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High-frequency electrocardiogram analysis in the ability to predict reversible perfusion defects during adenosine myocardial perfusion imaging

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ABSTRACT

Background: A previous study has shown that analysis of high-frequency QRS components (HF-QRS) is highly sensitive and reasonably specific for detecting reversible perfusion defects on myocardial perfusion imaging (MPI) scans during adenosine. The purpose of the present study was to try to reproduce those findings.

Methods: 12-lead high-resolution electrocardiogram recordings were obtained from 100 patients before (baseline) and during adenosine ^{99m}Tc-tetrofosmin MPI tests. HF-QRS were analyzed regarding morphology and changes in root mean square (RMS) voltages from before the adenosine infusion to peak infusion.

Results: The best area under the curve (AUC) was found in supine patients (AUC=0.736) in a combination of morphology and RMS changes. None of the measurements, however, were statistically better than tossing a coin (AUC=0.5).

Conclusion: Analysis of HF-QRS was not significantly better than tossing a coin for determining reversible perfusion defects on MPI scans.

Keywords:

HF-QRS, MPI, adenosine, myocardial ischemia

INTRODUCTION

Analysis of the electrocardiographic (ECG) signal has shown that particularly the QRS complex contains frequencies higher than the 0.05-150 Hz range used in the standard ECG (1). These high-frequency QRS components (HF-QRS) have been studied mainly in the 150-250 Hz range. Analysis of HF-QRS has been shown to provide promising clinical information, particularly in patients with ischemic heart disease. A previous study has documented reduced HF-QRS in patients with ischemic heart disease compared to normal individuals, but the inter-individual variation in HF-QRS was large (2). Analysis of HF-QRS has been shown to have a higher sensitivity than ST-segment elevation for detecting coronary artery occlusion (3, 4). Standard ECG, however, seems to be a better method for identifying the location of the ischemic area compared to HF-QRS (4).

Rahman et al. (5) investigated the ability of HF-QRS to estimate perfusion defects during adenosine myocardial perfusion imaging (MPI). They found that analysis of HF-QRS is highly sensitive (94 %) and reasonably specific (83 %) for detecting perfusion defects on MPI, and significantly more sensitive than analysis of conventional ST segments (18 %). This study used a new, advanced, real-time ECG software application developed by the National Aeronautics and Space Administration (NASA) based on HF-QRS root mean square (RMS) voltage values and reduced amplitude zones (RAZ) measurements (6, 7). Beker et al. (8) found that analysis of HF-QRS was 72 % sensitive and 73 % specific for identifying coronary artery disease in 62 subjects during treadmill exercise tests. Thus, these studies indicate that analysis of HF-QRS could provide an adjunctive tool in the diagnosis of coronary artery disease.

The use of adenosine myocardial perfusion imaging has been firmly established in numerous clinical studies and has become an essential component of clinical practice (9).

The purpose of the present study was to try to reproduce the findings of Rahman et al. (5) in another study population, thus investigate the ability of HF-QRS to predict perfusion defects at adenosine MPI.

METHODS

Study population

The study population consisted of 100 patients admitted for MPI at the department of Clinical Physiology, Lund University hospital, Sweden. Patients with pacemaker were excluded from the study. Of the 100 patients, 29 were excluded due to high noise levels in the ECG recording (root mean square (RMS) value within the QRS complex less than 3x the RMS isoelectric noise level) and 2 due to atrial fibrillation. After exclusions, 69 patients were therefore included in the study.

The study protocol was approved by the local research ethics committee and complies with the Declaration of Helsinki. Informed consent was obtained from each subject before enrolment.

MPI acquisition and analysis

During pharmacological stress, patients were injected intravenously with a body-weight adjusted dose (450-820 MBq) of ^{99m}Tc-tetrofosmin. Stress was performed with adenosine, infused at a rate of 140 μg/kg/min for 3 minutes before tracer injection, and continued for 2 minutes following injection. Low-load exercise on bicycle was performed when possible, to avoid side effects of adenosine. The ^{99m}Tc-tetrofosmin rest study was performed within 4 days (450-820 MBq).

