Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 61, No. 2, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.10.012

Biomarkers of Chronic Cardiac Injury and Hemodynamic Stress Identify a Malignant Phenotype of Left Ventricular Hypertrophy in the General Population

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Objectives The goal of this study was to determine if biomarkers of subclinical myocardial injury and hemodynamic stress identify asymptomatic individuals with left ventricular hypertrophy (LVH) at higher risk for heart failure (HF) and death.

Background The interaction between LVH, low but detectable cardiac troponin T (cTnT), and elevated N-terminal pro–B-type natriuretic peptide (NT-proBNP) on cardiovascular (CV) outcomes in the general population is unknown.

Methods Participants in the Dallas Heart Study without clinical HF, LV dysfunction, or chronic kidney disease underwent measurement of LV mass by magnetic resonance imaging (MRI), cTnT by highly sensitive assay, and NT-proBNP analysis (n = 2,413). Subjects were stratified according to LVH and by detectable cTnT (≥3 pg/ml) and increased NT-proBNP (>75th age- and sex-specific percentile) levels. For each analysis, participants were categorized into groups based on the presence (+) or absence (–) of LVH and biomarker levels above (+) or below (–) the predefined threshold.

Results Nine percent of participants were LVH+, 25% cTnT+, and 24% NT-proBNP+. Those LVH+ and cTnT+ and/or NT-proBNP+ (n = 144) were older and more likely to be male, with a greater risk factor burden and more severe LVH compared with those who were LVH+ biomarker– ($p < 0.01$ for each). The cumulative incidence of HF or CV death over 8 years among LVH+ cTnT+ was 21% versus 1% (LVH– cTnT–), 4% (LVH– cTnT+), and 6% (LVH+ cTnT–) ($p < 0.0001$). The interactions between LVH and cTnT ($p_{interaction} = 0.0005$) and LVH and NT-proBNP ($p_{interaction} = 0.014$) were highly significant. Individuals who were LVH+ and either cTnT+ or NT-proBNP+ remained at >4-fold higher risk for HF or CV death after multivariable adjustment for CV risk factors, renal function, and LV mass compared with those who were LVH– biomarker–.

Conclusions Minimal elevations in biomarkers of subclinical cardiac injury and hemodynamic stress modify the association of LVH with adverse outcomes, identifying a malignant subphenotype of LVH with high risk for progression to HF and CV death. (J Am Coll Cardiol 2013;61:187–95) © 2013 by the American College of Cardiology Foundation

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Manuscript received August 16, 2012; revised manuscript received September 25, 2012, accepted October 9, 2012.

JACC Vol. 61, No. 2, 2013
January 15, 2013:187–95

Abbreviations and Acronyms

BSA = body surface area
CI = confidence interval
cTnT = cardiac troponin T
CV = cardiovascular
ECG = electrocardiogram
eGFR = estimated glomerular filtration rate
HF = heart failure
HR = hazard ratio
LV = left ventricular
LVEF = left ventricular ejection fraction
LVH = left ventricular hypertrophy
MRI = magnetic resonance imaging
NT-proBNP = N-terminal pro–B-type natriuretic peptide

Left ventricular (LV) hypertrophy (LVH), most commonly due to chronic hypertensive heart disease, is associated with substantial morbidity and mortality, including the development of heart failure (HF) and death from cardiovascular (CV) disease (1,2). LVH develops in response to chronic pressure and volume overload and may ultimately progress to pathological systolic or diastolic dysfunction and symptomatic HF (3). Maladaptive LV remodeling plays a central role in the transition from asymptomatic LVH to clinical HF and results from cardiomyocyte injury and tissue fibrosis (4), as well as increased diastolic wall stress and neurohormonal activation (5).

Although clearly a risk factor for HF and CV death, the natural history of LVH is heterogeneous, with a progressive course in some individuals but an uncomplicated course in many others. Identification of biological pathways that contribute to the transition from LVH to clinical HF, and biomarkers that accurately represent these pathways, may help to identify individuals at high risk for adverse outcomes and to develop therapeutic targets to prevent disease transition. Biomarkers of myocardial injury and neurohormonal activation due to hemodynamic stress may therefore play key roles in defining the transition from asymptomatic LVH to clinical HF (6–8).

