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The effect of reduced intercellular coupling on electrocardiographic signs of left ventricular hypertrophy ☆

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Abstract

Background: The electrocardiographic (ECG) diagnosis of left ventricular hypertrophy (LVH) is based on the assumption that QRS voltage increases with left ventricular mass. However, most of patients with echocardiographically detected LVH do not have increased QRS voltage. Reduced intercellular coupling has been observed in LVH patients and animal models. The purpose of this study was to show that this uncoupling can explain relatively low QRS voltage in LVH patients.
Methods: Electrocardiograms and vectorcardiograms (VCG) were simulated with a realistic large-scale computer model of the human heart and torso that reliably represented the effects of reduced coupling on both propagation and ECG voltage.
Results: Uncoupling reduced QRS voltage in all leads except aVL, reflecting a decrease in vector amplitude as well as a leftward axis deviation that suggested left anterior fascicular block.
Conclusions: Low QRS voltage does not necessarily contradict a diagnosis of LVH but may be an indication for electrical uncoupling. The diagnostic value of this "relative voltage deficit" needs to be demonstrated in clinical studies.

Keywords: Intercellular coupling; Electrocardiogram and vectorcardiogram; QRS complex; Computer model

Introduction

The electrocardiographic (ECG) diagnosis of left ventricular hypertrophy (LVH) is based mainly on QRS voltage criteria and postulates that QRS voltage increases proportionally with left ventricular mass (LVM). However, ECG criteria for LVH have low sensitivity: only a minority of patients with increased LVM has increased QRS voltage.[1-3] This discrepancy between LVM and QRS voltage is perceived as a limitation of electrocardiography in LVH diagnosis. However, in cases when increased LVM is detected by a cardiac imaging method, the missing increase in left ventricle (LV) voltage may provide important clues about altered electrogenesis[4] of which the prognostic relevance is presently unknown.

The accepted theoretical framework for linking the recorded QRS voltage to the activation of the ventricles is provided by the solid-angle theory.[5-7] Predictions of the solid-angle theory agree with those of the more general bidomain theory when tissue anisotropy and torso inhomogeneities are ignored.[8,9] Solid-angle theory relates the recorded voltage to both spatial determinants (the spatial angle, determined by the extent of activation front and the position of the recording electrode relative to this front) and nonspatial determinants (source strength and electrical conductivity of the body).

The interpretation of the ECG in LVH focuses on the spatial determinants, although tending to neglect the modified electrical properties of the myocardium. However, it has been well documented that both active and passive electrical properties in LVH are altered (for review, see, for example, Bacharova[4] and Kleber[10]). Studies in several experimental models have shown that reduced expression of connexin 43 (Cx43) leads to a decrease in QRS voltage.[11,12] It has also been

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shown that the reduction in Cx43 expression in spontaneously hypertensive rats is associated with decreased QRS voltage.[13] Apparently, the reduced intercellular conductivity caused by a lower content in Cx43 can more than counterbalance the expected effect of increased LVM.

Although an increased QRS voltage is considered specific for the ECG diagnosis of LVH, the changes in QRS complex in LVH patients cover a broader spectrum, including increased QRS voltage in different leads, left axis deviation, and ECG signs of intraventricular conduction defects such as left anterior fascicular block (LAFB) or left bundle-branch block. These changes imply alterations in the impulse propagation in the left ventricle during depolarization.[14,15]

The purpose of this study was to evaluate mathematically the hypothesis that reduced intercellular coupling leads to an attenuation of QRS voltage in the 12-lead ECG that may offset the voltage amplification that increased LVM is thought to cause.

Methods

Model description

We used a highly realistic large-scale computer model of the human heart and torso that reliably represented the 3 interacting mechanisms by which reduced intercellular coupling affects the QRS complex: (1) reduction of the depolarization wave front velocity, (2) attenuation of the current generator associated with the wave front, and (3) modification of current flow through the thorax.

A monodomain reaction-diffusion equation[16] was used to simulate propagating activation based on ionic transmembrane currents at 0.25-mm resolution in a model of the human ventricles. Membrane ionic currents at each of the 25 million points that represented the ventricular myocardium were computed with a specific membrane model for human ventricular myocytes.[17] Computed transmembrane currents were injected in a realistic 1-mm resolution bidomain model of a human torso[8,18] (Fig. 1).

