QRS area monitoring during stress test: a novel index to separate normal to ischaemic patients?

Mario Curione[1], Camillo Cammarota[2], Giambattista Cardarelli[1], Simonetta Di Bona[1], Teresa Montesano[3], Laura Travascio[3], Marzia Colandrea[3], Marco Colotto[1], Massimo Ciancamerla[3], Giuseppe Ronga[3]

[1]Department of Clinical Siences, University of Rome "La Sapienza", Rome, Italy
[2]Department of Mathematics, University of Rome "La Sapienza", Rome, Italy
[3]Nuclear Medicine Service, Policlinico Umberto I University "La Sapienza", Rome, Italy

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Corresponding author:
Mario Curione
Department of Clinical Siences
University of Rome "La Sapienza"
Rome, Italy
Phone: +39 068 6207489
Fax: +39 0649978443
E-mail:
mario.curione@uniroma1.it

Abstract

QRS amplitude is correlated with ventricular volume. During stress test ventricular volume changes differently in normal subjects and in ischaemic patients, in relation to different ventricular compliance. The aim of the study is to test whether monitoring of QRS area profile during stress test is able to discern ischaemic from non-ischaemic patients. 28 patients underwent SPECT myocardial perfusion imaging at rest and during bicycle stress test. Two groups were selected: group A (control), 15 subjects with normal distribution of tracer uptake at rest and after stress; group B (ischaemic patients), 13 patients with reduced or absent tracer uptake at rest in one or more areas. QRS total area time profile shows a clearly recognizable difference in patients with ischemia vs. controls. A linear correlation was found between QRS rest total area and cardiac mass in normal subjects but not in ischaemic patients (r=0.53 and r=–0.27 respectively); an inverse correlation was also found between QRS rest total area and rest left ventricular volume and left ventricular section area, evaluated with SPECT (r=–0.52 and r=–0.58 respectively). We can hypothesize that QRS total area is linked to haemodynamic changes. It might be useful to employ in clinical practice QRS area in addition to the standard ST criterion to increase diagnostic capability of the ECG stress test.

Key words: QRS area, myocardial ischaemia, stress test, ventricular filling.

Introduction

Repolarization abnormalities, during exercise stress test (ST segment displacement), are the principal electrocardiographic signs to detect myocardial ischaemia [1].

Less employed in clinical practice are QRS changes in shape and/or amplitude during stress test. Sensitivity and specificity of isolated QRS changes in ischaemic patients are very low; only the "QRS score" increases diagnostic capability of the exercise stress test [2-5].

Pathogenetic aspects of depolarization abnormalities during ischaemia are still unclear and controversial [6]. Diastolic or systolic compliance defects in ischaemic patients, via abnormal intraventricular filling changes [7, 8], could be able to modify QRS amplitude, also during stress test, with a mechanism already observed during arrhythmias [9-11] or haemodialytic treatment [12-14].

The aim of the study is to test whether monitoring of QRS area profile is able to discern ischaemic from non-ischaemic patients during stress test. So far "QRS area" has been employed in standard ECG to detect myocardial hypertrophy [15].

We chose "QRS area" assuming that this variable can show different changes in intraventricular filling occurring during stress test in the patients enrolled. In contrast to isolated R amplitude or S deep modification to evaluate ventricular filling, "QRS area" should avoid bias due to the balance between radial and tangential forces diffusion (Brody Effect) as a consequence of modifications in electrical resistivity induced by intracardiac volume changes [16].

As an experimental model we choose a "single stress test" for each patient to avoid possible bias due to change in electrodes' position or to other variables linked to intraventricular volume, i.e. weight, haemoglobin and haematocrit, able to modify QRS amplitude, studied by Madias and Narayan in another experimental model [13].

Material and methods

Patients with a history of chest pain referred to the ECG Laboratory of the Department of Clinical Sciences, University "La Sapienza" of Rome, between April 2006 and December 2006, underwent clinical examination, standard 12-lead ECG and echocardiography.

