Is Electrocardiography-Left Ventricular Hypertrophy an Obsolete Marker for Determining Heart Failure Risk With Hypertension?

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Hypertension is a major risk factor for heart failure (HF), preceding it in 75% of patients, and present in 60% to 89% of people with HF with preserved ejection fraction, perhaps representing the main causative factor.\(^1\) Left ventricular hypertrophy (LVH), an increase in left ventricular mass (LVM), is an adaptive response proven to be a strong marker of cardiovascular disease (CVD) morbidity, including HF, and mortality.\(^1\)

Since the development of electrocardiography (ECG), this ubiquitous, low-cost test is utilized in most patients with hypertension undergoing health assessments. Nonetheless, to confirm hypertension-related LVH, costlier echocardiography is now widely available and, for most providers, the technique of choice. Moreover, cardiac magnetic resonance (CMR) is now the criterion standard for LVM measurement, providing excellent quality and quantification. These multiple tools, however, demonstrate a weak correlation, and present-day US health plans may require time-consuming prior authorization processes as cost-saving measures, underlining the utility of CMR and echocardiography.

Regardless of the utilized method, LVH is associated with increased CVD outcomes, although the specific linkage from hypertension and LVH to HF is not well elucidated. In this issue of the Journal of the American Heart Association (JAHA), Johnson et al.\(^2\) analyzed the largest randomized hypertension outcomes trial, ALLHAT (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial),\(^3\) to reveal the relationship between ECG-LVH, blood pressure (BP) lowering, and incident HF, noting the superiority of chlorthalidone for BP control and reducing HF incidence. Strengths of this report include a large, diverse cohort, and well-validated techniques. It comprised 29 892 subjects with hypertension, including 32% blacks, randomized to chlorthalidone, doxazosin, amlodipine, or lisinopril. Blinded reviewers determined ECG-LVH using the Minnesota code classification, Cornell voltage, Cornell product, Sokolow-Lyon, sum of 12 leads, and 12 leads product; serial changes were identified by a computer algorithm and confirmed visually. Inclusion of multiple ECG criteria probably increased the sensitivity. A potential limitation is that echo-LVH, despite its prognostic implications, was not used for follow-up. Interestingly, a U-shaped association of BP lowering and HF was observed, and evolving ECG-LVH and BP change per se only explained 4% to 13% of HF prevention, suggesting that factors beyond these elements were behind the beneficial chlorthalidone effects.

Considering that ECG-LVH changes did not explain most of the chlorthalidone benefits preventing HF, an essential question is whether ECG-LVH retains its utility as a risk marker or is now obsolete. First of all, ECG-LVH has limited sensitivity, particularly among obese patients,\(^4\) and decreased specificity, especially in some racial/ethnic groups, as in blacks, displaying increased voltage.\(^5\) Nonetheless, ECG-LVH may unmask an abnormal electrophysiological substrate, associated with mortality and incident HF. In ALLHAT, chlorthalidone, amlodipine, and lisinopril were associated with similar small reductions in mean Cornell voltage, indicating that risk reductions with chlorthalidone cannot be attributed to improvement in ECG-LVH.\(^6\) However, a subsequent analysis found that ECG-LVH was associated with 29% to 98% increased risk of all-cause mortality, myocardial infarction, coronary heart disease, stroke, and HF.\(^7\) Similarly, in the LIFE (Losartan Intervention for Endpoint Reduction) study of hypertensive individuals with ECG-LVH, Cornell product and Sokolow-Lyon criteria separately predicted increased cardiovascular risk. A post-hoc analysis revealed that ECG-LVH by both criteria was associated with >3-fold

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increased risk of myocardial infarction, stroke, cardiovascular mortality, and all-cause mortality, suggesting that combining criteria concentrates the risk.\(^8\)

Echocardiography has higher sensitivity than ECG in identifying LVH. Currently, LVM evaluation has moved from M-mode to 2D-ECG because of easier acquisition and lower variability. Noted drawbacks, though, are the need for adequate windows and dependence on geometrical assumptions. Real-time 3D-imaging is more reliable, although dependent on equipment availability and image quality.

CMR offers several advantages, including obtaining precise measurements without geometric assumptions. In 1 analysis including 4748 participants from MESA (Multi-Ethnic Study of Atherosclerosis), CMR- and ECG-LVH were present in 10.5% and 6.7%, respectively. ECG-LVH alone was predictive of CVD events, but LVH on both ECG and CMR had the strongest link.\(^9\) Furthermore, in another analysis from the same cohort, both ECG-LVH and CMR-LVH were predictive of HF, and CMR-LVH improved the predictive ability of a model similar to the Framingham Heart Failure Risk Score.\(^10\)

Therefore, ECG-LVH and imaging-LVH are different entities with common underlying pathophysiology, but independent prognostic value, supported by a genome-wide linkage analysis in families with hypertension revealing stronger genetic signals for ECG-LVH than echo-LVH.\(^11\) Potentially, an abnormal electrical substrate eventually translates in factors that may determine subsequent HF: increased myocardial tension, neurohumoral/biochemical changes, slowed conduction, and altered ventricular activation with regional wall motion abnormalities.