The resulting potential fields in the torso were computed to obtain the 12-lead ECG and vectorcardiogram (VCG). Intercellular and interstitial conductivities and heterogeneous fiber orientation were the same in the heart and torso models. The torso model also included intracavitary blood, lungs, and a skeletal muscle layer. The heart and torso models were previously adapted to the anatomy of a specific subject, and we verified that the model adequately reproduced the subject's 12-lead ECG.[18]

Changes introduced

In both the heart and torso models, the intercellular coupling was reduced in steps of 10% from its normal value, to represent reduced gap-junctional coupling. The reported coupling values refer to the compound electrical conductivity of the cytoplasm and the gap junctions (for a discussion of these concepts, we refer to Jongsma and Wilders[19]). This compound value depends on the expression level of Cx43 but is not proportional to it.

Electrocardiogram analysis

The QRS spatial vector magnitude and the electrical axis in the frontal plane were determined automatically and verified by an expert observer (L. B.). QRS amplitude and QRS duration in each lead were measured manually by the same observer.

The following ECG-LVH criteria were evaluated: Sokolow-Lyon index,[20] Cornell voltage,[2] and Cornell voltage-duration product,[21] and the maximum QRS spatial vector magnitude (QRSmax).[22]

Results

QRS duration

The gradual decrease in coupling caused a gradual prolongation of the QRS complex reaching 30 milliseconds at 60 % reduced coupling (Table 1).

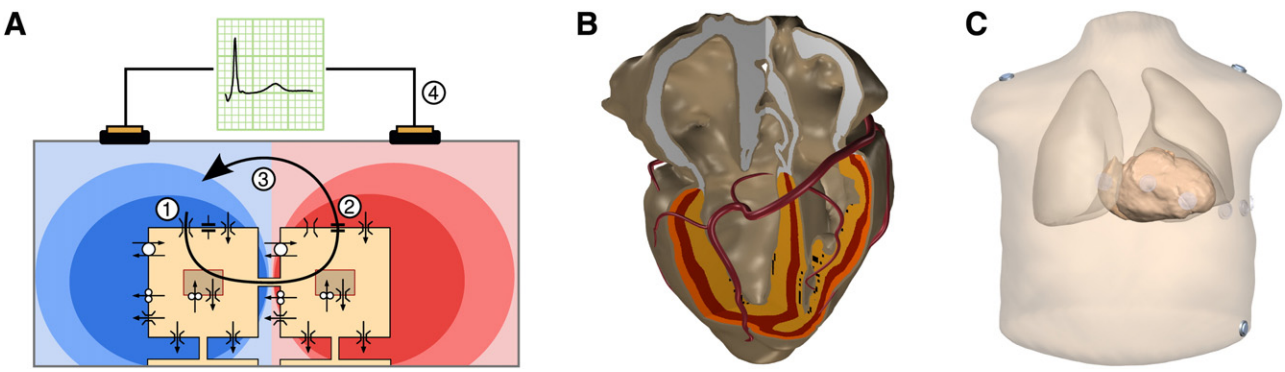

Fig. 1. A, Principle of the simulation technique: 2 model cells are depicted schematically, with their ion channels, pumps, and exchangers. Gap junctions connect the cells. (1) In depolarizing cells, a large inward sodium current flows. (2) This current passes through gap junctions to neighboring cells where it charges the cell membrane until the threshold for the sodium current is reached. (3) The current loop is closed in the interstitium and outside the heart, where it generates a potential field, schematically indicated here in red for positive potentials and blue for negative potentials. (4) This potential field is picked up as an ECG. In this model, the current that causes propagating activation is also used to compute the ECG, without simplifying assumptions about source strength. B, Anatomy of the heart model. Posterior view with part of the posterior wall and septum removed to show the layering of subendocardial cells (yellow), midmyocardial cells (red), and subendocardial cells (orange). C, Anatomy of the complete thorax model with heart, lungs, and standard ECG electrodes. The skeletal muscle layer is not shown.

