Velocity tracking of cardiac vector loops to identify signs of stress-induced ischaemia

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Abstract

Coronary artery disease (CAD) is among the leading causes of death worldwide. Initial studies require an electrocardiogram stress test often followed by cardiac imaging procedures. However, conventional indices still show insufficient diagnostic performance. We propose quaternion methods to evaluate abnormal alterations during ventricular depolarization and repolarization. Assessment was conducted during a Bruce protocol treadmill stress test and after the end of the exercise. We developed an algorithm to automatically determine the beginning and end of exercise and then, computed the angular and linear velocities. Statistical analysis for feature selection and classification between ischaemic and non-ischaemic patients was used. The most significant markers were maximum linear velocity during ventricular depolarization ($p < 5E\text{-}9$) and maximum angular velocity during the second half of the repolarization loop ($p < 5E\text{-}16$). The latter reached sensitivity / specificity pair of 78 / 92 (AUC 0.89). A linear classifier showed a trend of reduction in cardiac vector velocity in at-risk patients after the end of exercise. The sensitivity / specificity pair reached was 86 / 100. Trajectory deviations of depolarization / repolarization loops that result from ischaemia effects, could be responsible for the observed reduction in dynamic changes during exercise. Further studies could provide non-invasive complementary tools to detect CAD risk.

Keywords Exercise-induced myocardial ischaemia · Vectorcardiogram · Angular velocity · Quaternion theory

1 Introduction

Coronary artery disease (CAD) is among the leading causes of death worldwide and is the most prevalent among cardiovascular diseases [12]. Moreover, inducible myocardial ischaemia during stress tests is one of the most reliable predictors of future coronary events in patients with CAD [15].

Initial studies in patients with suspected CAD can require an electrocardiogram (ECG) stress test or cardiac imaging procedures in order to detect the presence of inducible ischaemia and stratify the risk. Coronary angiography via cardiac catheterization is the gold standard for the evaluation of coronary anatomy and severity of cardiac disease. It can also be used therapeutically since it allows reperfusion of the heart with the use of balloon angioplasty and stent placement. It is used in high-risk situations because it is the most invasive method and has harmful side effects such as myocardial infarction, stroke, induction of arrhythmias and vascular complications [21].

The modern cardiac imaging methods allow evaluation of the myocardium at risk to determine the need for catheter intervention. Cardiac computed tomography (CT) can provide good definition images through the use of x-ray beams collected by a detector array. However, this method leads to ionizing radiation exposure and usually offer net negative results, unnecessarily augmenting absorbed dose in healthy individuals and thus increasing probabilistic effects (cancer developing and genetic mutations)[14]. Care must be taken to ensure the need of this method especially with repeat imaging studies and in performing these tests in patients at a young age.

High-definition images can also be obtained from magnetic resonance imaging (MRI). It uses a magnetic field to alter the spin of the protons in hydrogen molecules and thus build an image. Conversely, metallic hardware is a

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contraindication for this method, such as permanent pacemarkers or implantable defibrillators [21]. Also, radioactive tracers are often used as agents that allow to assess myocardial perfusion in scintigraphy studies. However, it can result in a serious complication such as the contrast-induced nephropathy or other renal dysfunctions [19].

On the other hand, diagnosis methods based on ECG measurements, such as the ST segment depression during a stress test, are non-invasive and also inexpensive as compared to imaging methods. They are widely used in clinical routine but unfortunately, have shown insufficient diagnostic performance [3]. In this sense, much scientific effort has been expended into recent years to improve the diagnostic power of the stress test, using more complex techniques than just amplitude ECG measurements.

Recent studies have proposed complementary stress ECG markers based on high-frequency QRS analysis, which requires singular ECG recording equipment [23]. These markers focus on QRS abnormalities provoked by slow conduction of action potential over the ischaemic myocardium region. They could favor ischaemia detection when used together with ST changes and clinical data [3, 22]. Other authors have shown that the study of QRS slopes could provide a better contribution than a high-frequency analysis to the challenge of detecting stress-induced ischaemia. These slopes were associated with the linear velocity of the ventricular depolarization loop, which is affected by the reduction in myocyte conduction velocity [10, 16, 20].

