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ScienceDirect

Journal of Electrocardiology 47 (2014) 630–635

JOURNAL OF Electrocardiology

www.jecgonline.com

Review

Regression of electrocardiographic left ventricular hypertrophy or strain is associated with lower incidence of cardiovascular morbidity and mortality in hypertensive patients independent of blood pressure reduction – A LIFE review☆,☆☆

Casper N. Bang, MD, PhD,[a,b,*] Richard B. Devereux, MD,[a] Peter M. Okin, MD[a]

[a] Department of Medicine, Weill Cornell Medical College, NY, USA
[b] Department of Cardiology, The Heart Center, Rigshospitalet, Copenhagen, Denmark

Abstract Cornell product criteria, Sokolow–Lyon voltage criteria and electrocardiographic (ECG) strain (secondary ST-T abnormalities) are markers for left ventricular hypertrophy (LVH) and adverse prognosis in population studies. However, the relationship of regression of ECG LVH and strain during antihypertensive therapy to cardiovascular (CV) risk was unclear before the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study. We reviewed findings on ECG LVH regression and strain over time in 9193 hypertensive patients with ECG LVH at baseline enrolled in the LIFE study.

The composite endpoint of CV death, nonfatal MI, or stroke occurred in 1096 patients during 4.8 ± 0.9 years follow-up. In Cox multivariable models adjusting for randomized treatment, known risk factors including in-treatment blood pressure, and for severity ECG LVH by Cornell product and Sokolow–Lyon voltage, baseline ECG strain was associated with a 33% higher risk of the LIFE composite endpoint (HR. 1.33, 95% CI [1.11–1.59]). Development of new ECG strain between baseline and year-1 was associated with a 2-fold increased risk of the composite endpoint (HR. 2.05, 95% CI [1.51–2.78]), whereas the risk associated with regression or persistence of ECG strain was attenuated and no longer statistically significant (both $p > 0.05$). After controlling for treatment with losartan or atenolol, for baseline Framingham risk score, Cornell product, and Sokolow–Lyon voltage, and for baseline and in-treatment systolic and diastolic blood pressure, 1 standard deviation (SD) lower in-treatment Cornell product was associated with a 14.5% decrease in the composite endpoint (HR. 0.86, 95% CI [0.82–0.90]). In a parallel analysis, 1 SD lower in-treatment Sokolow–Lyon voltage was associated with a 16.6% decrease in the composite endpoint (HR. 0.83, 95% CI [0.78–0.88]).

The LIFE study shows that evaluation of both baseline and in-study ECG LVH defined by Cornell product criteria, Sokolow–Lyon voltage criteria or ECG strain improves prediction of CV events and that regression of ECG LVH during antihypertensive treatment is associated with better outcome, independent of blood pressure reduction.

Keywords: Hypertension; Left ventricular hypertrophy; Cornell voltage criteria; Sokolow-Lyon criteria; Strain; Anti-hypertensive treatment; Cardiovascular outcome; Cardiovascular death; Atrial fibrillation; Congestive heart failure; Myocardial infarction; Stroke

Introduction

Several studies have shown that left ventricular hypertrophy (LVH), detected by echocardiography [1] or the 12-lead electrocardiogram (ECG) [2], is not only a cardinal adaptation to increased hemodynamic load in hypertension, but also a common manifestation of preclinical cardiovascular

☆ Clinical trial registration information: http://www.clinicaltrials.gov. Unique identifier: NCT00338260.

☆☆ Conflict of interest: Drs Okin & Devereux received grant support from Merck & Co Dr Devereux consults for Merck & Co, Inc and General Electric Medical Systems. The remaining authors report no conflicts.

* Corresponding author at: Department of Medicine, Division of Cardiology, Weill Cornell Medical College, New York, New York, USA.
E-mail address: casperbang@hotmail.com

http://dx.doi.org/10.1016/j.jelectrocard.2014.07.003
0022-0736/

(CV) disease that strongly predicts CV morbidity and mortality. Another ECG abnormality, the classic ECG pattern of left ventricular (LV) strain, consisting of lateral ST depression and T-wave inversion [3], is a well-recognized marker of the presence and severity of anatomic LVH that also independently predicts CV morbidity and mortality in a variety of populations including hypertensive patients [3]. However, before the prospective Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study there were only limited data on the prognostic impact of changes in ECG indices during antihypertensive treatment. This review integrates the findings of multiple LIFE publications that examined the relationship of changing levels of ECG LVH and strain to CV morbidity and mortality [4–8].

Methods

The LIFE study [9] enrolled 9193 hypertensive patients with ECG LVH by Cornell voltage-duration product [10] and/or Sokolow–Lyon voltage criteria [3] on a screening ECG in a prospective, double-blind randomized study that compared CV morbidity and mortality with use of losartan, as opposed to atenolol-based treatment, as previously described in detail [9].

