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Conventional and new electrocardiographic criteria for hypertension-mediated cardiac organ damage: A narrative review

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Abstract

Hypertension-mediated organ damage (HMOD) is frequently observed in hypertensive patients at different cardiovascular (CV) risk profile. This may have both diagnostic and therapeutic implications for the choice of the most appropriate therapies. Among different markers of HMOD, the most frequent functional and structural adaptations can be observed at cardiac level, including left ventricular hypertrophy (LVH), diastolic dysfunction, aortic root dilatation, and left atrial enlargement. In particular, LVH was shown to be a strong and independent risk factor for major CV events, namely myocardial infarction, stroke, congestive heart failure, CV death. Thus, early identification of LVH is a key element for preventing CV events in hypertension. Although echocardiographic assessment of LVH represents the gold standard technique, this is not cost-effective and cannot be adopted in routine clinical practice of hypertension. On the other hand, electrocardiographic (ECG) assessment of HMOD relative to the heart is a simple, reproducible, widely available and cost-effective method to assess the presence of LVH, and could be preferred in large scale screening tests. Several new indicators have been proposed and tested in observational studies and clinical trials of hypertension, in order to improve the relatively low sensitivity of the conventional ECG criteria for LVH, despite high specificity. This article reviews the differences in the use of the main conventional and the new 12 lead ECG criteria of LVH for early assessment of asymptomatic, subclinical cardiac HMOD in a setting of clinical practice of hypertension.

1 | INTRODUCTION

Essential hypertension (HTN) is one of the most common modifiable risk factors in the general population, being strongly and independently related to an increased risk of cardiovascular (CV) morbidity and mortality, independently by age and gender.[1] Indeed, high blood pressure (BP) levels are associated with increased risk of major CV outcomes, including myocardial infarction, stroke, congestive heart failure (CHF), and CV death.[1] In view of the progressive aging of the population, as well as of the increasing prevalence of CV and metabolic risk factors and comorbidities, early detection and prompt control of HTN represent key elements for reducing

CV morbidity and mortality in both high- and low-income countries. Recent observations, however, seem to suggest that lowering BP levels to targets may not be sufficient to reduce CV risk related to HTN.[2]

Clinical studies have consistently reported a high prevalence of markers of HTN-mediated organ damage (HMOD) among hypertensive patients at different CV risk profile.[3-5] These markers include structural and functional changes, mainly involving kidneys, arteries, brain, and heart.[6,7] At cardiac level, left ventricular hypertrophy (LVH) represents the main factor associated with a worse CV prognosis.[8]

From a pathophysiological point of view, persistently elevated BP levels are recognized to produce a hemodynamic overload, leading to functional adaptations and structural changes of LV geometry, which may, in turn, result into an increased LV mass and remodeling.[9,10] These adaptations, as well as the interactions with genetic, biochemical, neuro-hormonal, and metabolic factors, are responsible for the development of LVH.[11-13] Once established, LVH tends to promote the occurrence of unfavorable cardiac effects, such as atrial and ventricular arrhythmias, myocardial stiffness, diastolic dysfunction, reduced coronary blood flow, coronary artery disease, and congestive heart failure.[14] Therefore, given these clinical consequences, current HTN guidelines recommend to perform systematic global CV risk assessment in each individual patient with high BP, including the detection of LVH.[15]

Worldwide, the most common first-line method to evaluate LVH is the 12-lead conventional electrocardiography (ECG), due to its widespread availability, favorable cost-effective ratio and its ease of performance.[16] One of the major limitations of ECG screening, however, is the well-known relatively low sensitivity, despite a high specificity, with regard to the assessment of LVH,[17] mostly in special populations, such as obesity group.[18] In addition, the lack of concordance among the currently available ECG criteria for LVH, mostly related to the different thresholds and leads proposed by different criteria, may induce contrasting data on its prevalence and clinical implications.

