normal subjects to those with CR and to subjects with CH, whereas E/e' increased from normal subjects to those with CR and to subjects with CH (Figure 3). Subjects with an abnormal geometry demonstrated higher E/A values compared to normal subjects, and those with CR and CH demonstrated a higher deceleration time compared to normal subjects. In subjects with a normal LVMI (normal and CR groups), the LV e' was inversely associated with RWT (ρ=-0.411, P<0.0001) (Figure 4). A significant positive correlation was observed between the RWT and systolic blood pressure in all the subjects (ρ=0.299, P<0.0001), but this was not observed in CR (ρ=0.090, P<0.1299).

According to multivariate analysis, age, the waist circumference, and systolic blood pressure level remained significantly associated with CR formation (Table 3). Advanced age was the strongest independent predictor of CR, followed by an increased waist circumference and systolic blood pressure levels.

Discussion

We investigated the impact of CR on cardiac function in subjects who had a medical check-up. In the present study, the proportion of subjects

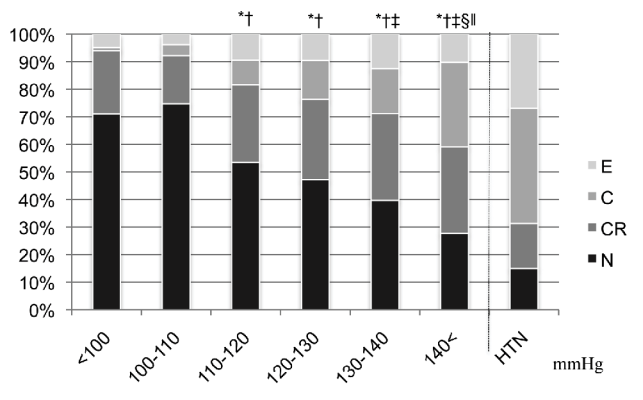

Figure 2: The proportion of eccentric hypertrophy (E, upper column), concentric hypertrophy (C, second column), concentric remodelling (CR, third column) and normal (N, lowest column) subjects in each of the six different systolic blood pressure ranges and hypertensive group.

*, vs. <100 mm Hg; †, vs. 100-110 mm Hg; ‡, vs. 110-120 mm Hg; §, vs. 120-130 mm Hg; ||, vs. 130-140 mm Hg; P<0.05 (chi-square test)

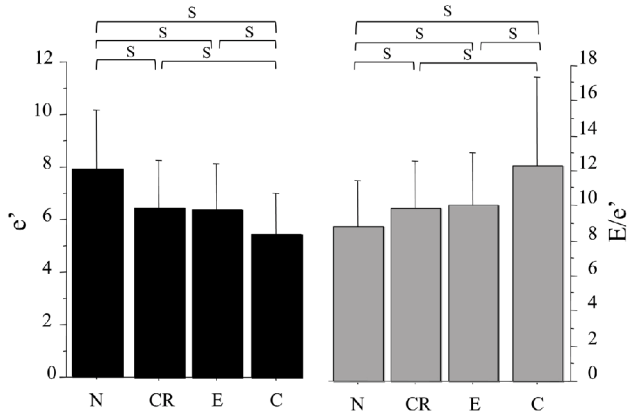

Figure 3: Left ventricular (LV) e' (black bar) and E/e' (grey bar) according to the LV geometry group.

LV e' is significantly decreased in the subjects with concentric remodelling (CR) compared to the subjects with a normal LV geometry (N). E/e' is higher in subjects with concentric remodelling compared to subjects with a normal geometry

	Normal (Range)	CR (Range)	CH (Range)	EH (Range)	p-value
LAD (mm)	32 (29-35)	33 (30-36)	39 (36-42)	36 (35-41)	<0.0001
IVST (mm)	8 (8-9)	10 (9-11)	11 (11-12)	10 (9-11)	<0.0001
PWT (mm)	8 (7-9)	9 (9-10)	11 (10-11)	10 (9-10)	<0.0001
LVEDD (mm)	45 (43-49)	42 (40-45)	47 (45-50)	51 (50-54)	<0.0001
LVESD (mm)	29 (26-31)	26 (24-28)	29.5 (27-31)	31 (30-35)	<0.0001
FS (%)	37 (35-40)	38 (35-40)	37.5 (35-40)	37.5 (35-39)	0.0270
EF (%)	67 (64-71)	69 (65-72)	68 (64-71)	67 (63-69)	0.0013
RVSP (mmHg)	28.7 (26.2-31.4)	28.7 (26.3-32.0)	30.3 (27.4-33.9)	29.4 (27.3-33.2)	0.0010
LVMI	36.9 (31.4-42.3)	41.3 (35.3-46.0)	59.5 (55.6-65.7)	56.7 (54.2-61.9)	<0.0001
RWT	0.36 (0.34-0.39)	0.45 (0.43-0.49)	0.46 (0.44-0.52)	0.38 (0.36-0.40)	<0.0001
e'	7.6 (6.3-9.2)	6.3 (5.3-7.4)	5.1 (4.2-6.5)	6.0 (5.2-7.3)	<0.0001
E/e'	8.5 (6.9-10.2)	9.5 (7.8-11.6)	11.6 (9.8-14.7)	10.1 (8.1-11.7)	<0.0001
DCT	212 (186-248)	243.5 (209-281)	245 (213.8-281.3)	222.5 (203-252)	<0.0001
E/A	1.00 (0.82-1.30)	0.83 (0.70-1.00)	0.80 (0.68-0.99)	0.83 (0.70-1.08)	<0.0001

Table 2: Echocardiographic variables of subjects grouped by the left ventricular geometric pattern.