Table 1
Amplitudes of the maximum QRS deflections of the standard 12-lead ECG (in millimeters; 10 mm = 1 mV) and QRS duration (in milliseconds)

	Reference	10%	20%	30%	40%	50%	60%
I	7	6	6	6	6	6	5
II	10	8	7	6	4	3	2
III	3	2	−2	−3	−4	−5	−6
aVR	−8	−7	−6	−5	−4	−4	−2
aVL	3	3	4	4	5	5	6
aVF	6	5	4	3	2	−2	−3
V_1	−15	−15	−15	−15	−14	−14	−13
V_2	−17	−16	−16	−15	−15	−14	−14
V_3	10	8	7	5	5	4	4
V_4	21	18	16	15	13	10	8
V_5	21	19	17	15	13	11	3
V_6	9	8	7	6	5	4	4
QRS_{dur}	90	90	98	98	105	112	120

QRS morphology

As shown in Fig. 2, the gradual decrease in coupling led to a gradual decrease in the QRS loop size visible in all planes. The QRSmax decreased gradually by 37.5% at 60% coupling reduction.

The QRS loop in the frontal plane was shifted gradually upward, and starting from the 50% coupling reduction, the main body of the QRS loop was dislocated to the upper left quadrant, creating a VCG pattern of LAFB.

The decrease in the QRS loop size was reflected in a gradual decrease of the QRS amplitude of the 12-lead ECG, except for lead aVL (Table 1, Fig. 2). The aVL amplitude increased gradually, reflecting the upward shift of the QRS loop in the frontal plane.

The upward displacement of the QRS loop was reflected in the 12-lead ECG as a gradual shift of the electrical axis to the left (Fig. 3). The electrical axis decreased with the coupling reduction, reaching the value of −32° at 60% coupling reduction.

Left ventricular hypertrophy–ECG criteria

As is shown in Fig. 4, the values of the Sokolow-Lyon index and QRSmax were reduced by the gradual coupling reduction. The Cornell voltage showed smaller changes, and the Cornell voltage-duration product remained essentially stable.

Discussion

In this computer-model study, we showed that a gradual reduction of intercellular coupling in the left ventricular myocardium caused a decrease in the QRS magnitude and an upward shift of the QRS vectorcardiographic loop. These changes were reflected in a decrease of the QRS amplitude in all leads of the 12-lead ECG, except aVL, and a gradual shift of the electrical axis in the frontal plane to the left.

QRS amplitude

It has been well documented that intercellular coupling is diminished in advanced stages of cardiac pathology and contributes to the substrate for lethal ventricular arrhythmias.[23] The evidence on the relation between coupling reduction and QRS amplitude is mainly anecdotal because side results of studies focused primarily on arrhythmias. Morley et al[12] showed a progressive diminution in the amplitude of the QRS complex in genetically engineered mice with cardiac-restricted knock-out of Cx43. Similarly, Danik et al[11] observed a gradual decrease in QRS amplitude closely paralleling the loss of Cx43 expression in a murine model, genetically engineered to express progressively decreasing levels of Cx43. We have previously studied the relation between QRS amplitude and Cx43 expression in spontaneously hypertensive rats and found 40% reduced Cx43 levels in 20-week-old spontaneously hypertensive rat as compared with normotensive Wistar rats.[13] This reduction was associated with 37% reduced values of QRSmax.

The results of our simulations support our concept of the relative voltage deficit in certain stages of LVH, postulating that the presence of a QRS amplitude within normal limits despite an increased LVM can be caused by electrical remodeling.[4,24] We showed that changes in electrical properties, in this case the reduced intercellular coupling, can lead to a decrease in the QRS amplitude. In LVH, it could counterbalance the effect of the increased LVM on the resultant QRS amplitude.

An unexpected finding of this study was the gradual shift of the QRS loop upward, with corresponding changes in the 12-lead ECG—the left axis deviation and the increase in R-wave amplitude in aVL—creating finally a pattern of LAFB. Danik et al[11] have demonstrated a gradual decrease in QRS amplitude in standard lead II. In a later study from this group,[12] 3 standard limb leads are presented, indicative of left axis deviation.

Left axis deviation and LAFB pattern are frequent findings in patients with LVH. Left axis deviation in patients with LVH is interpreted as an effect of increased LVM. However, as was pointed out by Liebman and Nadas,[25] the left axis deviation is not caused by LVH per se, that is, the increased LVM, but by a conduction defect. The LAFB pattern in our model study resulted from a diffuse reduction in coupling in the left ventricle and not from a conduction block restricted to the anterior fascicle. It cannot be excluded that the LAFB patterns in patients with LVH are caused by diffuse changes leading to altered conduction in left ventricular myocardium.

