Stress ECG Analysis for Ischemic Preconditioning Evidence

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Abstract

Ischemic preconditioning is one of the most powerful means to protect myocardial muscle after a prolonged episode of ischemia. Human models related to the idea of ischemic preconditioning are still under discussion, specially when the results reported in previous studies are diverging. The current study provides a useful methodology to clarify and support the evidence of ischemic preconditioning considering time series analysis of stress ECG derived parameters and multivariate analysis. The methodology was applied to a database composed of 14 Coronary Artery Disease (CAD) patients who underwent two consecutive stress tests within a 24-hour window. Preliminary results show that parameters obtained from the stress ECG are adequate to assess the ischemic preconditioning phenomenon. Based on both Wilcoxon signed rank test and Fisher discriminant analysis, it is possible to observe either a tendency of the electrocardiographic parameters evaluated or a marked difference between groups of stress ECG recordings corresponding to the first and second stress tests. These analysis allow to define differences between each particular stress ECG in the same patient and also differences between groups. Furthermore, comparison of results from healthy patients' stress ECG parameters, revealed that the second stress test results form a cluster that is oriented towards the healthy group cluster in the Fisher discriminant analysis.

1. Introduction

Ischemic preconditioning is defined as a "rapid, adaptive response to a brief ischemic episode, which slowed the rate of cell death during a subsequent prolonged period of ischemia" [1]. Evidence of ischemic preconditioning has been shown in a great number of previous studies developed in animal and human models, as well as in clinical protocols related to a history of angina before myocardial infarction [2], and during angioplasty with intermittent aortic cross-clamping [3]. Also, findings from hystochemical studies suggest the existence of a "second window" of benefits related to a reduction of myocardial infarct size 24 hours after a brief episode of ischemia [4].

Ischemic preconditioning phenomenon is a topic widely argued especially when we find differences between the results based on conventional electrocardiographic parameters and measurements reported in several previous research groups. There are evidences that a single observation in time is not enough to approach ischemic episodes. Therefore, information must be obtained from proper observation of trend behavior in the time domain of the several electrocardiographic parameters evaluated [8]. Since there has been disagreement in ECG evaluation of ischemic preconditioning, the methodology proposed in this work is based on electrocardiographic parameters extracted within a fixed recording interval that have both, clinical significance and quantitative relevance. This way of analysis provides additional patient specific information that enhances the parameters extracted.

The natural history of serial ischemic episodes is important to define the possible behavior of myocardial muscle on each ischemic episode, and its relation to the following one in evaluated series. Observations from studies based on 'heat stress protein' of a biphasic protective effect show a biochemical evidence, perhaps longer-lasting, of delayed ischemic preconditioning benefits [4].

The stress test represents a common physiological instrument which is able to elicit ischemic responses especially in people with history of risk factors or symptoms suggesting myocardial ischemia, making it a valuable noninvasive diagnostic tool in routine clinical practice. Initial findings of adaptation to angina were reported in the classical studies of *"warm up"* and *"walk through"* phenomena documented with exercise stress tests [5].

The framework of this study is the understanding of ischemic preconditioning and its influence in both diagnosis and therapeutics. In this report, a practical methodology has been developed to document and

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quantify the presence of the ischemic preconditioning phenomenon. The implemented methodology is based on optimized ECG signal processing instrumentation in order to obtain conventional and new clinical parameters that can be evaluated using multivariate discriminant measures and are helpful in characterizing this phenomenon.

2. Methodology

A clinical stress ECG database was obtained at the Cardiology Service of the *Hospital Universitario de Caracas* where stress tests are performed routinely on a daily basis. The procedure implemented to construct the database uses a methodology that closely follows the one presented by Wong et al. [6].

Considering Bayes' theorem, in which it is suggested that if the probability of a coronary event before testing is very low, the probability of positive diagnosis after testing does not increase even if the test has a good sensitivity and specificity. Therefore, previously diagnosed CAD male patients were selected to undergo stress tests, performed according to either the BRUCE or NEP protocols and always symptom-limited. Once the resulting stress ECG is defined as positive for a CAD diagnosis, a second stress test was performed 24 hours later. Each patient selected for the database and appointed for the second stress test must be under the same conditions and protocol as the day before. Patients with varying conditions, absent at the dated time, undergoing arrhythmic episodes or under different treatment conditions, were excluded from the study.

