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Increased Left Ventricular Mass and Decreased LV Systolic Function Have Independent Pathways to Ventricular Arrhythmogenesis in Coronary Artery Disease

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Abstract

Background—Following myocardial infarction, individual patients can have wide variations in extent of LV systolic dysfunction and increased LV mass. Both affect risk of sudden cardiac death but only LV ejection fraction is used for risk prediction.

Objective—We evaluated the independent as well as additive contributions of increased LV mass and decreased LV ejection fraction to sudden cardiac death in the general population.

Methods—In the ongoing Oregon Sudden Unexpected Death Study, we studied consecutive SCD cases (n=191) and coronary artery disease controls (n=203) from the Portland, Oregon metropolitan area (population approx. 1,000,000; 2002–2008). Comparisons of echocardiographic LV mass obtained prior and unrelated to SCD were conducted and a logistic regression model evaluated the relationship between SCD, severe LVSD, LV mass and other relevant clinical variables.

Results—In a multivariate model, both severe LVSD and LVH were associated with increased SCD risk (OR 1.9, 95% CI 1.1 – 3.2 for severe LVSD; OR 1.8, 95% CI 1.1 – 2.9 for LVH). In patients with coexisting severe LVSD and LVH, risk of SCD was additive (OR 3.5, 95% CI 1.7 – 7.2). In the same model, increased age, atrial fibrillation/flutter, elevated creatinine and diabetes independently increased risk, and use of angiotensin receptor blockers attenuated risk.

Conclusions—Reduced LV ejection fraction and increased LV mass had independent and additive effects on risk of sudden death. Despite the significant overlap between the two conditions, these findings point toward the existence of independent mechanistic pathways for ventricular arrhythmias that occur due to LV systolic dysfunction and LV hypertrophy.

Keywords

Death; Sudden; Hypertrophy; heart failure; arrhythmogenesis; population

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INTRODUCTION

A recent consensus conference ¹ has highlighted the growing concerns regarding the limitations of left ventricular ejection fraction (LVEF) for prediction of SCD risk ²⁻⁷. While severe LV systolic dysfunction (LVSD, LVEF≤35%) is the major risk determinant currently used in clinical practice to assess SCD risk among patients with CAD ^{8,9} it is critical to extend beyond the ejection fraction.

Left ventricular hypertrophy (LVH) defined by a critical increase in LV mass measured by echocardiography has been identified as a risk factor for sudden cardiac death (SCD) independent of coronary artery disease (CAD) risk factors ¹¹. While increased LV mass is often a component of LV remodeling in patients with severe LVSD, there are wide variations in the nature and extent of LV remodeling such that some patients will have severe LVSD but not meet criteria for LVH, but others will have both conditions ¹². We hypothesized that dissection of the LVSD-LV mass relationship among subjects with SCD is likely to provide useful information regarding the role of LV remodeling in ventricular arrhythmogenesis.

The primary prevention ICD trials were not designed to assess such a relationship, particularly since measurements of echocardiographic LV mass were not obtained. The Oregon Sudden Unexpected Death Study (Ore-SUDS) is an ongoing population-based case-control study of SCD among all residents of the Portland, OR metropolitan area ^{7,13,14}. We examined the role of severe LVSD, echocardiographic LVH (measured prior and unrelated to the SCD event) and other clinical factors in the occurrence of ventricular arrhythmogenesis by comparing SCD cases with CAD controls from the same population.

METHODS

Case and control ascertainment

From Feb 1st 2002 to Jan 31st 2008, cases of SCD in the Portland Oregon metropolitan area were identified. In the first three years, the Ore-SUDS study prospectively identified all cases of SCD among residents in this area (pop. approx. 1,000,000) through collaboration with the emergency medical response system (EMS), Medical Examiner's office, and local hospitals. During Feb 2005–Jan 2008, identification was limited to the majority subset with resuscitation attempts by first responders or investigation by the medical examiner. A detailed description of methods has been previously published ^{7,13}. SCD was defined as a sudden unexpected pulseless condition; if unwitnessed, subjects were to have been seen alive and symptom free within 24 hours of their sudden death. Subjects were assigned a diagnosis of SCD after a review of available medical records and the circumstances of arrest; survivors of SCD were included. Subjects with chronic terminal illnesses (e.g. cancer), known non-cardiac causes of sudden death (e.g. pulmonary embolism, CVA), traumatic deaths and overdoses were excluded. Case subjects for the present analysis were required to have documented CAD, defined as ≥50% stenosis of a major coronary artery by angiogram or postmortem evaluation; coronary artery bypass grafting or percutaneous coronary intervention; physician report of myocardial infarction; pathologic Q waves on ECG; or myocardial infarction history determined by any two of the following three: ischemic symptoms, ECG changes, or positive troponins/creatinine kinase-MB. During the same time period a control group of subjects from the same geographic region were identified who had CAD, but no history of SCD from the following sources: (1) patients transported by EMS for complaints suggestive of ongoing coronary ischemia, (2) patients visiting cardiology clinics or who received an angiogram at one of the participating health systems; these visits and angiograms were unrelated to the current study. Potential control subjects received an introductory letter and a follow-up telephone call. Those successfully