A retrospective study was carried out on 28 of those subjects, presenting symptoms and signs suggestive of myocardial ischaemia, who underwent myocardial SPECT at rest and after bicycle exercise test. During exercise test, 12-lead ECG monitoring was performed. According to results obtained, two groups of patients, homogeneous for anthropometric data, were selected: group A (control) – 15/28 subjects [6 male, 9 female, mean age 42±12.8 SD, mean body mass index (BMI) 23.5±2 SD] with normal distribution of tracer uptake at rest and after stress; group B (ischaemic): 13/28 patients (8 male, 5 female, mean age 50±9.6 SD, mean BMI 25±1.4) with reduced or absent tracer uptake at rest. Eight of them also presented reduced tracer uptake after stress.

The patients enrolled were not affected by myocardial hypertrophy, left bundle branch block or ventricular pre-excitation, and they were not pacemaker carriers.

Echocardiography

Standard M-mode and two-dimensional echocardiography was performed in all subjects. End-systolic, end-diastolic left ventricular (LV) diameters, LV wall thicknesses, and global and regional contractility were evaluated by two observers blinded to any clinical data. LV mass was calculated according to Devereux formula and used to normalize QRS total area and echocardiographic variables and to evaluate linear correlations with QRS Total Area [17].

Stress ECG

12-lead ECG was monitored during exercise stress test in all subjects of the study. Multistage Bruce protocol diagnosis of inducible ischaemia was used according to current guidelines [18].

SPECT acquisition protocol and image analysis

Myocardial SPECT was performed after stress test and repeated at rest, according to a "separate day" protocol. In both studies, patients were i.v. injected with 740 MBq of ^{99m}Tc MIBI (methoxy isobutyl isonitrile) (CardioliteTM, BMS/Dupont) [19].

In the interpretation of tomography images, the distribution of tracer uptake may be characterised visually as: normal (≥70%), mildly reduced (50-69%), moderately reduced (39-49%), severely reduced (10-29%), absent (<10%).

Dedicated software was employed to calculate LV Volume and section area of LV tomograms at rest and after exercise; these data were correlated with QRS total area data.

QRS area evaluation

Signal acquisition

Standard 12-lead ECG was performed using PC-ECG 1200 (Norav Medical Ltd.), which provides an output digital signal with resolution of 2.441 microV and 500 Hz sampling frequency.

Signal pre-processing

The 50 Hz power-line interference was removed using a linear filter according to Levkov et al. [20].

Signal processing and QRS detection

An automated method was used to detect the time locations of R peaks in the V5 lead recording. By visual inspection of one typical QRS complex, the two time intervals from the onset and the offset of the QRS complex to the R peak time location were identified. These two time intervals, whose sum is the duration of the QRS complex, were used to identify the onset and the offset of the QRS complexes in the entire V5 recording. In the other leads onset and offset of QRS were assumed to be the same as in V5.

QRS area evaluation

For any lead the QRS area was computed with the following method (Figure 1). For each QRS complex the baseline was defined as the mean of the two values of the signal in the onset and in the offset of the QRS. The absolute value of the

difference of the signal and the baseline was computed. The time voltage area of each QRS was computed as the integral of this absolute value from the onset to the offset of the QRS. This procedure was repeated for each of the 12 leads, and gives the areas A(i), i=1, 2, ..., 12. The Total Area (TA) of the QRS complex is computed as the sum of the areas of the 12 leads: TA = A(1) + A(2) + ... + A(12). We have considered the time series defined as the sequence of Total Area for each QRS of the stress ECG recording. This time series was smoothed by using a moving window average filter with span equal to 50 beats; the resulting series is called Total Area time profile. The same smoothing procedure was done for the RR sequence; the resulting RR time profile has a "V" shape with a well defined point of minimum, the Maximum Heart Rate (MHR) beat.

We describe the main quantitative features of the TA time profile using the following variables: a) Rest Total Area (RTA) is the value of the TA at resto, b) Early Recovery TA (ERTA) is the value of the TA at the 100th beat after MHR, c) Mean Total Area (MTA) is the temporal mean of TA value, d) Standard Deviation of TA (SDTA) is the temporal standard deviation of TA values. The TA values are measured in units of mV × ms, since the QRS area is computed by multiplying time (unit ms) and voltage (unit mV). The TA values are normalized for body mass index (BMI) by dividing its values for the BMI.

