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Intra-QRS Spectral Changes Accompany ST Segment Changes During Episodes of Myocardial Ischemia

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Abstract

Background—Coronary artery disease and myocardial ischemia cause substantial morbidity and mortality. While ischemia is traditionally diagnosed on the 12-lead electrocardiogram (ECG) by shifts in the ST segment, electrical changes are also produced within the QRS complex during depolarization of ischemic ventricular tissue, though these are often of small amplitude and can be missed in traditional ECG analysis. We explore the utility of an easily implemented spectral analysis method for detecting intra-QRS changes during episodes of myocardial ischemia, using Holter recordings from the European ST-T database.

Methods—Time-frequency distributions of QRS complexes from each recording were computed using the continuous wavelet transform. Indices corresponding to frequency content of four overlapping frequency bands were computed: F1 (24–35 Hz), F2 (30–45 Hz), F3 (40–60 Hz), and F4 (50–80 Hz). Values of these indices were compared during annotated episodes of ST change and during a baseline during the recording.

Results—Marked changes in intra-QRS frequency content were identified during ischemia, grouped by ECG lead analyzed. In lead III, a pronounced and statistically significant increase in the highest frequency sub-bands (F3 and F4) was consistently observed. Analysis of anterior precordial leads also showed significant increases in F4.

Conclusions—Intra-QRS time-frequency analysis using the continuous wavelet transform can identify a spectral signature corresponding to myocardial ischemia in the range 24–80 Hz. Intra-QRS spectral analysis has the potential for many clinical applications.

Keywords

electrocardiography; ambulatory ECG; myocardial ischemia; intra-QRS changes; depolarization; wavelet transform

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Introduction

Coronary artery disease is the leading global cause of death, claiming greater than 17 million lives annually, with rising prevalence [1]. Episodes of myocardial ischemia in patients with coronary artery disease are conventionally diagnosed by ST segment depression on the 12-lead electrocardiogram (ECG). However, ST segment criteria are imperfect for identifying ischemia. The specificity and sensitivity of ST-segment depression during exercise testing for ischemia has been estimated at 70% [2]. In this study, we investigate novel time-frequency (temporo-spectral) criteria that may serve as an adjunct to ST-segment criteria in the detection of coronary artery disease.

In addition to well-described changes in cellular repolarization, myocardial ischemia is known to cause changes in tissue depolarization, including depressed action potential upstroke, electrical uncoupling, and reduction of conduction velocity [3]. These changes influence the fine shape of the depolarization wavefront in the ischemic region, and can project themselves onto extracellular or body-surface recordings as low-amplitude intra-QRS components. These ischemia-related depolarization changes in the ECG are difficult to appreciate in time domain, but produce potentials with frequency content ranging from 40 to 250 Hz. Changes in this range have been demonstrated in various models of ischemia in preclinical and clinical settings [4–11]. However, the mode of detection, magnitude, direction, and frequency range of these changes have varied widely depending on the experimental and clinical conditions, with much attention devoted to the diminution of potentials seen using HFQRS analysis (in the range above 140 Hz) [12].

The wavelet transform, which converts time-domain representations of signals into the frequency domain, is known to be sensitive to small amplitude, short-lived signal components [13, 14]. The goal of the present study was to apply the wavelet transform and use spectral analysis to study real-world ambulatory recordings from patients during episodes of ischemia from the European ST-T database [15], with the hypothesis that intra-QRS changes in the ECG in the frequency range between 24 Hz and 80 Hz accompany ST deviations in ischemia.

