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Review

Electrocardiographic left ventricular hypertrophy and the risk of adverse cardiovascular events: A critical appraisal

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Abstract This review covers selected electrocardiographic left ventricular hypertrophy (ECG-LVH) studies which have evaluated their prognostic value for adverse cardiovascular (CVD) events. Most ECG-LVH studies have used echocardiographic left ventricular mass (Echo-LVM) as the gold standard for evaluating ECG-LVH criteria. More recently, LVM from magnetic resonance imaging (MRI-LVM) has evolved as the new gold standard. The reported risk of adverse CVD events is generally highest for ECG-LVH criteria which combine high amplitude QRS criteria with repolarization abnormalities such as in LV strain pattern. Evolving coronary heart disease (CHD) may account in part for the increased risk for ECG-LVH. However, one large coronary arteriography study found that 5-year survival was significantly lower in coronary artery disease (CAD) patients with ECG-LVH than without LVH regardless of CAD status. The utility of Echo-LVH as a standard is limited by the large intra- and inter-reader variability and the lack of standardization of allometric formulations for adjustment of LVM to body size. Newer evaluation data with MRI-LVM as the standard show that for most ECG criteria CVD event rates are significantly higher for study subgroups with ECG-LVH than those without ECG-LVH. However, the performance results differ when comparing the risk for CVD events from those for the overall LVH classification accuracy according to sensitivity and specificity. Large short-term variability of ECG amplitudes due to electrode placement variability is a common limiting factor for ECG-LVH criteria performance regardless of the gold standard. Clinical trials for hypertension control rely largely on monitoring Echo-LVH rather than ECG-LVH.

Keywords: Electrocardiography; Left ventricular hypertrophy; Classification accuracy; Left ventricular mass; Echocardiography; Magnetic resonance imaging

Introduction

The early electrocardiographic left ventricular hypertrophy (ECG-LVH) criteria were developed with ECG as its own standard by using the upper limits in subjects considered clinically normal and comparing the measurements in patients with conditions clinically likely to lead into LVH. In the next phase, M-mode echocardiographic LVH (Echo-LVH) became the gold standard, and more recently magnetic resonance imaging (MRI) has evolved into a new more accurate standard for LVH using LV mass for evaluation of ECG-LVH criteria and for development of new improved criteria. The present review is an appraisal of these developments. In selecting the papers for review preference was given to major epidemiological studies, particularly those which have considered prognostic value of ECG-LVH criteria.

ECG-LVH and adverse outcome events

Table 1 summarizes data on adverse outcome events for a selected set of observational and intervention studies.

Framingham Heart Study

The first four studies in Table 1 are observational longitudinal studies. The study covered in more detail here is the often-cited Framingham report by Levy et al. [1]. Logistic regression analyses of nine successive pooled, biennial examinations were performed to assess the associations with outcome both for baseline ECG voltage

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and repolarization features and for serial changes in these features. The authors note that this approach has been shown to closely resemble the Cox proportional hazard regression. The outcome was CVD mortality and morbidity including a variety of documented nonfatal CVD events listed in the table.

Comparing Cornel Voltage (CV) quartile 4 vs. quartile 1 in each index biennial for the risk at the next biennial examination, the risk for incident CVD events was over 3-fold in men and women. In evaluation of serial changes between successive biennial examinations by comparing transition to a higher CV quartile vs. no change, the risk for incident CVD events was associated with a significantly increase risk in men (relative risk (RR) 1.86, 95% confidence interval (CI) (1.14–3.03) but not in women. Similarly, a change to a lower CV quartile vs. no change was associated with a significant reduction in the risk for CVD events in men but not in women. A worsening of repolarization (from normal to mild or from mild to severe abnormality) was associated with an approximately 2-fold increase in the risk for CVD events in both sex groups. An improvement in repolarization abnormalities was not associated with a significant decrease in the risk of CVD events in either sex group.

BIRNH Study

This report is from the Belgian Interuniversity Research on Nutrition and Health by De Bacquer et al. [2] in a random sample of the Belgian population. CVD death was defined according to the International Code for Diseases (ICD), 9th Revision, codes 390–459. The study evaluated the risk of CVD death for high-amplitude QRS associated with ST depression or flat or negative T waves by the Minnesota Code. As noted in Table 1, the prevalence of high amplitude QRS combined with repolarization abnormalities was low, 0.8% in men and 0.5% in women. CVD risk was increased over 2-fold in both sex groups in multivariable-adjusted risk model, including adjustment for other ECG abnormalities. The risk was not significantly increased for CHD or all-cause mortality.