contacted who were willing to participate were mailed a consent form. After consent was obtained, medical records for each potential control subject were reviewed; those with documented CAD were enrolled. Subjects were recruited from these two sources to produce a control group consisting of individuals with both stable and acute coronary disease. By requiring all cases and controls to have documented CAD, we sought to efficiently control for the presence of CAD in analyses, so that observed differences between cases and controls would isolate the factors that increase SCD risk among patients with CAD.

To be included in the current analysis, case and control subjects were required to have an echocardiogram available from existing medical records prior to the SCD event that included an evaluation of ejection fraction and quantitative measures of left ventricular size, internal diameter, and wall thickness to calculate LV mass. Since this observational study relied on existing medical records, all echocardiograms analyzed for both cases and controls were performed in clinical settings unrelated to the subject's ascertainment and enrollment in the current study. If more than one echocardiogram met criteria, the echocardiogram closest to and prior to arrest/ascertainment was used. Case subjects without an echocardiogram prior to arrest were excluded. For control subjects, echocardiograms up to 5 days post-ascertainment were used if no prior echocardiogram was available. Case and control subjects with hypertrophic cardiomyopathy were excluded.

This study conforms with the declaration of Helsinki and was approved by the Institutional Review Boards of Oregon Health and Science University and all other participating hospitals and health systems.

Data collection and definitions

Medical records, including dates and results of relevant tests, were reviewed for case and control subjects. Left ventricular dimensions were obtained from echocardiograms performed prior to cardiac arrest for cases, and up to 5 days post-ascertainment for control subjects. LVM was calculated using the American Society of Echocardiography modified equation: $0.8\{1.04[(IVSd + PWTd + LVIDd)^3 - (LVIDd)^3]\} + 0.6g$ ¹⁵, where IVSd is interventricular septum thickness in diastole, PWTd is posterior wall thickness in diastole, and LVIDd is left ventricular internal diameter in diastole. LVM was indexed to body surface area (BSA). LVH was defined as $LVM/BSA > 134 \text{ g/m}^2$ for men and $> 110 \text{ g/m}^2$ for women¹⁶. The LV ejection fraction was obtained from the same echocardiograms. Severe LVSD was defined as an ejection fraction (EF) of $\leq 35\%$ or a qualitative assessment of LV function as being moderate to severely or severely impaired. Hypertrophic cardiomyopathy was defined as a chart history of HCM, autopsy findings of asymmetric septal hypertrophy, or extreme hypertrophy with cavity obliteration or echocardiographic findings of asymmetric septal hypertrophy or LV outflow tract obstruction. Medical history of hypertension, diabetes, history of atrial arrhythmias, and other structural heart disease were noted. Serum creatinine, cholesterol, and current medications were recorded from medical records closest to but unrelated to the arrest/ascertainment. Height, weight, and smoking history were obtained from the most recent medical history.

Statistical analysis

Univariate case-control comparisons were performed using independent samples t-tests for continuous variables and chi-square tests for categorical variables. A logistic regression model was used to estimate the odds of SCD associated with severe LVSD, controlling for age and all covariates associated ($p < 0.10$) with case status in univariate analysis. Then, LVH was added to the model to determine the association of LVH with SCD, controlling for LVSD and the covariates; similarly, LV mass was entered into a model with LVSD and covariates to determine the incremental effect of increasing LV mass on SCD risk.

controlling for LVSD. Interaction terms were included in the model to test for multiplicative statistical interaction between LVH and severe LVSD. Terms were retained in the final adjusted model if they were significant at $p < 0.05$, or if they changed the LVH effect estimate by $> 10\%$. Finally, a logistic model with dummy variables for LVH only, severe LVSD only, and the joint presence of LVH and severe LVSD was used to estimate the independent and joint effects of these two conditions, controlling for age, gender, and the covariates considered in the original model. All statistical analyses were conducted using SAS version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Identification of subjects

During the six year period from Feb 1st 2002 to Jan 31st 2008, 1404 adult cases of SCD (age ≥ 18) were identified in the Portland, Oregon metropolitan area that had medical records available for analysis. Of these, 619 (44%) had documented CAD. Among case subjects with documented CAD, 193 (31%) had echocardiograms and met inclusion criteria. For the same time period, 528 adult control subjects with CAD were enrolled. All controls had medical records available, and 203 (38%) had echocardiograms. After exclusion of two cases with hypertrophic cardiomyopathy, 191 cases and 203 controls remained for the analysis.