Materials and Methods

We analyzed data from the European ST-T ischemia database [15]. This database contains data derived from patients with coronary artery disease and either stable angina or silent ischemia. The database contains recordings from two body surface ECG leads, which varied from patient to patient, lasting 120 minutes in duration, sampled at 250 Hz. Ischemic ST depression episodes were defined as annotated by two cardiologists, identifying episodes of at least 30 seconds during which ST depression is $> 100 \mu\text{V}$ (measured 80 ms after J-point for heart rate less than 120 beats/min, or 60 ms otherwise). All cases from the database with at least one ischemic episode and inferior (lead III) or anterior precordial leads (either lead V3 or V4) available were included. We used clinical information and cardiologist annotations from the database to further identify patients and signals for analysis. Patients with angiograms revealing normal coronary arteries and those with no reported clinical history of coronary artery disease were excluded from analysis. While the recordings were

generally of good quality and had minimal noise, episodes that the reviewing cardiologists annotated as containing significant noise or unreadable (due to “galvanic potentials” from poor or intermittent skin-electrode contact, significant myoelectric potentials, or rare large amplitude electromagnetic interference) were censored from analysis. These episodes of noise were present in a small fraction of the cases, and were usually brief episodes within the 120 minute recording. Also, annotations identifying ST depressions that resulted from axis shift or rate related intraventricular conduction delay were not included in analysis.

For each patient, signal traces and annotation information for both leads were read in from the database. A high-pass Butterworth filter of cutoff 2.5 Hz to minimize impact of baseline wander. The ST segment was computed, and Time-Frequency Distributions (TFDs) for each QRS complex within the recording were then calculated using the Continuous Wavelet Transform (CWT)[16] with window length of 140 ms and complex Morlet mother wavelet.

From the TFDs, intra-QRS sub-band energy indices were calculated by integrating the coefficients across the QRS complex, in four overlapping sub-bands: F1 (24–35 Hz), F2 (30–45 Hz), F3 (40–60 Hz), and F4 (50–80 Hz), with units of time-summed spectral density. Finally, each sub-band index was trended across the 120 min recording. A low pass filter cosine window of duration 140 seconds was applied to smooth these trends and account for beat-to-beat fluctuation. A case baseline interval was established using the ST segment by identifying an interval of at least 5 minutes at the beginning of the recording (shortly after hook-up to the patient) during which the ST deviation remained consistently less than 100 μ V with fluctuations less than 50 μ V. All annotated episodes of ischemia (both the mean value across the episode, and the maximal value during the episode) were compared against the corresponding value during the case baseline, using a paired t test. Statistical p values less than 0.05 were considered significant. All values are reported as mean, plus or minus standard error of the mean. All signal analysis software was developed in MATLAB (The MathWorks, Natick MA).

Results

Clinical characteristics

Clinical characteristics of the patients analyzed are represented in Table I, organized by leads available in the recording: lead III (N=30, 86 total ST depression episodes) or anterior precordial leads V3 or V4 (N=25, 73 total ST depression episodes). This patient population was predominantly male with mean age of 53, with a heavy burden of ischemia and typically multiple episodes of ST depression per two hour recording (average 2.9 per recording).

Changes in the time frequency distribution accompany episodes of ST-segment depression and ischemia

A representative case from the database, from a patient with triple vessel disease and prior myocardial infarction, was analyzed to compare the TFD derived from lead III during ischemia compared to baseline conditions. These are plotted in Figure 1A as a color-coded representation of a three-dimensional plot, depicting energy for each frequency at a given

time within the QRS complex, alongside the corresponding the QRS complex (Figure 1B). While gross changes within the QRS are not evident via time domain analysis between baseline and ischemia, the TFD shows the emergence of a high frequency peak centered at 50 Hz.

Several measures were considered to quantify the changes in frequency content. A “dominant frequency” was initially considered, but this metric is insensitive to finer changes in subcomponents of the TFD, particularly the higher frequency ranges of interest that may comprise a smaller fraction of the total energy of the QRS complex. We therefore analyzed frequency content over the sub-bands outlined in “Methods” F1 through F4. For a typical undiseased QRS complex, these pass bands account for <15% of the total energy. The trends for the ST segment computed from our algorithm are plotted for bands F2, F3 and F4 for the same case from the database in Figure 2. The episode duration (by ST segment criteria) is denoted by the shaded area. The frequency indices clearly show a correlation with the ST episodes, with a sharp rise during the episode. Other ST segment shifts are also detected (for example at 85 minutes and 100 minutes) but did not meet criteria for labeling as an ischemic ST depression by reviewing cardiologists. Similar data is produced with analysis of data from lead V4 in Figure 3, from a patient with single vessel left anterior descending artery disease. A sharp and sustained rise in F3 and F4 is noted, in this case preceding ST segment depression by several minutes and illustrating that changes can persist after the ST segment has returned to normal. These trends demonstrate a clear and consistent rise in high frequency components during episodes of annotated ischemia.