Such improper diagnostic and therapeutic approach in daily clinical management of hypertensive outpatients.[19,20] On the basis of these considerations, the aim of this narrative review is to discuss the main conventional and novel 12-lead ECG criteria for the assessment of LVH, in order to improve the diagnostic work-up in hypertension.

1.1 | Pathophysiology of left ventricular hypertrophy in essential hypertension

1.1.1 | Early stages of left ventricular hypertrophy

Left ventricular hypertrophy is a maladaptive response to hemodynamic overload and neuro-hormonal imbalance that can be observed at cardiac level in hypertensive patients.[21-23] In the early stages of HTN, LVH counterbalances the abnormal cardiac wall stress, whereas in the subsequent stages of the disease, long-standing and elevated BP may lead to an increase of LV wall thickness without altering LV mass.[21-23] This condition is referred as concentric LV remodeling, and may lead toward the development of subsequent stages of LVH, which have been related to markedly higher risk of major CV complications compared to LV remodeling or normal LV geometry.[24-26]

Although the mechanisms underlining this process have not been fully elucidated, several studies demonstrated that it is mainly characterized by both in parallel growth of new sarcomeres along the longitudinal axes, thus expanding the cross-sectional area of myocytes, and by the deposition of new fibrous tissue in the interstitial compartment.[24-26] Diwan et al (2007) showed that the workload of this process requires an elevated oxygen consumption; therefore, LVH is eventually vulnerable to decompensation.[27]

1.1.2 | Non-hemodynamic factors for left ventricular hypertrophy

It should be also noted, however, that other non-hemodynamic factors may substantially contribute to modulating the hypertrophic response of the LV.[28] Among these factors, abnormal neuroendocrine stimulation plays a major role in the development and progression from normal LV geometry toward LVH.[29] Grassi G et al (2006) demonstrated that the sympathetic nervous system, activated by mineralocorticoids, leads to baroreceptor dysfunction, impaired arterial compliance, abnormal myocardial, vascular fibrosis, metabolic effects (eg, insulin resistance).[30] All these factors may promote development and progression of LVH.[30] On the other side, the activation of the renin-angiotensin-aldosterone system (RAAS)[31,32] and the imbalance of endothelin-1[33,34] and natriuretic peptides[35] network is also responsible for the generation of reactive oxygen species, vascular inflammation, and cardiac remodeling, which further promote this abnormal response to increased BP load. In particular, current evidence suggests that the RAAS significantly contributes to the development of diastolic dysfunction in HTN and plays an important role in its progression toward CHF by promoting an increase in collagen production with a subsequent enhancement of myocardial fibrosis and stiffness.[36]

1.1.3 | Subsequent stages of left ventricular hypertrophy

Although LVH is initially an adaptive process to the increased pressure overload, the presence of LVH is also the primary element responsible for the progression from HTN to hypertensive heart disease (HHD).[37] Indeed, the prototypal outcome of HHD progression is the well-known "burned-out" effect of the LV.[14,38] This process is characterized by an evolution from LVH associated with diastolic dysfunction, abnormal LV relaxation, and impaired filling properties, toward LV enlargement and systolic dysfunction.[36,39] Thus, HHD includes a wide range of clinical manifestations from asymptomatic LVH to symptomatic CHF, which, in turn, may occur as preserved ejection fraction (HFpEF > 50%), mid-range ejection fraction

(HFmEF 40%-50%), and reduced ejection fraction (HFrEF < 40%).[40] It should be also noted, however, that echocardiographic assessment of LVH has distinct prognostic value with respect to that obtained by ECG-detected LVH.[41,42]

1.2 | Hypertension-induced LVH and related cardiovascular complications

Left ventricular hypertrophy is an independent risk factor for CV morbidity and mortality.[43-45] It has been also related to a significantly higher and independent risk of non-fatal CV events, including arrhythmias, coronary artery disease, myocardial infarction, peripheral atherosclerotic disease, and CHF.[46]

