Spatial Indices of Repolarization Correlate with Non-ST Elevation Myocardial Ischemia in Patients with Chest Pain

By

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ABSTRACT (200 words)

Mild-to-moderate ischemia does not result in ST segment elevation on the electrocardiogram (ECG), but rather non-specific changes in the T wave, which are frequently labelled as non-diagnostic for ischemia. Robust methods to quantify such T wave heterogeneity can have immediate clinical applications. We sought to evaluate the effects of spontaneous ischemia on the evolution of spatial T wave changes, based on the eigenvalues of the spatial correlation matrix of the ECG, in patients undergoing nuclear cardiac imaging for evaluating intermittent chest pain. We computed T wave complexity (TWC), ratio of second to first eigenvalues of repolarization, from 5-minute baseline and 5-minute peak stress Holter ECG recordings. Our sample included 30 males and 20 females aged 63±11 years. Compared to baseline, significant changes in TWC were only seen in patients with ischemia (n=10) during stress testing, but not among others. The absolute changes in TWC were significantly larger in the ischemia group compared to others, with a pattern that seemed to depend on the severity or anatomic distribution of ischemia. Our results demonstrate that ischemia-induced changes in T wave morphology can be meaningfully quantified from the surface 12-lead ECG, suggesting an important opportunity for improving diagnostics in patients with chest pain.

Keywords: ischemia; ventricular repolarization dispersion; T wave; electrocardiogram

Glossary of Terms:

AMI:	Acute Myocardial Infarction
AP:	Action Potential
CAD:	Coronary Artery Disease
ECG:	Electrocardiogram
LAD:	Left anterior descending coronary artery
LCX:	Left circumflex coronary artery
PCA:	Principal Component Analysis
PCI:	Percutaneous coronary intervention
RCA:	Right coronary artery
ROC:	Receiver operator characteristics curve
R_{TWC}:	Changes in T wave complexity relative to baseline variations
SPECT:	Single photon emission computed tomography
SDNN:	Standard Deviation of normal-to-normal R-R interval
TWC:	T wave complexity
VRD:	Ventricular repolarization dispersion

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1. INTRODUCTION

Chest pain is the leading cause for emergency department visits among U.S. adults [1]. Initial patient evaluation and risk stratification aims at differentiating those who are in severe cardiac distress from those who are not, which is necessary for improving patient outcomes and allocating limited resources. Although the 12-lead electrocardiogram (ECG) remains the most powerful tool for initial patient assessment [2, 3], the absence of concrete ECG indices that can quantify myocardial ischemia in the absence of ST segment elevation constitutes a longstanding challenge in clinical cardiology [4-6]. This means that non-ST elevation myocardial ischemia cannot be ruled out until more invasive diagnostics, for instance coronary angiography or nuclear imaging, are ordered, performed, and interpreted [7, 8]. Therefore, there is a great clinical need for developing more cost-effective, rapid assessment diagnostic tools for patients with chest pain, and novel ECG markers of ischemia are a great opportunity for improving such diagnostics.

Progressive atherosclerosis can result in a critical narrowing of a coronary artery, eventually leading to supply-demand mismatch and oxygen-deprivation in the myocardial region supplied by that coronary artery [9, 10]. This process results in acute ischemia in the affected myocardial region, with corresponding electrophysiological changes in ventricular repolarization [11]. These changes include reduction of duration, resting potential, and propagation velocity of action potentials (AP) in the ischemic myocardial region. Thus ischemia alters ventricular repolarization by (a) shortening repolarization time (i.e., temporal changes) and (b) slowing the conduction speed across different myocardial regions (i.e., spatial changes) [12]. Ultimately, acute ischemia induces changes in STT morphology and timing. In fact, it has been shown that myocardial ischemia affects the AP in the epicardial and endocardial regions differently, which means that ischemia can precipitate ventricular repolarization dispersion (VRD) not only within the ischemic region itself, but also between ischemic and non-ischemic fibers [13]. As such, severe ischemia can cause dramatic depression of epicardial, but not endocardial, AP and

hence transmural conduction delays, manifested as undefinable QRS complex and T wave on leads whose positive poles are facing the ischemic region [14]. Such ECG pattern is clinically defined as massive ST elevation. Consequently, it can be inferred that mild to moderate ischemia does not typically result in transmural conduction delays (i.e., lesser degree of *temporal* VRD) and hence manifest no ST elevation on the surface ECG.

Methods tailored at quantifying the *spatial* inhomogeneity in VRD can constitute a promising alternative for detecting and quantifying non-ST elevation myocardial ischemia in high risk clinical populations [15]. Accordingly, we have previously shown that spatial indices of VRD correlate with biomarkers of myocardial necrosis during the evolution of acute myocardial infarction (AMI) [16]. In addition, others have shown that short-term simulated ischemia (no flow) during percutaneous coronary interventions (PCI) significantly alters spatial indices [12], as well as T vector and loop indices [17], of ventricular repolarization. However, these studies used the PCI as an ischemic model in order to analyze VRD changes during induced ischemia in patients who were already ischemic, without considering the values of the indices in control subjects. The PCI procedure, although it induces profound transmural ischemia, is not a perfect model of spontaneous myocardial ischemia and does not have a solid gold standard for quantifying the extent and severity of myocardial ischemia. In this study, we sought to evaluate the effects of mild-to-moderate myocardial ischemia on the evolution of spatial T wave changes, based on the eigenvalues of the spatial correlation matrix of the ECG, in patients undergoing nuclear perfusion imaging, using Tc-99m sestamibi single-photon emission tomography (SPECT), for evaluating intermittent chest pain. We hypothesized that the ratio of 2nd to 1st eigenvalues of T wave, as a spatial measure of VRD, correlates with the onset, evolution, and severity of myocardial ischemia in patients with positive SPECT scans compared to controls.

2. METHODS

2.1 Study Sample

This was a prospective observational study of patients referred for functional cardiac evaluation at UPMC Presbyterian Hospital, Pittsburgh PA. We recruited consecutive patients meeting the following inclusion criteria: (1) aged >30 year-old, (2) present with chief complaint of chest pain or other symptoms suggestive of acute coronary distress (e.g., shortness of breath), (3) undergoing SPECT myocardial perfusion imaging with both a resting baseline scan and a post stress scan (i.e., treadmill exercise or pharmacological stimulation), and (4) are in normal sinus rhythm at baseline. The exclusion criteria included patients who are (1) hemodynamically unstable, or (2) with atrial fibrillation and/or extrinsic heart rhythms (i.e., pacing). This study was approved by the Institutional Review Board of the University of Pittsburgh and all subjects signed a voluntary informed consent prior to participation.