Cardiac troponin T (cTnT) and N-terminal pro–B-type natriuretic peptide (NT-proBNP) are released from cardiac myocytes in response to a variety of pathological stimuli, including increased LV wall stress and hypertrophy, and are markers of cardiac injury and ventricular wall stress (9,10). Both biomarkers have been shown to associate strongly with incident HF (11,12) and mortality (13,14) in the general population; however, the impact of minimally elevated circulating levels of cTnT and NT-proBNP among individuals with LVH is unknown. Our goal was to test the hypothesis that biomarker evidence of subclinical myocardial injury and hemodynamic stress could identify asymptomatic individuals with LVH at higher risk for transition to HF and CV death.

Methods

Study population. The Dallas Heart Study (DHS) is a multiethnic, probability-based, population cohort study of Dallas County adults in which deliberate oversampling of African-Americans was performed. Detailed methods of the DHS have been described previously (15). Briefly, between 2000 and 2002, a total of 3,072 subjects completed the 3 DHS visits, including a detailed in-home survey, laboratory testing, and imaging studies. Participants were then followed up for the occurrence of predefined clinical events and death. For the current study, we excluded participants with an LV ejection fraction (LVEF) <40%, estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, and those with prevalent clinical HF (defined by self-report of "congestive heart failure, an enlarged heart, a weak heart, or cardiomyopathy") at baseline, yielding a final sample size of 2,413. Participants provided written informed consent, and the protocol was approved by the institutional review board of University of Texas Southwestern Medical Center.

Biomarker, imaging, and body composition measurements. Detailed methods describing measurements of cTnT by using a highly sensitive assay (Elecsys-2010 Troponin T hs STAT, Roche Diagnostics, Indianapolis, Indiana) and NT-proBNP (Elecsys, Roche Diagnostics) in the DHS have been published previously (14,16). The lowest concentrations within the analytical measurement range of the assays were 3 pg/ml and 5 pg/ml for cTnT and NT-proBNP, respectively. Cardiac magnetic resonance imaging (MRI) was performed by using a 1.5-T system (Intera, Philips Medical Systems, Best, the Netherlands). LV mass, wall thickness, end-diastolic and end-systolic volumes, and LVEF were calculated from short-axis sequences. LV concentricity was defined as the ratio of LV mass to end-diastolic volume (17).

Fat-free mass was measured with dual-energy x-ray absorptiometry (Delphi W scanner, Hologic, Inc., Bedford, Massachusetts, and Discovery software [version 12.2]) (18). Body mass index was calculated as weight (kilograms)/height (meters)^2 based on weight and height measured at study entry. Body surface area (BSA) was calculated by using the method of Tikuisis et al. (19). Twelve-lead electrocardiograms (ECG) were recorded at 25 mm/s and 1 mV/cm standardization, with a sampling rate of 0.5 kHz, by using the Marquette 12SL ECG analysis program version 229 (GE Marquette Medical Systems, Milwaukee, Wisconsin). Voltage measurements were obtained electronically by using median voltages from an aligned group of all beats from each lead. Two DHS investigators blinded to demographic and clinical information reviewed each ECG to verify the computer-identified parameters and to provide a clinical interpretation.

Definitions. LVH was defined as LV mass/BSA ≥89 g/m^2 in women and ≥112 g/m^2 in men, based on a phenotypically normal subpopulation of the DHS cohort, as previously described (17). As a sensitivity analysis, LVH was also defined by indexing LV mass to height$^{2.7}$ (LV mass/height$^{2.7}$ ≥39 g/$m^{2.7}$ [women] and ≥48 g/$m^{2.7}$ [men]) and fat-free mass (LV mass/fat-free mass ≥3.7 g/kg [both men and women]). Analyses of LVH according to the Sokolow-Lyon ECG criteria, defined as the sum of the S-wave amplitude in lead V_1 plus the maximum R-wave amplitude