

Diagnosis of Ischemic Heart Disease Using High Frequency ECG – Literature Review

Introduction

Several attempts have been made by researchers to expand the diagnostic capabilities of the electrocardiogram (ECG). One of the most promising methodologies to date is the analysis of the high frequency spectral components of the QRS complex (HFQRS). Investigations of changes in the HFQRS in multiple clinical conditions revealed a close relation between HFQRS and myocardial ischemia. Specifically, ischemia was associated with reduction in the intensity of the HFQRS in rest and stress ECG, as well as during coronary balloon occlusion. Consequently, HFQRS has been considered an excellent candidate for enhancing the limited capabilities of the standard ECG to diagnose ischemic heart disease (IHD).

The purpose of this review is to briefly summarize the knowledge that has been gained in this field to date. The paper presents the clinician with an evidence-based literature review aimed at facilitating an effective use of this methodology in the clinical setting.

Historical and technical overview

In everyday clinical practice, changes in ECG morphology occurring during the repolarization phase of the cardiac cycle (ST segment and T wave) are used for diagnosing ischemia. It seems only natural that ischemia also causes morphological changes to the depolarization phase (QRS complex) of the cardiac cycle, and thus can be identified by these changes.

The early work of Langner was the first to suggest that important clinical information can be obtained from the high frequency QRS signal.^{1,2,3} Later on, several comparative clinical studies suggested that certain waveform features of the HFQRS indicate myocardial disease. In the early papers, the terms “notches” and “slurs” were often used to describe waveform features within the QRS portion, when ECG recorders were used at high amplification and at high paper speeds. These early studies were done using analog equipment for recording and analyzing the data, and included the whole range of frequencies > 80 Hz. It is important to note that these frequencies are usually filtered out by standard ECG equipment. The development of digital ECG equipment and digital signal processing methods, together with the appearance of micro-computers, paved the way to a more quantitative approach in analyzing HFQRS signals.

It is important to note that standard ECG analysis is performed in the 0.05 - 100 Hz frequency band. However, spectral analysis^{4,5} of the ECG signal showed that higher frequency spectral components are present in the ECG waveform and notching within the QRS complex is caused by frequencies both above and below 100Hz. The terms “high frequency,” “high fidelity,” and “wideband electrocardiography” have

been used by several investigators to refer to the process of recording ECG with an extended bandwidth of up to 1,000 Hz. The amplitude of the HFQRS signal is measured in microvolts, whereas the standard ECG is measured in millivolts. In addition, the ECG signal typically includes noise components of several origins. While the environmental noise can only partially be reduced, if at all, skeletal muscle activity contributes noise in the high frequency range that cannot be filtered out. Therefore, this type of noise needs to be reduced using signal averaging techniques. The high frequency components are extracted from the averaged QRS complex by bandpass filtering. Different studies used different bandpass frequency ranges. Abboud et al. studied acute myocardial ischemia, using 150 - 250 Hz,⁶⁻¹² whereas Goldberger et al. used 80 - 300 Hz frequency range to study the effect of previous myocardial infarction (MI) on the HFQRS.^{13,14}

The quantification of the HFQRS signal was done using multiple approaches, including: peak-to-peak amplitude,^{13,15} reduced amplitude zone,^{6,10,16} and the integral of the signal.^{17,18} The most widely used approach for HFQRS quantification is calculating the root-mean-square (RMS) value of the signal.^{7,8,12,14,17,19-24} The RMS value of the HFQRS represents the average power of the signal over the entire QRS duration.

The inter-subject variation in HFQRS levels in all leads limit the clinical use of the calculated "normal" baseline values. Therefore, each subject needs a personalized reference baseline value to identify ischemia. The temporal variation in the HFQRS was found to be very low by several workers,^{13,21,25,26} indicating the high reproducibility of the signal.

In several studies, spatial variation was noticed between leads, with the highest HFQRS amplitude found in the precordial leads. It is believed that there is an increase in HFQRS as leads are set closer to the heart.^{7,25}

Bhargava and Goldberger reported that in healthy individuals the HFQRS increased during and immediately after exercise.²³

Simulation experiments, described by Abboud et al.²⁷ were used to investigate the physiological origin of HFQRS related phenomena. The conclusion was that the HFQRS signal is related to the fragmentation of the electrical activation wavefront, as well as to morphological changes in the myocardial action potential. When ischemia was simulated in the model, there were changes similar to those observed during ischemia in animal and human studies, namely, decreased HFQRS amplitude. Therefore, it was concluded that the HFQRS changes in ischemia are explained by slowing of conduction velocity in the ischemic region. The slowed conduction supposedly reduces the fragmentation of the activation wavefront and thus shifts the high-frequency components to lower frequencies.