We constructed the group mean TA time profile and the group mean RR time profile of each of the two groups of patients according to the following method. The time profiles were translated both in abscissa and in ordinate, so that the MHR points were positioned in the axes origin. Then the average of these time profiles was computed separately for subject groups A and B and TA and RR. The group mean time profiles are shown in Figure 2.

Statistical analysis

Statistical analysis was performed with statistical software R [21]. Differences between means were compared by using the t test and p value <0.05 was considered to indicate statistical significance. The linear correlation between variables was tested using Pearson's correlation coefficient.

Results

QRS total area variables

Mean values of RTA, ERTA, MTA, SDTA in ischaemic patients were significantly different than mean value in normal subjects (Table I).

A linear correlation was found between RTA and cardiac mass in normal subjects but not in ischaemic patients (r=0.53, p=0.042 and r=–0.27, p=0.37 respectively). An inverse correlation was found between RTA and left ventricular section area, evaluated with SPECT, in ischaemic patients (r=–0.58, p=0.038). An inverse correlation was also found in the same group between RTA and rest left ventricular volume, evaluated with SPECT (r=–0.52), but in this case the p value is not significant (p=0.069).

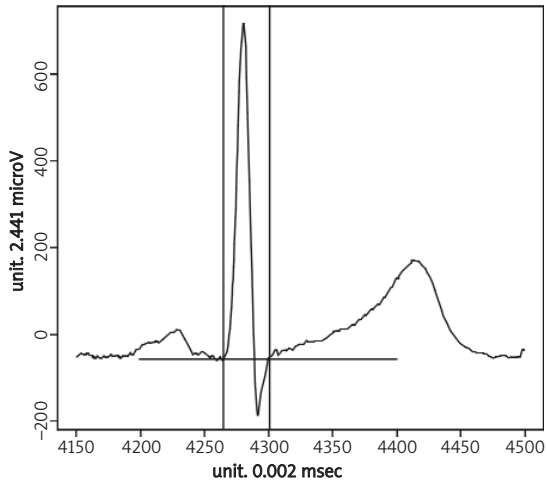

Figure 1. The two vertical lines mark the onset and the offset of the QRS complex; the horizontal line is the baseline; the area of QRS is the sum of two positive quantities: the area delimited by the signal above the baseline and the area delimited by the signal below the baseline

QRS total area time profile

A different time profile was clearly recognizable during test, in both the stress and recovery phase, between the two groups. During the stress phase normal subjects show a more stationary profile than ischaemic patients. After Maximum Heart Rate, in the early recovery phase, normals show a deeper profile than ischaemic patients. In the late recovery phase normals show a more increasing TA than ischaemic patients (Figure 2a-c).

Table I. Statistical tests of the QRS total area (QRS TA) variables between: (group A) 15 normal subjects, (group B) 13 patients with ischaemia

QRS area variables	Group A (control) mean	SD	Group B (ischaemic) mean	SD	Value p
RTA	14.5	±4.1	9.9	±2.4	<0.0059
ERTA	–0.6	±0.5	–0.2	±0.2	<0.0371
MTA	14.7	±4.1	10.2	±2.5	<0.0071
SDTA	0.8	±0.2	0.5	±0.1	<0.0263

