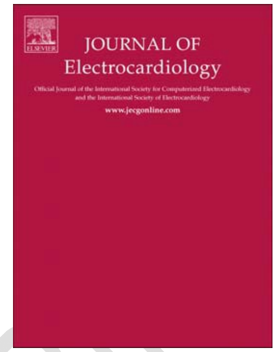

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Abstract

In this work we studied a computer-aided approach using QRS slopes as unconventional ECG features to identify the exercise-induced ischemia during exercise stress testing and demonstrated that the performance is comparable to the experts' manual analysis using standard criteria involving ST-segment depression. We evaluated the performance of our algorithm using a database including 927 patients undergoing exercise stress test sand simultaneously collecting the ECG recordings and SPECT results. High resolution 12-lead ECG recordings were collected continuously throughout the rest, exercise, and recovery phases. Patients in the database were classified into three categories of moderate/severe ischemia, mild ischemia, and normal according to the differences in sum of the individual segment scores for the rest and stress SPECT images. Philips DXL 16-lead diagnostic algorithm was run on all 10-second segments of 12-lead ECG recordings for each patient to acquire the representative beats, ECG fiducial points from the representative beats, and other ECG parameters. The QRS slopes were extracted for each lead from the averaged representative beats and the leads with highest classification power were selected. We employed linear discriminant analysis and measured the performance using 10-fold cross-validation. Comparable performance of this method to the conventional ST-segment analysis exhibits the classification power of QRS slopes as unconventional ECG parameters contributing to improved identification of exercise-induced ischemia.

Introduction

Exercise stress testing is the routine approach to identify and evaluate coronary artery disease (CAD) by gathering the ECG information during physical activity while potentially inducing myocardial ischemia. It has been used for many years as a common inexpensive approach to initial evaluation of the CAD and assessment of its extent. However, diagnostic power of this technique is limited by the low performance of conventional ST-segment depression analysis in identification of coronary disease [1].

A potential solution to improve the performance of exercise stress testing is implementation of unconventional features extracted from ECG during different phases of exercise testing. Sharir et al[2] studied employment of the High-frequency mid-QRS (HFQRS) analysis and demonstrated improved diagnostic performance compared to the conventional ST-segment analysis in identification of exercise-induced ischemia. The authors incorporated pretest likelihood of coronary artery disease in their analysis using a model developed by Pryor et al [3] based on pretest parameters including age, gender, smoking, diabetes, hyperlipidemia, baseline ECG abnormalities, type of chest pain, and history of myocardialinfarction. Their model also contained exercise parameters such as exercise duration, exercise stage, heart rate at rest, maximal heartrate, percent maximum age-predicted heart rate, exercise-induced chest pain, and magnitude of ST-segment depression, which along with the pretest parameters and HFQRS analysis provided significant improvement in diagnosis over ST-segment deviation alone.

QRS slopes were defined as unconventional features associated with the maximum absolute value of the ECG signal slope around each wave (Q, R, and S) and were initially used in percutaneous coronary intervention (PCI) application.Pueyo et al [4]used the QRS slopes as the

ECG features for detection of balloon inflation induced ischemia and found that QRS slopes are significantly less steep during artery occlusion. The authors defined the upward and downward slopes of the R-wave in QRS complex by fitting a pair of lines in the least-squares sense to the ECG signal in windows centered around the global maxima of derivatives ofthe upward and downward R-wave deflections, respectively. The slope reduction during PCI, associated with the increase in QRS width and decrease in its amplitude, demonstrated more contribution to induced ischemia identification than reduction of high-frequency contents, thus improving the performance more than high-frequency QRS features. The authors suggested using the QRS features as an adjunct to the conventional ST segment analysis in ischemia detection.

In an advanced study of induced ischemia identification during PCI by Romero et al [5], the authors used three QRS slopes by measuring the upward slope of the S-wave in addition to the other two R-wave slopes. They fitted three lines in the least-squares sense to the ECG signal in windows centered at the global maxima of the ECG signal derivatives of R-wave upward and downward deflections and S-wave deflection. QRS slopes were evaluated for the standard leads, as well as the leads derived from the vector cardiogram (VCG) and principal component analysis (PCA) QRS loops. The results indicated that QRS slopes and their variations are highly stable at resting state after normalization and are suitable for identification of ischemia-induced dynamic changes.