Both high-frequency and QRS slope methods detect velocity components during ventricular depolarization. We have previously shown that conduction slowdowns in heart tissue caused by acute coronary syndrome can be assessed efficiently via the study of linear and angular velocities of the cardiac electrical vector [5, 6]. Moreover, the latter velocity can be more accurately obtained by means of quaternion methods even in the presence of noise [4]. We propose to extend our quaternion methods to the evaluation of exercise-induced ischaemia. We hypothesize that the ischaemia arising in risk patients subjected to a stress test can degenerate the conduction paths, causing the alteration of both ventricular depolarization and repolarization loops. In this sense, a complementary study of both linear and angular velocity during the QRS complex and T-wave could capture more significant predictors of stress-induced ischaemia. Moreover, we suppose that once the maximum effort of the test has been reached, the return to normal conduction paths will be carried out slowly in patients with ischaemia. This work could provide non-invasive complementary tools for the detection of CAD risk and thus contribute significantly to the reduction of cumulative danger of unnecessary radiation exposure or nefrotoxicity with a consequent reduction in morbidity and costs.

2 Materials and methods

2.1 Dataset

The “Exercise Testing and Perfusion Imaging” database used in this work compiled the ECG recordings from 927 consecutive patients (55.2 ± 10.1 $y.o.$, 33% Female), who were referred to exercise myocardial perfusion single-photon emission computed tomography (SPECT) in two medical centers. Data were obtained from a project with Telemetric and ECG Holter Warehouse (THEW) [24]. Subjects underwent the Bruce protocol treadmill stress test previously described in detail [23]. Patients with a cardiac pacemaker, atrial fibrillation at the time of the stress test or QRS duration over 120 ms were excluded. Standard 12-lead ECG (sampling frequency of $1000Hz$ and 16-bit resolution with a sensitivity of $0.15\mu V$) was continuously recorded in three stages of the stress test: (1) Control, before exercise; (2) procedure, during the exercise; (3) recovery, a few minutes of recording after the end of the test. Exercise duration was symptom limited ($8.7 \pm 2.4\, min$). The recovery phase has a short registration duration and there were only 21 patients with just over 5 min of recording.

Along with ECG recordings, the database provided‘the percent ischaemic myocardium (IM) obtained from perfusion images and the patients were classified as moderate / severe ischaemia (IM $>$ 10%); mild ischaemia (5% $<$ IM $<$ 10%); no ischaemia or equivocal (IM $<$ 5%). In addition, in order to compare the performance, the ST level was measured 60 ms after J point. The diagnosis was considered positive following conventional criteria [1, 25]: ST segment elevation in two or more contiguous leads with a cut-off value of >0.1 mV in all leads other than V2/V3, where the values were >0.15 mV for women and >0.2 mV in men; or ST-segment depression >0.05 mV in at least two contiguous leads.

2.2 Preprocessing

The XYZ spatial signals were computed from ECG leads I, II, V1-V6 using the Kors inverse transform [13]. An 80-Hz Butterworth low-pass filter was applied to remove high-frequency noise and preserve the velocity information of the QRS complex. Also, a 0.5-Hz Butterworth high-pass filter was applied for baseline wander correction. Both were 5th order bidirectional to reduce phase distortion.

The delineation of the fiducial points was carried out using a wavelet-based ECG delineator included in the ecg-kit, an open-source MATLAB toolbox for cardiovascular signal analysis [9, 16]. In this work, the QRS event marks were only needed, which are the least uncertain fiducial points and were obtained using multilead criterion. Using these marks, an RR series was constructed from the difference between marks, and an algorithm was developed to automatically determine the beginning and end of the exercise. The algorithm computes RR mean (μ) and the standard deviation (SD) during the control phase. When the subjects begin exercise, RR begins to drop.Then, the first RR below μ - 3.SD represents the onset of the procedure (see Fig. 1). On the other hand, the lowest RR value determines the end of the exercise.

Given that the signals are immersed in a noisy environment, partly due to the nature of the exercise procedure itself, it is suggested to obtain the velocity parameters from an average beat [5, 23]. Therefore, for the construction of the data series of both linear and angular velocities throughout the procedure, an average beat is computed every ten beats, requiring a correlation greater than 0.9 among the QRS complexes. If that correlation is not reached, that segment is discarded. This can occur in recordings where the power of the unwanted noise interferes with the signal to the point of making it unreliable to other morphologies. ECG recordings that do not reach a correlation over 0.9 in more than 50% of the signal are discarded. Under this restriction, 94 patients (10%) had to be ruled out, ultimately resulting in a total population of 833 subjects.

