Electrocardiographic diagnosis of left-ventricular hypertrophy: good news for the clinician?

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In this issue of the Journal Gosse *et al.* [1] report the findings of a study aimed at investigating the value of several electrocardiographic (ECG) criteria in detecting left-ventricular hypertrophy (LVH) previously documented by echocardiography and in predicting cardiovascular disease in a large cohort of untreated hypertensive patients. Before addressing the details of the study, available evidence on this topic should be analyzed.

Left-ventricular hypertrophy, either detected by standard 12-lead ECG or echocardiography, is a cardinal manifestation of preclinical organ damage related to hypertension and a strong predictor of cardiovascular morbidity and mortality in several clinical settings [2,3]. In the 2007 European Society Hypertension/European Society Cardiology guidelines detection of LVH in hypertension allows classification of the patient in the high-risk category, because of the evidence, collected in large-scale prospective studies, that this biomarker of organ damage is associated with an incidence of cardiovascular events equal to or higher than 20% in 10 years [4]. Regression of ECG or echocardiographic LVH has been shown to occur during long-term effective antihypertensive treatment and to drive a variety of beneficial effects on left-ventricular function, myocardial tissue network, coronary reserve, and arrhythmias, thus resulting in an improved cardiovascular prognosis [5,6]. The Cardio-Sis study was planned in more than 11 000 nondiabetic hypertensive patients recruited in 44 centers in Italy to investigate the beneficial effects of tight versus usual blood pressure (BP) control [7]. The study showed that a tight control of systolic BP below 130 mmHg compared to the usual control below 140 mmHg decreased the likelihood of ECG-graphic LVH and clinical events (11.4 and 5.4% versus 17.0 and 9.4%, respectively) at the end of a 2-year follow-up period [7]. A recent meta-analysis of five studies including 2449 hypertensive individuals showed that LVH regression or persistence of normal left-ventricular mass was associated with a 46% reduction of cardiovascular events as compared to persistent or newly developed LVH; the difference remained significant after adjustment for several covariates [8]. Overall, these findings indicate that LVH regression or prevention of new-onset LVH may reliably predict the efficacy of antihypertensive therapy and the decreased risk of cardiovascular complications. Thus, detection of LVH either at the initial evaluation or during antihypertensive treatment may improve cardiovascular risk stratification and decision-making strategies.

Several techniques are currently available for LVH assessment, including ECG, chest radiography, mono/two-dimensional echocardiography, computerized tomography, magnetic resonance, and, more recently, three-dimensional echocardiography. All these tools differ in diagnostic accuracy, availability and cost. ECG is easily performed, widely available, inexpensive and provides additional data of clinical relevance because associated with a worse prognosis, such as signs of ventricular overload or 'strain' or ischemia, presence of conduction defects or arrhythmias. LVH may alter ECG pattern either by increasing QRS voltage and duration or by modifying instantaneous and mean QRS vectors, ST segment, T-wave and P-wave. Since the pioneering observations by Einthoven [9] and Lewis [10] that were based on the measurement of QRS voltages (i.e. R-wave and S-wave amplitudes in standard limb leads I and III), using clinical and necropsy data as reference standards, numerous voltage and nonvoltage criteria have been developed for clinical and research purposes. The 2009 American Heart Association/American College Cardiology Foundation/Heart Rhythm Society listed as many as 35 ECG-LVH criteria based on the following: limb lead voltage; precordial lead voltage; combinations of limb and precordial voltage; combinations of voltage and nonvoltage criteria; specific criteria for patients with left anterior fascicular block and right bundle-branch block [11]. However, the existence of so many criteria for LVH diagnosis tends to limit their application in daily practice. Moreover, the sensitivity of ECG criteria is limited, as documented in numerous studies based on the

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simultaneous estimation of left-ventricular mass by echocardiography or less often by computerized tomography or magnetic resonance. In a systematic review of 21 studies carried out in the hypertensive setting aimed at assessing the accuracy of six ECG-graphic criteria compared to echocardiography Pewsner *et al.* [12] found that the median sensitivity ranged from 10.5% for the Gubner index to 21% for the Sokolow-Lyon index and the median specificity ranged from 89% for the Sokolow-Lyon index to 99% for the Romhilt-Estes score. Multiple factors other than left-ventricular size or mass have been shown to influence the amplitude of QRS voltages and negatively impact the diagnostic value of ECG criteria. They include biologic and methodological ECG variability (this latter substantially depending on sites of electrodes application), age, sex, race and body size. In the Ikaria study the age-dependent performance of ECG criteria in predicting LVH, as assessed by echocardiographic left-ventricular mass indexed to either body surface area or height$^{2.7}$, was examined in a population-based sample of 570 middle-aged and 507 elderly participants [13]. The Cornell voltage had a higher sensitivity against echocardiographic left-ventricular mass indexed to height$^{2.7}$ in middle-aged participants compared to elderly ones; the opposed trend was observed for the Sokolow-Lyon voltage. Of note, when echocardiographic LVH was defined by indexing left-ventricular mass to body surface area, the age-related differences in sensitivity between ECG criteria lost their statistical significance. Taken together these observations indicate that age should be taken into account in the selection of ECG criteria for LVH detection in the general population and indexation criteria of echocardiographic left-ventricular mass may influence the sensitivity of ECG criteria. Sex may also affect the ability of ECG criteria to detect LVH due to sex-related differences either in body size as in left-ventricular compensatory responses to chronic pressure overload. For instance, the upper limit of QRS voltage is slightly lower in adult women as compared with men, even after adjustment for body size and cardiac mass. In the Losartan Intervention For Endpoint study, ECG-LVH defined by Cornell product was more frequently observed in women; in contrast, the Sokolow-Lyon voltage criterion was more frequently positive in men [14]. This finding has been recently confirmed by Barrios *et al.* [15] in a group of 264 patients with mild to moderate hypertension. These sex differences may be related to the application of sex-specific diagnostic cut-offs in the Cornell product criterion, as opposed to the use of a single nonsex-specific partition value in the Sokolow-Lyon voltage.

