Relation of Concentric Remodeling to Adverse Outcomes in Patients With Stable Coronary Artery Disease (from the Heart and Soul Study)

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Concentric remodeling (CR) is defined as increased left ventricular (LV) wall thickness with normal total LV mass. When encountered in populations with hypertension or patients undergoing aortic valve replacement, some studies have shown that CR predicts cardiovascular (CV) events and stroke. To expand our understanding of the prognostic implications of this common echocardiographic finding, we examined the association of CR and adverse CV events in ambulatory patients with coronary artery disease (CAD). We tested the hypothesis that finding CR on echocardiogram in ambulatory CAD independently predicts heart failure hospitalizations and CV death. Transthoracic echocardiograms were recorded in 973 participants from the Heart and Soul Study. Participants were divided into 4 groups: normal, CR, concentric LV hypertrophy, and eccentric LV hypertrophy. CV events were determined by 2 independent adjudicators and these were analyzed by Cox proportional hazards models. After mean 4.9 ± 1.5 years of follow-up, adverse outcomes occurred more frequently in those with concentric and eccentric LV hypertrophy but not in those with CR. After multivariate adjustment, concentric and eccentric LV hypertrophies were associated with increased risk of death and heart failure hospitalization, whereas CR was not. In conclusion, our hypothesis was not supported because CR was not associated with adverse CV events in our cohort of patients with stable CAD. **(Am J Cardiol 2011;107:1579–1584)**

The left ventricle remodels in response to long-term increased volume or pressure, most commonly resulting in hypertrophy. This transformation allows the left ventricle to decrease systolic wall stress and preserve contractile function.[1] The American Society of Echocardiography categorizes left ventricular (LV) remodeling as concentric remodeling (CR), concentric LV hypertrophy, and eccentric LV hypertrophy and defines CR as increased relative wall thickness with normal LV mass.[2] It is known that CR predicts cardiovascular (CV) events and stroke[3,4] and is associated with adverse CV outcomes in patients with hypertension[5–7] and in those undergoing aortic valve replacement[8]; however, these relations have not been defined in patients with established coronary artery disease (CAD). Therefore, we sought to determine the prognostic value of CR in a contemporary population of ambulatory patients with stable CAD and hypothesized that CR independently predicts heart failure hospitalizations and CV death.

Methods

Patients were enrolled in the Heart and Soul Study, a prospective cohort study investigating the influence of psychosocial factors on CV events. Methods have been described previously.[9] Administrative databases were used to identify outpatients with documented CAD at 2 Department of Veterans Affairs medical center databases (San Francisco and Palo Alto, California), a university-based medical center (University of California Medical Center–San Francisco), and 9 public health clinics in the Community Health Network of San Francisco, California. Criteria for enrollment included (1) history of myocardial infarction that healed, (2) angiographic evidence of ≥50% stenosis in ≥1 coronary artery (with or without previous myocardial infarction), (3) previous evidence of exercise-induced ischemia using treadmill electrocardiography or stress nuclear perfusion imaging, or (4) previous coronary revascularization. Patients were excluded if they deemed themselves unable to walk 1 block, had an acute coronary syndrome in the previous 6 months, or were planning to move from the local area within 3 years.

We performed standard echocardiography using a commercially available ultrasound system with harmonic imaging (Acuson Sequoia, Siemens Corporation, Mountain

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Table 1
Baseline characteristics of participants according to left ventricular geometry remodeling type