2.2 Study Protocol

After completing the resting SPECT myocardial perfusion scan, consented subjects were escorted to a private room where they underwent 5-minute baseline 12-lead Holter ECG recording while in a supine, resting position. Torso positions were used for limb leads. Recordings were obtained using H12+ digital Holter recorders (Mortara Instrument, Milwaukee WI) with high-fidelity sampling resolution of 1,000 samples per second, and at a frequency response rate of 0.05-300 Hz. The Holter monitor was then paused without detaching the cables or electrodes, and resumed again for 5-minutes when subjects reached their maximum heart rate during the peak of stress test (Figure 1). Whereas subjects undergoing pharmacological stress test remained supine during the entire test, subjects undergoing exercise stress testing were instructed to lie supine only when they reached their maximum heart rate and after abruptly stopping the stress test (no cool down). This window of ECG recording is more likely to provide noise and artifact-free signal, for reliable T wave analyses, while still capturing the majority of the critical ischemia phase. Subjects were then monitored until their vital signs returned to baseline before undergoing the post-stress SPECT myocardial perfusion scan.

2.3 SPECT Scans

The specific methods for quantifying myocardial ischemia using Tc-99m sestamibi SPECT imaging were detailed elsewhere [18]. In short, stress-rest protocol was used with either a Bruce treadmill exercise or Regadenoson stimulation stress testing. Initially, a radiotracer substance (i.e., 600 Mbq of Tc-99 sestamibi) is injected intravenously, a substance that gets absorbed by healthy myocardium. SPECT imaging is performed with a large field-of-view gamma camera equipped with a high-resolution collimator. Images are acquired in 32 frames and are reconstructed by back projection with a Butterworth filter. For image processing, the myocardium is divided into 17 segments and each segment is then graded according to perfusion with a 4-point system (1=normal, 2=mildly reduced, 3=severely reduced, 4=absent). During stress testing, areas with reduced blood flow, due to blocked or partially blocked coronary arteries, will be unable to absorb the radiotracer and will show up on imaging differently. The difference in grading between the stress scan and the resting scan defines the location, extent, and severity of myocardial ischemia. All SPECT images were interpreted by a board-certified nuclear cardiologist as a part of routine medical care.

2.4 ECG Pre-processing

All ECG streams obtained during study protocol were stored on a field laptop computer for offline analysis, and ECG annotator was blinded from the SPECT scan results. First, ECG streams were automatically filtered and previewed using H-Scribe v5.11 (Mortara Instrument), followed by manual annotation for cleaning noise and artifacts, and for rejecting abnormal or ectopic beats. A baseline 12-lead ECG was then captured and printed on standard ECG paper for interpreting cardiac rhythm, chamber hypertrophies, and conduction defects. Digital ECG signals were then pre-processed using Super-ECG v2.0 (Mortara Instrument) to compute beat-to-beat ECG intervals (e.g., QRS duration, QT interval, RR interval), as well as to compute 10-second averaged beats for each of the 12-leads for the duration of the recording. Beat

averaging has been shown to reduce the variance of T-wave morphology indices based on the principal component analysis (PCA) technique [19]. Consecutive normal beats were aligned by R-maxima to compute the required average beats in each lead, and these averaged beats were used for subsequent analysis.

2.5 ECG Features Extraction

The spatial dispersion of ventricular repolarization was quantified as previously described by Priori and colleagues [20]. To ensure the inclusion of the entire repolarization waveforms, the voltage of the ST-T complex was algorithmically defined as beginning at QRS offset and ending at the rate-expected end of T according to Bazett's formula + 0.1 second. The voltage of this repolarization window was samples every 1 ms, and the principal component analysis (PCA) technique as previously described by Lux et al [21] was performed on these amplitudes. The PCA was applied at each averaged beat on a set of 8 leads (I, II, V1-V6) that represent the relative magnitude of the spatial components of repolarization. The spatial complexity of repolarization was quantified using T wave complexity (TWC) index. TWC resembles the roundness of the repolarization loop and is calculated as the ration of 2nd to 1st eigenvalues of repolarization,

$$\text{TWC} = \frac{\lambda i,2}{\lambda i,1},$$

whereas λ resembles the repolarization eigenvalue of the corresponding ith averaged beat. These eigenvalues constitute the square root of the diagonal values of the covariance matrix of the ST-T waveforms of the ECG. A TWC value closer to 0 suggests that the 1st eigenvalue accounts for most variability (i.e., very homogenous ventricular repolarization), whereas a value closer to 1 suggests that the 2nd eigenvalue contributes significantly to the variability of repolarization (i.e., very dispersed ventricular repolarization). In healthy myocardium, the 1st eigenvalue accounts for most variability in the ST-T signal, so smaller TWC values are expected

in controls and larger TWC values are expected in ischemia group. TWC was measured at every 10-second averaged beat, and hence each recording (baseline ECG and peak-stress ECG) had 30 values (6 values per minute for 5 minutes).

Finally, to evaluate the ability of TWC to assess ischemic changes during stress testing, we computed an ischemic change index, R_{TWC}, as previously described by Arini et al [12]. This index evaluates the relative variation in TWC during peak stress to the normal variability observed in baseline recording. The index R_{TWC} was computed as the absolute magnitude of change in TWC with respect to averaged baseline (denoted as Δ_{TWC}) every ith averaged beat during peak stress (denoted as t) divided by the standard deviation of TWC at baseline recording (denoted as σ):

$$R_{TWC}(t) = \left| \frac{\Delta TWC\ (t)}{\sigma} \right|.$$

2.6 Data Analysis

Statistical significance was set at $p < 0.05$ (two-tailed). Descriptive statistics were reported as mean ± standard deviation for continuous variables and as frequency (%) for categorical variables. Patients were divided into three groups: those with positive SPECT results (i.e., ischemia group), those with negative SPECT result but high probability of CAD (i.e., Hx of CAD group), and those with negative SPECT results and low probability of CAD (i.e., control group). For some post-hoc analyses, the ischemia group was further sub-divided according to severity of ischemia (mild vs. moderate) and according to the anatomical distribution of affected coronary artery (left anterior descending, LAD, left circumflex, LCX, vs right coronary artery, RCA). Groups were compared using chi-square for categorical variables, or using one-way analysis of variance with Tukey's post-hoc comparisons for continuous variables. Variable significant at $p<0.20$ at the univariate level were entered in a multivariate logistic regression model with backward selection to identify predictors of ischemia. The diagnostic performance of

variables significant in the final multivariate model were evaluated using area under the ROC curve (AUC). ROC-optimized cutoff values were used to calculate sensitivity and specificity to detect pre-SPECT probability of ischemia. Finally, to analyze the evolution of beat-to-beat changes in index variable R_{TWC} , we used repeated measures analysis of variance with time-group interaction comparisons. Tukey's post hoc comparisons were used to identify significant differences between ischemia and control groups during the course of Holter recording.