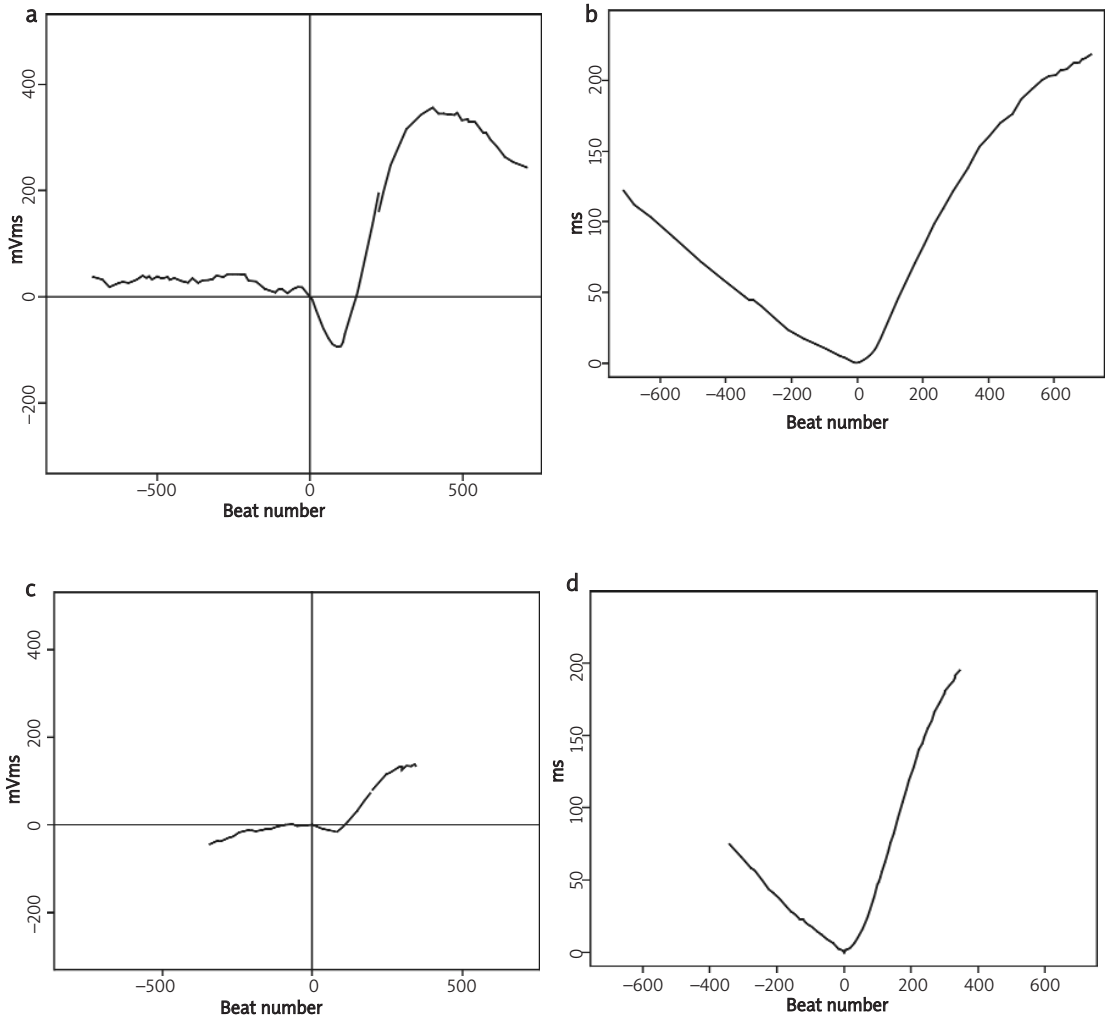

Figure 2. QRS total area (QRS TA) profile and RR interval in Normal Subjects (panels a and b) and in ischaemic patients (panel c and d) during exercise stress test. Physiopathological interpretation of difference between QRS Area profiles in normal and in ischaemic patients are explained in Figure 3

Discussion

Our data, shown as monitoring of QRS TA profile during stress test, discern ischaemic from non-ischemic patients (Figure 2a-c). Mean time profile of QRS TA, during increase in heart rate, is stable in normal subjects, and this finding could be referred to normal diastolic ventricular function. During ERT, sudden decrease in heart rate, associated with sudden increase in intraventricular volume, is linked to reduction in QRS TA mean values (Figure 3a). Inversely, in ischaemic patients (Figure 3b) QRS TA mean values profile shows, during increase in heart rate, an increasing trend, due to abnormal diastolic function leading to reduced ventricular filling. During ERT, a sudden decrease in heart rate is associated with a lower reduction of mean QRS TA than normal subjects, according to decreased diastolic compliance.

Also, our results confirm, as previously reported, a positive correlation between QRS TA and excitable cardiac mass [15]. Rest QRS TA value was lower in ischaemic patients than normal subjects, probably as a consequence of loss in excitable cardiac mass. Only in normal subjects, as expected, was a linear correlation found between RTA and cardiac mass.