Based on the preponderance of the evidence, modern clinicians should not abandon ECG-LVH as an outcome prediction tool, despite displaying modest accuracy diagnosing anatomic-LVH. Only validated criteria should be used and, although no single measurement can be recommended, combination of these has been shown to increase sensitivity. Going forward, use of criteria incorporating repolarization abnormalities should be encouraged, like the Romhilt-Estes score or the Framingham score, indicating higher risk for incident CVD than assessment based solely on increased QRS amplitudes. Likewise, other variables (eg, P-wave indexes) may help clarify the discrepancy between ECG-LVH and imaging-LVH. In addition, optimal evaluation should be adjusted for factors known to alter accuracy (sex, race, body habitus), and the diagnosis of LVH in the presence of left bundle branch block should be made with caution.\(^12\)

It is important to contemplate how these key concepts affect practicing clinicians. The current American College of Cardiology/American Heart Association guideline for management of hypertension recommends a target BP of <130/80 mm Hg for those at increased risk or with HF.\(^1\) Also, based on conclusions from ALLHAT,\(^3\) thiazide-type diuretics are recommended as first-line agents.\(^1\) Nevertheless, if thiazide-type diuretics are to be considered superior to reduce, specifically, new-onset HF, the question to be addressed is whether this is indeed a class quality. The mechanism by which chlorthalidone lowers BP is obscure, but likely related to extracellular fluid contraction, followed by inhibition of carbonic anhydrase leading to vasodilation; additionally, chlorthalidone reduces pulse-wave velocity, a measure of aortic stiffness and marker of cardiovascular events.\(^13\) On the other hand, hydrochlorothiazide is undoubtedly the most widely used thiazide for hypertension, often perceived as a safer option for metabolic derangements. Despite lack of head-to-head trials, a systematic review found a 23% risk reduction in HF for chlorthalidone versus hydrochlorothiazide, and 21% reduction in CVD events.\(^14\)

Moreover, indapamide, also underutilized, appears to share some of the superior effectiveness for BP reduction and CVD outcome reduction compared with hydrochlorothiazide.\(^15\)

Additionally, LVM is associated with body size, tobacco use, and diabetes mellitus,\(^7\) with LVH being highly prevalent among diabetics, even normotensive individuals. Future considerations for approaching LVH may include the sodium-glucose cotransporter-2 inhibitors,\(^16\) since empagliflozin use in diabetics with atherosclerotic CVD demonstrated an impressive 38% and 35% reduction in cardiovascular mortality and HF hospitalization, respectively.\(^17\) Although the mechanisms behind these striking results remain unclear, 1 proposed pathway is regression of LVH through reduction in preload, afterload, and weight. An ongoing study seeks to explore this, examining changes in LVM by CMR in diabetics with LVH randomized to dapagliflozin versus placebo.\(^16\)

Notably, both ECG-LVH and anatomical LVH are tied to increased CVD risk; hence, prevention and treatment of either form is expected to have a positive impact. A substudy from LIFE demonstrated that regression of LVH by Cornell product, Sokolow-Lyon voltage, or ECG strain during antihypertensive treatment was associated with better prognosis, independent of traditional risk factors and BP reduction.\(^18\) Furthermore, in SPRINT (Systolic Blood Pressure Intervention Trial),\(^19\) including 8164 individuals with hypertension without diabetes mellitus, the intensive control arm had 46% lower risk of developing ECG-LVH, and they were more likely to have regression of this entity. The beneficial effects on LVH in the intensive control group agree with the results of improved CVD outcomes; nevertheless, they did not wholly explain the reduction in CVD events.

The results from Johnson et al\(^12\) offer new insights indicating how much we still do not understand about the complex underlying pathophysiology leading to HF and the importance of addressing not only BP control, but also other potential contributors to HF. At this time, routine imaging evaluation of
LVH is not recommended because of limited data on the cost-effectiveness for risk classification and management; in fact, routine evaluation of hypertension with echocardiogram received a score of 3 on the Appropriate Use Criteria from 2011, considering it inappropriate.20 Contrarily, imaging can be helpful in young individuals, those with secondary hypertension, uncontrolled hypertension, or HF symptoms.1

For curtailing the persistent morbidity and mortality because of uncontrolled hypertension, the most prevalent and potent CVD risk factor, some questions related to LVH determination remain unanswered. Future research should help clarify whether beyond ECG-LVH measurements, screening for LVH with echocardiogram, or even CMR, in patients with hypertension is useful, how we can adjust for factors that affect accuracy, and what is the best way and time to follow up and approach these patients therapeutically.

Disclosures
Dr Ferdinand has served as a consultant for Amgen, Sanofi, Boehringer Ingelheim, Novartis, Quantum Genomics, and Janssen. Dr Maraboto has no disclosures to report.

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