A three channel (II, V5 and V6) stress ECG database has been built from 14 male subjects at the moment. The tests were performed using a QUINTON 5000® from Quinton Instruments Co.. The analog output signals were digitized using SISPAS [6] (Portable Acquisition Signal System, a prototype system developed in our group) as illustrated in *Figure 1*. Sampling rate was at 250 Hz and at 12 bits resolution, during the 30 minutes duration of the test. After acquisition, all patient's files were transferred to a 90 Mb removable hard disk unit and to a 250 Mb backup tape unit.

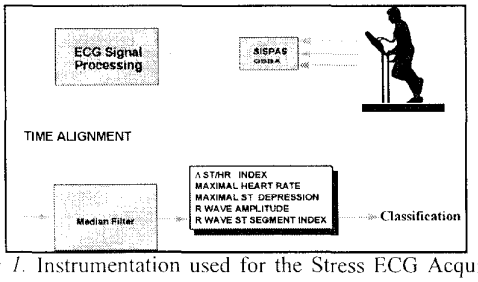

Figure 1. Instrumentation used for the Stress ECG Acquisition and parameter extraction.

All three leads were preprocessed in order to filter noise, to perform QRS detection, to carry out classification and temporal alignment. Normal beats detected on intervals of 10 seconds were averaged to measure ST-level deviation and R amplitude. From these measurements; ST segment level, R amplitude trend curves and RR interval series were constructed for further analysis and parameter extraction. All software was developed in Borland C++ 3.1™.

Once we have obtained the measurements related to ST level, R wave amplitude and RR interval series, trend analysis of the desired electrocardiographic parameters was possible. Time series were built for the ST level, R wave amplitude and Heart Rate as seen in *Figure 2*, allowing to mark any moment during the test.

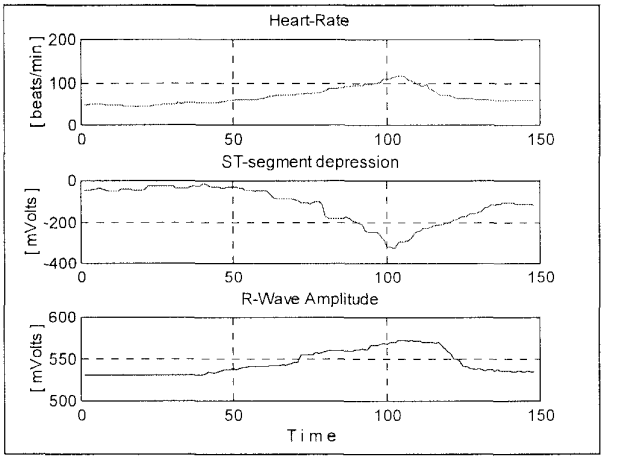

Figure 2. ST level, R wave amplitude and Heart Rate Time series from one lead of a patient's Stress ECG.

From the time series, for each channel and patient record, the following parameters were calculated: maximum ST-level depression, maximum heart rate, R wave amplitude change vs. ST-level change [7] and maximum ST-level change vs. maximum HR change (Delta Index) [6].

3. Statistical management

Comparability between each pair of stress test is possible once the double product (Maximal Heart Rate x Corresponding Systolic Heart Pressure) achieved in the second stress test is confirmed to be at least the same as the first stress test. This selection rule is a good estimate of the myocardial oxygen consumption (VO_{max}) in both tests.

In order to contrast the expressed null hypothesis as the *Absence of the ischemic preconditioning phenomenon* and therefore, to demonstrate a tendency in the electro-

cardiographic parameters measured and obtained from ST level, R wave amplitude and Heart Rate time series, the Wilcoxon signed rank test [9] was applied. This test based on ranks allows to define the difference between both groups of stress tests. This can be achieved trough the determination of a meaningful measurement in the distance of each pair of observations, thus, differences between each bivariate matched pair of electrocardiographic parameters are calculated. A one-tailed decision rule was expressed since the null hypothesis is defined in one way according the ischemic preconditioning concept.

Also with the goal of making a discriminant analysis between the groups, Fisher Discriminant Measure was used in order to obtain the hyperplane that best separates the two groups of extracted stress ECG parameters, allowing a satisfactory differentiation of the stress test series. Discriminant analysis of the data was applied to the set of measured parameters for both the first recording group (labeled ***u***) and the second recording group (labeled ***d***) using OLPARS™ (Version 7.2) qualitative analysis of the Fisher Pairwise Projections [10].