Magnitude of ischemia-related frequency shifts by electrocardiographic lead

Since ischemia-related frequency shifts may differ depending on the electrocardiographic vector utilized, analysis was conducted in groups according to lead analyzed: inferior frontal (lead III) and anterior precordial (leads V3-V4). The mean value of each index is shown for each episode of ischemia and compared to the mean value during baseline in Table II. For lead III, ischemia was associated with an upward shift in the energy of the highest frequency sub-band indices (F3 and F4). The mean increase in the F3 index was 1.30 ± 0.45 compared to baseline ($p = 0.005$), and the mean increase of the F4 index was 0.77 ± 0.26 ($p=0.004$). Similar findings were seen for lead V3-V4, with a statistically significant mean increase in the F4 index (increase of 0.25 ± 0.07 , $p = 0.0003$).

For the above analysis, the mean value of each index was used, simply averaging the frequency index across the period of annotated ST depression. This had the effect of decreasing the power to detect changes, since the change in the frequency index often did not perfectly align with the start and stop of the annotation (see for example the shaded region in Figure 3). As an additional method of analysis, the change in the maximal value achieved during the annotated episode (compared to the maximal value during the baseline) is displayed in Table III. With this analysis, pronounced changes again occurred in F3 and F4, but statistically significant changes also occurred in the F2 and F1 bands. For F2, though the mean value during ischemia was not significantly different, the maximum value achieved during the episode was 3.04 ± 0.81 greater for lead III ($p=0.0003$) and $1.23 \pm$

0.57 greater for leads V3-V4 ($p=0.033$). For F1, for lead III this index increased 8.29 ± 2.51 and for leads V3-V4, 2.83 ± 1.40 ($p=0.001$ and 0.046 , respectively).

These findings overall suggest that for both leads, across frequencies between 24 and 80 Hz, ischemia was associated with an increase in fractional energy. The effect was most pronounced for the highest frequency bands.

Outlier analysis for high frequency sub-bands

In Figure 4, for both leads III and V3-V4, we assigned a sequential episode number for all annotated ischemic episodes identified (abscissa), and plotted the change in mean F4 index on the ordinate in a Manhattan bar plot. We performed analysis on the 10 episodes for both the inferior and anterior leads which had an opposite behavior during episodes of ischemia (shaded in panels A and B). For lead III, we surprisingly found that out of these 10 episodes, in 5 (50%) concomitant massive ST elevations were present during the episode, whose concomitant ST depressions were being annotated. Furthermore, when sorted by magnitude of shift, episodes with ST elevation accounted for the 3 most discordant outliers in the Figure (highlighted in red, in the shaded portion of the plot). Similarly, among the outliers in lead V3 analysis, in 6 of the 10 of the episodes with most discordant shift (60%), a concomitant annotated episode of ST elevation was noted, including 3 of the most discordant 4 observations. In panel C of the figure, two representative outlier QRS complexes and corresponding TFDs derived from lead III are shown, demonstrating a marked downward shift in frequency content. Though these cases were not removed from our analysis in order to be inclusive, these findings suggest that when ischemia is present and extensive enough to produce ST elevation, it may produce different shifts in frequency content of the QRS complex (see Discussion).

Discussion

In this study, we assessed for intra-QRS changes during episodes of ischemia identified by changes in the ST-T segment of the ECG using a real-world database of patients with coronary disease. We show that spectral analysis using the continuous wavelet transform can identify important shifts in frequency content of the QRS complex that correlate with annotated episodes of ischemia. Analysis of the depolarization phase of the 12-lead ECG may therefore serve as an adjunct to ST segment analysis in the diagnosis of myocardial ischemia.