In the field of induced-ischemia detection during exercise stress testing, Llamedo et al [6] made use of four QRS slopes (around Q, R, and S waves)in addition to14 other unconventional ECG features including the amplitudes around Q, R, and S waves, the estimates of the P and T wave widths, QRS complex width, and other features related to the ST segment. They also included 11 pretest features and 10 exercise parameters in their model and showed higher performance compared to the HFQRS model presented in [2]. Although this reference achieved a great performance in detection of stress induced ischemia, it does not provide the distinct contribution of their four QRS slope parameters to the final performance among many other features.

In this work we aimed to specifically study the classification power of QRS slopes in exercise stress testing and the contribution of these features to the identification of induced ischemia without presence of other features. We evaluated the upward and downward slopes of R-wave in our 12-lead ECG database. By means of a statistical approach, the leads with highest discrimination power at the peak exercise and the rest phase were nominated and used for classification.

Materials and Methods

Database

Data used in this research was provided by the Telemetric and Holter ECG Warehouse of the University of Rochester (THEW), NY [7]. We performed our study on the patients from 'exercise testing and imaging perfusion' database which contains recordings from 927 patients. High resolution 12-lead ECG signals were recorded continuously throughout all phases of rest, exercise (stress), and recovery. We removed 18 recordings marked in the database as the files with low quality, incomplete data, or image problems.

Patients in the database were classified manually by two experts according to the differences in sum of the individual segment scores for the stress and rest SPECT images, Ischemia

Myocardiumscore (IM), into three categories: moderate/sever ischemia (IM $\geq$ 10%), mild ischemia (10% > IM $\geq$ 5%), and normal (IM < 5%).

The IM score, manually-determined by two experts, is our gold standard for ischemia identification. Selecting the classifier threshold at 10%, our analysis identifies a positive case (moderate/severe ischemia) if IM $\geq$ 10%, and a negative case (normal or mild ischemia) if IM <10%. The database was accordingly split into 34 positive cases and 875 negative cases.

Method

The Philips DXL 16-lead ECG algorithm admits 10-second ECG segments as input. The 12-lead ECG recordings in the database are several-minutes long and cover all three phases of the exercise stress testing. The long ECG recordings were divided into 10-second 12-lead segments of data and our algorithm was run on all segments. The DXL algorithm generated12-lead representative beats for each 10-second segment, their ECG fiducial points, and the ECG parameters such as heart rate, ST amplitude, and ST slope, as well as the onset, end, and the amplitude of all ECG waves including Q, R, and S. The ECG representative beats were then averaged by a smoothing filter which returned the exponentially weighted average of the current and previous beats.

As an example, Figure 1 shows the evolution of a representative beat during all phases of a 16-minute-long exercise stress test. The representative beats were generated every 10 second by the DXL algorithm on lead II and were averaged with the previous beats by an exponentially weighted summation. All representative beats are displayed in 1200ms intervals. The initial representative beat is the leading edge of the 3-D plot at the preliminary ECG recording time. The next averaged representative beats are lined up in parallel to the initial representative beat.

All QRS complexes are aligned at the middle of representative beat intervals. Initially, the P-wave is located around 420ms and T-wave is around 800ms.Increase in heart rate brings the QRS complexes closer together and the adjacent QRS complexes become visible in the 3-D plot. Displacement of adjacent QRS complexes, P-wave, and T-wave, are observable in the 3-D plot with the test progress.

The contour mapping of the 3-D plot is shown in Figure 2 where therest, exercise, and recovery phases are annotated on the plot. During the exercise phase, QRS complexes become closer together by increase in the heart rate. After the peak exercise, the heart rate drops rapidly in the recovery phase. A gradual reduction in T-wave amplitude is observed during the exercise phase which is followed by the amplitude increase in the recovery phase.ST depression is also visible around the end of the exercise phase.