HFQRS in Various Clinical Scenarios

Rest: Abboud et al.²⁸ found decreased amplitudes of the HFQRS in patients with asymptomatic coronary artery disease, compared to healthy subjects during rest.

Acute myocardial ischemia: Several studies, first with animals and later in human subjects, showed reduction in HFQRS amplitude during acute myocardial ischemia. Mor-Avi et al.⁷ obtained recordings from epicardial and body-surface electrodes in dogs subjected to balloon occlusion of left anterior descending

artery. The HFQRS recorded from the left-ventricular epicardial surface exhibited a considerable reduction in amplitude, compared to the non-ischemic right-ventricular surface recording, which remained unchanged. Importantly, ECG recorded using body surface electrodes exhibited concomitant reduction in HFQRS amplitude. Other animal studies showed similar results.^{6,9 - 11}

Old MI: Several studies have looked into the HFQRS signal in healthy patients versus that of subjects with old MI. Most investigators noticed reduced HFQRS amplitude in subjects having old MI.

Goldberger et al.^{13,14,29} reported that HFQRS levels were significantly lower in leads V2 and V5 in patients with old anterior and old inferior MI. In patients with old inferior MI, the HFQRS was lower in leads II, aVF and III. Similar results were reported by Talwar et al.,³⁰ investigating the HFQRS in lead III in patients with old inferior MI.

Using X, Y and Z leads, Berkalp et al.¹⁹ showed reduced HFQRS amplitude in patients with old inferior or anterior MI in the frequency band of 150-250 Hz. Novak et al.³¹ contradicted these findings, reporting HFQRS (>90 Hz) to be higher in leads X, Y, and Z in post-MI patients compared with healthy subjects. Pettersson et al.³² found no change in the HFQRS between normal and post MI patients regardless of infarct location or size. This was the case for frequency ranges of 150-250 Hz or 80-300 Hz.²⁵

The conflicting results could possibly be explained by the fact that the controls in the last study were IHD patients and not healthy subjects. Another point is that the above-mentioned studies diagnosed MI using ECG analysis only, which is known for its limited accuracy in differentiating between healthy and MI groups. Multiple cardiac imaging techniques could have better differentiated the groups and thus resolve some of the conflicting results. Goldberger¹³ suggested that the decrease in HFQRS in patients with old MI is due to overall loss of the electromotive force, or a slowing of conduction associated with the scar tissue. However, it is possible that the HFQRS decreases only when there is an associated ischemic region in the same area, similar to residual ischemic regions around the MI, the patient remaining asymptomatic. Alternatively, the scar tissue may not produce or propagate any electrical activity. Thus the overall activation time of the myocardium is prolonged due to the "detour" the electrical activation takes in front of the scar tissue, and not due to conduction slowdown.

HFQRS in Different Tests and Procedures

Reperfusion: Studies during thrombolytic therapy, using a reduced number of ECG leads in acute MI patients, showed increase in HFQRS after reperfusion. This suggested that the analysis of HFQRS may offer a more potent method for detecting successful reperfusion than the commonly practiced methods (ST-T and/or chest pain changes).^{20,21} Aversano et al.²¹ studied changes in HFQRS with reperfusion and reported 100% sensitivity and 92% specificity in identifying failed-reperfusion therapy in the ST elevation acute coronary syndrome.

Exercise induced ischemia: Abboud et al.³³ compared changes in HFQRS between the rest period (before exercise testing) and the recovery period (after exercise), in nonischemic and asymptomatic subjects and in patients with known IHD. It was found that the normalized cross-correlation coefficient of the HFQRS signal was significantly higher in the control group. Analysis of the QRS power spectrum showed that HFQRS increased with exercise in non-ischemic subjects.²³ In a comparative study by Beker

et al.,²² the HFQRS was recorded continuously during the exercise testing. Healthy subjects had higher HFQRS RMS values during and after the exercise test compared with subjects with angiographically proven ischemic heart disease (>75% obstruction in at least two main coronary arteries).