3. RESULTS

3.1 Baseline Characteristics

Our sample included 50 patients aged 63±11 years (range 30-89), and there were 40% females and 10% African Americans. Around two thirds of patients had hypertension and hyperlipidemia, and more than one third had diabetes, a history of myocardial infarction, and a prior coronary revascularization procedure. On the stress test (60% treadmill exercise and 40% pharmacological stimulation), 12 patients (24%) developed symptoms and manifested significant changes on their peak ECG. On the SPECT imaging, however, 10 patients (20%) had diminished myocardial perfusion indicative of myocardial ischemia (40% with mild and 60% with moderate ischemia). Table 1 compares the baseline demographic and clinical characteristics between groups. Compared to control group, ischemia group was more likely to be older males with higher systolic blood pressure and a past history of AMI with a prior revascularization procedure. However, no baseline characteristic differentiated the ischemia group from patients with a known history of CAD.

3.2 Holter ECG Characteristics

Table 2 compares the ambulatory Holter ECG characteristics of 5-min baseline recording and 5-min peak-stress recording between the study groups. At baseline, there were no differences between groups regarding heart rate variables or temporal or spatial ECG waveform variables. Though, the control group seemed ($p<0.20$) to have higher average heart

rate and higher heart rate variability compared to other groups. There were no differences in average TWC between groups at baseline. At peak-stress recording, however, the ischemia group had significantly higher TWC values compared to controls and to those with Hx of CAD (0.37±0.17 vs. 0.20±0.12 and 0.20±0.15, $p<0.01$, respectively). There were no differences in heart rate variables or other temporal ECG waveform variables, but ischemia groups seemed ($p<0.20$) to have slower heart rate, wider QRS duration, and more pronounced ST depression.

3.3 Univariate & Multivariate Predictors of Ischemia

At the univariate level, only baseline systolic blood pressure and mean TWC values during peak-stress were significant predictors of ischemia. Other demographic (i.e., age, sex), clinical (i.e., history of CAD), and Holter ECG (i.e., peak-stress heart rate, QRS duration, and ST depression; and baseline heart rate variability) characteristics were not significant predictors of ischemia (Table 3). In the multivariate model, higher mean TWC value during peak-stress was the only significant predictor after controlling for other demographic and clinical characteristics. Using ROC analysis, mean TWC during peak-stress was a very good classifier of pre-SPECT probability of ischemia (AUC = 0.853, Figure 2-A). A cutoff value of 0.235 predicted outcome with sensitivity and specificity of 80% and 83% respectively (Figure 2-B).

3.4 Beat-to-Beat Evolution of Spatial Indices of Repolarization

Figure 3-A shows the trend of TWC at baseline and its evolution during peak stress test in the different study groups, measured every ith averaged beat of recording. At baseline, the relevant contribution of the second principal component (λ_2) to the repolarization variability was equivalent among all groups, suggesting morphological similarities in T loop roundness. At peak of stress test, only the ischemia group had a significant increase in the value of second principal component (λ_2), resulting in increased spatial complexity of repolarization (TWC), and hence increased T loop roundness. Although not significant, patients with a past history of CAD also had a similar trend of change (i.e., increase in second principal component, λ_2). The control

group, however, had an initially opposite trend during peak of stress test (i.e., increase in first principal component, λ_1), which was not significant though.

Figure 3-B illustrates the absolute relative changes in spatial dispersion of ventricular repolarization in the three study groups at every ith averaged beat of peak stress recording. Compared to controls and other patients with a past history of CAD, the ischemia groups had a significantly greater change in TWC throughout the peak of stress and early recovery period. This suggests that myocardial ischemia induces greater spatial dispersion of ventricular repolarization manifested as significant relevant increase in the second principal component (λ_2) and subsequent absolute change in TWC index. In summary, only the ischemia group had a significant increase in the spatial dispersion of repolarization during peak of stress test, which continued through the early recovery phase. Figure 4 compares the 12-lead ECG and corresponding principal component waveforms and their T loops at different time points in a control patient and in a case with moderate ischemia of the LAD artery.

3.5 Post-hoc Subgroup Analyses

We sought to evaluate the different patterns of change in TWC in few clinically-important subgroups. With regard to type of stress test, those completing exercise stress test (n=33, 66%) achieved higher max heart rate during peak of stress compared to those completing pharmacological test (116±21 vs. 87±14, $p<0.01$). However, there were no significant differences in the behavior of R_{TWC} changes between the two tests in patient with ischemia or without ischemia (Figure 5-A and 5-B). Two observations can be made from Figure 5-B. First, although not significant, changes in R_{TWC} seen in patients with ischemia induced by regadenson stress testing seemed to be more pronounced and persistent than those changes seen with exercise stress testing. Second, the changes in R_{TWC} seen in patients with ischemia induced by exercise stress testing seemed to be more pronounced during the initial minute of peak stress test. These observations can be possibly explained by (1) the clinically-known nature of

exercise testing that tends to provoke more transient (<1 minute) ischemia during the peak of stress test, and (2) the design of the protocol that recorded the peak-stress Holter ECG after stopping the treadmill to capture a noise and artifact-free signal for reliable T wave analyses.

With regard to severity and location of ischemia, , although underpowered, our post-hoc analyses suggest that there is a relationship between the severity of ischemia and the magnitude of change in spatial repolarization dispersion (Figure 5-C), as well as between the behavior of change in repolarization dispersion and the location of affected coronary artery (Figure 5-D). More severe ischemia, or ischemia involving the left ventricle from a partially occluded LAD or LCX arteries, but not RCA, seemed to augment the observed ischemia-induced changes in TWC.

