DETERMINATION OF THE ABILITY OF HIGH-FREQUENCY ECG TO ESTIMATE LEFT VENTRICULAR MASS IN HUMANS, DETERMINED BY MAGNETIC RESONANCE IMAGING

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Short title: High-frequency ECG vs LVM in humans

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ABSTRACT

Background Previous studies have shown a significantly higher correlation between left ventricular mass index (LVMi) and high-frequency QRS components (HF-QRS) than between LVMi and QRS amplitudes in the standard frequency range in rabbits. The purpose of the present study was to compare electrocardiographic measurements from standard and high frequency ranges with left ventricular mass (LVM) and LVMi determined by magnetic resonance imaging in humans.

Methods 62 normal subjects were studied. Signal-averaged electrocardiograms (ECGs) from the 12 standard leads were analyzed in the standard frequency range (0.05-150 Hz), in the middle (25-100 Hz) and high end (50-150 Hz) of the standard frequency range and in the 150-250 Hz range. Root mean square (RMS) values from the HF-QRS and QRS amplitude measurements from the standard ECGs were compared with LVM and LVMi.

Results The correlations between LVMi and HF-QRS were similar to those between LVMi and standard ECG. When regarding LVM, however, the correlations found in standard ECG were higher than those found in HF-QRS.

Conclusions Contrary to previous results in animals, we found in humans no better correlation between HF-QRS and LVM/LVMi than between standard ECG and LVM/LVMi.

Keywords: signal-averaged ECG, high-frequency QRS components, healthy subjects

INTRODUCTION

The electrocardiographic diagnosis of left ventricular hypertrophy is an important clinical problem. The standard 12-lead electrocardiogram (ECG) remains one of the most widely used diagnostic tools for detecting left ventricular hypertrophy. However, based on echocardiographic standard, the sensitivity is poor at high levels of specificity, limiting the utility of the ECG for left ventricular hypertrophy detection (Devereux *et al.*, 1984; Reichek & Devereux, 1981).

The standard ECG by convention contains frequencies between 0.05 and 150 Hz, but the ECG signal also includes higher frequencies (Golden *et al.*, 1973). The highest amplitudes of the high-frequency components are found within the QRS complex (Abboud, 1993). Okin et al found a significantly higher correlation between the left ventricular mass index (LVMi) and high-frequency QRS components (HF-QRS) than between LVMi and standard ECG QRS amplitudes (Okin *et al.*, 1992). Signal-averaged orthogonal lead recordings in normal rabbits and in those with left ventricular hypertrophy were used in their study. The high-pass filtered vector integral was significantly correlated with LVMi even among the normal rabbits. The results suggest that assessment of HF-QRS could improve the electrocardiographic diagnosis of left ventricular hypertrophy.

Magnetic resonance imaging is a three-dimensional imaging technique that is not dependent on geometric assumptions and not limited in the position or orientation of the image sections. Magnetic resonance imaging has become gold standard in the assessment of left ventricular volumes, function and mass. Excellent results for both accuracy (Caputo *et al.*, 1987; Maddahi *et al.*, 1987; Lund *et al.*, 2000) and reproducibility (Firmin *et al.*, 1987; Semelka *et al.*, 1990; Grothues *et al.*, 2002) of measurements have been demonstrated.

A previous study by Carlsson et al (Carlsson *et al*, in press) showed a statistically significant correlation, but poor correlation coefficients, between left ventricular mass (LVM) and established left ventricular hypertrophy criteria. With the results of that study and the study by Okin et al (Okin *et al.*, 1992) in mind, we therefore wanted to test the hypothesis that RMS values from HF-QRS correlate better with magnetic resonance imaging-determined LVM and LVMi than does standard ECG.

