Left ventricular electromechanical function
Ventricular depolarization (the QRS complex

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Background

QRS duration and morphology are key diagnostic and prognostic determinants in several cardiac pathological conditions. Despite the widespread use of noninvasive imaging techniques, the assessment of left ventricular (LV) hypertrophy and the prognostic evaluation of patients with heart failure still rely on the QRS morphology. In these conditions, electrocardiography (electric) and echocardiography (mechanical) are complementary tools for defining anatomical and functional cardiac disturbances.

QRS morphology and left ventricular dimensions

QRS duration is the time required for myocardial depolarization down the Hiss-Purkinje system then throughout the myocardium. Clinical studies in individuals without heart failure have demonstrated that the QRS duration, both within and above the normal reference range, was directly related to LV mass and volume measured by echocardiography or cardiac magnetic resonance.[1,2] All patients included in those studies had LV mass within the normal values[3], suggesting that QRS duration is related to physiological increase in mass in normal cardiac structure and function which is quite different from the pathological cardiac hypertrophy.[4]

The effect of LV anatomical dimensions on the QRS morphology are influenced by several factors, including age, gender, race, body habitus, as well as pathological conditions such as ischemic heart disease, cardiomyopathies, infiltrative myocardial disease, myocardial fibrosis and pulmonary disease.[5] Acute fall in blood volume and consequently LV dimensions and volumes affect QRS morphology and causes increased amplitude, both in normal individuals and in hemodialysis patients.[6-8] The opposite occurs with rapid increase in LV dimensions which results in reduction in QRS amplitude.[9] These electrocardiographic changes are opposite to those expected according to the Brody effect on the relation between the body surface potential and intraventricular blood volume.[10] However, the exact mechanism underlying these changes of QRS morphology is not fully understood.

Another measure of QRS is its duration. This has been proposed to be related to the anatomic position of the papillary muscles in healthy individuals.[11] With the anterior and posterior fascicles of the left bundle branch course toward the papillary muscles, their relative distance from the lateral ventricular wall has been postulated to be directly related to QRS duration on the basis of longer distance for the electrical wave-front to travel before reaching LV lateral wall. This method has been proposed for prediction of individual normal QRS duration, thus distinguishing abnormal QRS duration from normal variants.[12,13]

LVH is a well-established independent risk factor for heart failure, coronary heart disease, stroke, arrhythmias, sudden cardiac death and cardiovascular and all-cause mortality.[14] It is not a simple adaptive process of the LV to pressure overload but is considered a marker of preclinical organ damage. Regression of LVH is associated with lower cardiovascular event rates independent of the degree of blood pressure reduction or other risk factors.[15-17] Therefore, detection of LVH has significant clinical relevance for the assessment of the cardiovascular risk and management strategy.

LVH has been conventionally assessed for over forty years. The Framingham Heart Study showed that ECG evidence of hypertrophy was associated with a threefold increase in symptomatic coronary heart disease and sudden cardiac death, even after adjusting for associated hypertension.[18] Subsequent studies confirmed that ECG derived LVH is an independent cardiovascular risk factor both in general population and in hypertensive patients. [19-21]

Clinically, the use of ECG in the diagnosis of LVH has been used to estimate myocardial mass. Several ECG criteria developed for diagnosing LVH,[5] which assume that the increase in QRS voltage and duration reflect an increase in the activation front of the electrical impulse due to an enlarged LV and a prolongation of the time required for an electrical impulse to pass through a thickened ventricular wall. [22] However, none of these criteria had been shown to have high diagnostic accuracy. In addition, using such criteria in clinical practice resulted in high percentage of false negative (normal ECG criteria for LVH in the presence of anatomical hypertrophy) cases due to low sensitivity (the proportion of positive LVH criteria when there is anatomic hypertrophy) ranging between 0 and 68%[23-25] and specificity (the proportion of negative LVH criteria when there is no anatomical hypertrophy) ranging between 53 and 100%. This is also consistent with high percentage of false positive (ECG criteria for LVH with no anatomical hypertrophy) diagnoses, especially in populations where the true prevalence of anatomical hypertrophy is low.[26] The level of false negative and false positive results reflect the discordance between ECG derived LVH and ventricular hypertrophy detected by echocardiography or magnetic resonance imaging, which are considered the reference standards for the assessment of LV mass. Overall, the agreement between ECG LVH criteria and echo LVH is rather low.[24,25] This raises doubt about the importance of LV mass as the only or the main factor influencing ECG diagnosis of LVH.