Variable	Normal (n = 304)	CR (n = 262)	Concentric LV Hypertrophy (n = 322)	Eccentric LV Hypertrophy (n = 85)	p Value
Age (years)	66 ± 11	66 ± 10	67 ± 11	68 ± 10	0.19
Men	228 (75%)	227 (87%)	258 (80%)	77 (91%)	0.0005
Race					
White	178 (59%)	168 (64%)	181 (56%)	54 (64%)	0.22
Black	40 (13%)	45 (17%)	62 (19%)	16 (19%)	0.21
Asian	46 (13%)	25 (10%)	33 (10%)	9 (11%)	0.14
Other	39 (13%)	24 (9%)	46 (14%)	6 (7%)	0.12
Medical history					
Hypertension	183 (60%)	189 (72%)	253 (79%)	61 (73%)	<0.0001
Diabetes mellitus	61 (20%)	67 (26%)	105 (33%)	91 (23%)	0.004
Myocardial infarction	155 (51%)	119 (46%)	175 (55%)	69 (82%)	<0.0001
Stroke	39 (13%)	37 (14%)	48 (15%)	15 (18%)	0.68
Heart failure	35 (12%)	28 (11%)	66 (21%)	39 (46%)	<0.0001
Revascularization	180 (59%)	143 (55%)	189 (59%)	54 (64%)	0.47
Medications					
Diuretic	67 (22%)	61 (23%)	121 (38%)	34 (40%)	<0.0001
β Blocker	167 (55%)	141 (54%)	197 (61%)	59 (69%)	0.03
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	121 (40%)	124 (47%)	190 (59%)	62 (73%)	<0.0001
Systolic blood pressure (mm Hg)	128.9 ± 18.8	132.2 ± 18.4	139.2 ± 23.5	127.8 ± 20.5	<0.0001
Body mass index (kg/m^2)	26.9 ± 4.4	29.6 ± 5.2	29.2 ± 5.6	26.3 ± 4.3	<0.0001
Left ventricular end-diastolic volume index (ml/m^2)	46.1 ± 10.9	44.8 ± 10.3	50.8 ± 12.1	93.9 ± 19.5	<0.0001
Left ventricular mass index (g/m^2)	80.0 ± 11.9	84.7 ± 10.2	120.4 ± 41.5	139.5 ± 27.9	<0.0001
Left ventricular ejection fraction	64.5 ± 6.9	64.8 ± 5.9	61.0 ± 9.2	45.8 ± 12.1	<0.0001
Septal thickness (cm)	1.1 ± 0.1	1.3 ± 0.2	1.4 ± 0.3	1.2 ± 0.3	<0.0001
Posterior wall thickness (cm)	1.0 ± 0.1	1.2 ± 0.4	1.2 ± 0.2	1.2 ± 0.2	<0.0001

Data are expressed as mean ± SD or number of subjects (percentage).

View, California). LV volumes and ejection fraction were measured quantitatively using the 2-dimensional (2D) echocardiographic biplane method of disks.[10,11] LV mass was measured using the 2D echocardiographic truncated ellipse method.[12] LV posterior wall thickness was measured at end-diastole from 2D recordings according to recommended methods.[12]

Normal LV end-diastolic volume index was defined as ≤75 ml/m^2.[2] Normal LV mass index was defined as ≤88 g/m^2 for women and ≤102 g/m^2 for men.[2] Normal LV posterior wall thickness was defined as <1.1 cm.[2] Participants were classified into 4 groups of LV geometry: normal, CR, concentric LV hypertrophy, and eccentric LV hypertrophy. CR was defined as normal LV mass index, normal LV end-diastolic volume index, and increased LV posterior wall thickness; concentric LV hypertrophy was defined as increased LV mass index and normal LV end-diastolic volume index; and eccentric LV hypertrophy was defined as increased LV mass index and increased LV end-diastolic volume index. We excluded participants with normal LV mass index and increased LV end-diastolic volume index and those without complete echocardiographic measurements caused by technical difficulty. A single cardiologist (N.B.S.) blinded to clinical and laboratory information evaluated all echocardiograms.

Each participant completed a detailed questionnaire that included age, gender, race, medical history, level of physical activity, current smoking, and level of alcohol consumption. Study personnel recorded all current medications and measured height, weight, and blood pressure. Medication categories were categorized using Epocrates Rx. (San Mateo, California).