2.3 Velocity computation

Spatial velocity signals can be obtained applying quaternion methods, as we have previously described in [5]. At this instance, an alternative formula was used for the computation of the angular velocity which is more efficient in terms of processing speed, since it is obtained with fewer operations. As can be seen in Eq. 1, for the nth sample ($\vec{P}_n(x, y, z)$) in the three-dimensional space obtained from Kors transformation, a quaternion $\vec{q_n}$ was built.

$$\mathbf{q_n} = \frac{(0, \mathbf{P_n})}{\|\mathbf{P_n}\|} \implies \dot{\mathbf{q}}_\mathbf{n} = (\mathbf{q_{n+1}} - \mathbf{q_n}) \cdot Fs \tag{1}$$

Then, using the temporal differentiation of $\vec{q_n}$

$$\boldsymbol{\omega}_\mathbf{n} = \dot{\mathbf{q}}_\mathbf{n} \times \bar{\mathbf{q}}_\mathbf{n} \tag{2}$$

Herein, $\bar{\mathbf{q}}_\mathbf{n}$ indicates the quaternion conjugate and the '$\times$' symbol refers to the Hamilton multiplication rule which follows the fundamental formula of quaternion algebra, ie: $i^2 = j^2 = k^2 = ijk = -1$. This results in a sequence of quaternions $\vec{\omega}$ where the imaginary parts represent the angular velocity in space, that is, a three component vector.

On the other hand, the linear velocity can be obtained by direct differentiation of the vectors $\vec{P_n}$.

$$\vec{v_n} = (\vec{P_{n+1}} - \vec{P_n}) \cdot Fs \tag{3}$$

Recent works, as described in Section 1, have shown evidence of abnormal ventricular depolarization changes during ischaemic events [10, 22]. Additionally, significant alterations in ventricular repolarization were observed during angioplasty procedures [6]. In this sense, it is necessary to study both ventricular depolarization and repolarization waves. Therefore, from each ith beat two subsignals were selected: QRS complex and T-wave. The first is composed of all the samples included in the interval $Q\widehat{R}S \pm 60ms$. The latter includes all the samples from $Q\widehat{R}S_i + 60ms$ to $Q\widehat{R}S_{i+1} - 150ms$.

Figure 2 shows a descriptive graph of the velocities based on two subjects from the database herein used. On the left side panel (Fig. 2a), a T-wave loop (ventricular