QRS duration

Theoretically, conduction velocity is proportional to the square root of the electrical conductivity of the tissue.[10] Therefore, the effect of the gradual increase in coupling reduction on QRS duration was an expected result. It is also consistent with results of experimental and model studies showing statistically significant effects on the conduction velocity only after considerable decrease in Cx43.[11,12,19,26] Consistent with the theoretical square-root relationship, the slower transverse conduction velocity was more strongly affected than the relatively fast longitudinal conduction velocity.[26] Reported increases in QRS duration in Cx43

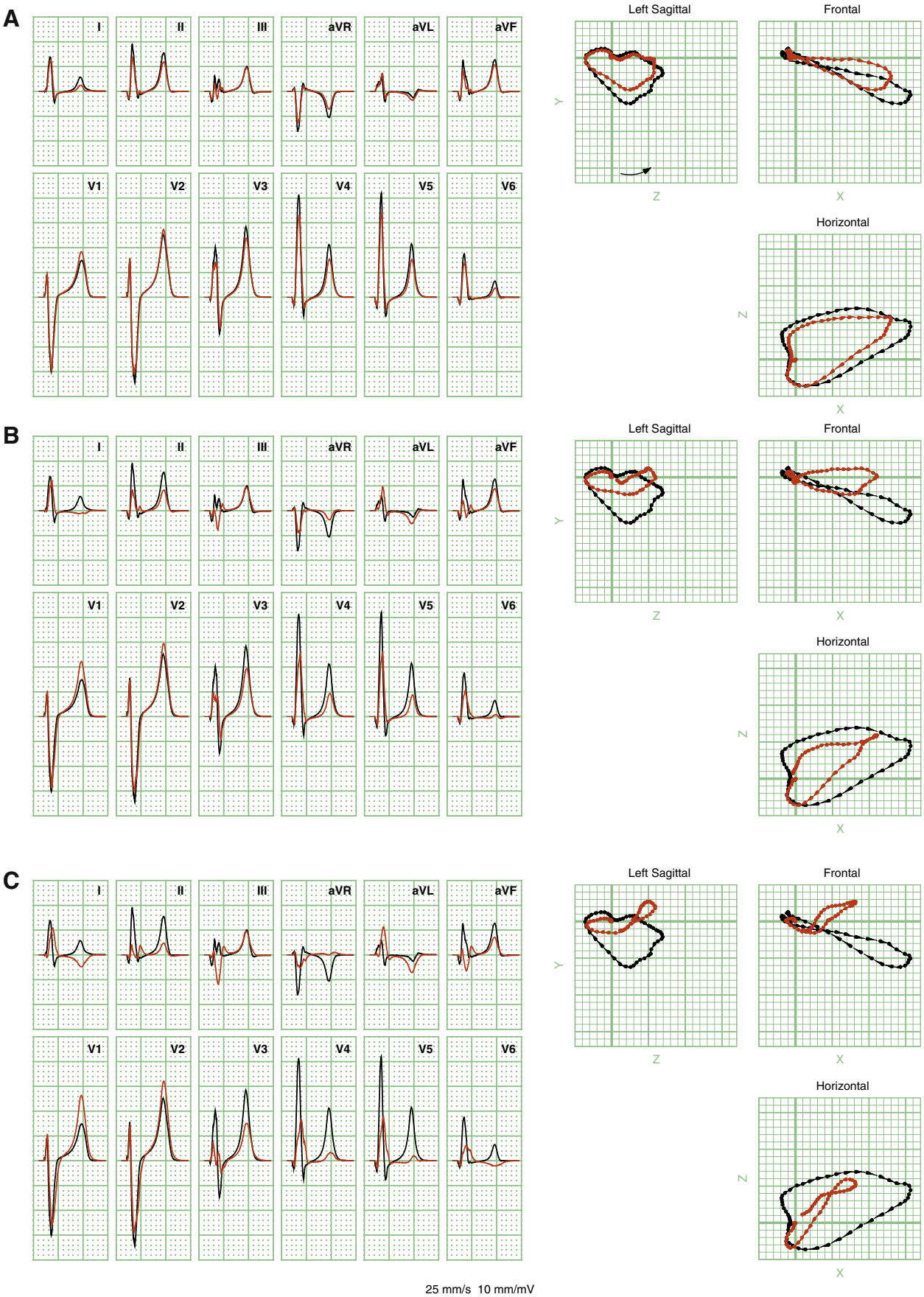

Fig. 2. Simulated standard 12-lead ECG and VCG for 20 % (A), 40 % (B), and 60% (C) coupling reduction (red) compared with baseline (black). For each panel: left, standard 12-lead ECG; and right, VCGs in left sagittal, frontal, and horizontal planes.

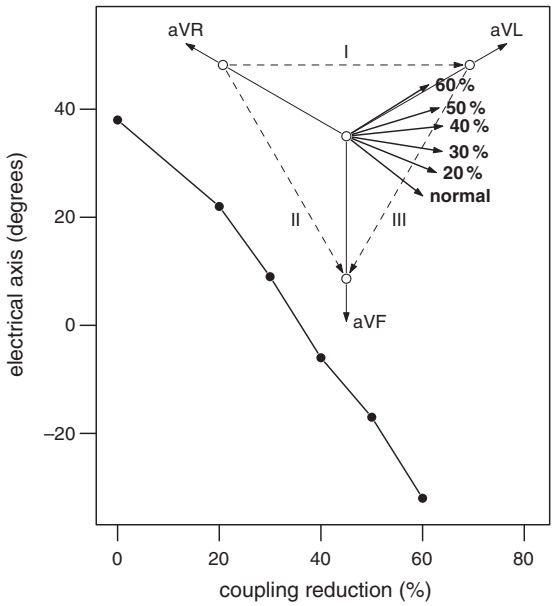

Fig. 3. Values of the electrical axis in the frontal plane. The inset shows the angles graphically and in relation to the standard ECG leads.

knockout mice range from 0% to 72%.[11,27] The reported baseline QRS durations also differ greatly. These differences may be caused by the difficulty of determining the end of the QRS complex in the murine ECG, which lacks an isoelectric interval between the QRS complex and the T wave.

Prolongation of QRS duration is a frequent finding in LVH patients and is incorporated into several composite ECG-LVH criteria, for example, Romhilt-Estes score[28] or Cornell voltage-duration product.[21] In clinical studies, QRS prolongation is a predictor of adverse outcome. Classically, the QRS prolongation is interpreted as a longer time required for the spread of an electrical impulse across the enlarged left ventricle. Our results show that slowed propagation caused by reduced coupling can be an additional factor.