Prespecified end points included incident heart failure hospitalization, all-cause mortality, and death from heart disease during follow-up. We conducted annual telephone follow-up interviews with participants (or their proxies) to ask about death or hospitalization for "heart trouble." For any reported event, medical records, electrocardiograms, death certificates, and coroner's reports were retrieved and reviewed by 2 independent and blinded adjudicators. If the adjudicators agreed on the outcome classification, their classification was binding. In the event of disagreement, the adjudicators conferred, reconsidered their classification, and requested consultation from a third blinded adjudicator.

All-cause mortality was determined by review of death certificates. Myocardial infarction was defined using standard diagnostic criteria.[13] Death was considered caused by CAD if (1) the participant died during the same hospitalization in which acute myocardial infarction was the primary diagnosis or (2) the participant had sudden CAD death defined as an unexpected, otherwise unexplained fatality within 1 hour of onset of terminal symptoms.

Hospitalization for heart failure was defined as hospital admission for a clinical syndrome involving ≥2 of the following: paroxysmal nocturnal dyspnea, orthopnea, increased jugular venous pressure, pulmonary rales, third heart sound, cardiomegaly on chest x-ray, or pulmonary

Table 2
Baseline characteristics of participants according to normal left ventricular geometry and concentric remodeling

Variable	Normal (n = 304)	CR (n = 262)	p Value
Age (years)	66 ± 11	66 ± 10	0.47
Men	228 (75%)	227 (87%)	0.0005
Race			0.06
White	178 (59%)	168 (64%)	—
Black	40 (13%)	45 (17%)	—
Asian	46 (13%)	25 (10%)	—
Other	39 (13%)	24 (9%)	—
Medical history			
Hypertension	183 (60%)	189 (72%)	0.002
Diabetes mellitus	61 (20%)	67 (26%)	0.11
Myocardial infarction	155 (51%)	119 (46%)	0.19
Stroke	39 (13%)	37 (14%)	0.64
Revascularization	35 (12%)	28 (11%)	0.76
Heart failure	180 (59%)	143 (55%)	0.31
Medications			
Diuretic	67 (22%)	61 (23%)	0.72
β Blocker	167 (55%)	141 (54%)	0.79
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	121 (40%)	124 (47%)	0.07
Systolic blood pressure (mm Hg)	128.9 ± 18.8	132.2 ± 18.4	0.04
Body mass index (kg/m^2)	26.9 ± 4.4	29.6 ± 5.2	<0.0001
Left ventricular end-diastolic volume index (ml/m^2)	46.1 ± 10.9	44.8 ± 10.3	0.14
Left ventricular mass index (g/m^2)	80.0 ± 11.9	84.7 ± 10.2	<0.0001
Left ventricular ejection fraction	64.5 ± 6.9	64.8 ± 5.9	0.53
Septal thickness (cm)	1.1 ± 0.1	1.3 ± 0.2	<0.0001
Posterior wall thickness (cm)	1.0 ± 0.1	1.2 ± 0.4	<0.0001

Data are expressed as mean ± SD or number of subjects (percentage).

edema on chest x-ray. These clinical signs and symptoms must have represented a clear change from the normal clinical state of the patient and must have been accompanied by failing cardiac output as determined by peripheral hypoperfusion (hypotension in the absence of other causes such as sepsis or dehydration) or peripheral or pulmonary edema. Supportive documentations of decreased cardiac index, increasing pulmonary capillary wedge pressure, decreasing oxygen saturation, and end-organ hypoperfusion, if available, were included in adjudication. The study protocol was approved by the institutional review board at each participating site, and all participants provided written informed consent.

The goal of this study was to examine the association of CR with CV outcomes. Differences in participant characteristics by pattern of ventricular remodeling (normal, CR, concentric LV hypertrophy, and eccentric LV hypertrophy) were determined using analysis of variance of continuous variables and chi-square tests for dichotomous variables. Analyses were performed using SAS 9 (SAS Institute, Cary, North Carolina). We used Cox proportional hazard models to evaluate the independent association of LV geometry with CV events and included analysis of unadjusted data and multivariable adjusted outcomes. For these analyses, we report hazard ratios with 95% confidence intervals. A Kaplan–Meier plot aggregated CV events by date during follow-up for each group.