Acquisition was performed approximately 45-60 minutes after tracer injection for both stress and rest images, using a dual-head gamma camera (Vertex, ADAC Corporation, Milpitas, California, USA) equipped with high-resolution, parallel-hole collimators. Data were collected at 32 projections over a 180° orbit, 40 seconds per projection, and 64×64 matrix zoomed to a pixel size of 5 mm. The starting angle was 315°. Attenuation correction was not used. Single photon emission computed tomography images were reconstructed and post-filtered (Butterworth order, 5.0; cut-off frequency, 0.6 for supine images and 0.66 for prone images). The single-photon emission computed tomography reconstruction and reorientation were automatic (Autospect plus, ADAC), but an experienced operator checked reorientation into three orthogonal views and made correction if needed. The images were evaluated by an experienced nuclear cardiologist completely blinded to the HF-QRS results. MPIs were considered to represent reversible perfusion defects if there was a larger perfusion defect in the adenosine study compared with the resting study. Similar perfusion defects at rest and adenosine may represent infarction, hibernation or attenuation artifacts and were reported as "fixed defects" in the current study.

ECG acquisition and signal averaging

ECGs were recorded for 5 minutes before adenosine infusion, while the patient was resting in the supine position, and during the entire adenosine infusion. Electrodes were placed at standard locations for chest leads and at the proximal part of the arms and the left iliac crest for limb leads (10).

Data collection of the ECG was performed on a Windows XP-based laptop with software supplied by CardioSoft, Houston, TX. A frequency response range of 0.5 to 300 Hz and a sampling rate of 1000 Hz were used to acquire the ECGs. A signal-averaging algorithm was applied in each lead to identify and average the QRS complexes in order to reduce the noise

level. Premature complexes and noisy beats were automatically eliminated via a cross-correlation function that rejects beats with a cross correlation coefficient less than 0.90. The first 100 accepted beats during rest were used for baseline. During the infusion, a 100-beat sliding template was established, going forward in time (i.e. most recent beat in, oldest beat out), and the values at peak infusion were used for analysis. The signal was bandpass filtered by the software using a Butterworth filter (11) in the time domain to include only frequencies between 150 and 250 Hz. The QRS duration was delineated from the standard ECG.

Analysis of HF-QRS

The presence or absence of three types of RAZs of the HF-QRS was noted. The three types include the Abboud (RAZ A), Abboud Percent (RAZ AP) and NASA (RAZ N) RAZs (5, 9). A RAZ score, ranging from 0 to 108 was calculated (5, 7). This score was calculated from 2 subscores: the "general RAZ burden" (0-36) and the "RAZ contiguity" subscore (0-72). The general RAZ burden derives from the severest RAZ type that is present is any given lead, with 3 points for a RAZ N, 2 points for a RAZ AP, and 1 point for a RAZ A. The contiguity score was calculated as follows: if a RAZ N is present, 3 points were given, and then 3 additional points were also given for every nth RAZ N present that was spatially contiguous to another RAZ N. Similarly, 2 points were given for RAZ AP, and 1 point for RAZ A. For contiguity, the orderly (Cabrera) sequence was used for limb leads. RAZ scores at baseline (RSAB) were calculated for all patients, both for V leads and CR leads. CR leads are precordial leads referenced to the right arm electrode, and maximizes the QRS voltages (12, 13).

The RMS values of each HF-QRS were determined by 1) squaring the amplitude of each sample, 2) determining the mean of these squares, and 3) determining the square root of this mean. Changes in RMS values from the rest recording to the end of the adenosine infusion were expressed as a percentage (%ΔRMS). The three contiguous leads which had the greatest

change in %ΔRMS (positive and negative) were determined and their individual %ΔRMS was summed to create a %ΔRMS-3 score, both in V leads and CR leads. The same procedure was repeated for four contiguous leads to produce a %ΔRMS-4 score (5).