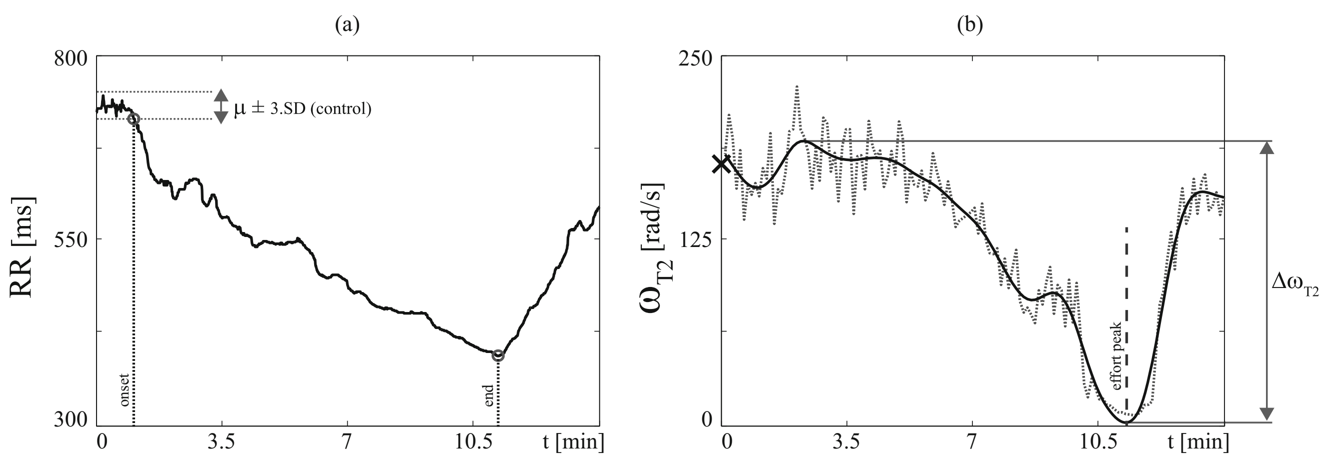
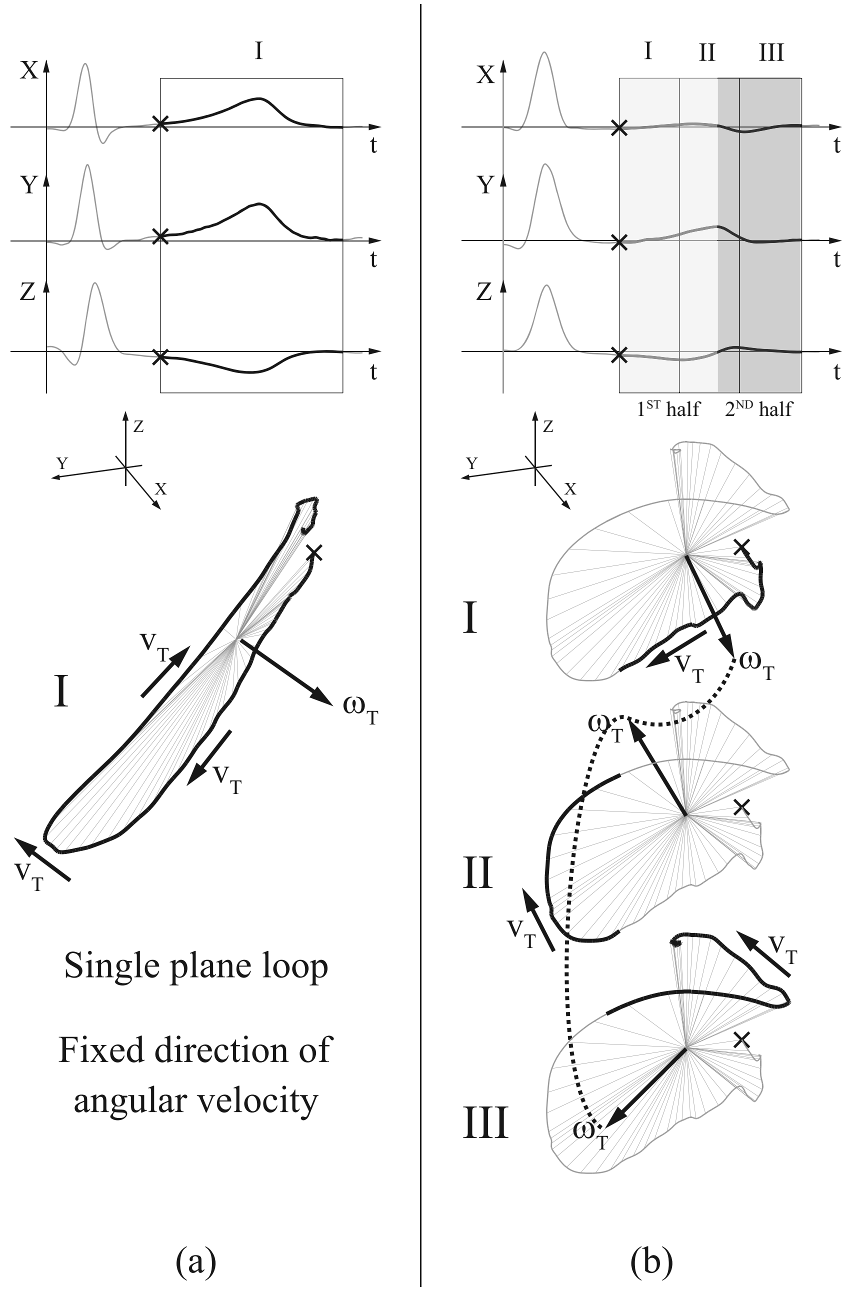


Fig. 1 **a** RR sequence for a patient in the database. Vertical dotted lines indicate the onset and end of the procedure. Mean (μ) and standard deviation (SD) during the control phase are used for automatic detection of the beginning of exercise. **b** Example sequence of angular velocity response to exercise. Maximum and minimum values in the filtered signal determine the index candidate for diagnosis