Comparison to prior studies

There is conflicting evidence in the literature regarding the presence, directionality, and consistency of intra-QRS potentials during myocardial ischemia. These discrepancies may reflect different experimental settings (ischemia induced via balloon inflation, versus clinically-identified ischemia), clinical versus pre-clinical setting (therapeutic balloon inflation in patients[6, 7, 13] versus arterial occlusion in canine models[17]), and technique used (signal averaged ECGs versus bandpass filtering [5]).

Our study analyzed patients with established coronary artery disease during episodes of ST depression, representing “real world ischemia”, and focused on frequency ranges between

24 and 80 Hz (which, given the Nyquist limitation on detectable frequency of half sampling frequency, permits use of the technique on standard ECGs). Importantly, the frequency band examined in our study differs markedly from prior studies using HFQRS analysis, which involves higher frequencies of up to 250 Hz[6, 12]. It is reasonable to consider that the type of analysis presented here could be complementary to HFQRS analysis, and the directionality of passband component changes may be different (see discussion below). Accounting for these factors, our findings are compatible with the idea of increased “abnormal intra-QRS potentials”[8] which emerge during ischemia, as has been reported in multiple preclinical and clinical studies of ischemia[7, 10, 19]. Use of the CWT, a transform which is well-suited to identifying low-amplitude higher-frequency components which simultaneously provides high resolution of time and frequency within the QRS, may have assisted in the identification of these potentials in our study.

Mechanism for generation of high frequency components in the QRS

The mechanism for intra-QRS changes remains incompletely understood, but given the cellular electrophysiologic changes that accompany ischemia, it is likely that locally altered electrical wavefront propagation plays a major role. In a two-dimensional computational modeling study incorporating regionally ischemic tissue, new frequency components in this range were observed in local electrograms corresponding to fractionation of the depolarization wavefront around ischemic tissue[20]. In that study, the ability to detect these potentials differed based on the local electrogram vector, with highest sensitivity using vectors orthogonal to the wavefront of propagation[20]. We find from the data from this study that there are changes in the magnitude of change that depend on the lead being analyzed. Since the potentials recorded on surface ECG reflect the relation between the recording vector and the vector representing electrical activation, both electrode configuration and the size and distribution of ischemic tissue may affect the frequency content within the QRS. This relation may allow for tailoring of spectral markers depending on coronary artery affected and lead used in analysis.

Reduction of higher frequency components within the QRS, as previously reported[12], may reflect slowed conduction velocity in ischemic myocardium which masks the contribution of wavefront fractionation within the QRS complex. It is reasonable to consider that our CWT-based analysis is able to detect emergence of new potentials in the 24–80 Hz range due to wavefront fractionation, whereas HFQRS analysis is sensitive to the abolition of higher frequency components that may occur due to reduced conduction velocity in the neighborhood of the ischemic region.

Timing of intra-QRS changes in relation to repolarization changes

In this study, we often observed episodes of intra-QRS changes that were not accompanied by annotated ST episodes. This is clearly seen in Figure 2, where the annotation identified 4 episodes of ST deviation, but several other ST shifts are clearly visible, though not meeting criteria for cardiologist annotation. As illustrated by the corresponding F3 band trend, and time frequency distribution during the unlabeled episode, frequency analysis responded to these episodes. Additionally, Figure 3 demonstrates that intra-QRS changes did not always temporally align with ST changes. Indeed, changes in intra-QRS frequency content often

preceded changes in the ST segment by several minutes for annotated segments of ischemia. In our analysis, we chose stringent criteria for difference of our marker, namely, the mean value during the annotated episode of ischemia (corresponding to the shaded area in the Figure). We did not attempt to align the episode of frequency change and seek the peak deviation of the indices (analysis which may have further accentuated a difference from baseline).