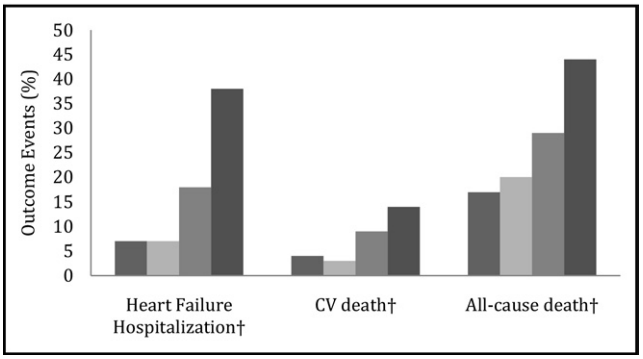

Figure 1. Outcome events of heart failure hospitalizations, cardiovascular death, and all-cause death in participants with normal ventricular geometry (n = 304) *(dark gray bars)*, concentric remodeling (n = 262) *(light gray bars)*, concentric left ventricular hypertrophy (n = 322) *(medium gray bars)*, and eccentric left ventricular hypertrophy (n = 85) *(black bars)*. Data are expressed as percentage (†p <0.001).

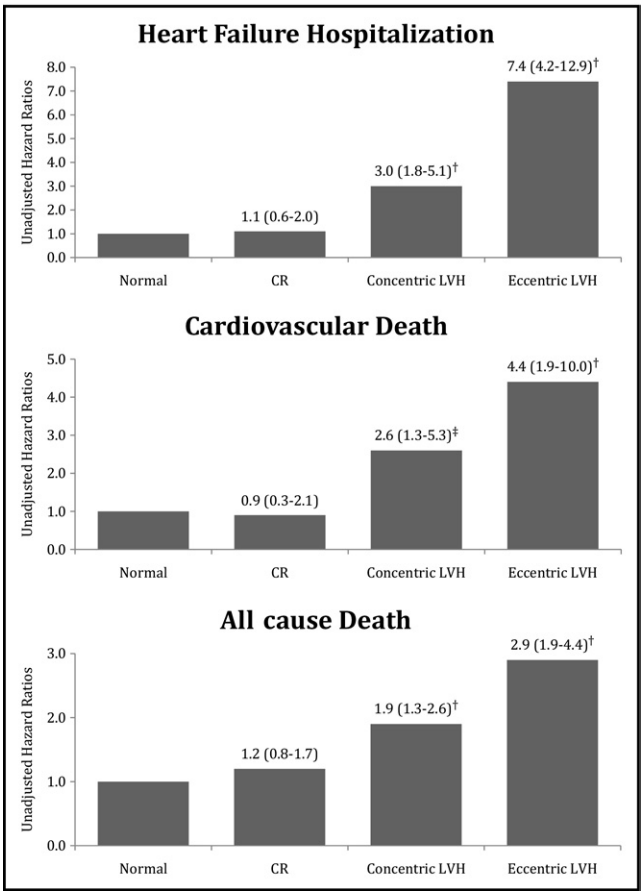

Figure 2. Unadjusted hazard ratio (95% confidence interval) for outcome events of heart failure hospitalizations, cardiovascular death, and all-cause death comparing concentric remodeling, concentric left ventricular hypertrophy (LVH), and eccentric left ventricular hypertrophy to normal left ventricular geometry (†p <0.001; ‡p ≤0.01).