Timing of echocardiogram relative to time of arrest or ascertainment

All included case subjects had an echocardiogram prior to arrest, with 76% within two years of arrest, and 24% more than two years prior (range 2.1 – 9.7 years prior). Over half (59%) of control subjects had echocardiograms prior to ascertainment (46% within two years and 13% more than two years prior (range 2.1 – 6.5 years prior), 14% had their echocardiogram performed on the day of ascertainment, and 27% up to 5 days post-ascertainment. There were no differences in mean LV mass or prevalence of LVH for control subjects with peri- or post-ascertainment echocardiograms vs. those subjects with echocardiograms performed prior to ascertainment ($p \geq 0.59$).

Clinical characteristics of cases and controls

Case subjects were slightly older than control subjects (72 vs. 67 years, $p = 0.0002$), but did not differ by gender, mean BMI, or prevalence of hypertension ($p \geq 0.08$) (Table 1). Diabetes and a history of atrial fibrillation or flutter were more common in cases ($p \leq 0.003$) (Table 1). Case subjects also had higher serum creatinine levels ($p < 0.0001$), but cholesterol levels did not differ ($p = 0.17$). Case subjects were slightly more likely to be taking beta blockers and ACE inhibitors, and slightly less likely to be taking angiotensin receptor blockers, but these differences did not reach significance ($p \geq 0.08$) (Table 1). Over one-half of control subject vs. one-quarter of case subjects had normal LVSD; mild-to-moderate and severe LVSD were more common in cases vs. controls ($p < 0.0001$).

Prevalence of LVH and increased LV mass in cases and controls

Case patients were more likely to have LVH than control patients (48% vs. 25%, $p < 0.0001$) (Table 2). When subjects were stratified by presence of severe LVSD, this difference was also observed in patients without LVSD (42% in cases vs. 21% in controls, $p < 0.0001$). While the overall prevalence of LVH was higher in patients with LVSD, case-control differences were attenuated (58% in cases vs. 42% in controls, $p = 0.10$) (Table 2). Figure 1 illustrates that LVH was more common among cases in each category of LV function.

Mean adjusted LV mass was also significantly greater among SCD cases than among control subjects (129 g/m^2 vs. 107 g/m^2 , $p < 0.0001$) (Table 2), with the distribution of adjusted LV

mass shifted toward higher values in the case group (Figure 2). These differences were observed in both men (136 g/m^2 vs. 110 g/m^2 , $p < 0.0001$) and women (113 g/m^2 vs. 100 g/m^2 , $p = 0.05$; data not shown). Mean adjusted LV mass was greater in cases than controls in both the presence and absence of severe LVSD (Table 2).

The severity of LVH appeared worse among cases as well; cases were much more likely than controls to have LV mass $\geq 25\%$ above the LVH cut-off ($p < 0.0001$, Table 2). When the joint distribution of severe LVSD and LVH were examined, patients with combined severe LVSD and LVH were significantly more likely to be found in the case group compared to the control group (28% vs. 8%), as were subjects who had LVH alone (27% vs. 17%) ($p < 0.0001$) (Table 2, Figure 3).

Severe LVSD and LVH independently increase odds of SCD

In the logistic regression model evaluating the relationship between SCD and LVSD and including all terms significant at $p < 0.10$ in univariate analyses, BMI, use of beta blockers, and gender were removed from the final model because they were not significant in the multivariate model ($p \geq 0.36$). Controlling for age, diabetes, serum creatinine level, history of atrial fibrillation/flutter, and a history of medication with angiotensin receptor blockers, severe LVSD doubled the odds of SCD (OR 2.1, 95% CI 1.3 – 3.5). When LVH was added to the full multivariate model with all terms significant at $p < 0.10$ in Table 1, there was no significant interaction between LVSD and LVH ($p = 0.74$). As in the previous model, BMI, use of beta-blockers, and gender were non-significant ($p \geq 0.25$) and were removed. In the final model controlling for all remaining covariates, both severe LVSD and LVH independently nearly doubled the odds of SCD (OR 1.9, 95% CI 1.1 – 3.2 for severe LVSD; and OR 1.8, 95% CI 1.1 – 2.9 for LVH) (Table 3).