4. DISCUSSION

In this study, we evaluated the evolution of spatial repolarization changes, using TWC index, in response to stress-induced ischemia in 50 patients referred to nuclear perfusion imaging for the evaluation of intermittent chest pain. We noticed a significant increase in spatial repolarization dispersion during stress testing among patients with ischemia on imaging scans, but not among others. These changes seemed to be influenced by the severity of ischemia and the location of the culprit coronary artery. Using ROC analysis of mean TWC during peak of stress test, we successfully predicted the pretest probability of ischemia with sensitivity and specificity ≥80%. This suggests a potential benefit of ECG indices of spatial repolarization dispersion in the early evaluation of patients with chest pain.

4.1 Myocardial Ischemia and Ventricular Repolarization

The ventricular myocardium is not homogeneous, it is comprised of three electrophysiologically distinct cell types, including: epicardial, endocardial, and M cells [22]. These cells have differences in ion channel properties and hence manifest different action potential durations. Different physiological and pathological derangements can aggravate these

differences in AP durations and result in various magnitudes of VRD. For example, both global and regional repolarization heterogeneity are increased at faster heart rates [23], which explains the observed slight changes in TWC seen in controls in this study (Figure 3-A). Progressive central sympathetic activation occurs during myocardial ischemia, but it does not affect intra- or inter-ventricular dispersion of ventricular repolarization during the early phase [24]. In fact, myocardial ischemia results in further accentuation of the AP notch and eventual loss of the dome in the epicardium but not endocardium, finally leading to transmural VRD. For instance, Figure 4-A shows how stress alters T waves on the 12-lead ECG by inducing biphasic morphology in more ECG leads than seen during baseline (i.e., increased dissimilarity in AP), which accentuates the second principal component and results in more round T loop. In absence of physiologic derangements (no ischemia and no CAD), sympathetic stimulation alters T waves on the 12-lead ECG (Figure 4-B) by increasing the T waves amplitudes as compared to baseline (i.e., increased similarity), and hence accentuating the first principal component and leading to less round T loop. This explains the greater heterogeneity of ventricular repolarization seen among ischemic patients in this study (Figure 3-B), which was independent from the heart-rate induced changes in repolarization observed in other groups. This is the first study to compare ischemia-induced VRD in ischemic patients while considering the values of the indices in control groups

Current literature on the evolution of VRD during myocardial ischemia is emerging rapidly. Although body surface mapping studies suggested that changes in myocardial repolarization dispersion resulting from localized ischemia are not reliably reflected in temporal indices [11], Rubulis and colleagues [17] have shown that PCI-induced ischemia had significant impact on T vector and morphology analysis, most prominently during LAD artery occlusion. Similarly, Arini and colleagues [12] have shown that PCI-induced ischemia alters spatiotemporal indices of repolarization on the surface ECG, namely T peak-to-end interval ($T_{P\text{-}E}$) and TWC, with a behavior which very much depends on the occluded coronary artery. Such observed

spatiotemporal changes were most prominent with the occlusion of the RCA and LCX arteries, rather than the LAD. In both studies, no flow ischemia induced during PCI resulted in transmural ischemia, and hence the observed spatiotemporal changes were associated with profound ST elevation on the surface ECG. In this study, however, we have interestingly shown that similar trends of spatial repolarization changes can be seen with mild-to-moderate ischemia in the absence of ST elevation on the surface ECG, which also seemed to follow a behavior which very much depends on the culprit artery.

The differences observed between our findings and previous studies with respect to which coronary artery induces the greatest heterogeneity in ventricular repolarization might be more complex to explain than previously thought. First, the relationship between affected artery and the magnitude of observed spatiotemporal changes suggests that the relative contribution of the second eigenvalue might be dependent on the direction of ischemic injury current with respect to the direction of repolarization current at baseline [12]. For example, if the repolarization direction is oblique to the right at baseline, then ischemic injury currents due to occluded RCA might not result in increased heterogeneity in repolarization as would be seen with the occlusion of the LAD. Second, such spatiotemporal changes cannot be fully explained by using the classic concept of an injury current that flows from injured to uninjured myocardium [25]. Rather, spatiotemporal changes may be largely secondary to a loss of the AP dome in the epicardium, but not endocardium, induced by severity of myocardial ischemia. Our findings (Figure 5-C) suggest that, with disregard to culprit artery, more severe ischemia induces greater heterogeneity in ventricular repolarization. Third, ischemia alters the AP duration differently in diseased than in normal myocardium [26]. Rubulis et al [27] have shown that patients with left ventricular hypertrophy (LVH), for instance, manifest more pronounced repolarization response during coronary occlusion compared to those without LVH. In this study, we have noticed that patients with a history of CAD tend to manifest, during stress, a pattern of repolarization heterogeneity in between those with ischemia and controls (Figure 3-A). As such, by using the

history of CAD as a covariate in our multi-variate model (Table 3), we have shown that ischemia induces spatial changes in ventricular repolarization independent from underlying cardiovascular pathology, yielding a predictive power to detect pretest probability of ischemia with sensitivity and specificity ≥80%.

4.2 Study Limitations

We used stress-testing to induce spontaneous ischemia and study dynamic changes in ventricular repolarization. Exercise is known to induce baseline and waveform noise artifacts, making ECG signal processing very challenging. To address this issue, we used three different strategies in the study design and data analysis steps. First, we only recorded ECG streams when patients were lying down in bed. Specifically, the Bruce exercise protocol did not include a cool down stage; when patients reached their max heart rate, the test was stopped abruptly and patients were instructed to step off the treadmill and lie flat on bed, during which the peak stress ECG was recorded. This window does guarantee a noise-free recording that captures most ischemic changes that are known to be prominent during early recovery phases (1 to 3 minutes after stopping the test) [28]. This may explain the more transient changes seen in TWC in patients who underwent exercise vs. regadenoson stress testing in this study (Figure 5-A and 5-B). Second, we manually annotated ECG recordings to delete abnormal and noisy beats. Third, we used 10-second signal averaging to compute reliable indices of T wave morphology; beat averaging has been shown to reduce the variance of T-wave morphology indices based on the principal component analysis (PCA) technique [19].