As a new finding, confirming our haemodynamic hypothesis, QRS TA at rest and at maximum heart rate was inversely correlated with rest and stress ventricular volume, evaluated by SPECT perfusion imaging. QRS TA seems to be able to also evaluate left ventricular filling.

According to these results, QRS TA is not only linearly linked to cardiac mass, but also inversely linked to ventricular filling. QRS TA could be expressed by the ratio: cardiac mass/ventricular filling.

So we could explain the low sensitivity and specificity in electrocardiographic diagnosis of left ventricular hypertrophy (Romhilt-Estes, Sokolow-Lyon and Cornell criteria) [22] by the underevaluation of "left ventricular filling" as a correction factor.

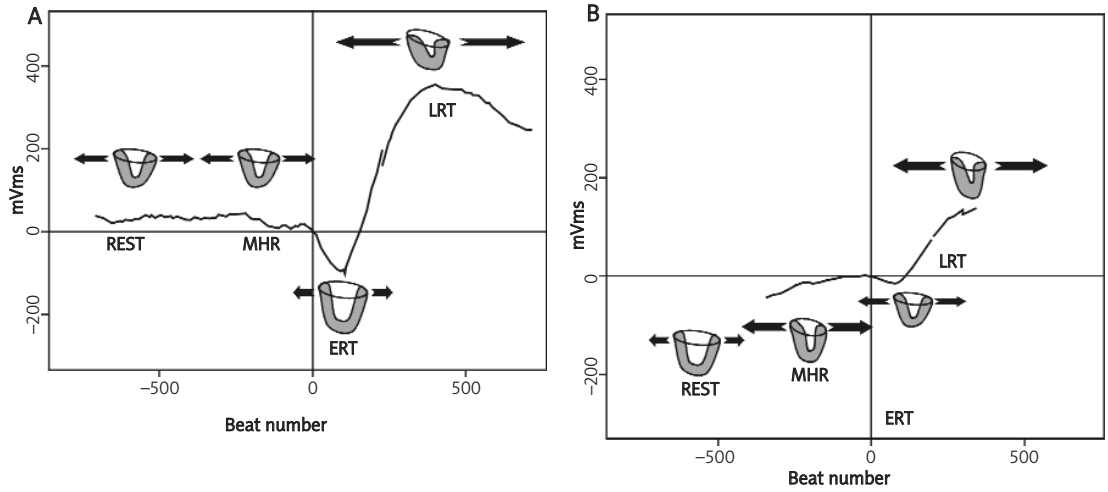

Figure 3. Haemodynamic hypothesis
Interpretation of differences in mean profile of QRS Total Area (QRS TA) during stress test in **normal subjects (A)** and **ischaemic patients (B)**. Intraventricular volume inversely correlates with vector power intensity (bolded arrows). In the panels are shown a sectional schematic image of left ventricle, during Rest, Maximum Heart Rate (MHR), Early Recovery Time (ERT) and Late Recovery Time (LRT) stages of stress test.
Panel A: Intraventricular volume and QRS TA profile, during increase in heart rate, are stable in normal subjects. This finding could be referred to normal ventricular compliance. As physiological behaviour, during ERT, sudden decrease in heart rate is associated with sudden increase in intraventricular volume, with associated reduction of QRS TA mean values.
Panel B: Inversely, in ischaemic patients, during increase in heart rate, intraventricular volume decreases and QRS TA profile shows an increasing trend due to abnormal ventricular compliance. Also during ERT in ischaemic patients, mean QRS TA is less reduced with respect to normal subjects; these findings could be referred to reduced ventricular filling as an effect of reduced diastolic compliance.
During LRT, mean QRS TA profile changes in the two groups according to the hypothesis proposed

In conclusion QRS TA profile identifies patients with abnormalities in haemodynamic performance during stress test, while the ST criterion, as known, better identifies patients with bioelectrical abnormalities. Monitoring of QRS TA and ST variables contemporaneously might be employed in clinical practice to increase diagnostic capability of the ECG stress test.

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