To validate our method, we employed two QRS slopes: R-wave upward(or positive) slope (sPR) and downward(or negative) slope (sNR).The QRS slopes were measured at the beginning of the rest phase as well as the peak exercise of the 12-lead averaged representative beats for each patient. The peak exercise is the time at which the maximum heart-rate is detected. Morphology of the averaged representative beats determines the R-wave slopesas described in [4]by applying the averaged fiducial points. Differences in the slopes at the peak exercise and the rest phase are specified as

$$\Delta sPR = sPR\,|Stress - sPR\,|Rest \qquad (1)$$

$$\Delta sNR = sNR\,|Stress - sNR\,|Rest \qquad (2)$$

By applying a statistical hypothesis test (t-test), statistical significance of the difference of QRS slopes for each lead was evaluated and the leads with the lowest p-values were selected for R-wave positive and negative slopes and were used in the classification process. The most significant differences were seen at lead $V2$ for ΔsPR and lead aVR for ΔsNR . These two parameters form the feature vector v as follows

$$v = [\Delta sPR \,|V2, \Delta sNR \,|aVR\,] \qquad (3)$$

Linear discriminant analysis (LDA) was applied to our feature vector to generate a classifier model. As a binary classification technique, LDA finds a model to the linear combination of the features with different Gaussian distributions, that best separates the input dataset into two classes. We can adjust the LDA classification threshold by changing the cost of misclassification of positive cases.

We made use of k-fold cross-validation method with k=10 where the database was randomly partitioned into 10 non-overlapping subsets with roughly the same size and the same proportion of the ischemic cases to the normal cases. The classifier was trained using 9 subsets and validated on the remaining subset. This process was repeated 10 times to use all subsets for validation while the other subsets trained the classifier. The advantage of k-fold cross-validation method is that all cases in database are used for training k-1 times and each case is used for validation once.

Results

The standard criterion to identify a positive exercise-inducedischemia case (coronary artery disease) in an exercise stress test is observing a horizontal or down-sloping ST-segment depression of 100μV or more at peak exercise or an ST elevation of 100μV or more in anonQ-wave lead during or after the exercise [8]. In manual analysis of ECG recordings by two experts, horizontal or down-sloping ST-segment depressions and ST-segment elevations at J+60 were annotated with maximum levels at 0μV, 50μV, 100μV, 150μV, 200μV, 250μV, and 300μV. Applying the standard criterion of 100μV to the manually annotated ST-segments provides 17 true positives and 785 true negatives, resulting in 24% sensitivity and 93% specificity marked by an asterisk in Figure 3. Selecting the classification threshold at other levels results in different performances which are marked with cross marks in Figure 3.

Philips DXL algorithm was run on 909 ECG recordings in the database and QRS slopes were measured from the averaged representative beats generated by the algorithm. In an iterative process, linear discriminant analysis with different classification thresholds (determined by the cost of misclassification of positive cases)was applied to the feature vector and 10-fold cross-validation method was implemented to classify the cases. As a result, a series of the specificity and sensitivity values were calculated for all classification thresholds generating the ROC curve displayed in Figure 3 with the positive event defined as the severe/moderate exercise-induced ischemia. We observe that the performance of manual ST-segment analysis at each classification threshold is close to the performance of our classifier shown by the ROC curve.

Discussion and Conclusions

QRS slopes have been studied as unconventional features versus conventional ST-segment analysis to improve the performance of identification of balloon inflation induced ischemia in PCI [4,5], or in combination with a large number of pretest, exercise and proposed features in exercise stress tests [6], but their distinct contribution to the ischemia detection was not studied.

In this work we performed an independent study on classification power of QRS slopes in exercise-induced stress testing by developing a classifier model based on these features only.

We demonstrated that the performance of our algorithm is comparable to that of manual ST-segment analysis performed by two experts. Although the performance of the ST-segment analysis was low with 24% sensitivity and 93% specificity at the standard classification threshold of 100µV,our computer-aided algorithm was capable of achieving the same performance without human intervention while the sensitivity and the specificity could be balanced by adjusting the ROC discrimination parameter.