One of the most frequent HTN-induced LVH complications is represented by the development of cardiac arrhythmias, which may be related to intrinsic modifications of the cardiac vasculature and structure, thus leading to an increased risk of sudden cardiac death and CHF.[47,48] The increased amount/accumulation of fibrous tissue represents the main cause of the genesis of arrhythmias.[48] The large amount of extracellular collagen deposition can lead to side-to-side electric coupling alterations between myocardial fibers, thus resulting in irregular cardiac contraction, increased dispersion of repolarization, and a vast array of intraventricular electrical pathways. Each one facilitates micro-re-entry and promotes arrhythmogenesis.[49]

Among supraventricular arrhythmias, atrial fibrillation is the most common electrical alteration in LVH patients. Instead, among ventricular arrhythmias, sustained ventricular tachyarrhythmia is considered the major cause of death in patients with LVH.[50] Once sustained and malignant ventricular arrhythmias have established, the risk of sudden cardiac death increases. In a recent meta-analysis, the incidence of ventricular arrhythmias was 5.5% in patient with LVH compared to 1.2% in patients without LVH. In addition, a recent study reported LVH as a potential risk stratification factor due to its association with sudden cardiac death.[51]

In the setting of HTN, proliferation and hypertrophy of the vascular smooth muscle cells can be observed, thus resulting in vascular wall thickening and consequently leading to a reduced coronary flow reserve.[52] These structural (vascular) changes along with low coronary blood flow can increase the risk of acute coronary syndrome and myocardial infarction.[53-55] Changes of extracellular matrix which promoted vascular dysfunction, as well as impaired mechano-elastic properties of cardiac myocytes, may culminate in the development of diastolic dysfunction.[56]

Furthermore, several studies underlined the importance to consider ECG-related LVH criteria as markers of electrical anomalies, because their presence is associated with a marked increase in severity of the disease and its complications, whereas the reduction of the ECG-detected LVH bears a more favorable prognosis.[57]

1.3 | Conventional electrocardiographic criteria for left ventricular hypertrophy

Several ECG criteria have been proposed for the diagnosis of LVH in a setting of clinical practice, mostly based on QRS voltage criteria

TABLE 1 Main electrocardiographic criteria for detection of left ventricular hypertrophy

Criterion	Definition	Cutoff values
Lewis voltage	R in I + S in III − R in III − S in I	≥17 mm
Gubner-Underleider voltage	R in I + S in III	≥25 mm
Sokolow-Lyon voltage	S in V1 + R in V5/V6	≥35 mm
R in aVL voltage	R in aVL	>11 mm
Cornell voltage	S in V3 + R in aVL	>20 mm (men); 28 mm (women)
Cornell product	(S in V3 + R in aVL) x QRS duration (msec)	≥2440 mm*msec
Romhilt-Estes score	0-7 items, including: (1) R or S wave in the limb leads ≥20 mm; or S wave in V1 or V2 ≥ 30 mm; (2) R wave in V5 or V6 ≥ 30 mm (3 points); (3) left atrial involvement—terminal deflection of P wave in V1 is 1 box wide, and 1 box deep or more (3 points); (4) left axis deviation; (5) QRS duration ≥ 0.09 second (1 point); (6) Intrinsicoid deflection in V5 and V6 ≥ 0.05 second (1 point); (7) ST-T segment changes (LV strain)	≥5
Left ventricular strain	ST segment depression and T wave inversion	
Framingham criterion	Left ventricular strain + at least one voltage criterion (R in aVL or Gubner-Underleider or Sokolow-Lyon or S in V1/V2 ≥ 25 mm or R in V5/V6 ≥ 25 mm)	
Perugia criterion	Left ventricular strain and/or Cornell voltage and/or Romhilt-Estes score ≥5	
VAT	Time interval between the beginning of the QRS complex to the peak of the R wave	>0.05
Tp-Te Interval	Time interval between the peak and the end of the T wave in one precordial lead (mostly V5)	Not available