ECGs were routinely obtained at study baseline, at 6-months, and at yearly follow-up intervals until study termination or patient death. Repolarization abnormalities in leads V5 and/or V6 were considered consistent with the presence of typical strain when there was a down-sloping convex ST segment with an inverted asymmetrical T-wave opposite to the QRS axis [11]. For consistency with prior LIFE publications we used the word strain instead of the recently recommended and maybe more appropriate term "secondary ST-T abnormalities" [12]. The product of QRS duration times the Cornell voltage combination (RaVL + SV3, with 6 mm added in women [10]) >2440 mm · ms or Sokolow–Lyon voltage (SV1 + RV5/6) >38 mm was used to identify LVH [3]. The 38 mm threshold was employed for Sokolow–Lyon voltage as it increased specificity of Sokolow–Lyon voltage to the same level as found for Cornell product in the original derivation populations without reducing sensitivity, thus increasing the number of patients with true anatomic LVH recruited for the study [13].

The LIFE trial used a composite endpoint of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke according to previously defined criteria [9]. These endpoints and secondary endpoints of sudden cardiac death [7], new-onset heart failure and [14] new-onset atrial fibrillation [8], were ascertained and then verified by an expert endpoint committee who were blinded to ECG results when classifying possible morbid events [9]. The relations of baseline as well as in-treatment levels of Cornell product and Sokolow–Lyon voltage, and baseline and year-1 ECG strain to the risk of CV events were assessed using Cox proportional hazards models in which baseline risk factors and a treatment group indicator were included as standard covariates, and baseline and subsequent systolic and diastolic blood pressure, Cornell product and Sokolow–Lyon voltage measurements were entered as time-varying covariates.

LIFE findings

During mean follow-up of nearly 5 years sudden cardiac death occurred in 190 patients (2.1%), new-onset atrial fibrillation in 701 (7.9%), new-onset heart failure in 265 (3.0%), death resulting from heart failure in 26 (0.3%), stroke in 541 (5.9%), MI in 386 (4.2%), CV death in 438 (4.8%) and the LIFE composite endpoint of CV death, MI, or stroke occurred in 1096 patients (11.9%) [4–6].

One of the prespecified secondary hypotheses of the LIFE study was that regression of ECG LVH per se would be associated with reduced CV morbidity and mortality. LVH can be defined by several ECG patterns, including the well-recognized Cornell product criteria, Sokolow–Lyon voltage criteria and the classic strain pattern of ST depression and T-wave inversion. Indeed, among 843 patients who had both baseline strain and echocardiographic LVH data, strain was present in 81% of patients with echocardiographic LVH (475/586) and in only 7% of patients with echocardiographic LV mass in the normal range (18/257). ECG strain is a well-recognized marker of the presence and severity of anatomic LVH, and incorporation of ECG strain into scores that include standard voltage criteria improves ECG detection of LVH [15]. Strain has also been associated with adverse prognosis in hypertensive patients. In the Progetto Ipetensione Umbria Monitoraggio Ambulatoriale (PIUMA) study including 1717 hypertensive patients, Verdecchia et al. [16] tested a variety of standard ECG methods for assessment of LVH, and concluded that several of these standard criteria were important for CV risk stratification in essential hypertension, including Cornell voltage criteria, Sokolow–Lyon criteria and ECG strain. However, no one had tested the ability of these ECG methods for assessment of LVH to predict CV outcome during aggressive treatment of hypertension independent of reduction in blood pressure before the LIFE study.

ECG strain and outcomes

ECG strain pattern of lateral repolarization abnormality was present in 923 patients (10.6%) at baseline, 876 (10.1%) patients at year one, 549 (7.4%) patients at both baseline and year 1, developed in 292 in the first year (3.9%) and regressed in 245 (3.3%) patients from baseline to year 1 [5]. In univariate Cox analyses, the presence of the strain on the baseline LIFE study ECG was associated with a >3-fold increased risk of developing congestive heart failure (CHF) (with a 5-year rate of 8.8% compared with only 2.7% in those without ECG strain), a 4-fold increased risk of CHF mortality (5-year CHF mortality of 1.2% vs. only 0.3%) [4] and a 2-fold increased risk of the composite CV endpoint (5-year event rate 21.0% vs. 11.2%) [6]. In addition, strain at baseline was associated with an increased risk of each of the component end points of the LIFE study: a 2.26-fold increased risk of CV death (5-year CV mortality 9.1% versus 4.3%), a 2.16-fold increased risk of MI (5-year infarction rate 8.1% versus 3.9%), and a 1.76-fold increased risk of stroke (5-year stroke rate 10.2% versus 5.8%) compared with patients without strain [6]. In addition,