A point to consider in exercise stress testing is presence of the high level of noise especially during the exercise phase. Although the DXL algorithm handles the analysis of noisy signals very well, we averaged the representative beats with their previous beats using a smoothing filter to reduce the variations generated by noise. Visual inspection of 3-D beat plots still shows some noisy cases even after smoothing. An advantage of our method over the traditional analysis is that QRS slope measurements are less prone to the noise than ST levels used in traditional ST-segment analysis.

The low number of ischemic cases within all patients undergoing the study is a common limitation in exercise stress testing. This ratio is 4% in our database with 34 moderate/severe ischemiccases out of 909 patients which is an inherent limitation.

Although the classification based on QRS slopes exhibits similar performance to that of the ST-segment analysis in exercise stress testing, here we do not intend to propose them as a replacement to the traditional method. Instead, we try to concentrate on the theoretical approach to exhibit the classification power of QRS slopes. The clinical application of these features alone or accompanied with other features is beyond the scope of this paper and needs a comprehensive investigation.

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Figure 1. An example 3-D plot of the evolution of a representative beat during all phases of a 16-minute-long exercise stress test. The representative beats were generated every 10 second by the DXL algorithm on lead II and were averaged with the previous beats by an exponentially weighted summation. The initial representative beat is the leading edge of the 3-D plot at the preliminary ECG recording time. The next averaged representative beats are lined up in parallel to the initial representative beat. Increase in heart rate brings the QRS complexes closer together and the adjacent QRS complexes become visible in the 3-D plot. Displacement of adjacent QRS complexes, P-wave, and T-wave, are observable in the 3-D plot with the test progress.

Figure 2. Example contour mapping of the evolution in the averaged representative beats during the rest, exercise, and recovery phases of an exercise stress test. During the exercise phase, QRS complexes become closer together by increase in the heart rate. After the peak exercise, the heart rate drops rapidly in the recovery phase. A gradual reduction in T-wave amplitude is observed during the exercise phase which is followed by the amplitude increase in the recovery phase.ST depression is also visible around the end of the exercise phase.

Figure 3. The ROC curve of our classifier with varying classification thresholds. Positive event is the severe/moderate exercise-inducedischemia. The ROC discrimination parameter is the LDA misclassification cost of positive cases. The asterisk shows the performance of manual ST-segment analysis with the standard 100μV threshold in ST depression or elevation criterion at 24% sensitivity and 93% specificity. The cross marks show the performance of manual ST-segment analysis with different thresholds in ST depression or elevation criterion at the other thresholds of 0μV, 50μV, 150μV, 200μV, 250μV, and 300μV, displaying higher sensitivity at higher thresholds. We observe that the performance of manual ST-segment analysis at each classification threshold is close to the performance of our classifier on the ROC curve.