(Table 1).[17] Sensitivity and specificity of different criteria have been discussed elsewhere.[58] Schematic representation of main conventional ECG criteria used so far has been reported on Figure 1 (panel A). Although negativity of the ECG criteria does not mean that anatomic LVH is ruled out, due to the low sensitivity of this method, they are considered a valid and independent prognostic marker of cardiac organ damage and increased CV risk.[15]

One of the most historically reliable ECG criterion is the Sokolow-Lyon voltage, which can be obtained by the sum of S wave detected in V1 lead and R wave measured in V5/6 leads (positive: ≥35 mm).[17]

This is characterized by relatively low sensitivity and high specificity. Among other criteria, Gubner-Ungerleider and Framingham[59] criteria have a very low sensitivity, although high specificity.[58] Similarly, Lewis voltage and the R wave in V6 lead/R wave in V5 lead ratio have high specificity and low sensitivity.[60]

The criterion with the highest specificity (98% in men and 95% in woman) is the Cornell Voltage, which can be derived by the sum of S wave in V3 and of R wave in aVL (positive: >28 mm in men, >20 mm in woman).[61] Analysis of the Framingham cohort reported a relatively low sensitivity of this criterion in this population (about 10% in men
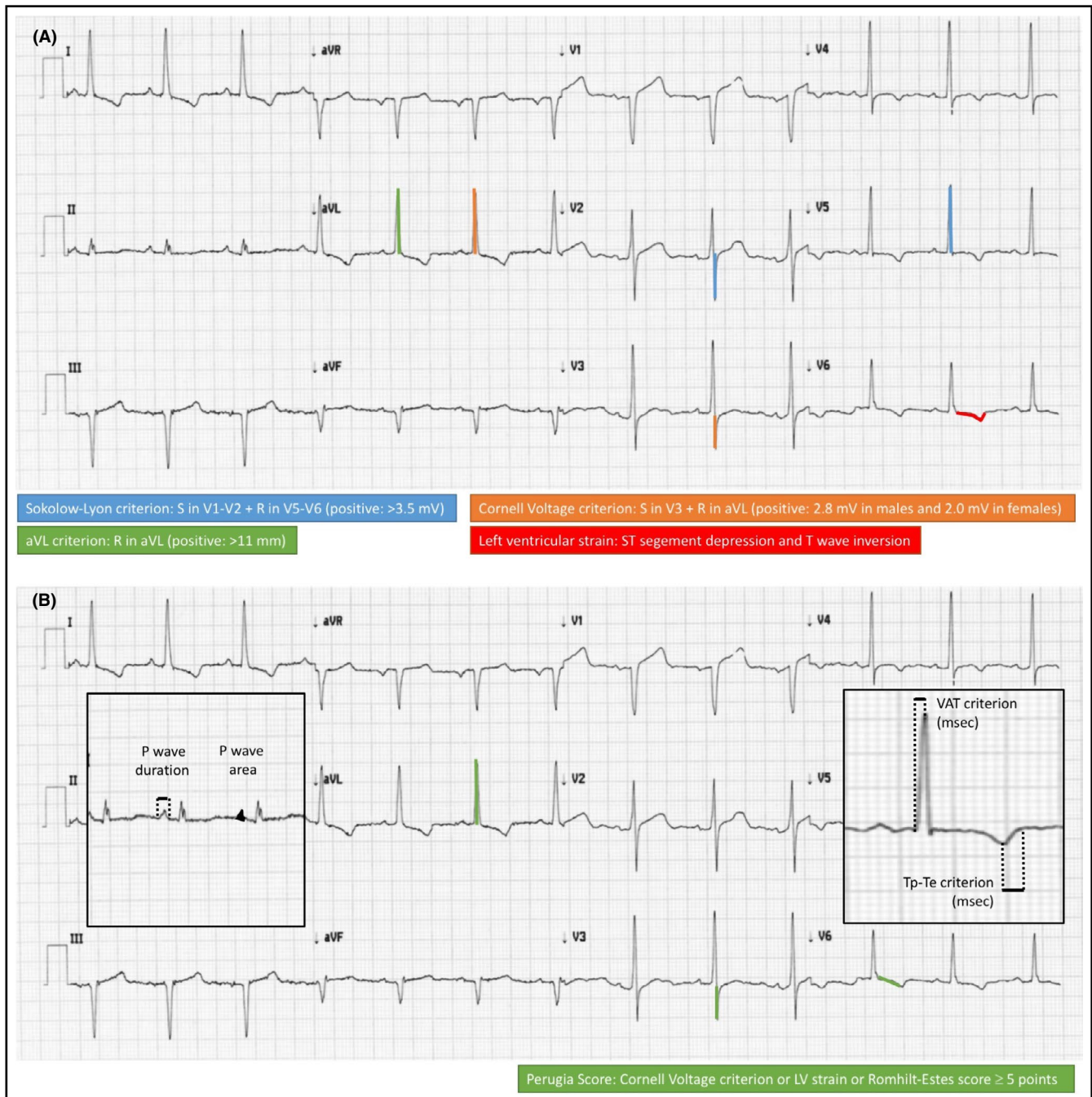