CR: Concentric Remodelling; CH: Concentric Hypertrophy; EH: Eccentric Hypertrophy; LAD: Left Atrial Diameter; IVST: Interventricular Septal Thickness; PWT: Posterior Wall Thickness; LVEDD: Left Ventricular End Diastolic Diameters; LVESD: Left Ventricular End Systolic Diameters; FS: Fractional Shortening; EF: Ejection Fraction; RVSP: Right Ventricular Systolic Pressure; LVMI: Left Ventricular Mass Index; RWT: Relative Wall Thickness; e': Septal mitral annular early diastolic velocity; E/e': Peak early diastolic left ventricular filling velocity to e' ratio; DCT: Deceleration Time of the peak early filling velocity; E/A: Peak diastolic left ventricular early filling velocity to the atrial filling velocity ratio

Variables	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Sex	0.59	0.44-0.79	≤ 0.0001			
Age	1.06	1.05-1.08	<0.0001	1.06	1.05-1.08	<0.0001
BMI	1.12	1.06-1.18	<0.0001			
WC	1.05	1.03-1.07	<0.0001	1.04	1.02-1.06	<0.0001
SBP	1.03	1.02-1.04	<0.0001	1.01	1.00-1.02	0.039
HDL	0.99	0.98-1.00	0.0350			
LDL	1.00	0.99-1.00	0.024			
TG	1.002	1.000-1.004	0.036			
FBS	1.02	1.00-1.03	0.018			
HbA1c	4.31	2.67-6.91	<0.0001			
CCR	0.99	0.98-0.99	<0.0001			

Table 3 Predictors of concentric remodelling geometry: Univariate and multivariate logistic regression analyses.

OR: Odds Ratio; 95% CI: 95% Confidence Interval; BMI: Body Mass Index; WC: Waist Circumference; SBP: Systolic Blood Pressure; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; TG: Triglycerides; FBS: Fasting Blood Sugar; HbA1c: Haemoglobin A1c; CCR: Creatinine Clearance (Cockcroft and Gault)

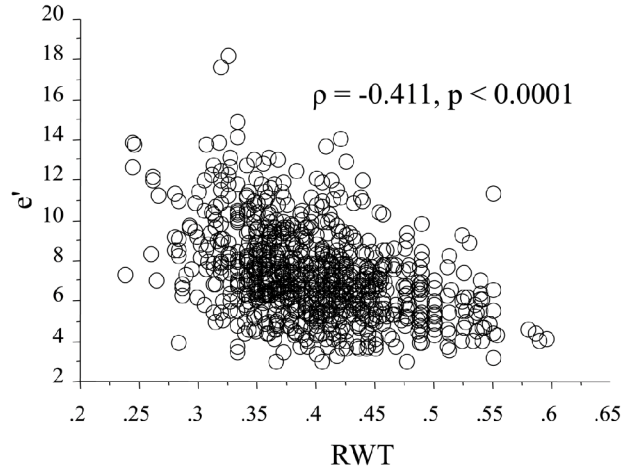

Figure 4: Relationship between the left ventricular (LV) e' and relative wall thickness (RWT).

LV e' is moderately correlated with RWT

with CR was higher than expected, and this proportion increased with age. For the first time, we determined that LV relaxation was impaired in non-hypertensive subjects with CR, despite the lack of obvious hypertrophy, as confirmed by tissue Doppler echocardiography. In our logistic analysis, advanced age was the strongest independent predictor of CR formation, followed by an increased waist circumference and systolic blood pressure.

Whether CR is physiological, pathological, or a reaction to other pathological conditions is not completely understood. Classical remodelling such as CH and EH is a physiological or pathological condition that may occur after myocardial injury, increased pressure, or volume loading [13]. In early-stage hypertension, LV geometry changes to CR, because the myocardial cells tend to enlarge with respect to the short axis [14]. CR appears to be an early response to LV pressure overload, which maintains normal LV systolic wall stress [5,15]. In patients with hypertension, delayed LV relaxation is independently associated with concentric LV geometry [4]. Myocardial relaxation is markedly influenced by pressure overload. CR has an adverse prognostic impact similar to that of CH, despite the lack of an absolute increase in LV mass [6,7]. In our study, CR was present in a considerable percentage of subjects during the medical check-up even though they did not have hypertension; however, their blood pressure was not within the normal range. However, the proportion of CH increased in relation to blood pressure and it was significant in hypertensive patients. CR demonstrated a trend toward a higher RWT and LVMI compared to a normal geometry and it was associated with systolic pressure according to multivariate analysis. It may be inferred that CR changes into other geometries (CH or EH) and its function decreases with an increase in blood pressure. CR appears to be a response to the LV pressure load in the context of normal systolic blood pressure and it is not always physiological and compensated.