Joint effects of LVSD and LVH

When severe LVSD and LVH were considered in a logistic model that estimated lone effects and joint effects separately, subjects with both LVH and severe LVSD had a much higher odds of SCD compared to subjects with neither condition (OR 3.5, 95% CI 1.7 – 7.2), indicating that the presence of both conditions additively increases the odds of SCD.

DISCUSSION

Among a group of subjects with established CAD, both severe LVSD and echocardiographic LVH (as defined by a critical increase in LV mass) were significantly more common among SCD cases than among controls. The prevalence of combined severe LVSD and LVH was also significantly higher in cases vs. controls. In a multivariable model controlling for age, diabetes, serum creatinine level, history of atrial fibrillation/flutter, and medication use, both severe LVSD and LVH were independently associated with a near doubling of SCD risk. The risk of SCD was more than tripled in patients with severe LVSD and coexisting LVH. These findings indicate that while there is overlap between occurrence of severe LVSD and LVH in patients with ischemic cardiomyopathy, these two conditions also confer independent risk of SCD. The fact that this risk is additive further suggests that there may be distinct processes involved in the pathobiology of LVSD and LVH that lead to ventricular arrhythmogenesis. To our knowledge this is the first study to make this distinction in the general population.

Ventricular arrhythmogenesis due to LV remodeling is a complex process with multiple components that involve myocytes as well as interstitium¹⁷. Clinical trials indicate that therapeutic regression of both LV systolic dysfunction¹⁸ as well as LV hypertrophy¹⁹ reduces the risk of ventricular arrhythmogenesis. The effective utilization of animal models

has already provided several distinct pathways leading to ventricular arrhythmogenesis due to increased LV hypertrophy^{20,21} and decreased LV systolic function²². More recently, a large number of novel genomic variants have also been identified from human populations that could further expand the list of distinct mechanistic processes leading to ventricular arrhythmogenesis in these two conditions^{23–26}. From the clinical perspective, selection of patients that are at high risk of future ventricular arrhythmogenesis based solely on the value of the LV ejection fraction is likely to be simplistic. A renewed focus on using existing and novel pathways, independently for LV systolic dysfunction and increased LV mass will likely translate into enhancement of predictive and therapeutic modalities for ventricular arrhythmogenesis.

This study confirms earlier reports that increased age¹³, diabetes^{27–29} and abnormal renal function³⁰ are independent predictors of increased SCD risk and that ARBs have beneficial effects on risk¹⁹. To our knowledge, the independent contribution of atrial fibrillation/flutter toward increased SCD risk in ischemic cardiomyopathy in the general population is a novel finding and also merits further evaluation.

Due to the population-based nature of this study, this analysis has some important limitations. Only the subset of SCD cases that had an echocardiogram performed with data adequate to calculate LV mass was analyzed. In addition, while echocardiograms were more commonly performed to evaluate acute coronary syndrome (ACS) in control subjects, we saw no differences in LV mass or LV function comparing echocardiograms performed to evaluate ACS vs. other indications in either cases or controls ($p \geq 0.16$). Based on these data, it is unlikely that potential bias due to indication for echocardiograms or their timing affected the validity of our findings. Case subjects were older than control subjects, and though multivariable models were adjusted for age, some uncontrolled confounding by age is possible.

One of the strengths of the present study is the relative proximity of the echocardiogram to the SCD event (at least three-quarters of cases and controls were evaluated within two years of SCD or ascertainment). In contrast, in the Framingham cohort study, mean follow-up after the baseline echocardiogram was 10.32 years¹¹. In addition, our study examined the role of LVSD and LVH in community-dwelling subjects with documented CAD.

CONCLUSIONS

In this investigation of sudden death mechanisms in the general population, increased LV mass and severe LVSD had independent and additive effects on SCD risk. These findings underscore the potential utility of considering these parameters independently when assessing mechanisms or enhancing risk stratification for SCD.

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Figure 1. Frequency of LV hypertrophy (LVH, by measurement of echocardiographic LV mass) among LV function sub-groups in cases and controls. A greater prevalence of LVH was observed in case subjects, across all categories of LV systolic function.

Figure 2. Distribution of LV mass (normalized for body surface area) in cases and controls shows a rightward shift toward higher values in the case group.

Figure 3. Distribution of severe LV systolic dysfunction (LVSD) and LV hypertrophy (LVH) in cases vs. controls. Case subjects were more likely than control subjects to have co-existing severe LVSD and LVH.