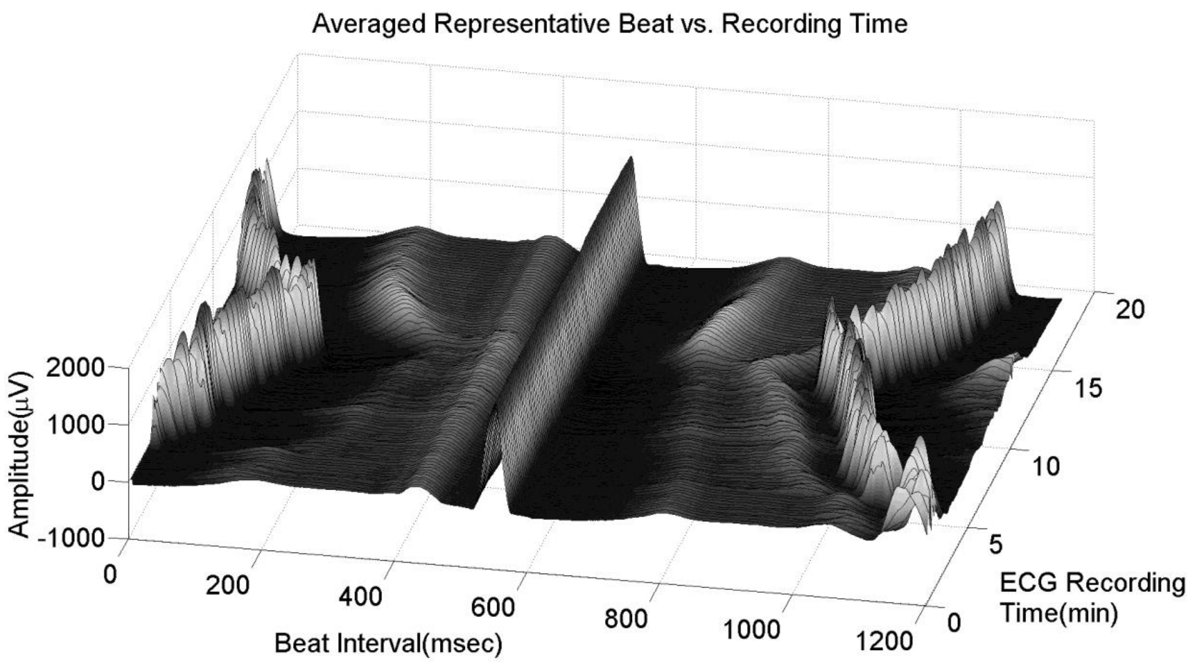
Averaged Representative Beat vs. Recording Time
Amplitude(μV)
2000
1000
0
-1000
0
200
400
600
800
1000
1200
Beat Interval(msec)
0
5
10
15
20
ECG Recording
Time(min)

Figure 1

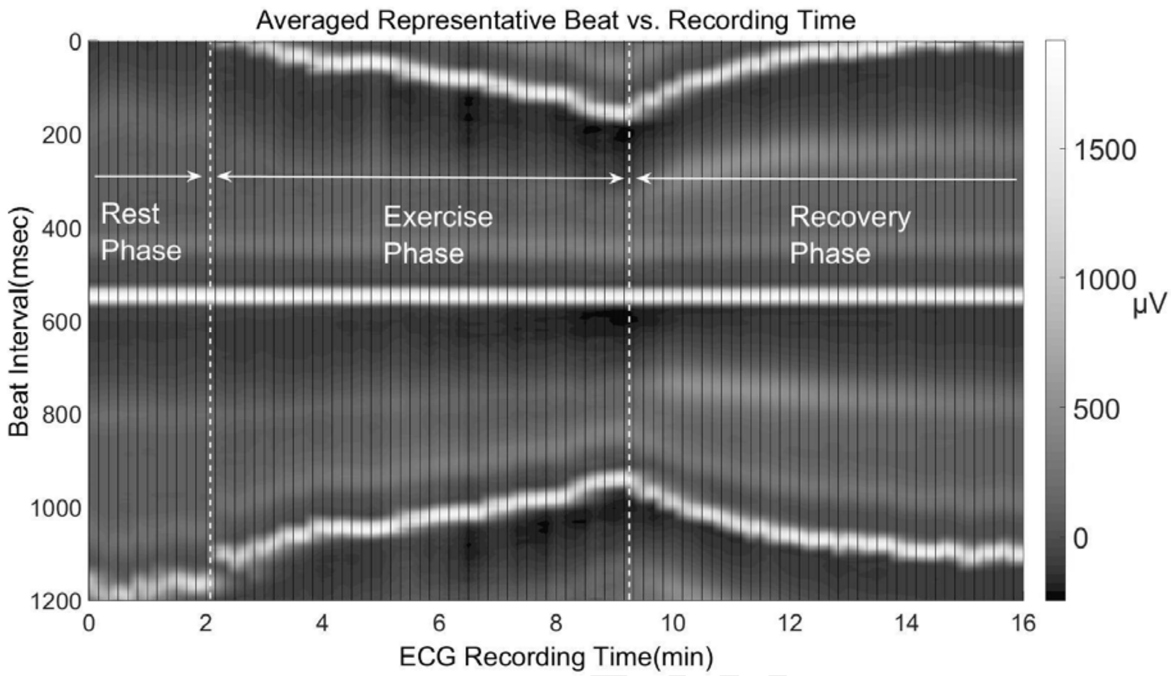
Averaged Representative Beat vs. Recording Time
Rest
Phase
Exercise
Phase
Recovery
Phase
Beat Interval(msec)
0
200
400
600
800
1000
1200
0
2
4
6
8
10
12
14
16
ECG Recording Time(min)
1500
1000
500
0
μV