Left ventricular hypertrophy criteria

In this study, we also showed how the decrease in the QRS loop size and its upward displacement affected the classic ECG-LVH criteria. As expected, the Sokolow-Lyon index reflected the decrease in the QRS vector magnitude in the horizontal plane, whereas in the case of the Cornell voltage-duration product, the decrease in the QRS size was balanced by the increased aVL amplitude and prolonged QRS duration. These findings could contribute to explaining the discrepancies in the diagnostic performance of these 2 classic ECG-LVH criteria.

Interpretation of this study

Computer modeling is a useful tool for evaluating whether observational results agree with existing theory. Our study showed that the observed decrease in QRS amplitude in spontaneously hypertrophic rats and/or genetically engineered mice[11-13] agrees with the observed reduction in Cx43 expression in these animals and that a similar decrease in intercellular coupling could potentially explain the lack of increased QRS amplitude in LVH patients, as well as leftward rotation of the QRS axis. This model study cannot prove that reduced coupling actually occurs in these patients, and it cannot exclude other explanations for the relative voltage deficit and the axis rotation, but it shows that reduced coupling is a viable explanation that merits further study. We made this prediction using a reaction-diffusion model of the human heart and torso, which reliably accounts for all effects that uncoupling has on the ECG. It would have been impossible to make this prediction with solid-angle theory because it cannot predict the magnitude of the current sources in the heart. This change in source strength is crucial in the explanation of the effects of uncoupling.