Fig. 2 Angular and linear velocities of the cardiac vector in a T-wave loop during exercise. **a** Non-ischaemic patient. Nearly planar loop produced by a healthy signal. **b** Ischaemic patient. Continuous deviations of the loop produced by ischaemic effects. The '×' mark indicates the beginning of the loop. The dotted line shows the variation of the angular velocity direction in different phases of the T-wave



repolarization) of a healthy subject is observed during exercise. This loop follows a curve that can be almost entirely contained in a plane. Thus, while the linear velocity changes its direction, the angular velocity remains in a fixed direction, changing only the module. On the other hand, on the right side panel (Fig. 2b), the repolarization loop of a patient with stress-induced ischaemia is shown. The loop has deviations along the entire curve causing the angular velocity to continually alter its direction as well. This implies that the rotations would be slower until the procedure ends and the recovery process begins. It should be noted that the second half of the T-wave exhibits more deviations effects.

2.4 Differential markers

Since the velocity of the cardiac electrical vector is slowed down as a consequence of the ischaemic process, the maximum value of the linear and angular velocities previously described were selected as candidate features for diagnosis. These are obtained for the following: (1) the QRS complex (ω_Q, v_Q), ventricular depolarization; (2) the first half of the T-wave (ω_{T1}, v_{T1}), apex-to-base repolarization; and (3) the second half of the T-wave (ω_{T2}, v_{T2}), transmural repolarization from epicardium to endocardium. This translates into a total of 6 candidate features. During the procedure, the heart rate of the subject increases due to exercise. This increase is accompanied by a natural change in velocities. If the heart begins to undergo an ischaemic process, this change should be affected. For this reason, change in velocity is characterized as:

$$\begin{cases} \Delta \mathrm{v} = max(\|\vec{v_n}\|_2) - min(\|\vec{v_n}\|_2) \\ \Delta \omega = max(\|\vec{\omega_n}\|_2) - min(\|\vec{\omega_n}\|_2) \end{cases} \tag{4}$$

Figure 1 shows an example of the change in the angular velocity of the second half of the T-wave. As can be seen, the maximum and minimum values are taken from the signal resulting from passing the signal through a low pass filter (3rd order bidirectional, Butterworth, cutoff frequency of 40Hz).

2.5 Velocity values during recovery

Previously, through an ischaemia model during an angioplasty procedure, we provided evidence that ischaemic processes would cause the deviation of conduction pathways during ventricular repolarization [6]. Under the assumption that after the end of ischaemia the restitution of these pathways to normal paths will occur more slowly in an affected tissue, we also propose herein that the absolute values of the velocity variables be observed after a period of 5 min from the end of the exercise has elapsed. Then, through a statistical analysis, we work on possible combinations of up to two parameters in order to separate the pathological group from the healthy group. The number of patients with sufficient registration time during recovery is low (21 patients with recovery records longer than 5 min) in relation to the total number of patients. Therefore, this section of the work may show a trend that should be evaluated in depth in future work.

2.6 Statistical analysis

The differences in the dynamic features of No ischaemia (IM $<$ 5%) and Mild/Severe ischaemia (IM $>$ 5%) populations were evaluated. In this sense, we constructed violin plots to compare the indices in both groups. For these results, a two-sided Wilcoxon signed rank test to obtain a significance value (p) on the group means was used.

On the other hand, we also used the Wilcoxon test to compare the value of each index after 5 min of recovery with the control value. We used combinations of the most significant indices to observe a possible linear classification on territorial maps from both populations.

3 Results

The automatic detection of the beginnings and ends of the stress tests using the algorithm and the RR series described in Section 2.2, showed a high efficacy. Both onset and end marks coincided by 99% with the time when RR values begin to drop due to exercise and the time when they begin to recover respectively. The marks had to be corrected in 8 subjects (1%) due to the high level of noise during the control and procedure phases. The total number of subjects after the construction of the series of averaged beats under the correlation restriction greater than 0.9 every 10 consecutive QRS complexes, was N = 833, including 773 non-ischaemic and 60 ischaemic (IM $>$ 5%) patients.