FIGURE 1 Illustrative representation of conventional (panel A) and novel (panel B) criteria for electrocardiographic detection of left ventricular hypertrophy

and 22% in woman).[24] Later, the Cornell product criterion (which is the Cornell Voltage criterion multiplied for the QRS duration; positive: >2.4 mV) has demonstrated to provide better sensitivity and specificity than those provided by Cornell Voltage in a large cohort of hypertensive patients with ECG evidence of LVH.[62]

Lately, the Romhilt-Estes score includes the following points[63]: (1) the R or S wave in the limb leads greater than or equal to 20 mm; or S wave in V1 or V2 greater than or equal to 30 mm; (2) R wave in V5 or V6 greater than or equal to 30 mm (3 points); (3) left atrial involvement—terminal deflection of P wave in V1 is 1 box wide, and 1 box deep or more (3 points); (4) left axis deviation—QRS axis is −30 degrees or more negative (2 points); (5) QRS duration greater than or equal to 0.09 second (1 point); (6) Intrinsicoid deflection in V5 and V6 greater than or equal to 0.05 second (1 point); (7) ST-T segment changes ("LV strain" = ST-T vector shifted opposite to QRS vector): without digitalis (3 points) or with digitalis (1 point). Indeed, it incorporates abnormalities in QRS axis, duration, amplitude, QRS onset-to-peak time, P wave, ST-T morphology.

However, a recent systematic review reports that conventional ECG criteria should not be used to rule out the presence of LVH in patients with HTN, because of their low sensitivity.[64]

1.4 | New electrocardiographic criteria for left ventricular hypertrophy

Over the last few years, several new ECG criteria have been proposed and tested in relatively small studies including both normotensive individuals and hypertensive outpatients, in order to overcome the intrinsic limitations of the above mentioned conventional ECG criteria and improve diagnostic accuracy of ECG detection of LVH.[65,66] Illustrative representation of novel criteria for ECG detection of LVH are shown in Figure 1 (panel B).