METHODS

Study population

The study population consisted of 62 healthy volunteers in different age groups recruited by advertisement in the University Hospital of Lund, Sweden. Volunteers were not considered for the study if they had either clinical or ECG evidence of an old myocardial infarction. To reduce any potential confounding factors in the ECG analysis, patients with the following abnormalities on standard 12-lead ECG were not considered: intraventricular conduction delay with QRS duration $\geq$ 120 ms, ventricular pre-excitation, left anterior fascicular block, or atrial fibrillation. Further, the individuals were normotensive (blood pressure: systolic < 140 mm Hg and diastolic < 90 mm Hg) and had no direct or indirect signs of systemic or metabolic disease. The study was approved by the local committee on human research and complies with the Declaration of Helsinki. Informed consent was

obtained from each patient prior to enrolment.

Determination of left ventricular mass

Throughout the study, magnetic resonance imaging was performed on a 1.5 T system (Magnetom Vision; Siemens, Erlangen, Germany) with a 25 mT/m gradient with a phased-array body coil. All subjects were placed in supine position and imaged using a protocol described earlier (Engblom *et al.*, 2004). In short, scout imaging was performed to enable identification of the cardiac long and short axes. Short axis cine images covering the entire left ventricle were then acquired using a turbo fast low-angle shot sequence (slice thickness 10 mm, field of view 380 mm, matrix 126x256, repetition time 100 ms (echo sharing resulting in phases every 50 ms), echo delay time 4.8 ms, flip angle 20°). The fast low-angle shot sequence was triggered by ECG, and image acquisition was undertaken during breath hold. Nine to twelve slices were required to completely cover the left ventricle, depending on heart size. Image acquisition time for the left ventricle was approximately ten minutes per subject.

The image analysis was performed with publicly available software (Scion Image Beta 4.0.2). The first frame of the cine image loop was selected as the end-diastolic image. The end-systolic image was chosen as the image containing the smallest left ventricular blood pool diameter. Endo- and epicardial borders were outlined manually on each end-diastolic and end-systolic image. The papillary muscles were included in the LVM (Pennell, 2002; Friberg *et al*, 2004). To obtain the LVM, the planimetered area of each slice was multiplied by slice thickness. LVM was determined both in end-diastole and end-systole for internal validation.

Besides LVM, LVMi (LVM (g) divided by body weight (kg)) (Okin, 1992), was used in the study.

ECG acquisition

The ECGs were recorded using equipment provided by Siemens-Elema AB, Solna, Sweden. The precordial leads were obtained using the standard electrode placement while the limb leads were obtained using the Mason-Likar electrode placement to reduce noise due to skeletal muscle activity (Mason & Likar, 1966). The signals were digitized at a sampling rate of 1 kHz, with an amplitude resolution of 0.6 μV and stored on a PC hard disc for analysis.

The ECG was acquired continuously for five minutes, at rest in supine position, within one hour after the magnetic resonance imaging.

Signal averaging

The five-minute recording from each patient was signal-averaged in order to minimize the noise level, which is essential for later analysis of the low-amplitude HF-QRS. The recordings were processed off-line, using software for ECG analysis developed by the Signal Processing Group, Department of Applied Electronics, Lund University, Sweden. For signal averaging only beats with similar morphology were accepted. Each beat in each recording was cross-correlated to a ”template beat”, representing the predominant morphology. In the beat alignment the highest cross-correlation value was determined by shifting each beat in relation to the template (Pahlm & Sörnmo, 1987). Beats with cross-correlation coefficient < 0.97 were not included.

Analysis of different frequency ranges

The amplitudes in the standard frequency range were automatically determined in the obtained signal-averaged ECG. The measurements used to estimate LVM were the Cornell voltage measurement (R(aVL) + S(V3)) (Molloy *et al.*, 1992) the Cornell product measurement ((R(aVL) + S(V3)) * QRS duration) (Molloy *et al.*, 1992) and the Sokolow-Lyon measurement (S(V1) + R(V5/6)) (Sokolow & Lyon, 1949). Two of the individuals had a QS complex in V1, its amplitude was used for the Sokolow-Lyon measurement.