Two kinds of observations may help explaining the different role of ECG and imaging in diagnosing LVH. It has been reported that ECG changes can precede the development of myocardial hypertrophy in relatives of patients with hypertrophic cardiomyopathy, in young athletes and in patients with Duchenne muscular dystrophy. [27-29] More importantly, evidence exists with respect to the independent accuracy of ECG and imaging criteria of LVH in predicting death from cardiovascular disease.[30-32] Similar observations have been made in patients free of objective cardiovascular disease, who developed atrial fibrillation. In these patients, ECG markers of LVH had prognostic significance, independent of LVH detected by cardiac magnetic resonance.[33] Taken together, these data may indicate that ECG and imaging markers of LVH reflect different pathological conditions, each with specific characteristics, but with some overlap between the two (Figure). [34,35]

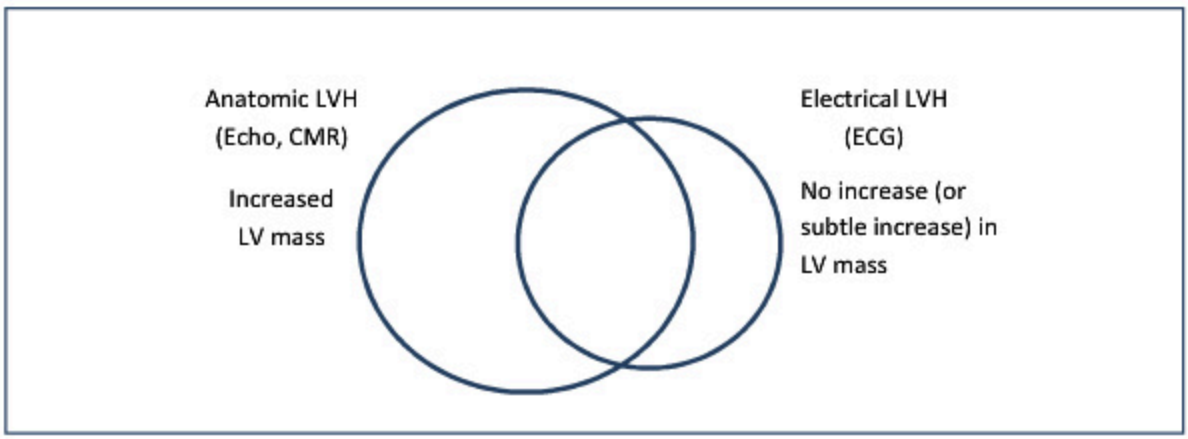

Figure: Overlap between anatomic LVH detected by echocardiography or cardiac magnetic esonance and electrical LVH detected by ECG. From[34] modified.
LVH: left ventricular hypertrophy, CMR: cardiac magnetic resonance

Ventricular hypertrophy represents a complex remodeling of the myocardium including structural, biochemical and electrical changes.[4] In addition to increased anatomical LV mass, the myocytes hypertrophy, cell apoptosis and interstitial fibrosis modify the electrophysiological properties of the myocardium determining an electrical remodeling. The main features are an increase in the action potential duration and a decrease in conduction velocity. [36-38] A model study showed that these electrophysiological changes produced QRS patterns consistent with those observed in LVH, even if the myocardial mass did not exceed the defined upper normal limits.[39] Thus the alteration of the sequence of electrical activation may account for the prolonged QRS duration, left bundle branch block and left anterior fascicular block frequently seen in patients with LVH.[40] Moreover, local non-uniform myocardial differences in these changes create the substrate for micro-reentry circuits which may trigger and maintain the arrhythmias.[41]

Therefore, the traditional association between increased anatomical LV mass and increased QRS amplitude would occur only in an "ideal hypertrophy" where the anatomical and electrical changes are uniformly distributed throughout the myocardium.[42] In real LVH, the QRS amplitude changes can result from a combination of anatomical and electrical remodeling. This is in accordance with the solid angle theory: the potentials recorded on the body surface depend on spatial determinants which are directly related to the anatomy of the heart, therefore detected by imaging, and non-spatial determinants which are related to the electrical properties of the myocardium. [43,44] Since LVH results in substantial electrical myocardial changes even before an appreciable increase in LV mass, the QRS changes cannot be expected to be in agreement with imaging diagnostics. In this context the false negative ECG results are not really "false". The electrical remodeling may

result in a reduction of the electrical field in the hypertrophied myocardium compared to the normal one. As a consequence, the QRS voltage is lower than expected according to the increased LV mass. This "relative voltage deficit" may contribute to the discrepancies between ECG and imaging assessment of LVH.[45-47]

The above data show that clinical LVH has two distinct pathophysiological components: the anatomical remodeling, diagnosed by imaging techniques, and the electrical remodeling, observed on ECG. Although many patients have both anatomical and electrical expression of LVH, there are subgroups that have isolated anatomical or electrical LVH. Whether patients with lone ECG LVH or lone echo LVH constitute different clinical entities with different cardiovascular risk is not known. Thus, assessment of LVH in clinical practice has relevant prognostic and therapeutic implications, with the QRS morphology unable to measure LV mass or dimensions but provides valuable information on the myocardial electrical changes.