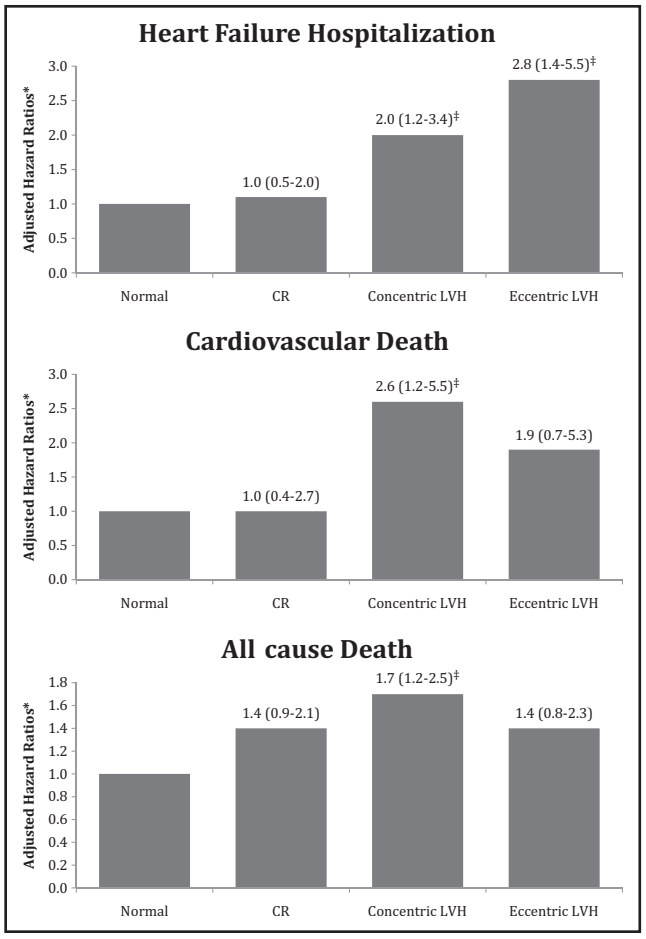

Figure 3. Multivariable-adjusted hazard ratio (95% confidence interval) for outcome events of heart failure hospitalizations, cardiovascular death, and all-cause death comparing concentric remodeling, concentric left ventricular hypertrophy, and eccentric left ventricular hypertrophy to normal left ventricular geometry (‡$p \leq 0.01$). *Hazard ratios were adjusted for gender, hypertension, diabetes mellitus, history of myocardial infarction, history of congestive heart failure, medications, systolic blood pressure, body mass index, and left ventricular ejection fraction. Abbreviation as in Figure 2.

Results

From September 2000 through December 2002, 1,024 participants were enrolled in the Heart and Soul Study. From this cohort, 973 participants remained in the analytic sample after exclusions, of which 304 (31%) were normal, 262 (27%) had CR, 322 (33%) had concentric LV hypertrophy, and 85 (9%) had eccentric LV hypertrophy.

Table 1 lists baseline characteristics of participants according to ventricular remodeling type. By definition, LV end-diastolic volume index was highest in participants with eccentric LV hypertrophy. In addition, LV wall thickness and LV mass index were highest in participants with LV hypertrophy. Table 2 lists baseline characteristics of those without remodeling ("normal") and those with CR only. By definition, LV wall thickness was greater in participants with CR. Furthermore, although patients with CR had LV mass indexes within normal limits, these were significantly higher than in normal participants.

After mean 4.9 ± 1.5 years of follow-up, participants without remodeling and those with CR had similar rates of heart failure hospitalizations, CV death, and all-cause death (Figure 1). In contrast, patients with concentric and with eccentric LV hypertrophy had significantly higher rates CV outcomes. Although CR showed no greater relative risk of adverse CV outcome, the 2 subgroups of hypertrophy were associated with increased risk of heart failure hospitalizations, CV death, and all-cause death (Figure 2).

After multivariable adjustment, concentric and eccentric LV hypertrophies were associated with an approximately twofold risk of heart failure hospitalizations and CV death, whereas CR was not (Figure 3). Figure 4 shows Kaplan–Meier survival free of heart failure hospitalization during follow-up for all groups.