The obtained 12-lead signal-averaged ECG was analyzed using a Butterworth filter (Proakis & Manolakis, 1996) within the frequency intervals of 25-100 Hz, 50-150 Hz, and 150 - 250 Hz. The signal was first filtered forward and then backward to ensure linear phase of the filtering process (Proakis & Manolakis, 1996). The QRS components in each of the 12 leads were expressed as RMS values during the entire QRS duration. RMS values were calculated by 1) squaring the amplitude of each sample, 2) determining the mean of these squares, and 3) determining the square root of this mean. The QRS onset and offset were automatically determined from the signal-averaged ECG in the standard frequency range before the filtering process (Jonson *et al.*, 1984; Xue *et al.*, 1995).

Trend samples of the signal-averaged ECG were obtained every 5 seconds. The noise level was calculated in each lead and expressed as an RMS value in an interval of 100 ms, starting 100 ms after the QRS offset. Trend samples for further analysis were obtained after one minute of registration, if the noise level did not exceed 3.2 μV in the frequency band 25-100 Hz. If the noise level exceeded 3.2 μV, the first subsequent trend sample with a noise level < 3.2 μV was used. The cut noise levels for the frequency band 50-150 Hz was 1.3 μV and 0.4 μV for 150-250 Hz.

For correlations with LVM, the RMS value in lead V1 and the highest RMS value in lead V5 or V6 was summed (RMS-Sokolow-Lyon). Likewise, the RMS value in lead aVL and V3 was summed (RMS-Cornell voltage), and RMS-Cornell product was calculated as QRS-duration, measured in the standard frequency range, times RMS-Cornell voltage. The correlations between LVM/LVMi and RMS-values in each individual lead were also investigated, as well as the sum of the RMS-values over all 12 leads ("Summed RMS").

Statistical methods

Continuous data were subjected to the Kolmogorov-Smirnov test to determine their distribution. Because of lack of Gaussian distribution among the RMS values, Spearman rank correlation coefficient, ρ, was used for correlations between LVM/LVMi and ECG measurements. A criterion level of $p < 0.05$ was considered statistically significant. All analyses were carried out using SPSS for Windows 11.5 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Study population

The study population consisted of 62 individuals (28 females and 34 males). Mean age was 46.4 years (SD 15.4 years, range 21-79 years). Body mass index ranged from 15.4 to 29.7 kg/m2 (mean 23.8 kg/m2, SD 3.5 kg/m2). The LVM varied between 96

and 223 g among the individuals (mean 167 g).

Comparison between LVM and standard ECG QRS amplitudes

The correlation between LVM and Cornell voltage was $\rho = 0.31$ ($p = 0.018$), versus $\rho = 0.40$ ($p = 0.002$) between LVM and Cornell product and $\rho = 0.35$ ($p = 0.006$) between LVM and Sokolow-Lyon. The highest correlation between peak-to-peak amplitude was found in lead V3 ($\rho = 0.41$, $p = 0.001$). Figure 1A shows the correlation between the peak-to-peak amplitude in V3 and LVM.

Comparison between LVM and RMS-values

In the 25-100 Hz frequency range, there was a significant correlation between LVM and RMS-Cornell product ($\rho = 0.35$, $p = 0.007$), but not between LVM and any of the other parameters (RMS values in individual leads, RMS-Cornell voltage and RMS-Sokolow-Lyon). Even when the two outliers in this frequency interval were excluded, the correlation was statistically significant ($\rho = 0.34$, $p = 0.010$). In the 50-150 Hz range, none of the correlations between RMS values and LVM was found to be significant. The highest correlation with LVM was found in lead V2 ($\rho = 0.20$, $p = 0.109$). In the 150-250 Hz frequency range, the only significant correlation was between LVM and Summed RMS ($\rho = 0.33$, $p = 0.011$). Figure 1B shows the best correlation in this set of correlations: the correlation between RMS-Cornell product and LVM in the 25-100 Hz range.

Comparison between LVMi and standard ECG QRS amplitudes

The correlation between LVMi and Cornell voltage was $\rho = 0.06$ ($p = 0.638$), versus $\rho = 0.08$ ($p = 0.528$) between LVMi and Cornell product and $\rho = 0.30$ ($p = 0.018$) between LVMi and Sokolow-Lyon. The highest correlation between LVMi and peak-to-peak amplitude was found in lead aVL ($\rho = 0.36$, $p = 0.004$). Figure 2A shows the correlation between the peak-to-peak amplitude in aVL and LVMi.