Table 1

Demographic and clinical characteristics of 191 cases and 203 controls with coronary disease

	Cases (n=191)	Controls (n=203)	p value *
Age (mean $\pm$ SD)	72 $\pm$ 12	67 $\pm$ 11	0.0002
Male (%)	71%	64%	0.16
BMI (mean $\pm$ SD)	28.7 $\pm$ 7.2	30.0 $\pm$ 6.9	0.08
Diabetes (%)	49%	34%	0.003
Hypertension (%)	81%	74%	0.14
History of atrial fibrillation / flutter	31%	14%	<0.0001
Serum creatinine, mg/dL (median, IQR) [†]	1.4 (1.0 – 1.8)	1.1 (0.9 – 1.4)	<0.0001
Cholesterol, mg/dL (means $\pm$ SD) [‡]	166 $\pm$ 45	174 $\pm$ 50	0.17
Use of beta blockers (%)	69%	61%	0.08
Use of ACE inhibitors (%)	53%	47%	0.23
Use of angiotensin receptor blockers (%)	6%	11%	0.08
Smoking [§]			0.56
Current smoker	30%	28%	
Former smoker	48%	45%	
Non-smoker	22%	27%	
LVSD			<0.0001
Normal (EF $\geq$ 55%)	26%	54%	
Mild to moderate (EF 36–54%)	38%	28%	
Severe (EF $\leq$ 35%)	36%	19%	

EF: Ejection Fraction; LVSD: Left Ventricular Systolic Dysfunction assessed by echocardiogram

* p values from independent samples t-test for continuous variables and chi-square test for categorical variables.

[†] Creatinine values available for 175 cases and 196 controls. Due to skewed distribution, creatinine values were log-transformed for all statistical tests.[‡] Cholesterol values available for 114 cases and 156 controls.[§] Smoking history available for 152 cases and 140 controls.

Table 2

Distribution of LV hypertrophy and LV mass in 191 cases and 203 controls with coronary disease

	Cases (n=191)	Controls (n=203)	p-value *
LVH (%)			
All subjects	48%	25%	<0.0001
Without severe LVSD (123 cases, 165 controls)	42%	21%	<0.0001
With severe LVSD (68 cases, 38 controls)	59%	42%	0.10
Adjusted LVM [†]			
All subjects	129 ± 45	107 ± 36	<0.0001
Without severe LVSD (123 cases, 165 controls)	120 ± 40	102 ± 32	<0.0001
With severe LVSD (68 cases, 38 controls)	145 ± 48	128 ± 43	0.07
LVH categories based in adjusted LV mass (%)			<0.0001
No LVH	52%	75%	
0–9% above LVH cut-off	10%	6%	
10–24% above LVH cut-off	15%	9%	
≥25% above LVH cut-off	23%	9%	
Joint Distribution, LVH & LVSD (%)			<0.0001
Neither	37%	65%	
Severe LVSD Only	15%	11%	
LVH Only	27%	17%	
Both LVH and Severe LVSD	21%	8%	

LVH: Left Ventricular Hypertrophy defined by quantitative measurements on echocardiogram;

LVSD: Left Ventricular Systolic Dysfunction assessed by echocardiogram

* p values from independent samples t-test for continuous variables and chi-square test for categorical variables.

[†] Adjusted LVM calculated as LVM / body surface area.

Table 3

Multivariate odds ratio estimates for sudden cardiac death (SCD) associated with severe LVSD and LVH.

	Odds ratios and 95% confidence intervals	
	Adjusted model with LVSD only*	Adjusted model with LVSD and LVH*
Severe LVSD	2.1 (1.3 – 3.5)	1.9 (1.1 – 3.2)
LVH	--	1.8 (1.1 – 2.9)
Age (1-year increase)	1.03 (1.01–1.05)	1.03 (1.01–1.05)
Diabetes	2.0 (1.2 – 3.3)	1.9 (1.2 – 3.1)
Creatinine (1-unit increase in log-value)	2.5 (1.5 – 3.9)	2.3 (1.4 – 3.6)
History of atrial fibrillation/flutter	2.3 (1.3 – 3.9)	2.3 (1.3 – 3.9)
Use of angiotensin receptor blockers	0.4 (0.2 – 0.8)	0.3 (0.1 – 0.8)

LVH: Left Ventricular Hypertrophy; LVSD: Left Ventricular Systolic Dysfunction

* Adjusted estimates obtained from multivariate model adjusted for all covariates in table. All other variables included in Table 1 were removed from the final models because they were neither significantly associated with SCD in the multivariate models, nor confounders of the association of LVSD or LVH with SCD.