Discussion

We found that CR was present in 27% of the ambulatory CAD population and, contrary to our hypothesis, was not associated with adverse CV events. At baseline, patients with CR were nearly indistinguishable from patients with normal geometry. These findings suggest that CR in CAD may be a benign response as LV volume decreases physiologically with aging, without the detrimental effects of frank hypertrophy.[14,15]

Supportive evidence for the adverse effects of fully developed hypertrophy is abundant and includes pathology-based and clinical studies.[16,17] However, association of CR with adverse events is less clear. A population-based study failed to find an independent association between CR and outcomes after multivariate analysis adjusting for confounding variables.[18] In addition, a study of patients with suspected CAD referred for coronary angiography found no association between CR and CV outcomes.[19]

Di Tullio et al[4] found that CR was associated with a modest increase in ischemic stroke. However, hypertension was present in most patients and was significantly more prevalent in patients than in controls. In a retrospective analysis of patients who underwent aortic valve replacement, presence of CR was associated with increased in-hospital mortality and morbidity.[8] A recent population-based study found that CR as defined by magnetic resonance imaging was predictive of stroke and CAD.[3] However, the subjects were community-dwelling participants free of clinically apparent CV disease.

Classification of LV geometry is an area of considerable interest and debate without consensus, although the American Society Echocardiography has published guidelines for categorization.[2] The complexity of this issue lies in the paradox that the left ventricle can increase in thickness without an increase in total mass. This relation can be explained by simply viewing increased wall thickness as an obligatory consequence of decreasing LV cavity volume and constant LV mass.

We believe the unique features of this study include its large sample, prospective design, rigorous 2D quantitation, comprehensive measurement of potential confounding variables, adjudication of events, and long-term follow-up. Nonetheless, potential limitations include a study popula-

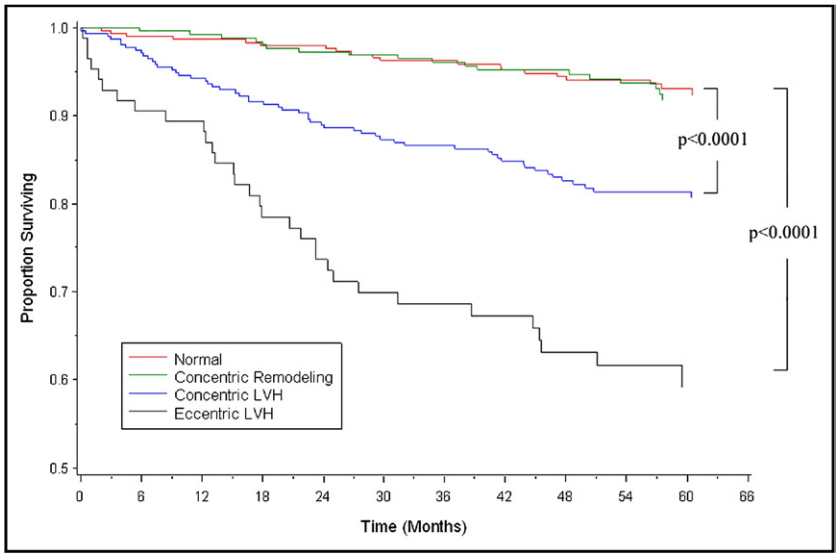

Figure 4. Kaplan–Meier survival free of heart failure hospitalization. Abbreviation as in Figure 2.

tion of older men with stable CAD. Thus, our results may be less applicable to other populations. In addition, a larger sample may have been able to detect adverse outcomes associated with CR. However, this possibility is unlikely because outcomes occurred in 32% of an adequately powered cohort. Another possible limitation is exclusion of traditional M-mode measurements such as internal dimension, which may make our results difficult to compare to previous studies. However, biplane volumetric measurements have been shown to be more fastidious compared to linear measurements.[20] In addition, studies of LV geometry have used different criteria to define CR including volume-to-mass ratios.[3]

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