Comparison between LVMi and RMS-values

The best correlation between LVMi and any RMS-value in the 25-100 Hz range was found in lead V2 ($\rho = 0.33$, $p = 0.009$). In this frequency range, the correlations in lead V1 and aVL, as well as Summed RMS were also found to be statistically significant. In the 50-150 Hz range, the best correlation was found in lead V1 ($\rho = 0.37$, $p = 0.003$). Here, also the correlations in lead V2, V3, Summed RMS, RMS-Sokolow-Lyon, RMS-Cornell voltage, and RMS-Cornell product were statistically significant. In the 150-250 Hz range, the only statistically significant correlation was found between LVMi and RMS-Cornell product ($\rho = 0.26$, $p = 0.039$). Figure 2B shows the best correlation in this set of correlations: the correlation between RMS-V1 and LVMi in the 50-150 Hz range.

DISCUSSION

It has previously been demonstrated that the high-frequency ECG correlates better with LVMi in rabbits than does the standard ECG, both when considering normal rabbits and those with left ventricular hypertrophy ($r = 0.71$, $p < 0.001$ in normal rabbits) (Okin *et al.*, 1992). The present study, however, shows similar results for standard ECG and HF-QRS. Surprisingly, the established electrocardiographic criteria for detecting left ventricular hypertrophy

were found to have a low correlation with LVMi, with only Sokolow-Lyon being statistically significant. When considering LVM, standard ECG correlated far better with LVM than did HF-QRS. The highest correlations found in the present study were between V3 and LVM ($\rho = 0.41$) and between Cornell product and LVM ($\rho = 0.40$). The results indicate that the standard frequency range is better suited to predict LVM than are higher frequency ranges. The reason for the different findings is not obvious. Okin et al used a 44 Hz high-pass filter and they used time-voltage integrals of the vector QRS complex instead of RMS values.

The most frequently used frequency band when studying HF-QRS has been 150-250 Hz. The only statistically significant correlation found in the present study in this frequency band was between LVM and Summed RMS. It is not clear if this is a "true" significant correlation or a type I error because of the many correlations investigated in. However, it is possible that LVM is a confounding factor for Summed RMS, which has been used in previous studies (Pettersson *et al.,* 2000; Ringborn *et al.*, 2001; Trägårdh *et al.*, 2004).

A previous study (Carlsson *et al.*, in press) showed that there is a statistically significant correlation between LVM and established electrocardiographic left ventricular hypertrophy criteria in the same healthy study population used in this study, but that QRS duration alone is more strongly correlated to LVM than are other ECG criteria.

The basic physiology of HF-QRS is not fully understood, but Abboud et al have suggested that the morphological changes in HF-QRS seen in ischemic hearts can be attributed to a slowing of conduction velocity in the region of ischemia (Abboud *et al.*, 1991). If this is true, there is no obvious reason why patients with left ventricular hypertrophy should have higher RMS values than normal individuals.

For unknown reasons, a large inter-individual variation in RMS values has been found in the 150-250 Hz range (Pettersson *et al.*, 2000). It is possible that this variation could hide any potentially real additional effects of LVM in this frequency range. However, HF-QRS have been demonstrated to be quite reproducible within individuals (Batdorf *et al.*, 2004), which probably makes the method more useful for monitoring situations or when a previous HF-QRS recording is available.

It has been suggested that HF-QRS can be a diagnostic tool in various heart diseases. It has previously been shown that diminution of HF-QRS is a more sensitive detector of acute myocardial ischemia than changes in the ST segment of standard ECG (Abboud *et al.*, 1987; Pettersson *et al.*, 1998; Pettersson *et al.*, 2000). Several investigators have documented reduced HF-QRS in patients with old myocardial infarction compared to healthy individuals (Goldberger *et al.*, 1980; Bhargava *et al.*, 1981). Ringborn et al, however, found no difference in HF-QRS when comparing patients with ischemic heart disease, with and without old infarction (Ringborn*et al.*, 2001). It has also been shown that this entire group of patients with ischemic heart disease has lower HF-QRS than healthy individuals (Trägårdh *et al.*, 2004), suggesting that some pathophysiological process, other than healed myocardial infarction, diminishes HF-QRS in this group. The National Aeronautics and Space Administration has developed a software program that is able to analyze

and display changes in HF-QRS in real time, and their results on detecting coronary artery disease are promising (Schlegel *et al.*, 2004).