RIFLE Study

This study comes from the Italian Risk Factors and Life Expectancy study in 12,180 men and 10,373 women [3]. The risk of CVD mortality for high-amplitude QRS was significantly increased in multivariable-adjusted model in men (RR 1.86 (1.13, 3.07) but not in women. Similarly, for high-amplitude QRS combined with abnormal ST-T the CVD risk was over 6-fold for men (RR 6.33 (3.02, 13.3)). The risk increase in women was nearly as high as in men (RR 5.91 (0.70, 49.9)) but not statistically significant.

NHANES 1

The first US National Health and Nutrition Study evaluated the risk for CVD death for high-amplitude QRS combined with repolarization abnormalities (MC3.1 + MC 4.1–4.3, 5.1–5.3) [4]. CVD mortality risk was increased for white men and back men (RR 3.26 (1.91, 5.56) and 4.29 (2.00, 9.18), respectively, and for white women (RR 2.59 (1.29, 5.19) but the risk was not significantly increased for black women. The study also evaluated the risk of CVD death for ECG estimate for left ventricular mass index (ECG-LVMI) derived using multiple ECG wave amplitudes and echocardiographic LV mass index (LVMI) as the standard [5]. The risk for CVD death for LVMI quintile 5 vs. quintile 1 in a risk model adjusted for age, systolic blood pressure and history of heart attack was 1.39 (1.21–1.39) in white men, 1.26 (0.81–1.96) in black men, 1.36 (1.08–1.70) in white women and 1.95 (1.44–2.66) in black women (not shown).

Glasgow Blood Pressure Clinic Study

The Glasgow study by Dunn et al. [5] in 3783 hypertensive men and women evaluated all-cause mortality by Sokolow–Lyon criteria. LVH prevalence at baseline was 34.5% for men, and 12.8% had ST-T changes. The corresponding figures for women were 21.5% and 8.8%. All-cause age-adjusted mortality, expressed as deaths per 1000 patient-years, was 27.6 for men with normal ECG, 43.2 for men with ECG-LVH by voltage criteria only ($P < 0.001$) and 56.9% for voltage criteria combined with abnormal ST-T ($P < 0.001$). The authors concluded that ECG-LVH, with or without ST-T changes is a predictor of mortality in hypertensive patients independent from other risk factors (age, blood pressure at referral and smoking) evaluated in regression analyses separately or in combination with ECG-LVH.

PIUMA Study

Verdecchia et al. [6] evaluated the risk for incident CHD for a variety of ECG-LVH criteria in connection with the co-operative study of Italian hypertension clinics PIUMA (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale) in 1717 white hypertensive men and women. The endpoints CVD events were incident CHD (MI or angina with ischemic ECG changes, stroke, transient ischemic attack (TIA), aortoiliac occlusive disease documented at artiriography, occlusion of retinal artery documented at arteriography, HF requiring hospitalization or renal failure requiring dialysis. The risk for CVD events was not significant for CV or Sokolow–Lyon (S–L) voltage. LV strain by Framingham criteria was associated with increased risk but not by stricter PIUMA criteria (ST depression ≥ 100 μV), evidently because of lower prevalence. The risk for CVD events was high, over 4-fold for Romhilt–Estes Score ≥ 4 or ≥ 5 or for Perugia Score (ECG-LVH by CV, Romhilt–Estes Score ≥ 5 or PIUMA LV strain).

MRFIT Study

The Multiple Risk Factor Intervention Study was the first large clinical trial with simultaneous intervention on multiple CHD risk factors in 12,866 men considered at high risk of CHD [7]. One part of the analyses of the risk for CVD death (including fatal MI and sudden cardiac death) included evaluation of the risk for a significant change exceeding 95th percentile limit for short-term variation established as 900 μV for S–L voltage and 400 μV for CV [8]. Significant change was measured as the average value the first 6 annual visits as the baseline value and the risk for CVD and CHD death for the significant change was evaluated during the subsequent 10 years of follow-up. A significant increase in CV was associated with over 2-fold increase in the risk for CVD death but a not for a significant increase in S–L voltage. In turn, a significant decrease in S–L voltage was associated with an