Clinical implications

We showed that reduced intercellular coupling, which is a part of the hypertrophic remodeling of myocardium, would result in QRS changes that are consistent with a number of findings in LVH patients:

- A decrease in QRS amplitude of the 12-lead ECG except for the increase of R-wave amplitude in aVL. This finding could contribute to the explanation of the "discrepancies" between the QRS voltage and increased LVM.
- QRS prolongation.
- Left axis deviation and LAFB pattern.

Our results, therefore, draw attention to the effect of the altered electrical properties leading to QRS characteristics that are presently not considered in the interpretation of ECG changes in LVH patients. It is well documented that Cx43 reduction contributes to the formation of an arrhythmogenic substrate and increases vulnerability to ventricular arrhythmias. The recognition of the early stages of its reduction may therefore have diagnostic significance.

A less intuitive result of our study was that reduced coupling in the LV led to leftward QRS axis orientation, which is frequently observed in LVH patients and is included in scoring systems and recommended criteria for LVH.[28,29]

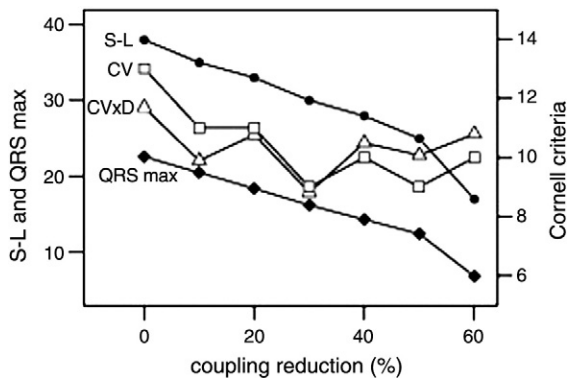

Fig. 4. Selected voltage criteria for LVH: Sokolow-Lyon index (S-L), Cornell voltage (CV), estimated QRSmax, and Cornell voltage-duration product (CVxD). (CVxD is divided by 100 to fit the graph.)

Limitations of the study

In this study, only the effect of reduced coupling was investigated. Despite the possible relevance of our results for diagnosis in LVH patients, we did not include other factors affecting the electrical properties of myocardium that are the part of electrical remodeling in LVH. Changes that could lead to reduced QRS amplitude include reduced expression of sodium channels and increased electrical conductivity of the interstitium.

The effect of reduced coupling was demonstrated on a normal cardiac anatomy. We did not introduce changes in LVM, LV anatomical characteristics, or thoracic geometry and conductivity to demonstrate the interplay of changes in anatomical size and electrical properties (spatial and nonspatial factors in terms of the solid angle theory). It means, on the other hand, that the results are also applicable to other cardiac pathologies associated with reduced intercellular coupling, for example, diffuse ischemic changes.

Conclusion

In this computer-model study, we showed the effect of a reduction in intercellular coupling on the QRS voltage and morphology, and we concluded that low or normal QRS voltage does not necessarily contradict a diagnosis of LVH but rather indicates electrical remodeling of the hypertrophied left ventricle. The described QRS changes could contribute to the understanding of the variability of ECG findings in LVH patients and consequently to the early detection of electrical remodeling in patients and interpretation of the effect of antihypertensive therapy.