The total variation between the maximum and the minimum values of linear velocity showed significant differences (p $<$ 5E-9) between the at-risk population (IM $>$ 5%) and the population without ischaemia (IM $<$ 5%), as shown in Table 1. These differences can be understood as the difficulty of increasing or decreasing the conduction velocity due to the increase in axial resistance on coupling between myocytes in the damaged tissue area [17].

On the other hand, significant differences were found (see Table 1) in the changes of angular velocity during the second half of the T-wave (p $<$ 5E-16). The second half of the T-wave has been associated with transmural repolarization, which would indicate that ischaemia causes more notable damages in the internal tissues of the ventricles than in epicardial ones. However, the relationship between ventricular dispersion and the ECG waveform is still under debate [2].

In Fig. 3a, we show violin graph representations for the two parameters with the greatest statistical significance. Herein, a decision threshold, taken from the intersection of the kernel probability density curves, is observed with which a sensitivity / specificity pair of 50/88 for $\Delta \mathrm{v}_{\mathrm{Q}}$ and 78/92 for $\Delta \omega_{\mathrm{T2}}$ is reached. Additionally, the performance of the standard diagnostic ST measure, reached a sensitivity / specificity pair of 65.2/60.9 in this dataset. The improvement in performance can be appreciated in Fig. 3b, where the ROC curves of $\Delta \mathrm{v}_{\mathrm{Q}}$ and $\Delta \omega_{\mathrm{T2}}$ show an

Table 1 Mean (μ) and standard deviation (SD) of differential markers in both groups. Last column shows p-values of Wilcoxon rank-sum tests

Index	No ischaemia	Ischaemia	p-value
	$\mu \pm SD$	$\mu \pm SD$	
$\Delta \mathrm{v}_{\mathrm{Q}}$ $[mV/s]$	14.8 ± 7.7	10.2 ± 7.5	<5E-9
$\Delta \mathrm{v}_{\mathrm{T1}}$ $[mV/s]$	3.6 ± 1.4	3.2 ± 1.9	<0.05
$\Delta \mathrm{v}_{\mathrm{T2}}$ $[mV/s]$	3.7 ± 1.5	3.2 ± 1.9	<0.005
$\Delta \omega_{\mathrm{Q}}$ $[rad/s]$	138.1 ± 94.2	135.2 ± 101.3	ns
$\Delta \omega_{\mathrm{T1}}$ $[rad/s]$	58.8 ± 61.8	49.7 ± 43.6	ns
$\Delta \omega_{\mathrm{T2}}$ $[rad/s]$	259.4 ± 123.2	134.9 ± 75.2	<5E-16