A third set of 8 healthy patients (labeled ***healthy***) obtained from a group of asymptomatic male volunteers without history of cardiovascular disease, was also analyzed in order to compare with the results obtained in the preconditioning database.

4. Results

Based on the Wilcoxon signed rank test and a defined α=0.05, statistical significant tendency in some electrocardiographic parameters such as : maximum ST-level depression (MST), R-wave amplitude change vs. ST-level change (Delta R) and maximum ST-level change vs. maximum HR change (DST/HR) were found. These evidences allow us to reject the expressed null hypothesis and accept the alternative hypothesis of ischemic preconditioning phenomenon evidence with the selected parameters.

As seen in *Figures 3 and 4*, results obtained with the sample of 14 CAD patients and comparison with the 8 healthy subjects are included respectively. In *figure 3*, it is possible to observe clear clusters for the first and second records making possible a classification of the first and the second stress tests. *Figure 4* illustrates the alignment of the three groups.

These preliminary findings show that the proposed methodology is able to determine slight differences in a series of stress tests as we can see in *Figure 3*. The separation of the ***d*** cluster from the ***u*** cluster, suggest that patients were subject to preconditioning. Inclusion of the healthy patients in the former analysis, shows the alignment of clusters seen in *Figure 4*, where the ***d*** cluster is oriented towards the healthy group, suggesting that the parameters obtained in the ***d*** group were closer to values from healthy subjects than those in the ***u*** group.

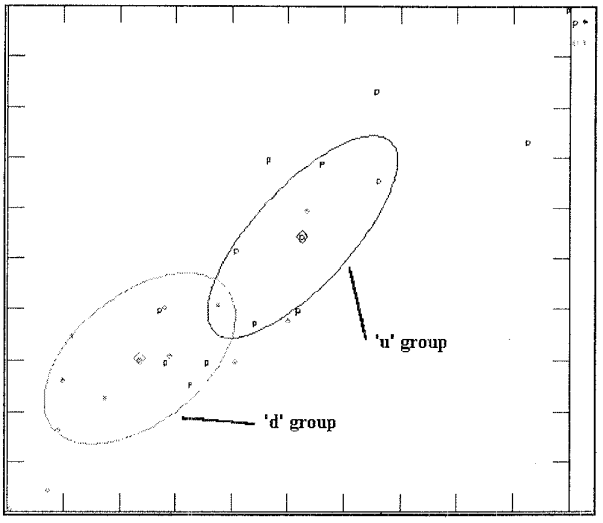

Figure 3. Comparison of clusters for the ***u*** and ***d*** groups.

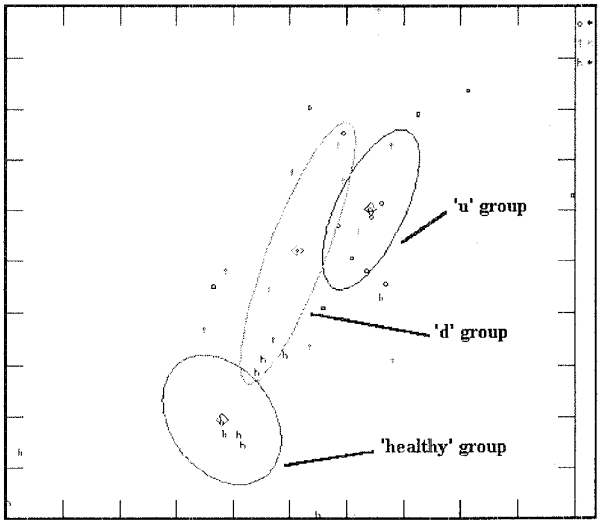

Figure 4. Fisher Pairwise Projection for the three groups.

In *Figure 5* we can see a boxplot graph based on the values of signed rank differences obtained from both, the last and the first stress ECG parameters of the sample evaluated. It can be observed that there is a tendency in the difference distribution. The medians of the signed ranks obtained from the difference in each pair of matched sample, show a behavior that could support the idea of ischemic preconditioning.