Statistical analysis

Receiver operating characteristics (ROC) analysis was performed, using a non-parametric approach, for the HF-QRS measurements (RSAB, %ΔRMS-3, %ΔRMS-4, RSAB+%ΔRMS-3, RSAB+%ΔRMS-4 in CR and V leads). The area under the ROC curve (AUC) with 95% confidence interval (CI) was calculated to express the overall diagnostic accuracy of the test. The level of significance was set at $p<0.05$. Analyses were carried out using SPSS 11.5 (SPSS Inc., Chicago, IL, USA).

RESULTS

After exclusions, the study population consisted of 69 patients (n = 47 male, 68%). Mean age was 64 years (range 10-85 years). Of the 69 patients, 19 had at least 1 reversible defect on their MPI scan (MPI-positive group) and 50 did not (MPI-negative group). Seven patients, of whom 2 were in the MPI-positive group, had either a left (n=5) or right (n=2) bundle branch block. In the MPI-positive group, 6 patients were examined in the supine position and 13 did a light-load exercise on a bicycle. In the MPI-negative group, 23 patients were examined in the supine position. In total, 27 patients had fixed defects on their MPI scans (13 in the MPI-positive group and 14 in the MPI-negative group).

The patients were examined in different combinations: all patients (n=69), cycling patients (n=40), supine patients (n=29), patients with fixed defects (n=27), patients without fixed defects (n=42), and supine patients without fixed defects (n=16, most similar to the study

group in reference (5)). ROC diagrams for RSAB, %Δ-RMS-3, %Δ-RMS-4, RSAB+ %Δ-RMS-3, and RSAB+ %Δ-RMS-4 for both V leads and CR leads were established. Overall, the RSAB contributed more to the area under the curve (AUC) than did %Δ-RMS, and the best individual measure was found to be RSAB+%Δ-RMS-4 in CR leads for all subgroups but one. However, none of the measurements were found to be statistically better than "tossing the coin" (i.e. AUC = 0.5). The best AUC was found for all supine patients (AUC=0.74, CI 0.48-0.99, p=0.080), figure 1. For all patients the best AUC was found to be 0.60 (CI 0.45-0.75, p=0.202); for cycling patients 0.52 (RSAB in V-leads) (CI 0.34-0.71, p=0.806); for patients with fixed defects 0.71 (CI 0.52-0.91, p=0.058); for patients without fixed defects 0.55 (CI 0.27-0.82, p=0.719); for supine patients without any fixed defects 0.72 (CI 0.31-1.0, p=0.253). Excluding patients with bundle branch block had only a small influence on the results.

DISCUSSION

The main result of the present study is that RSAB contribute more to the possible detection of reversible perfusion defects on MPI scans than does %ΔRMS, but none of the measurements (neither V leads nor in CR leads) were found to be statistically better than AUC = 0.5.

The findings that RSAB perform better than %ΔRMS (and that the individually best combination was RSAB+%ΔRMS-4 in CR leads) was consistent with previous findings from Rahman et al. (5). Their results, however, showed that analysis of HF-QRS are highly sensitive and reasonably specific for detecting reversible perfusion defects on MPI scans. There are several possible reasons for the different results. It is known that sitting up causes changes in HF-QRS compared to lying in the supine position (for example RMS voltage

decreasing significantly in lead V3, and the number of RAZs lost in the 12 leads significantly exceeding the number of RAZs gained) (14). The %ΔRMS values might therefore be different in the supine patients than in the cycling patients. Other differences in study population between the two studies could be a different number of patients with old myocardial infarction or ischemic cardiomyopathy. Ischemic heart disease has been shown both to decrease RMS voltages (15-17) and increase the RAZ counts (7), and ischemic cardiomyopathy has been shown to increase RAZ counts (18). Other possible explanations could also be differences in the prevalence of left ventricular hypertrophy, which could affect HF-QRS (19). The subpopulation in the present study most similar to the population in the previous study (supine patients without fixed defects) was very small (n=16), so no certain conclusions can be drawn from that group.