Figure 2

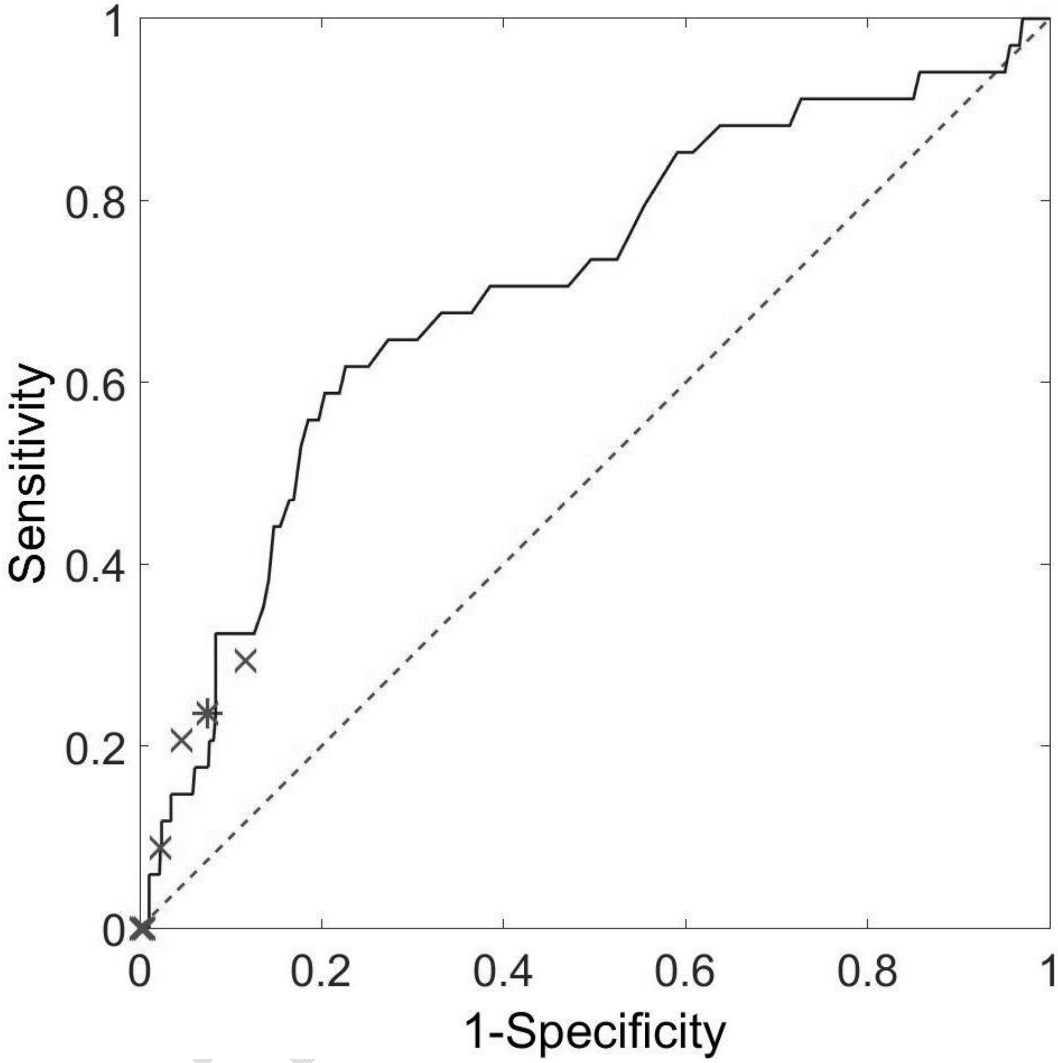

Figure 3