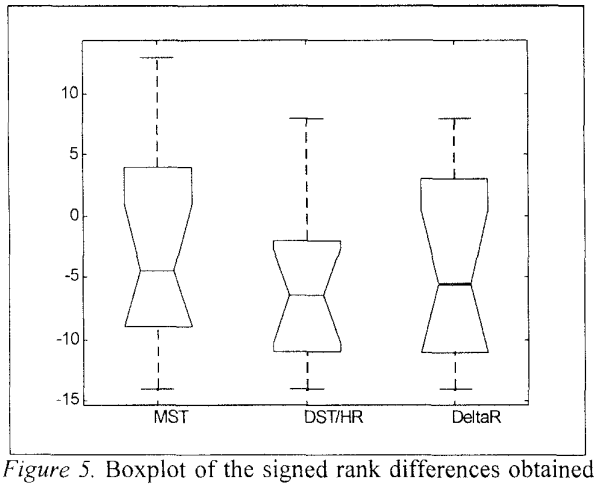

Figure 5. Boxplot of the signed rank differences obtained from the electrocardiographic parameters evaluated.

5. Discussion

The results obtained, support the adequacy of this methodology and allow the possibility of further research in the ischemic preconditioning phenomenon widely described in recent studies. More clinical trials are required before drawing a better understanding of the preconditioning phenomenon. Also, the study of the clinical implications of these results, in particular in relation to the stress test protocols and cardiac rehabilitation programs is subject to further research.

In previous reports where ECG measurements were developed with conventional electrocardiographic equipment and parameters to determine ischemic preconditioning in myocardial infarction with prodromal angina model[2], the statistical analysis could not achieve significance. Contrariwise, the findings obtained in enzymatic measurements and ventriculography could achieve statistical significance in the approach of the ischemic preconditioning. As the former report, also exist a wide variety of disagreement among the ischemic preconditioning approach based on electrocardiographic parameters or models to elicit this phenomenon.

Although the stress ECG is a low cost, noninvasive and reproducible way to elicit ischemic episodes, its clinical value is limited when it is only based on ST changes[11]. The extraction of other electrocardiographic parameters by an enhanced system of acquisition in the time domain and trend analysis of several parameters, makes it a valuable aim to asses the ischemic preconditioning phenomenon in humans.

This approach to ischemic preconditioning evidence will allow further evaluation of the potential benefits of this phenomenon. Currently it is difficult to evaluate the wide possibilities and implications of ischemic preconditioning either in the cardiac rehabilitation programs or in several therapeutic applications such as Percutaneous Transluminal Angioplasty preparation, Transplantation programs, etc. Nevertheless, a better understanding of ischemic preconditioning phenomenon will enhance the possibilities of developing further research on ischemic preconditioning mimetic agents and their use in the preventive and therapeutic clinical practice.

Acknowledgments

This study was supported by project BID/CONICIT E08 (SIC).

References

[1] Kloner R, Derek Y. "Does Ischemic Preconditioning occur in patients?", J. Am Coll Cardiol. 1994; 24: 1133-42.

[2] Ottani, F. Galvani M. "Prodromal angina limits infarct size", Circulation 1995; 91:291-297.

[3] Ezra D., Berger M. "Adaptation to ischemia during percutaneous transluminal coronary angioplasty", Circulation 1990; 82:2044-2052

[4] Marber M.S., et al. "Cardiac stress protein elevation 24 hours after brief ischemia or heat stress is associated with resistance to myocardial infarction", Circulation. 1993 ; 88 :1264-72.

[5] Jaffe MD, Quinn NK. "Warm up phenomenon in angina pectoris", Lancet 1980; 2:934-6.

[6] Wong S. , Almeida D., Mora F.. "Computerized analysis of ST vs. HR for assesing myocardial ischemia in the stress ECG" , IEEE EMBS 1995, Montreal-Canada.

[7] Hopkirk J., Uhl G., "Limitation of exercise induced R wave amplitude changes in detecting coronary artery disease in asymptomatic men" ,J. Am Coll Cardiol. 1984; 3:821-6.

[8] Krucoff M., Jackson Y. , Kehoe M., Kent K.,. "Quantitative and Qualitative ST segment Monitoring During and After Percutaneous Transluminal Coronary Angioplasty", Circulation. 1990; 3:IV-20-IV-26.

[9] Conover, W J. "Practical nonparametric statistics". John Wiley & Sons, Inc..USA. 1980

[10] Olpars 7.2™. "On Line Pattern Analysis and Recognition System". PAR Government Corporation. 1993.

[11] Severi S.,Micelassi C.;"Prognostic Impact of Stress Testing in Coronary Artery Disease". Circulation. 1991; 83:III-82-III-88.

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