There is no information on the predictors of left ventricular CR in non-hypertensive subjects. In our multivariate analysis, age, the waist circumference and systolic blood pressure were independent predictors of CR. Advanced age was more prevalent in our subjects with CR and it was a predictor of CR formation. Thus, we must consider the effects of aging on the development of CR. Structural remodelling of the left ventricle is part of the normal aging process even in the absence of disease, which includes hypertension and aortic stenosis. With aging, a moderate increase in the myocyte size and thickening and fibrosis of the LV wall are observed even in the absence of arterial hypertension or any other cause of afterload increase [16]. One possible explanation of this mild hypertrophy in the elderly is an increased systolic blood pressure, although neurohormonal and/or other factors may equally contribute. Echocardiographic studies have demonstrated that an increase in the LV mass occurs with age; in contrast, on magnetic resonance imaging, RWT either increases or does not change, whereas the LV mass decreases or does not change with age [17]. In addition, the mass-to-volume ratio, which is nearly equivalent to RWT, markedly increases with a substantial decrease in the end-diastolic volume, although the LV mass decreases with age [18]. Furthermore, myocardial hypertrophy with aging is not necessarily physiological, because diastolic function decreases with aging, whereas LV systolic function is preserved across one's lifespan [16]. In obese subjects, changes in the total blood volume, and myocardial metabolism and fatty infiltration are thought to influence LV structural remodelling [19]. It has been reported that CR is the most prevalent abnormal pattern (34%) in obese patients, using the body surface area (BSA) to normalize LV mass [20]. However, using BSA to normalize LV mass in obese patients may potentially lead to substantial errors and shift the concentric hypertrophy pattern to the CR pattern [19]. Cardiac remodelling is complicated by inadequate cardiac mass (i.e., atrophy), which is induced by hemodynamic unloading (e.g. protracted bed rest, prolonged weightlessness during space

travel, heterotopic transplantation, and mechanical unloading with a ventricular assist device) and by metabolic unloading (e.g. starvation, nutrient deprivation and cachexia) [1,2]. In addition, a sedentary lifestyle and volume loss may lead to cardiac atrophy and decrease in LV dispensability in daily life [21,22]. Myocardial contraction and relaxation are preserved, but chamber stiffness increases because of a relative increase in the interstitial compartment [23]. In an atrophic heart, LVMI is significantly lower, but RWT is higher compared to healthy controls, which indicates a natural tendency toward CR [21]. Interestingly, transcriptional signatures of atrophy and hypertrophy are the same [24,25]. The balance of protein synthesis and degradation determines the size and function of cardiomyocytes [25,26]. Therefore, hypertrophic and atrophic remodelling comprises a series of events, and they reflect the extreme aspects of cardiac plasticity [27]. Besides hemodynamic overload, metabolic loading (e.g. obesity and diabetes) contributes to myocardial hypertrophy and cardiac remodelling and function [1]. Hemodynamic and metabolic loading, unloading, and reloading are related to cardiac plasticity, irrespective of whether it is physiological or pathological in origin [1]. No discrete thresholds can be used to define the boundaries of hypertrophy or atrophy. CR can be considered as a consequence of a shift in the balance between atrophy and hypertrophy signalling, which may occur because of aging, obesity, insulin resistance, blood pressure, arterial stiffness, excessive exercise, disability, poor nutrition, altered plasma volume or several other factors.

Conclusion

Several limitations to the present study are worth emphasizing. First, this analysis was a single-centre study with a very high prevalence of senior citizens. Second, data regarding the mechanism of abnormal relaxation in CR geometry were not available. Third, physical inactivity, which may have an impact on ventricular remodelling or cardiac plasticity, was not recorded. Finally, since our subjects were recruited from a Japanese population, it is uncertain whether our findings can be extrapolated to other ethnicities.

It is noteworthy that our analysis was performed using relatively elderly urban dwellers, a demographic that is predicted to increase in the future. Patients with CR, particularly the elderly, are considered to be at high risk for developing heart failure. An increase in RWT is fundamental to CR and can be easily and inexpensively calculated with the help of M-mode ultrasound cardiography.

In conclusion, left ventricular concentric remodelling is frequently present and is associated with impaired myocardial relaxation in healthy subjects. Age, waist circumference, and systolic blood pressure were independent predictors of concentric remodelling. A prospective study is needed to determine whether the existence of concentric remodelling can be used to predict mortality and morbidity in non-hypertensive subjects.

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