‘ns’ indicates non-significant differences (p $>$ 0.05) between groups

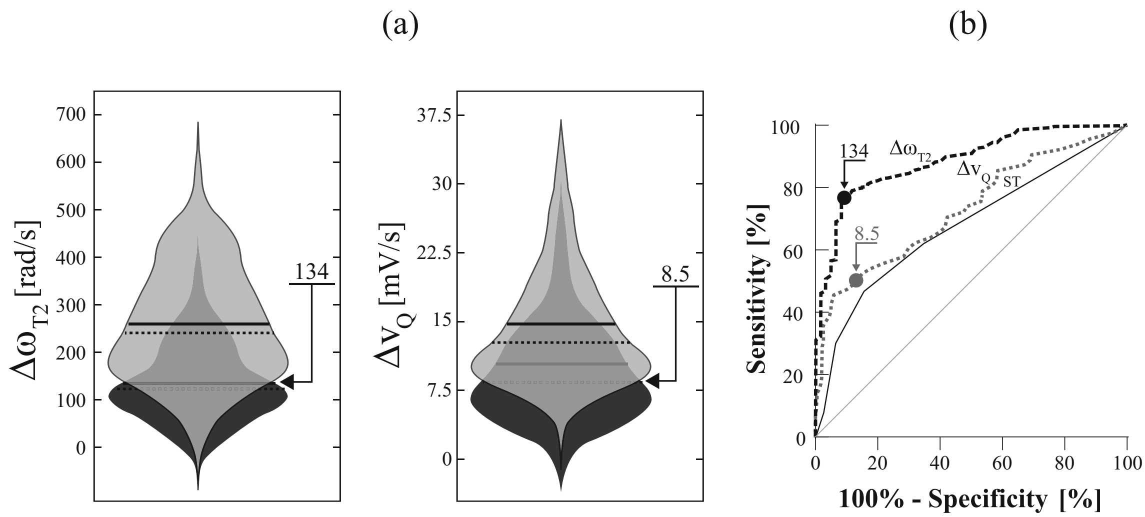


Fig. 3 **a** Violin graphs for the variations in angular velocity of the second half of the T-wave and linear velocity of the QRS complex. Light gray plots correspond to non-ischaemic patients (IM < 5%) and the dark gray ones to at-risk patients (IM > 5%). Dotted lines indicate the medians of populations and solid ones, the means. The intersection values 134 rad/s and 8.5 mV/s are possible threshold limits for classification; **b** ROC curves of the velocity markers ($\Delta\omega_{T2}$ dashed black line and Δv_Q dotted gray line) compared to the level ST-segment measurements (solid black line)

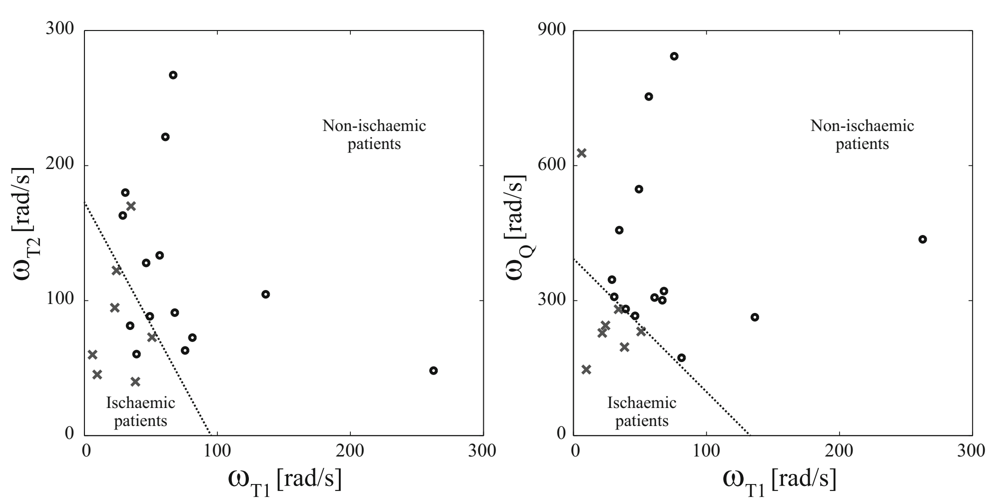
area under the curve (AUC) of 0.73 and 0.89 respectively, while the ST curve reaches only 0.69.

Finally, two-dimensional territorial maps are shown in Fig. 4 for the most significant indices during the recovery phase (5 min after the end of the exercise). ω_{T1}showed the most significant differences ($p < 0{,}005$). Through a simple linear classification, the pair (ω_{T1}, ω_{T2}) reached sensitivity / specificity levels of 86 / 86 while the pair (ω_Q, ω_{T1}) reached levels of 86 / 100.

4 Discussion

In this work, we studied the dynamic changes in the cardiac electrical vector induced by a stress test. The assessment was conducted during the procedure and also, after the end of the exercise, during the recovery phase. We obtained the angular and linear velocities in the QRS complex and both halves of the T-wave. The distinction between the T-wave halves is relevant given that the phenomenon of abnormal increased ventricular repolarization dispersion is strongly linked to cardiac risk [2]. However, it has not yet been determined whether the origin of the risk lies in early or late repolarization. Moreover, its measurement using the temporal parameters of the ECG, such as the interval from T-wave peak to T-wave end, has been called into question, among other reasons, because of the uncertainty in the delineation of the T-wave end [11, 18]. Therefore, more robust measurements of ventricular repolarization dispersion, as the velocity markers in the halves of the T-wave, could

Fig. 4 Territorial maps for the best indices during the recovery phase. The '**x**' marks indicate the ischaemic patients (IM > 5%) and the '**o**' marks, the non-ischaemic ones (IM < 5%). Dotted lines show a linear classification



shed light on this question. We have previously shown the potential of the velocity indices as ventricular repolarization heterogeneity markers both on acute coronary syndrome [6] and on drug effects [7, 8].