The observations that intra-QRS frequency changes can precede ST changes, and that sub-criteria ST depression is associated with frequency change, raises the question as to whether intra-QRS changes could serve as an independent early marker of ischemia that may be more sensitive than ST depression. In the current study, we did not have access to an independent marker of ischemia that could be used to test this hypothesis. Future work by our group will focus on using this analytic technique in real world situations with patients experiencing angina and ischemia established by an alternative modality (such as nuclear SPECT perfusion imaging with simultaneous 12-lead ECG). This may establish whether the sensitivity of the exercise ECG may also be improved by adding intra-QRS analysis.

Insight derived from outliers

As discussed in Results and in Figure 4, a minority of episodes of ST depression in our analysis were associated with downward shift in the high frequency components, which was directionally discordant from the rest of the database cases. Surprisingly, we noted marked ST elevation and reciprocal ST depression in a substantial proportion of these discordant responses (which is reflective of the severity of ischemia in this database). In these cases (see Figure 4 panel C), the time frequency distribution showed opposite shifts. It is reasonable to consider that transmural ischemia and infarction may affect wavefront propagation differently than subendocardial ischemia, leading to abolition (rather than emergence) of fine propagation modulation, and thereby high frequency potentials, within the QRS. Our current study was not designed to study frequency shifts in setting of ST elevation. The observation in prior studies of reduced high frequency components during balloon inflation may mimic this situation and corroborate our findings[10]. Our outlier analysis thus suggests that separate analysis may be appropriate for ischemia occurring in the setting of ST elevation or transmural arterial occlusion.

Clinical implications

We believe our findings have several important clinical implications. The demonstration that the CWT can identify changes in frequency content that accompany myocardial ischemia identified by ST analysis provides important proof-of-concept for a novel adjunctive marker of coronary artery disease that assays for changes in depolarization. This technique can be applied to standard ECGs and only requires a sampling rate twice the highest frequency of interest, well within nominal 12-lead standards for commercially available ECG machines. Since the CWT based effectively on band-pass filtering, it inherently removes DC and baseline wander, features that make it useful for ambulatory applications or exercise electrocardiography. Use of this adjunctive marker thus may help tailor diagnostic procedures and guide appropriate therapy.

Limitations of the study

One limitation of this study is that we rely on the annotated ST/T episodes in the database to identify analyzed episodes of myocardial ischemia. While we cannot totally exclude that the annotated episodes in the database could reflect false positives, the database is composed of a patient population with heavy burden of coronary disease, and the majority of ST depressions were annotated as ischemic according to the original description[21]. Given the high pre-test probability of ischemia in this population, we therefore expect a very low incidence of false positive ST depressions. Our current study is also not designed to investigate the specificity of intra-QRS changes, which in a future study would require an independent marker of ischemia and its absence (without which, our technique cannot serve as an independent marker of ischemia).

We only used two electrocardiographic leads for each case in this study, because there were no other leads available in the database, and the leads used varied from case to case. Future studies will seek to use all 12 leads of an ECG for analysis. It is conceivable that availability of all 12 leads will alter the performance characteristics to further increase both sensitivity and specificity when analyzed in combination.

This is the first study utilizing CWT intra-QRS analysis in a database of patients with known ischemia. As such, in the absence of further data, we developed fixed pass-bands for use across all database patients. In the real world, a given patient may develop shifts in frequency content within bands that are patient-specific, which may in turn correlate with the size, distribution and even chronicity of ischemia within the tissue. Future work will focus on identifying which of these clinical factors contribute to given frequency shifts, using an independent marker of ischemia (such as SPECT perfusion imaging).

Conclusion

Intra-QRS changes in the ECG accompany ST depression in ambulatory recordings during episodes of ischemia, which are readily detected as increase in HF components using spectral analysis and the CWT. These changes may serve as adjunct to ST analysis providing an additional noninvasive marker of ischemia with multiple potential clinical applications.

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Highlights

- Ischemia is known to affect the repolarization phase of the myocardium and the ST segment, but can also produce changes during depolarization within the QRS complex.
- Spectral time-frequency analysis using the continuous wavelet transform is able to resolve small amplitude, transient intra-QRS changes effectively.
- In real-world recordings of patients with known coronary disease, we demonstrate that an increase in frequency components in the range of 40 Hz to 80 Hz can be detected accompanying ST segment depression.
- These findings have the potential to serve as an adjunctive measure for the detection of ischemia. Intra-QRS spectral analysis has many clinical applications, including analysis of the ECG during exercise stress testing

Figure 1.