Limitations of the study

The present study only includes normal individuals. It is possible that the range of LVM is too small in the study and that a better correlation could be found if including patients with left ventricular hypertrophy as well.

There are previously defined criteria for determining left ventricular hypertrophy in the standard ECG. In other frequency bands, however, no such criteria have been established. In the present study, RMS analogs of established standard ECG criteria for detecting left ventricular hypertrophy were used for estimating LVM in the 25-100, 50-150 and 150-250 Hz intervals, as were also RMS values from individual leads. It is possible that other measurements in these frequency bands correlate better with LVM.

In summary

Contrary to previous results in animals, we found no better correlation between HF-QRS and LVM/LVMi than between standard ECG and LVM/LVMi in healthy human individuals.

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FIGURES

Figure 1. Scatter plots of the best correlation between measurements based on standard ECG and LVM (A) and between HF-QRS and LVM (B). The best correlation between standard ECG and LVM was found to be the peak-to-peak amplitude in lead V3 and between HF-QRS and LVM RMS-Cornell product in the 25-100 Hz range.

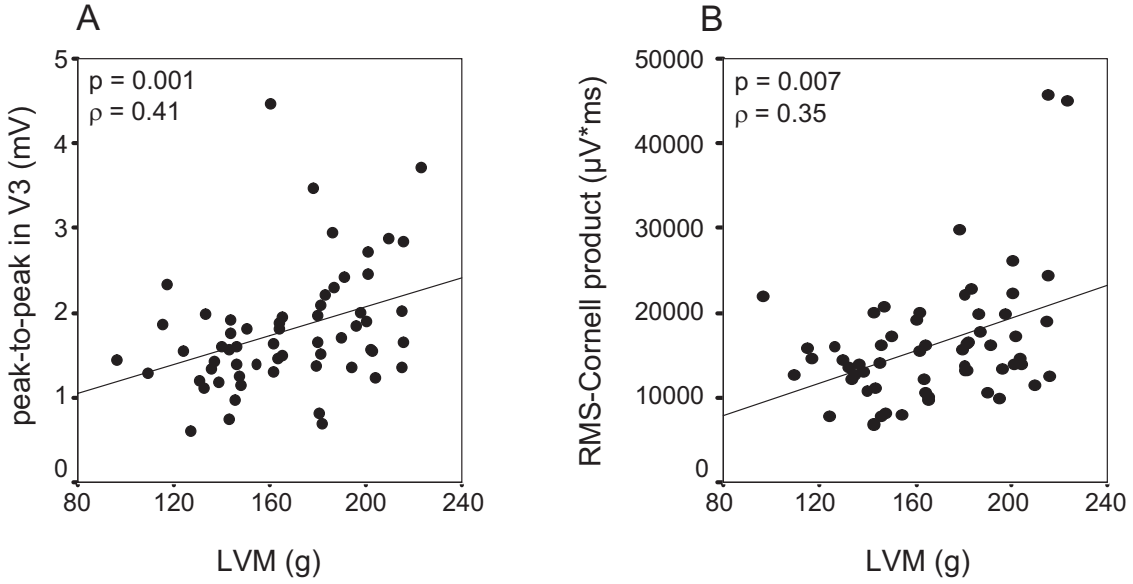

Figure 2. Scatter plots of the best correlation between measurements based on standard ECG and LVMi (A) and between HF-QRS and LVMi (B). The best correlation between standard ECG and LVMi was found to be the peak-to-peak amplitude in lead aVL, and between HF-QRS and LVMi RMS-V1 in the 50-150 Hz range.