Among these new criteria, the Perugia criterion has firstly been introduced to ameliorate the sensitivity of ECG findings for LVH diagnosis.[66] It includes at least one of the following: S wave in V3 lead + R wave in aVL lead >24 mm (men) and >20 mm (women) or LV strain or Romhilt-Estes score ≥5 points, yielded values of sensitivity, specificity, and accuracy of 34%, 93%, and 73%, respectively, in subjects with uncomplicated essential hypertension.[60] This criterion was firstly tested in a clinical study aimed at comparing the accuracy and prognostic value of different ECG criteria by including 1717 Caucasian adult hypertensive patients, who were prospectively followed up for up to 10 years (mean 3.3) in Italy.[67] At entry, the prevalence of LVH was 17.8% (Perugia score), 9.1% (Cornell), 3.9% (Framingham), 5.2% (Romhilt-Estes), 6.4% (strain), and 13.1% (Sokolow-Lyon).[67] During follow-up event rate of major CV events was higher in the subjects with than in those without LVH (all P < .001) according to any criteria, with the only exception of the Sokolow-Lyon index.[67] At multivariate analysis, an independent association between LVH and CV risk was observed for both the Perugia score (hazard ratio [HR] 2.04, 95% confidence interval [CI] 1.5-2.8) and the Framingham (HR 1.91, 95% CI 1.1-3.2), Romhilt-Estes (HR 2.63, 95% CI 1.7-4.1) and strain methods (HR

2.11, 95% CI 1.4-3.2).[67] However, Perugia score showed the highest population-attributable risk for CV events, accounting for 15.6% of all cases, whereas the Framingham, Romhilt-Estes and strain methods accounted for 3.0%, 7.4%, and 6.8% of all events, respectively. In particular, LVH diagnosed by the Perugia score was associated with an increased risk of CV mortality (HR 4.21, 95% CI 2.1-8.7).[67]

Another important prognostic index is the value of R wave in aVL lead (positive: ≥11 mm),[68] which has been also recommended by the latest set of European guidelines on HTN.[15] Indeed, recent studies have demonstrated the importance of R wave in aVL due to its significant correlation with the LV mass.[61,68] Moreover, significant correlation between QT interval and LVH has been observed in several studies. In the CARdiovascular Living and Ageing in Halle (CARLA) study, prolonged QT interval adjusted for heart rate (QT corrected, QTc) >500 ms was associated with increasing LV mass.[69]

In the few last years, new parameters, closely related to an increased LV mass, LV diastolic dysfunction and risk of cardiac arrhythmias, have been proposed. These parameters include the time interval between the peak and the end of the T wave (Tp-Te) [70] and ventricular activation time (VAT).[71]

In the Tp-Te interval, the peak of the T wave represents the end of the epicardial action potential, whereas the end of the T wave represents the end of the mid-myocardial action potential, thus reflecting the transmural dispersion of repolarization.[70] Despite the fact that a clear cutoff value has not been established yet, longer Tp-Te interval has been observed in untreated hypertensive outpatients than in normotensive individuals, being significantly related to increased LV mass and high 24-hour ambulatory BP levels.[72] Moreover, prolonged Tp-Te (91 ± 12.24 vs 74 ± 9.96; P < .001), Tp-Te/QT (0.24 ± 0.027 vs 0.20 ± 0.025; P < .001) and Tp-Te/QTc (0.22 ± 0.023 vs 0.18 ± 0.023; P < .001) were significantly increased in non-dipper hypertensive patients than dippers with metabolic syndrome.[73] In addition, abnormal Tp-Te interval has been reported in patients with coronary artery disease.[74-76] Indeed, a more recent analysis from the PAMELA study has shown that Tp-Te interval is independently correlated with an increased risk of CV events.[77] It should be noted, however, that in this latter study, Tp–Te measurements were adjusted for heart rate using the modified Bazett's formula, that is $cT_p - T_e = \sqrt{T_p - T_e}/RR$ interval.