The other main limitation was the small sample size (n=50) and the corresponding small number of positive ischemic events (n=10, 20%). Accordingly, our findings suggest a promising, novel approach to ischemia detection rather than conclusive. In addition, we found a trend between the magnitude of TWC and severity and location of ischemia, but we were underpowered to detect significant group differences in our post hoc analyses. This interesting

observation suggests that spatial T wave changes might be less accurate in detecting mild ischemia or ischemia due to partial RCA occlusion, which has an important clinical implication for the potential use of spatial repolarization indices for screening chest pain patients. Finally, our findings, although are similar to those previously reported [11, 12, 17], still need to be confirmed in larger prospective studies.

5. CONCLUSIONS

When compared to chest pain patients with no ongoing myocardial ischemia, those with active ischemia have greater spatial heterogeneity of repolarization, which can be quantified on the surface ECG in the absence of ST elevation. The magnitude of this heterogeneity seems to follow a pattern that much depends on the severity of ischemia and location of culprit artery. This suggests that spatial indices of VRD are a rich opportunity for improving diagnostics in patients with chest pain very early during care, which needs to be tested in future prospective studies.

FIGURE LEGENDS

Figure 1: Study Protocol

Study participants completed a baseline SPECT scan followed by a 5-min baseline Holter ECG recording. Then they underwent a stress test followed by 5-min peak Holter ECG and stress SPECT scan.

Figure 2: Diagnostic Performance of Peak-Stress T wave Complexity

(A) The receiver operator characteristics (ROC) curve and area under the curve (AUC) for classifying pre-SPECT probability of ischemia using peak-stress mean T wave complexity. (B) ROC-optimized cutoff value of 0.235 has a sensitivity of 80% and specificity of 83% to predict pre-SPECT probability of ischemia in this learning dataset.

Figure 3: Trends of T wave complexity at baseline, stress, and recovery in study groups

(A) At baseline, groups had similar trends in T wave complexity (TWC) values. During stress and early recovery, the ischemia group had significant changes in TWC compared to controls (denoted by *). (B) This figure shows the changes in T wave complexity during peak of stress test relative to their baseline values. Significant changes were observed in the ischemia group when compared to other groups (denoted by *). Error bars indicate 95% CI of standard error.

Figure 4: Comparison of Changes in T wave Complexity Between two Patients

This figure compares the 12-lead ECG, principal ECG components, and corresponding T loop at baseline, peak, and recovery of stress test in a control patient and a case with moderate ischemia of the anterior wall (disease of the left anterior descending artery). Horizontal panels are adjusted on the same amplitude scale for each patient.

Figure 5: Relationship between type of stress test, and severity and location of ischemia on the evolution of spatial repolarization changes

This figure compares the absolute changes in TWC between (A) exercises vs. regadenoson stress testing in patients without ischemia, (B) exercises vs. regadenoson stress testing in patients with ischemia, (C) mild vs. moderate ischemia in patients with positive SPECT, and (D) the anatomic distribution of culprit artery in patients with positive SPECT..

TABLE 1: Baseline Demographic and Clinical Characteristics

Variable	***All Patients (n=50)***	***Groups***			***p***
		Ischemia (n=10)	**Hx of CAD (n=16)**	**Controls (n=24)**	
Age (years)	62.6±11.4	**65.9±9.7**	**68.1±10.9**	57.5±10.4	**.007**
Sex (Male)	30 (60%)	**8 (80%)**	**12 (75%)**	10 (42%)	**.038**
Race (Black)	5 (10%)	0	1 (6%)	4 (17%)	.258
BMI (kg/m^2)	30.7±6.3	28.6±5.2	29.7±5.5	32.3±7.1	.23
Resting HR (bpm)	65±13	61.7±11.5	62.4±11.8	69.0±13.7	.178
Systolic BP (mmHg)	142±24	**159±26**	144±22	133±20	**.011**
Diastolic BP (mmHg)	81±8	85±10	79±5	81±9	.251
Past Medical History					
Hypertension	36 (72%)	9 (90%)	13 (81%)	14 (64%)	.218
Diabetes	19 (38%)	6 (60%)	7 (44%)	6 (29%)	.236
Dyslipidemia	32 (64%)	9 (90%)	12 (75%)	11 (50%)	.058
Ever Smoker	30 (60%)	7 (70%)	10 (63%)	13 (59%)	.840
Myocardial Infarction	14 (28%)	**4 (40%)**	**8 (50%)**	2 (9%)	**.016**
Prior PCI/Stent	21 (42%)	**7 (70%)**	**13 (81%)**	1 (5%)	**.001**
Prior CABG	11 (22%)	**4 (40%)**	**7 (44%)**	0	**.002**
COPD/Asthma	10 (20%)	1 (10%)	3 (19%)	6 (29%)	.475
Current Medications					
Beta Blockers	17 (34%)	5 (50%)	7 (44%)	5 (21%)	.107
ACE Inhibitors	14 (28%)	2 (20%)	6 (38%)	6 (29%)	.105
Chief Complaint					
Chest Pain	42 (84%)	10 (100%)	12 (75%)	20 (87%)	.202
Shortness of Breath	22 (44%)	3 (30%)	7 (44%)	12 (52%)	.497
Resting 12 Lead ECG					
Sinus Rhythm	50 (100%)	-	-	-	-
LVH with NSSTTC	3 (6%)	0	2	1	-
RBBB/LBBB	2 (4%)	0	2	0	-
Stress Test					
Treadmill Exercise	33 (66%)	6 (60%)	8 (50%)	19 (79%)	.147
Stress Time (min)	8.0±2.7	7.0±2.4	7.4±2.4	8.6±2.8	.328
%max HR	76±20	**70±18**	**67±22**	86±15	**.004**
Symptoms Response	12 (24%)	**6 (60%)**	4 (25%)	2 (8%)	**.007**
+ve ECG Response	12 (24%)	**6 (60%)**	4 (25%)	2 (8%)	**.002**
SPECT Scan					
LVEF (%)	66±12	**57±10**	67±14	69±11	**.026**
Abnormal Wall Motion	14 (28%)	**7 (70%)**	**7 (44%)**	0	**.001**
Positive for Ischemia	10 (20%)	-	-	-	-
Mild Ischemia		4 (40%)	-	-	-
Moderate Ischemia		6 (60%)	-	-	-
LAD Disease		4 (40%)	-	-	-
LCX Disease		3 (30%)	-	-	-
RCA Disease		3 (30%)	-	-	-