It has been shown previously that changes in HF-QRS are more sensitive than the standard ECG for detecting myocardial ischemia during angioplasty-related coronary artery occlusion (3, 4, 6). It has been debated whether administration of adenosine causes “true myocardial ischemia” (oxygen deficit) or only reflects the impairment of flow reserve caused by the atherosclerotic stenosis. One study has shown that cardiac output doubles in healthy individuals during adenosine infusion (20), thus causing a real workload on the heart, whereas others argue that true ischemia during adenosine administration only occurs in the presence of coronary steal (21). It is not possible to know whether true ischemia occurred or not in the present study or in the previous study by Rahman et al. (5). It is possible that the number of patients with real ischemia in the two studies differs, thus causing different results.

It is well known that the presence of ST-segment depression with exercise has reasonable sensitivity and specificity for predicting coronary artery disease (22, 23). The interpretation of these changes is not reliable when there is electrocardiographic evidence of left ventricular hypertrophy or in patients taking digitalis (22, 23). During adenosine infusion, however, it has

been shown that the majority of patients with reversible MPI scans do not have ST-segment depression. Its presence, however, has been shown to be predictive of significant coronary artery disease (24-26). This has also been found to be true in the presence of left ventricular hypertrophy but not in patients taking digitalis (26). It is possible that the small increase in myocardial oxygen consumption during adenosine infusion, as reflected in an increase in rate-pressure product (26), may be sufficient to generate ischemia in patients with severe stenoses. This might explain ST-segment depression some patients during adenosine infusion.

The physiological mechanisms underlying HF-QRS are still not fully understood. One theory is that HF-QRS are related to the conduction velocity and the fragmentation of the depolarization wave in the myocardium. In a three-dimensional model of the ventricles with a fractal conduction system, high numbers of splitting branches were shown to be associated with more HF-QRS. This experiment also showed that the changes seen in HF-QRS in patients with myocardial ischemia might reflect slowing of the conduction velocity in the region of ischemia (27). This mechanism has been tested by Watanabe et al. (28), who infused sodium-channel blockers into the left anterior descending coronary artery in dogs. In their study, 60 unipolar ECGs were recorded from the entire ventricular surface and were signal-averaged and filtered in the 30–250 Hz frequency range. The decrease noted in the HF-QRS correlated linearly with the local conduction delay. The results suggest that HF-QRS is a potent indicator of disturbed local conduction. An alternative theory is that HF-QRS reflect the shape of the original electrocardiographic signal. Bennhagen et al. (29) showed that RMS values of the depolarization signal correlate poorly with the signal amplitude but highly with the first and second derivatives, i.e., the velocity and the acceleration of the signal. The autonomic nervous system also might affect HF-QRS. For example, changing from supine to upright position causes significant change in HF-QRS in some leads compared with the supine position (14).

Twenty-nine per cent of the patients in the present study were excluded due to high noise levels. The majority of these were in the group doing light-load exercise on a bicycle during the adenosine infusion. To be able to analyze HF-QRS in more patients during exercise therefore a better handling of signal-to-noise issues is required.

CONCLUSIONS

The present study could not establish that analysis of HF-QRS is significantly better than "tossing a coin" for determining reversible perfusion defects on MPI scans, but in consistency with previous studies, the best individual measurement was a combination of RAZ score at rest and RMS changes during stress in CR leads.

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Figure legends

Figure 1. ROC diagram of the best individual measure based on AUC (RSAB+%ΔRMS-4) in the best subgroup (all supine patients); AUC=0.74, CI 0.48-0.99, p=0.080. In this group, 6 patients were in the MPI-positive and 23 in the MPI-negative group.