Percutaneous coronary intervention (PCI): Abboud et al.⁸ showed a reduction in HFQRS amplitude in both intracoronary and surface ECG tracing in a sample of patients undergoing PCI (n=11). In contrast, some of the patients (6/11, 54%) showed no change in the surface ST-T segment in any lead during the procedure. In addition, HFQRS reduction occurred earlier than changes in the ST segment, indicating improved sensitivity of the HFQRS signal to detect ischemia over conventional ECG analysis.

In an elaborate study by Pettersson et al.,²⁵ it was found that HFQRS amplitude significantly reduced ($29 \pm 18\%$) in at least one lead (bipolar, pseudo-orthogonal) in all 19 patients recorded during coronary balloon inflation. The HFQRS reduction was most common in lead X. An increase in HFQRS amplitude was also found, most often in lead Y. This result was also reported by Abboud et al.⁹ in dogs where reduced amplitude of HFQRS was seen in leads X, Z but not in Y. There was no relationship between the lead showing the maximal decrease and the occluded vessel. In 15/19 procedures, there was $\geq 0.1\text{mV}$ ST segment deviation in at least one of the 12 standard leads during inflation. There was no significant correlation between the maximal ST deviation and the maximal absolute or percentage decrease in HFQRS RMS value in any lead.

In a recent study by Pettersson et al., HFQRS was obtained from standard 12 lead set in 52 patients³⁴ during coronary balloon occlusion. It was shown that the HFQRS amplitude decreased significantly in at least one lead in 46 of the 52 patients during coronary balloon inflation (88% sensitivity). The criteria for significant HFQRS decrease were taken from Aversano et al.²¹: Absolute RMS change of more than $0.6\mu\text{V}$ or relative change above 20%. In contrast, significant changes in the ST segment were observed only in 37 patients (71% sensitivity, $p > 0.01$). Sensitivity was highest in the occluded left anterior descending coronary artery (LAD), both for ST-elevation (94%) and HFQRS (100%). The right coronary artery (RCA) showed the largest difference between the methods, in that the ST-elevation reached a sensitivity of 61% versus 87% for HFQRS.³⁴ When ST-deviation (depression or elevation) criteria were used, the sensitivity of the ST method reached 79% (41/52), thus causing the difference from the HFQRS technique to be non significant ($p = 0.09$). In seven patients, the HFQRS criteria, but none of the ST-segment criteria, were met although the patients had chest pain during inflation. Two patients met only the ST-deviation criteria. In a more detailed analysis of a subgroup of patients (n=37), the HFQRS exhibited a significant increase in one or more leads during balloon inflation in 24/37 patients. Furthermore, an increase in HFQRS amplitude was observed in four out of the five patients with no HFQRS decrease. The increase was typically observed in only a few of the leads (2.4 ± 1.6 leads). The highest increase was found in patients with occlusion of the left circumflex artery (LCX) (seen in the anterior leads); the smallest increase was in the LAD group. The authors' explanation was that the conduction velocity increases in the non-ischemic myocardium (as seen previously in healthy subjects²⁴), in association with the hyperdynamic compensatory wall motion (after reperfusion).³⁴ The distribution of leads showing decreased HFQRS was wider than that of the standard leads showing ST changes. The presence of proximity effect when recording from the anterior chest leads is supported by their findings that both the marked decrease in HFQRS during LAD occlusion and the increase during LCX occlusion, are seen in those leads. Abboud et al.⁹ noted a reduction in the HFQRS in dogs 20 sec after artery occlusion. These changes were not

accompanied by a significant change in the standard ECG. Pettersson found the HFQRS to be less indicative of the location of the ischemic region than the standard ECG. A criticism of this finding is that sub-grouping according to the artery occluded, during the PCI, gave a small number of participants in each group.

Conclusion

The studies reviewed here indicate the significant amount of knowledge on HFQRS that has accrued during the last three decades. It was shown repeatedly that HFQRS is a highly sensitive indicator of myocardial ischemia. Moreover, HFQRS related phenomena were shown to be manifested at lower levels of ischemia, compared with ST-T changes.

HFQRS has been investigated in a variety of clinical settings. These studies provide a sound scientific basis for a clinical application aiming at accurate detection of ischemia.

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The HyperQ™ Stress System received US FDA clearance (510K) and CE marking.