Table 2: Holter ECG Characteristics

Variable	***All Patients (n=50)***	***Groups***			***p***
		Ischemia (n=10)	**Hx of CAD (n=16)**	**Controls (n=24)**	
Baseline Holter Recording					
Average Heart Rate	67±11	62±7	66±11	71±12	0.11
5-min SDNN	39±22	33±11	32±19	46±25	0.09
Average QRS Duration	96±14	102±16	92±11	95±15	0.27
Average QTc Interval	424±24	431±23	418±21	423±27	0.45
Average JTc Interval	340±58	335±23	330±17	344±30	0.27
Number of PVCs	2.9±6.2	3.2±7.0	2.6±5.2	3.0±6.7	0.97
Max ST depression	0.28±0.43	0.50±0.20	0.21±0.06	0.50±0.11	0.77
Average TWC	0.19±0.11	0.18±0.10	0.17±0.09	0.20±0.13	0.69
Peak Stress Holter Recording					
Average Heart Rate	89±15	85±14	85±14	95±15	0.10
Max Heart Rate	106±23	100±22	97±21	115±23	0.05
5-min SDNN	44±22	41±14	38±22	49±24	0.29
Average QRS Duration	98±16	106±22	96±16	95±12	0.14
Average QTc Interval	413±34	417±35	406±40	416±32	0.70
Average JTc Interval	338±27	335±33	336±30	340±22	0.85
Number of PVCs	6.7±17.6	2.5±5.9	6.5±12.6	8.5±22.9	0.67
Max ST depression	0.70±1.1	1.20±1.7	0.80±1.4	0.40±0.3	0.16
Average TWC	0.23±0.16	0.37±0.17	0.20±0.12	0.20±0.15	**<0.01**

Table 3: Univariate & Multivariate Predictors of Pre-SPECT Probability of Ischemia

PREDICTOR	UNIVARIATE		MULTIVARIATE	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age (per 1 year)	1.03 (0.97–1.01)	0.308	–	–
Male Sex	3.3 (0.6–17.4)	0.164	2.4 (0.3–18.6)	0.148
History of CAD	4.4 (0.8–23.5)	0.081	4.79 (0.55–41.9)	0.115
SBP (per 10 mmHg)	1.5 (1.1–2.0)	**0.017**	1.51 (0.99–2.30)	0.124
Baseline 5-min SDNN	0.98 (0.94–1.02)	0.338	–	–
Peak-Stress Max Heart Rate	0.99 (0.95–1.02)	0.375	–	–
Peak-Stress Max QRS Duration	1.04 (1.00–1.09)	0.068	1.05 (0.96–1.15)	0.301
Peak-Stress Max ST depression	1.0 (0.99–1.01)	0.155	1.0 (0.99–1.01)	0.601
Peak-Stress mean TWC (per 1%)	1.07 (1.02–1.12)	**0.008**	1.08 (1.01–1.16)	**0.029**