Obese individuals have larger echocardiographic left-ventricular masses, but lower ECG-graphic QRS voltages in comparison to nonobese counterparts. The amount of thoracic adipose tissue tends to reduce QRS voltage by increasing the distance between the heart and electrodes on the chest wall. Obesity may differently impact the diagnostic accuracy of ECG criteria. In a study conducted in 852 nonobese and 352 obese hypertensive patients the Sokolow-Lyon voltage and Romhilt-Estes criteria as well as the strain pattern had a reduced sensitivity in obese patients, whereas the Cornell voltage, Cornell product, Perugia score and aVL R-wave overall exhibited a similar diagnostic accuracy in both groups [16]. Dominiek-Karlowicz *et al.* [17] evaluated the performance of 11 ECG criteria in detecting echocardiographic-documented LVH in 95 severely obese patients (body mass index $\geq$40 kg/m^2) before elective bariatric surgery. The authors found that none of the voltage-based criteria was of value for diagnosing LVH; also the Cornell product showed a very low sensitivity.

The disagreement between left-ventricular mass estimated by echocardiography as well as other cardiac imaging techniques and ECG findings is mostly related to the intrinsic limitations of ECG performance; it should be noted, however, that ECG provides no direct measurements of left-ventricular mass but only indirect evidence about changes of cardio-electric properties associated with the hypertrophic process [18]. Notably, ECG-LVH and echocardiographic-LVH have been documented to predict cardiovascular and all-cause mortality independently from each other and from other cardiovascular risk factors. The different prognostic indications provided by these cardiac phenotypes further support the combined value of ECG-LVH and echocardiographic LVH for improving cardiovascular risk stratification [19,20].

NEW INSIGHTS FROM THE STUDY BY GOSSE *ET AL.*

In their study Gosse *et al.* examined the association of multiple ECG indexes (i.e. QRS voltage, QRS duration and QRS voltage-duration product) with left-ventricular mass and the risk of cardiovascular disease in 958 uncomplicated, untreated hypertensive patients (mean age 48 years, 61% men) from the Bordeaux cohort with a relatively high 41% prevalence of LVH as defined by the nonsex-specific echocardiographic partition value of 51 g/h$^{2.7}$.

The main findings of the study can be summarized as follows: the amplitude of R-wave in lead aVL showed the closest correlation with left-ventricular mass among the eight ECG criteria included in the analysis, followed by the product aVL R-wave$*$QRS duration and Cornell voltage; similar behavior was observed for the ability of ECG criteria to identify left-ventricular mass changes during the follow-up period; height of R-wave in aVL was the best predictor of incident cardiovascular events in terms of sensitivity and specificity, as suggested by the receiver-operating characteristic (ROC) curves analysis, compared with the remaining ECG voltages.

These results are in keeping with previous findings from a hypertensive cohort without ECG-graphic signs of LVH [21] and extend the observation to a mixed population of individuals with and without ECG-LVH, who more closely reflect the 'real word'. These results reinforce the value of a simple ECG criterion for stratifying cardiovascular risk in clinical practice. It should be noted that in the above-mentioned study by Verdecchia *et al.* [21] the aVL R-voltage value displaying the best compromise between sensitivity and specificity in predicting cardiovascular events was 5.7 mm, a value close to the 6.0 mm voltage identified by ROC curves analysis as the best LVH predictor in the study by Gosse *et al.* [1]. Thus, a nonsex-specific threshold of 6.0 mm may be considered a reliable ECG criterion for

identifying high-risk hypertensive individuals. The better performance of R-voltage in aVL lead in detecting LVH and in predicting cardiovascular risk as compared to more complex and time-consuming ECG criteria as documented in both studies may be ascribed to the fact that either R-voltage mostly reflects the vectors originating from left-ventricular activation or the amplitude of precordial voltages tends to decrease in the presence of obesity, lung and thoracic diseases.

A few aspects and limitations of this study deserve to be mentioned. Additional analyses focusing on sex influence on the relationship between ECG criteria and left-ventricular mass did not show significant differences between men and women. The superior ability of aVL R-wave in detecting LVH was independent of age, as shown by the analysis across three different age strata. In a clinical perspective, this implies that the index can be effectively applied independently of sex and age categories. It is also important to underline that intra-reader and day-to-day variability was lower for R in aVL as compared to other leads and calculated indexes.

Unfortunately, the results of the present study cannot be extended to hypertensive patients with prevalent cardiovascular disease, renal insufficiency, older age and from different racial samples. Furthermore, as the relationship between left-ventricular mass and ECG changes during the follow-up period was based on data collected only in a small fraction of patients (14%), this aspect of the study should be considered with caution. Finally, no information was provided about the performance of R-voltage in aVL according to body mass index.

In conclusion, the study by Gosse *et al.* provides good news for clinicians taking care of hypertensive patients in their everyday practice by showing that the simple assessment of R-wave voltage in lead aVL has a greater diagnostic value in detecting LVH and estimating cardiovascular risk than other more complicated, time-consuming and less reproducible ECG criteria. This approach, simpler and much less expensive than others, may thus allow clinicians to detect cardiac organ damage in hypertensive patients and to identify the high or very-high-risk category more easily.

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Conflicts of interest

The authors report no conflicts of interest.

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