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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).

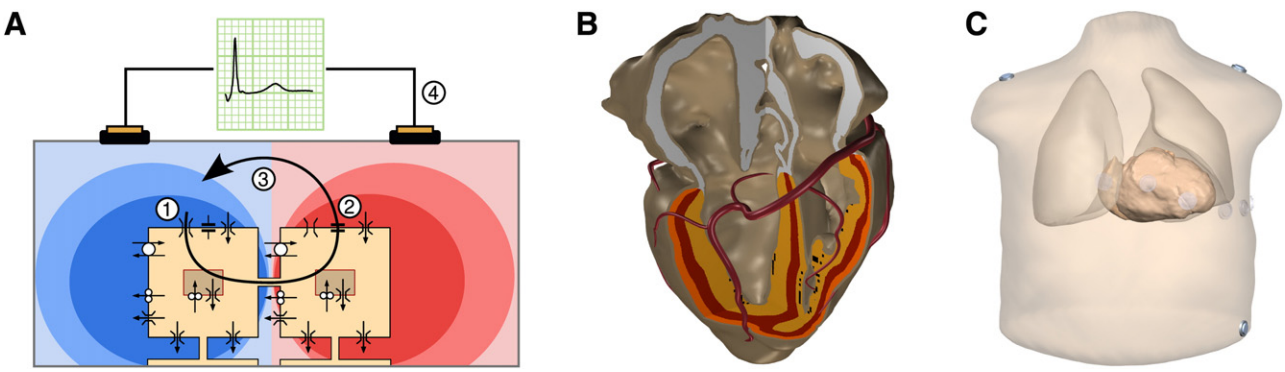

Fig. 1. A, Principle of the simulation technique: 2 model cells are depicted schematically, with their ion channels, pumps, and exchangers. Gap junctions connect the cells. (1) In depolarizing cells, a large inward sodium current flows. (2) This current passes through gap junctions to neighboring cells 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.