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Figure 1: Study Protocol

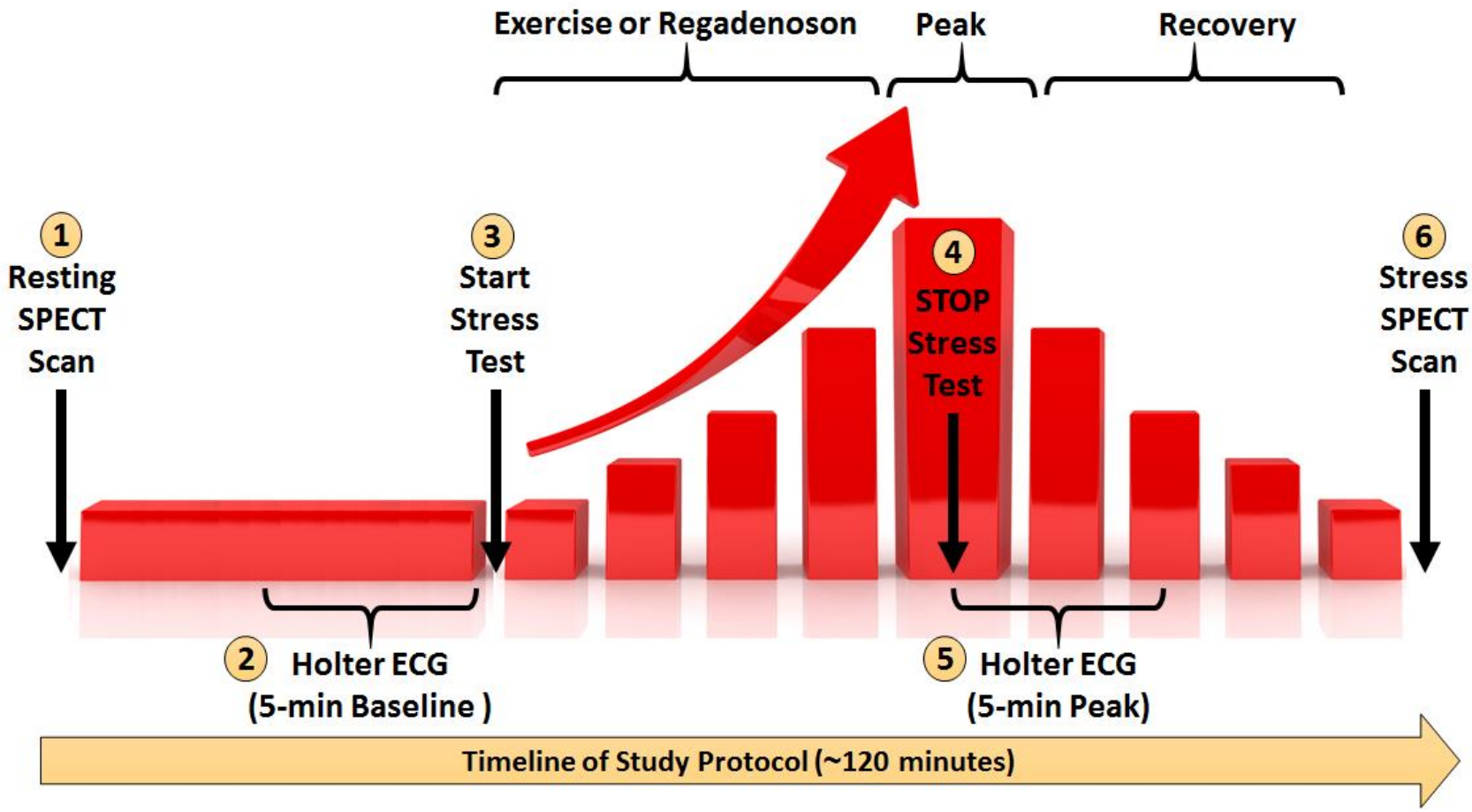

Figure 2: Diagnostic Performance of Peak-Stress T wave Complexity

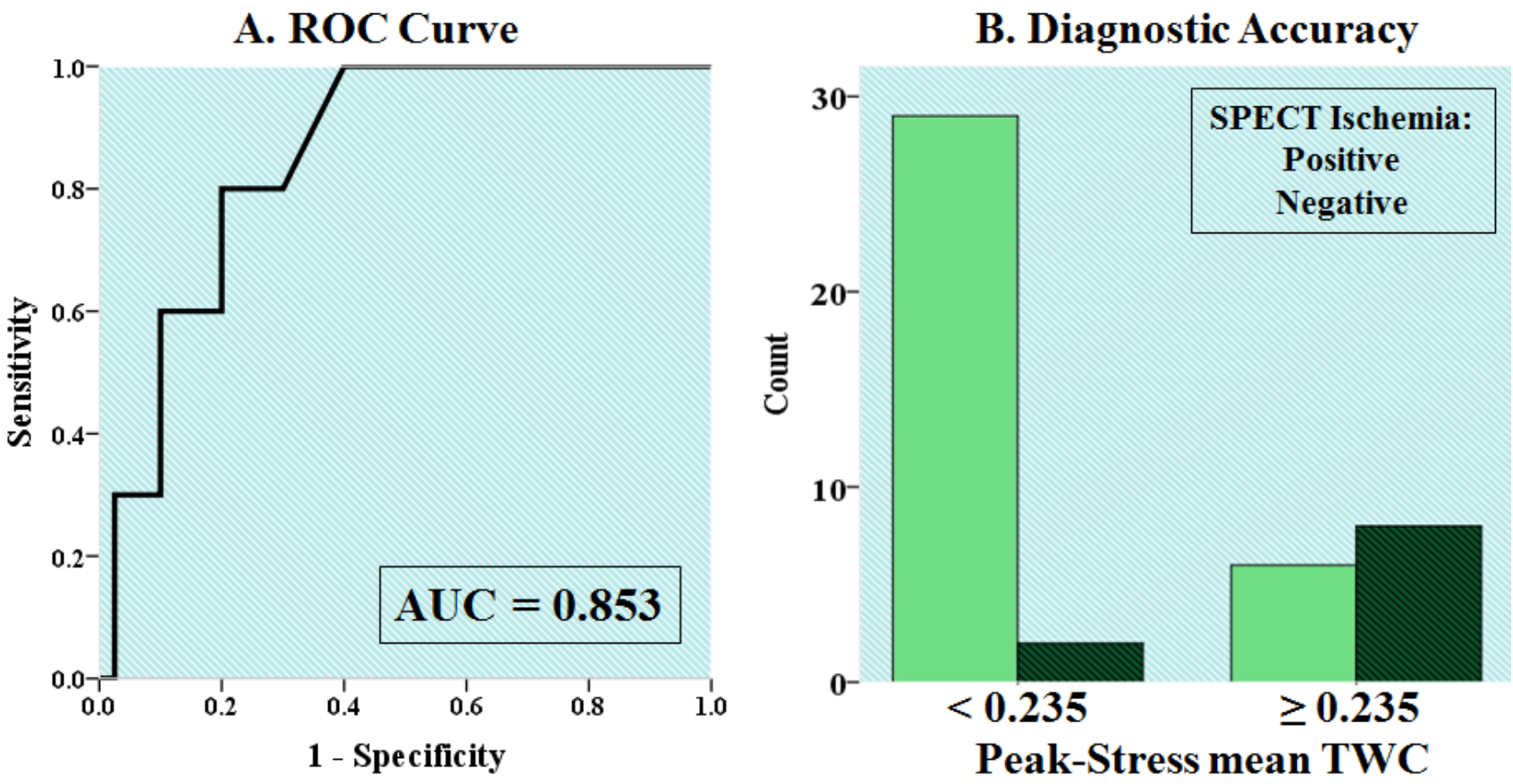

Figure 3: Trends of T wave complexity at baseline, stress, and recovery in study groups