Analysis of baseline and ischemic QRS-T complexes and corresponding time-frequency distributions for a representative case. Changes in the ST segment are present during ischemia. While difficult to identify in time-domain, intra-QRS changes are evident in the time-frequency distribution from lead III as a separate peak centered at 50 Hz (frequencies between 40 Hz and 80 Hz outlined in the square).

Figure 2.

Annotated trends from representative case analyzing lead III. Panel A) shows the ST segment level with symbols identifying onset and end of the cardiologist-annotated episode (the duration of which is shaded). In panel B) the corresponding frequency indices for F2, F3, and F4 are plotted, showing good correlation with the ST segment trend.

Figure 3.

Annotated trends from a representative case analyzing lead V3. Panel A) shows the ST segment level with symbols identifying onset and end of the cardiologist-annotated episode (the duration of which is shaded). In panel B) the corresponding frequency indices for F2, F3, and F4 are plotted, showing an upward shift in correlation with the annotated ST episode.

Figure 4.

Analysis of outliers. All episodes of annotated ischemia for lead III analysis (panel A) and lead V3-V4 analysis (panel B) are assigned an episode number, plotted on the abscissa, with the corresponding shift in F4 index for ischemia versus baseline illustrated by the height of the bar (ordinate), sorted in increasing order. The 10 episodes representing outliers (shaded) are analyzed, with red bars representing those with concomitant ST elevations. Panel C) shows representative QRS complexes and time-frequency distributions for two such episodes with ST elevation in lead V4 (left) and lead III (right), demonstrating marked downward shift in frequency content.

Table I

Patient characteristics. CCB, calcium channel blocker; BB, beta-blocker.

	Lead III cases (N=86 episodes)	Lead V3-V4 cases (N=74 episodes)
Age	52.3 +/- 10.5	53.5 +/- 9.8
Gender	Male 30/30 (100%)	Male 23/25 (92%)
Single vessel disease	8/30 (26.7%)	12/25 (48%)
Number episodes per recording	2.9+/-2.1	2.9 +/- 2.0
Medications	17/30 CCB/BB (57%) 16/30 nitrates (53%) 12/30 unknown (40%)	16/25 CCB/BB (64%) 17/25 nitrates (68%) 7/25 unknown (28%)

Table II

Summary data for mean change in frequency sub-band indices during annotated episodes of ischemia. SEM, standard error of the mean. F1–F4, sub-band indices as defined in methods.

	Difference in Mean (ischemia versus baseline)	SEM	p value
Lead III			
F1 (24–35 Hz)	1.096	2.700	0.68
F2 (30–45 Hz)	0.300	0.736	0.68
F3 (40–60 Hz)	1.295	0.447	0.005
F4 (50–80 Hz)	0.768	0.255	0.004
Leads V3-V4			
F1 (24–35 Hz)	−0.247	1.186	0.84
F2 (30–45 Hz)	0.097	0.446	0.83
F3 (40–60 Hz)	0.128	0.150	0.39
F4 (50–80 Hz)	0.248	0.065	<0.001

Table III

Summary data for maximal value achieved of frequency sub-band indices during annotated episodes of ischemia. SEM, standard

	Difference in Maximum (ischemia versus baseline)	SEM	p value
Lead III			
F1 (24–35 Hz)	8.293	2.507	0.001
F2 (30–45 Hz)	3.044	0.811	<0.001
F3 (40–60 Hz)	2.448	0.481	<0.001
F4 (50–80 Hz)	1.414	0.270	<0.001
Leads V3-V4			
F1 (24–35 Hz)	2.831	1.395	0.046
F2 (30–45 Hz)	1.230	0.566	0.033
F3 (40–60 Hz)	0.597	0.210	0.006
F4 (50–80 Hz)	0.510	0.095	<0.001