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References

1. Reichek N, Devereux RB. Left ventricular hypertrophy: relationship of anatomic, echocardiographic and electrocardiographic findings. Circulation 1981;63:1391.
2. Casale PN, Devereux RB, Kligfield P, et al. Electrocardiographic detection of left ventricular hypertrophy: development and prospective validation of improved criteria. J Am Coll Cardiol 1985;6:572.
3. Pewsner D, Jüni P, Egger M, Battaglia M, Sundström J, Bachmann LM. Accuracy of electrocardiography in diagnosis of left ventricular hypertrophy in arterial hypertension: systematic review. BMJ 2007;335:711.
4. Bacharova L. Electrical and structural remodeling in left ventricular hypertrophy—a substrate for a decrease in QRS voltage? Ann Noninvasive Electrocardiol 2007;12:260.
5. Holland RP, Arnsdorf MF. Solid angle theory and the electrocardiogram: physiologic and quantitative interpretations. Prog Cardiovasc Dis 1977;19:431.
6. Bayley RH. Biophysical principles of electrocardiography. New York: Paul B Hoeber; 1958. p. 237.
7. Scher AM. Trends in electrocardiographic recording. In: Schlant RC, Hurst JW, editors. Advances in electrocardiography. New York: Grune & Stratton; 1972. p. 1.
8. Potse M, Dubé B, Vinet A. Cardiac anisotropy in boundary-element models for the electrocardiogram. Med Biol Eng Comput 2009; 47:719.
9. Van Oosterom A. Solidifying the solid angle. J Electrocardiol 2002;35 (Suppl):181.
10. Kléber AG, Rudy Y. Basic mechanisms of cardiac impulse propagation and associated arrhythmias. Physiol Rev 2004;84:431.
11. Danik SB, Liu F, Zhang J, et al. Modulation of cardiac gap junction expression and arrhythmic susceptibility. Circ Res 2004;95:1035.
12. Morley GE, Danik S, Bernstein S, Sun Y, Rosner G, Gutstein DE. Reduced intercellular coupling leads to paradoxical propagation across the Purkinje-ventricular junction and aberrant myocardial activation. PNAS 2005;102:4126.
13. Bacharova L, Plandorova J, Klimas J, Krenek P, Kyselovic J. Discrepancy between increased left ventricular mass and "normal" QRS voltage is associated with decreased connexin43 expression in early stage of left ventricular hypertrophy in spontaneously hypertensive rats. J Electrocardiol 2008;41:730.
14. Bacharova L, Estes EH. Electrocardiographic diagnosis of left ventricular hypertrophy: depolarization changes. J Electrocardiol 2009; 42:228.
15. Bacharova L, Szathmary V, Kovalcik M, Mateasik A. Effect of changes in left ventricular anatomy and conduction velocity on the QRS voltage and morphology in left ventricular hypertrophy: a model study. J Electrocardiol 2010;43:200.
16. Potse M, Dubé B, Richer J, Vinet A, Gulrajani RM. A comparison of monodomain and bidomain reaction-diffusion models for action potential propagation in the human heart. IEEE Trans Biomed Eng 2006;53:2425.
17. Ten Tusscher KHWJ, Noble D, Noble PJ, Panfilov AV. A model for human ventricular tissue. Am J Physiol Heart Circ Physiol 2004;286: H1573.
18. Hoogendijk MG, Potse M, Linnenbank AC, et al. Mechanism of right precordial ST-segment elevation in structural heart disease: excitation failure by current-to-load mismatch. Heart Rhythm 2010; 7:238.
19. Jongsma HJ, Wilders R. Gap junctions in cardiovascular disease. Circ Res 2000;86:1193.
20. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am Heart J 1949;37:161.
21. Molloy TJ, Okin PM, Devereux RB, Kligfield P. Electrocardiographic detection of left ventricular hypertrophy by the simple QRS voltage-duration product. JACC 1992;20:1180.
22. Murata K, Kurihara H, Hosoda S, Ikeda M, Seki M. Frank lead vectorcardiogram in left ventricular hypertrophy. Jpn Heart J 1964; 82:543.
23. Severs NJ, Bruce AF, Dupont E, Rothery S. Remodelling of gap junctions and connexin expression in diseased myocardium. Cardiovasc Res 2008;80:9.
24. Bacharova L, Kyselovic J. Electrocardiographic diagnosis of left ventricular hypertrophy: is the method obsolete or should the hypothesis be reconsidered? Med Hypotheses 2001;57:487.
25. Liebman J, Nadas AS. An abnormally superior vector (formerly called marked left axis deviation). Am J Cardiol 1971;26:777.
26. van Rijen HVM, Eckardt D, Degen J, et al. Slow conduction and enhanced anisotropy increase the propensity for ventricular tachyarrhythmias in adult mice with induced deletion of connexin43. Circulation 2004;109:1048.
27. Thomas SA, Schuessler RB, Berul CI, et al. Disparate effects of deficient expression of connexin43 on atrial and ventricular conduction: evidence for chamber-specific molecular determinants of conduction. Circulation 1998;97:686.
28. Romhilt DW, Estes Jr EH. A point score system for the ECG diagnosis of left ventricular hypertrophy. Am Heart J 1968;75:752.
29. Verdecchia P, Angeli F, Cavallini C, et al. The voltage of R wave in lead aVL improves risk stratification in hypertensive patients without ECG left ventricular hypertrophy. J Hypertens 2009;27:1697.