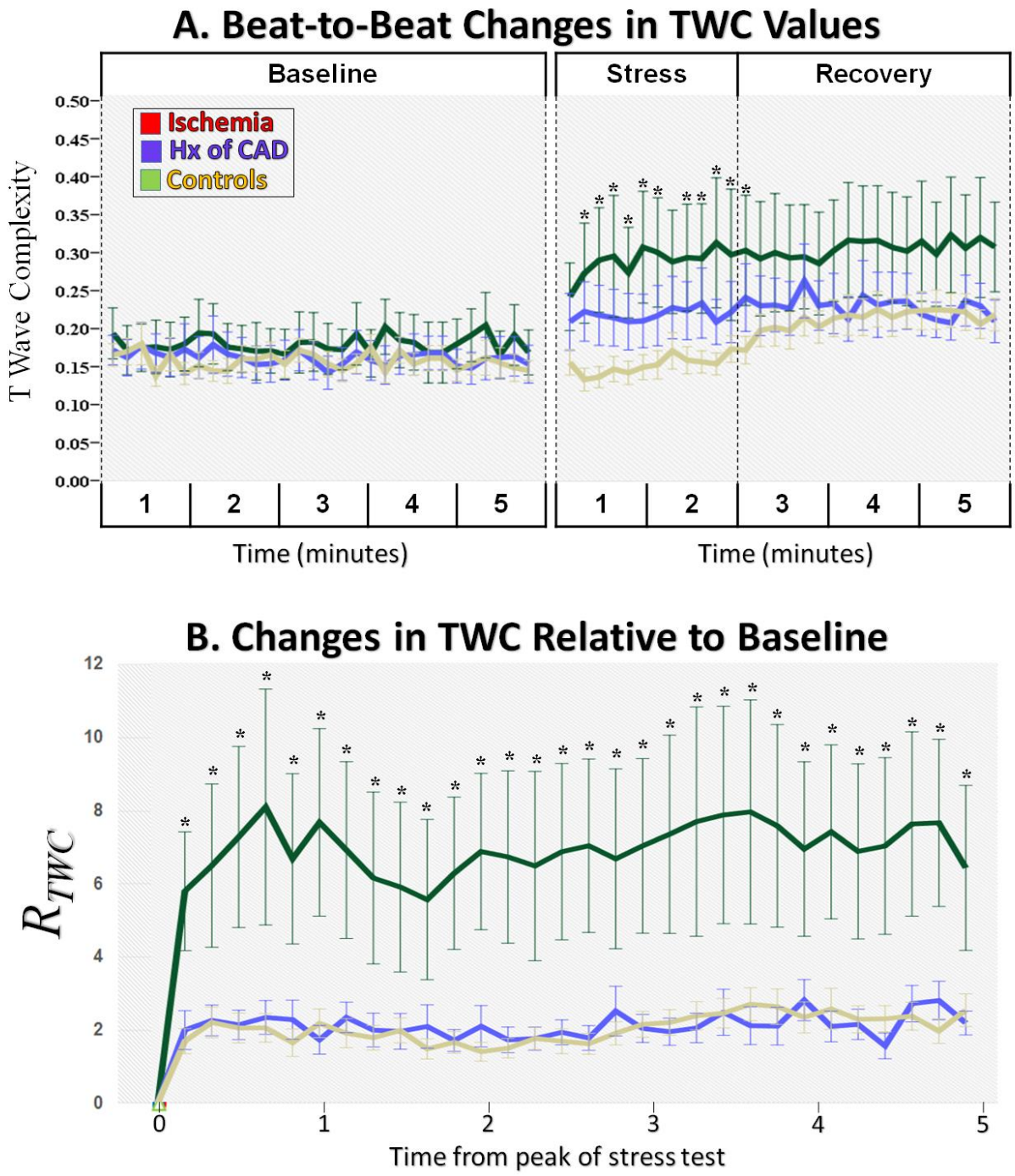

Figure 4: Comparison of Changes in T wave Complexity Between two Patients

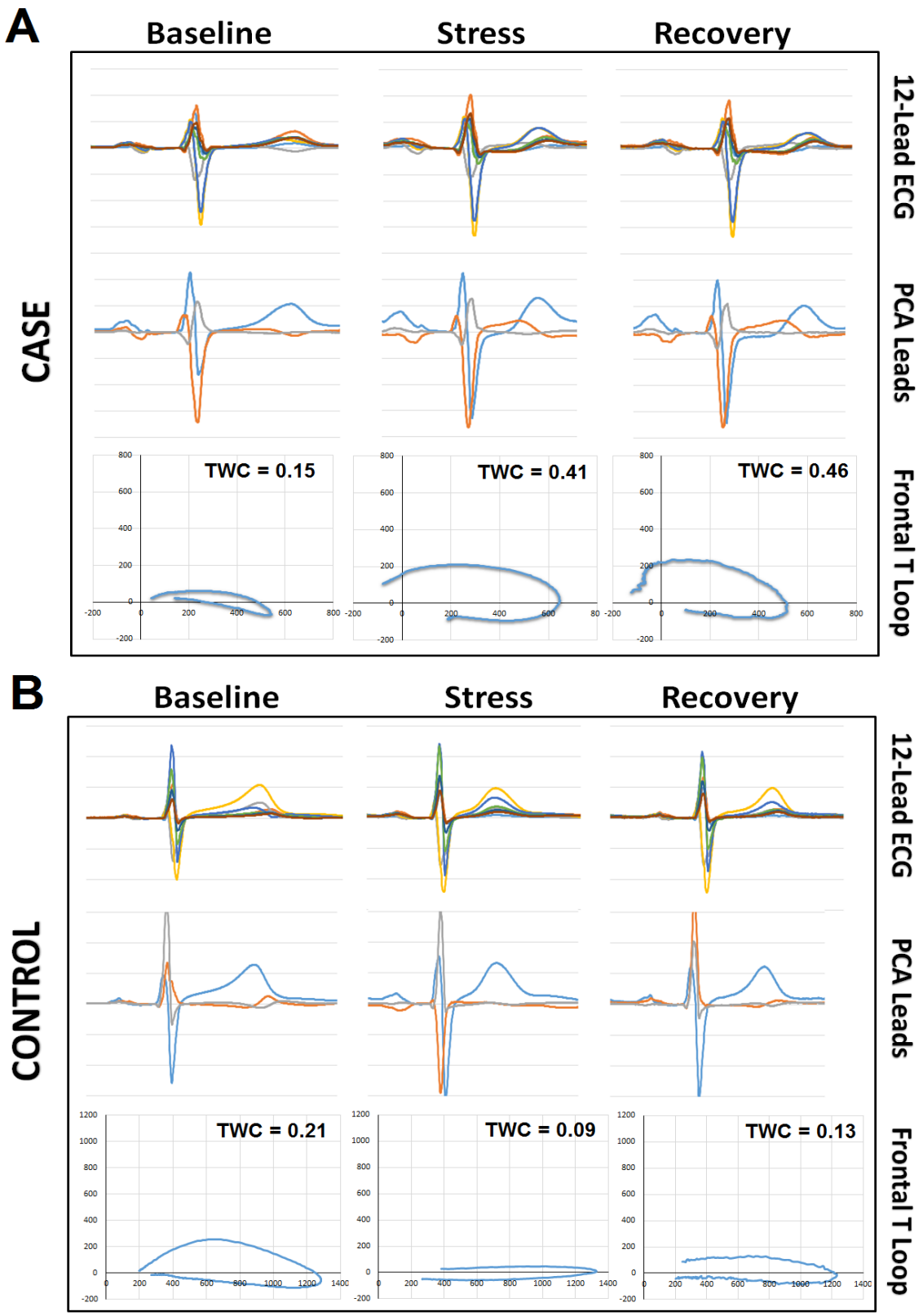

Figure 5: Relationship between type of stress test, and severity and location of ischemia on the evolution of spatial repolarization changes