Available evidence has also demonstrated that Tp-Te interval may be considered a reliable measure of transmural dispersion of the LV repolarization, which is increased in LVH and responsible for the increased risk of arrhythmogenesis.[78] In recent clinical studies, the Tp-Te interval has been analyzed in the precordial leads, particularly V5,[72] and this might be responsible for the higher able to detect the diffusion of the electrical field through the ventricle walls. The choice to use the precordial leads as the main referral gives a high sensitivity to the Tp-Te interval with respect to the peripheral leads, where this interval may represent a dispersion index of the global repolarization, by including the apical-basal and the interventricular dispersion.[79] An increased LV transmural

dispersion is linked to a high probability of developing cardiac arrhythmias, because the repolarization dispersion and the refractory time may be at a short distance to each other, thus generating a very rapid repolarization gradient.[80,81] Thus, it is the rapidity of the repolarization gradient that determines the arrhythmogenesis potential rather than the total width of the dispersion. The apical-basal or the interventricular dispersion, in this context, may be less indicative, since it may be or not be associated to a rapid repolarization gradient with or without the associated risk of arrhythmogenesis. Further, the Tp-Te interval is considered as a predictive index of ventricular tachyarrhytmias [82] and of an high risk of mortality in patients with LQTS, Brugada syndrome [83] and in patients treated with primary coronary intervention after 1 year from the ischemic event.[84]

Other finding of a recent study showed that smoking is associated with hyperactivity of the sympathetic system and LV repolarization abnormalities, including abnormal Tp-Te interval, thus contributing to the increasing prevalence of ventricular arrhythmias among smokers.[85] The clinical significance of Tp-Te interval justifies the need of additional studies to better clarify its prognostic value in terms of CV risk.

Another not conventional parameter recently found is the intrinsicoid deflection or the ventricular activation time (VAT).[71] It is the time required by the ventricle to depolarize and it can be estimated by measuring the interval from the beginning of the QRS complex to the peak of the R wave. In a recent study, VAT was considered as a potential marker for diastolic dysfunction, one of the major cardiac functional alteration in the course of hypertension.[71] A value of VAT in V5 and V6 >0.05 seconds is a criterion used in the Romhilt-Estes score regarding the LVH. It has been shown that an increase of VAT is associated with an increase in atrial and septum diameters, an increase in left ventricle mass index and a low e' velocity at TDI, besides a minor e'/a' ratio at the echocardiography.[71]

Finally, it has been evaluated also the P wave, since in literature it has been correlated at the echocardiographic level to left atrial alteration, which is associated with the presence of left ventricular diastolic dysfunction. In particular, four criteria (average duration, maximum duration, dispersion, and area of the P wave) are increased in patients with diastolic dysfunction and in patients with left atrial diameter >40 mL/m^2 respect to those without diastolic dysfunction and a left atrial volume <40 mL/m^2, by attributing to P wave parameters a predictive role of increased risk of left atrial enlargement, LV diastolic dysfunction and atrial arrhythmias.[86]

2 | PERSPECTIVES AND CONCLUSIONS

Electrocardiographic assessment of LVH represents an easy to perform, widely available, repeatable, and cost-effective method to assess the presence of LVH in the setting of clinical practice of HTN. In view of the mounting prevalence of HTN at global level, we suggest that this method is used in large screening evaluations of hypertensive patients, as also recommended by current guidelines. Up to date, several studies have been performed to assess the most reliable ECG criteria to diagnose LVH and to prevent its related complications. On the basis of the currently available evidence, several new ECG criteria can be proposed for being applied in routine practice, among which the assessment of Tp-Te interval can be considered one of the most promising tool for early identification of electrophysiology risk in hypertensive patients with LVH. However, further studies are needed to improve and ameliorate the prognostic relevance of these new ECG criteria, as well as to test the potential effects of different antihypertensive therapies on ECG-detected LVH regression and CV prognosis.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

Francesca Miceli: involved in conception and design, drafting, and reviewing the manuscript. Vivianne Presta: involved in data searching and reviewing the manuscript. Barbara Citoni: involved in data searching and reviewing the manuscript. Flaminia Canichella: involved in data searching and reviewing the manuscript. Ilaria Figliuzzi: involved in data searching and reviewing the manuscript. Andrea Ferrucci: reviewed the manuscript. Massimo Volpe: reviewed the manuscript. Giuliano Tocci: involved in conception and design, drafting, reviewing and approving the final proofs.

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