The results observed during the stress test suggest that an incipient ischaemic process could moderate the velocity variations of the cardiac vector (see Table 1). From the linear velocity perspective, this observation agrees with the results of other authors [3, 22, 23] who have shown a relationship between high-frequency phenomena in the QRS complex and conduction velocity in the tissue. In this sense, these studies have concluded that a reduction in the changes of the high-frequency components appears as a consequence of the presence of ischaemic tissue. Other authors have also observed that the slopes of the QRS complex, which are directly related to the velocity of the electrical cardiac vector, could reach a performance classification of exercise-induced ischaemia comparable to that of manual analysis by an expert [10].

Concerning angular velocity, our study shows that its variations have a fundamental role in the effects of ischaemia on ECG tracing. During the stress test, the maximum total variation in angular velocity of the second half of the T-wave showed the highest statistical significance ($p < 5\text{E-}16$) between at-risk patients (IM $> 5\%$) and non-ischaemic patients (IM $< 5\%$). This is consistent with our previous observations of latent repolarization abnormalities in an ischaemia model based on angioplasty trials [6]. Both this marker and the linear velocity marker are independent of the high-frequency measurements. Moreover, quaternion methods ensures robustness to noise in the calculation of angular velocity [4]. Additionally, both Δv_Q and $\Delta\omega_{T2}$ performed better than the standard diagnostic ST measure.

Moreover, the angular velocity of the first half of the T-wave and the QRS complex showed promising performance values (sensitivity/specificity levels of 86/100) during the physical recovery phase (see Fig. 4). Regardless of the decrease in the total number of subjects due to the fewer recordings during the last phase, we can observe a general decrease trend of velocities in patients with ischaemia. This could indicate that returning to normal values may be more time-consuming in an affected heart.

Finally, more work is needed to generalize our findings. These results meaningfully contribute to the study of the spatial velocity of the cardiac electrical vector from a quaternion perspective. Future efforts should be made to integrate both linear and angular velocities with other features into a single index in order to assess abnormalities during exercise-induced myocardial ischaemia more accurately. The proposed automatic algorithm for the detection of rhythm changes achieved high performance and allows us to hypothesize its integration to Holter routine studies in the near future. Also, it could be convenient to make prospective studies to define the normal limits of these new markers that characterize exercise-induced ischaemia.

5 Study limitations

The nature of the stress test involves high noise levels in relation to the power of the ECG signal. Quaternion algebra provides a robust tool for obtaining velocities in signals that lie in a noisy environment. However, in the first part of this work we had to rule out 94 patients (10%) who did not reach reasonable levels of correlation (> 0.9) between consecutive QRS complexes through the whole procedure. Future work should evaluate possible algorithms that allow noise reduction during exercise. These algorithms should be tested together with the indices studied here in order to evaluate reproducibility in independent databases.

On the other hand, the trend observed in the maximum value of the linear and angular velocities suggests that the return to normal values is slower in ischaemic patients. However, in the second part of this work, the number of patients with sufficient registration time during recovery is low ($N = 21$). Further studies should be conducted to verify whether this trend can extend to considerable statistical significance.

6 Conclusion

By studying the dynamics of the electrical cardiac vector from a velocity approach, we have extended our previous observations and the results of other authors to improve the identification of stress-induced ischaemia. The results presented here could complement the classical indices and routine studies in order to optimize the diagnostics and avoid invasive procedures. The trajectory deviations of the QRS complex and T-wave loops that arise as a consequence of ischaemia effects, as shown in Fig. 2, could be responsible for the observed reduction in dynamic changes during exercise. This fact suggests a moderation effect on the velocity change ability of the cardiac electrical vector. Additionally, the trend observed in the recovery phase suggests that valuable information could be obtained in the post-exercise recordings. In this sense, it would have the additional advantage of presenting less noisy signals. We are confident that a further deepening of these ideas could substantially improve the diagnosis of stress-induced ischaemia.

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Declarations

Competing interests The authors declare no competing interests.

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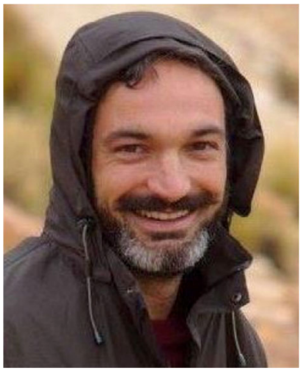

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