QRS morphology in heart failure

QRS duration is a strong independent predictor of cardiovascular mortality, future pacemaker implantation and sudden cardiac death in hypertensive patients as well as in the general heart failure (HF) population.[48-50] In middle aged and older adults without cardiovascular disease there is a continuous graded relation between QRS duration >100 ms and risk of heart failure.[51,52] A prolonged QRS duration >120 ms is associated with significant reduction of ejection fraction.[53-55] More than one third of HF patients with reduced ejection fraction (HFrEF) have QRS duration ≥120 ms.[53,56,57] In the Swedish HF Registry, QRS prolongation or left bundle branch block (LBBB) were found in 39% of patients with reduced EF (<40%), 25% of those with mildly reduced EF (40-49%) and 18% with normal EF (≥50%).[58] In addition, QRS duration was strongly related to age, male gender and dilated cardiomyopathy, and was associated with higher risk of cardiovascular and all-cause mortality.[55]

HF is also associated with progressive ventricular remodeling which may be accompanied by QRS prolongation. However, ECG changes do not reflect anatomical remodeling per se. A discordance between QRS duration and LV size has been demonstrated in patients with left bundle branch block and dilated cardiomyopathy.[59] In these patients the progression over the years of QRS duration was associated with worse prognosis, whereas increased LV cavity size did not carry significant prognostic information. In a large study, cardiovascular death or hospitalization from HF was more frequent in patients with bundle branch block (42.6%) compared to those with normal ECG (18.6%)[56], thus suggesting a pivotal role for QRS monitoring in addition to conventional LV size and EF regular follow up.

In the HF setting, QRS prolongation is also considered a clinical marker of inter- and intra-ventricular mechanical dyssynchrony which impairs the appropriate sequence of contraction and relaxation, hence reducing cardiac efficiency.[60,61] Inter-ventricular dyssynchrony assessed by tissue Doppler imaging has been observed in more than 70% of patients with QRS >120 ms.[62] This function disturbance has been shown to respond favorably to cardiac resynchronization therapy (CRT) which restores ventricular mechanical synchrony, resulting in significant clinical and overall cardiac function improvement [63,64] However, almost one third of patients with guidelines based indications (symptomatic patients with reduced ejection fraction (<35%), ECG pattern of left bundle branch block with QRS

duration >150 ms) fail to respond to CRT.[60] In addition, about 30% of HF patients with a wide QRS (>120 ms) do not show significant ventricular dyssynchrony [65,66], a percentage that corresponds to that of non-responders to CRT. On the other hand, significant mechanical dyssynchrony has been shown in HF patients with narrow QRS.[62,67-69] These patients have a substantial increase in the risk of cardiac events, independent of the QRS width.[70,71] Therefore it seems that QRS duration or morphology cannot be taken as the whole mark for the severity of LV mechanical dyssynchrony.[62,67,70,72] A finding that makes the precise mechanism by which CRT improves the cardiac function, the relation between electrical dyssynchrony (QRS >120 ms), mechanical dyssynchrony, and the relative importance of QRS duration and morphology in identifying patients who may benefit from CRT, not completely understood.

Most randomized controlled trials of CRT enrolled HF patients according to QRS duration. Overall, there was a progressive increase in CRT benefits with broadening QRS (>120-150 ms).[73-77] However, when the beneficial effect of CRT was evaluated according to the echocardiographic evidence of mechanical dyssynchrony in patients with narrow QRS (<120/130 ms), there was no benefit.[78-80] These results confirm that QRS duration is an important indicator of ventricular dyssynchrony, although other mechanisms may be involved in predicting the response to CRT. Furthermore, patients with LBBB morphology had the best response to CRT compared to those with right bundle branch block (RBBB) who had the least favorable response, and those with intraventricular conduction delay (IVCD) having intermediate response.[81] When the combined effect of QRS morphology and mechanical dyssynchrony were considered, it was observed that non-LBBB patients with significant mechanical dyssynchrony had greater benefits from CRT, similarly to LBBB patients.[82]

Registers have shown that approximately 50% of HF patients have preserved ejection fraction (HFpEF) but do carry similar prognosis to those with HFrEF patients.[83] This finding raised concern about identifying patients at greater risk of adverse cardiovascular events. However, the role of QRS duration in those patients has received little attention. Recent findings suggest that both electrical and mechanical dyssynchrony are present in HFpEF patients,[84] with mechanical dyssynchrony associated with wider QRS.[85] Prolonged QRS ≥120 ms has been reported in about 18% of HFpEF patients. [58,82,84] In a small study the prevalence of inter- and intra-ventricular dyssynchrony in HFpEF patients with QRS duration ≥120 ms was comparable to that of HFrEF (42% vs. 55% respectively).[86] In addition, analysis of the association between QRS duration and outcomes demonstrated that QRS ≥120 ms was significantly associated with an increased risk of cardiovascular and all-cause mortality,[87] suggesting that QRS duration in HFpEF patients is a clinical marker that identifies patients at higher risk of adverse events.

In conclusion therefore, in HF patients, QRS duration and morphology have great diagnostic and prognostic relevance. However, as in patients with cardiac hypertrophy, electrical dyssynchrony is not a direct reflection of mechanical dyssynchrony and cannot be interpreted as a surrogate of cardiac dysfunction. Both electrical and mechanical dyssynchrony should be taken into account to provide the best clinical assessment of HF patients.

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