Effects of coronary revascularization on T-wave amplitude variability in patients with non ST elevated acute myocardial infarction

Edoardo Moro1, Sebastiano Belletti1, Marco Cesarano1 and Federico Lombardi2,*

1 UO Cardiologia – UTIC, A.O. San Paolo, Milan, Italy
2 UOC Malattie Cardiovascolari, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Dipartimento di Scienze Cliniche e di Comunità, University of Milan, Milan, Italy

Abstract

Introduction: T-wave amplitude variability (TAV) is a noninvasive index of beat-to-beat variations in ventricular repolarization. Aim of the study was to evaluate whether this parameter might reflect the changes in ventricular repolarization process induced by myocardial reperfusion, in the setting of acute myocardial ischemia. Methods and results: 97 patients with diagnosis of non-ST-elevation myocardial infarction (NSTE-MI) eligible for coronary revascularization were studied. In each patient, a 20 minute three pseudo-orthogonal lead recording was obtained at admission and within few hours from angiography. TAV was computed with SyneTVar 3.10a software (ELA medical, SORIN Group, Paris, France). Twenty patients were excluded for technical reason. The remaining 77 patients, aged 68 ± 12.2 years, had a preserved left ventricular ejection fraction (54 ± 10.9%). In comparison to the first measurement, there was a significant increase in mean TAV (from 20.4 ± 6.7μV to 23.2 ± 9.4μV, P = 0.02) only in patients who underwent coronary revascularization. The increase was more easily detectable in patients with revascularization of left anterior descending coronary artery (from 19.2 ± 7.4μV to 24.3 ± 10.2μV, P = 0.01). No differences were instead observed in patients who were not revascularized for either the lack of critical coronary stenosis or anatomical reasons. Conclusions: Percutaneous coronary revascularization in NSTE-MI patients is associated with a significant increase in TAV, which is likely to reflect the alterations of cardiac electrical properties induced by myocardial tissue reperfusion.

Keywords: myocardial ischemia; reperfusion arrhythmias; T-wave variability; ventricular repolarization; Holter recording

Introduction

Identification of patients at risk for malignant ventricular arrhythmias is a main clinical challenge [1, 2]. Among noninvasive techniques developed to identify patients at risk, measurements of alterations in ventricular repolarization process have provided promising results [3-6]. Microvolt T-wave alternans (mTWA) has long been considered a sensitive and efficient noninvasive methodology to detect alterations in repolarization process and to predict arrhythmic events [1, 7-9]. Whereas negative predictive value is consistently above 95% [7, 8, 10-12], its positive predictive value remains unsatisfactory [7, 13]. As a result, several high risk patients with normal left ventricular ejection fraction (LVEF) are not appropriately identified, treated and therefore remain exposed to an increased arrhythmic risk. In this context, a recent technique named T-wave amplitude variability (TAV) has been proved effective in identifying arrhythmic risk in heart failure [14, 15], Chagas disease [16], long-QT syndrome [17], dilated cardiomyopathy [18] and in malignant arrhythmia survivors without structural heart disease [19]. Unlike the mTWA, this approach does not look for a repeating pattern in repolarization process, but it quantifies the amount of beat-to-beat changes in ST-segment and T-wave amplitude. This phenomenon can be considered an expression of a non-periodic variability in ventricular recovery, which, conceptually, is likely to be prodromal to T-wave alternans [14].

The aim of this study was to evaluate whether TAV might reflect the changes in ventricular repolarization process induced by acute myocardial reperfusion in the setting of non-ST-elevation acute myocardial infarction (NSTE-MI).

*Corresponding author: Federico Lombardi, UOC Malattie Cardiovascolari, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Dipartimento di Scienze Cliniche e di Comunità, University of Milan, Milan, Italy. Tel./Fax: +39 02 50320483; Email: federico.lombardi@unimi.it

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Methods

Patients' population

Patients' recruitment was carried out at Coronary Intensive Care Unit of Azienda Ospedaliera San Paolo, University of Milan, Milan, Italy. We enrolled patients hospitalized over one year for non-ST-elevation acute coronary syndrome (NSTE-ACS) with elevation of cardiac biomarker troponin I, eligible for diagnostic coronary angiography [20, 21]. Exclusion criteria were: (i) atrial fibrillation or flutter, artificial paced ventricular rhythm or any other non-sinusual rhythm; (ii) left bundle branch block; (iii) major significant comorbidity (i.e., acute renal failure, hepatic failure).

Study protocol and general procedures

This investigation was designed as an observational cohort study. The Research Ethics Board of the hospital approved the study protocol. All subjects signed a written informed consent before enrollment. All patients were submitted to the common clinical and instrumental procedures performed in patients admitted for NSTE-MI (chest X-ray, standard 12-lead ECG, blood tests, echocardiogram), received standard pharmacological therapy (double antiplatelet therapy, beta-blockers, angiotensin-converting enzyme inhibitors, statin) consistent to their clinical conditions, and underwent diagnostic coronary angiography within 72h from admission, as recommended by current guidelines [21]. For each patient, a 3-lead Holter-ECG recording was recorded at admission and within 24h after coronary angiography, during the daytime, in resting condition and in absence of noise.

T-wave amplitude variability

Holter ECG recordings were performed using SpiderView digital Holter recorder (ELA medical, SORIN Group, Paris, France) at a sampling rate of 1000Hz, with a resolution of 2.5 μV, for a period of 20 minutes. Electrodes were placed in a pseudo-orthogonal x, y, z lead configuration. ECG files were converted to standard Holter format defined by International Society for Holter and Noninvasive Electrocardiography [22] and analyzed using the Holter reading software SyneScope 3.10 (ELA medical, SORIN Group, Paris, France). T-wave amplitude variability was evaluated using SyneTVar 3.10a software (ELA medical, SORIN Group, Paris, France) based on the vector magnitude \( \mathbf{v}_F = \sqrt{x^2 + y^2 + z^2} \), as previously described [14-19, 23]. In brief, ECG signal was first preprocessed by the software, including a down sampling to 200Hz, an estimation of the baseline and respiratory components as well as a digital filtering removal of recording sections characterized by: (i) noise level >10μV, (ii) ventricular or atrial premature beats, or (iii) high RR interval variability (standard deviation >150ms). Multiple clusters made of 60 QRS-T consecutive cycles were created and every repolarization phase (i.e., ST-segment and T-wave) was subdivided in 8 consecutive 50ms segments (T1-T8) following QRS offset (defined as QRS onset + 120ms). Level of variability is computed basing on the variance of the average amplitude of every T1-T8 segment across the consecutive 60 QRS-T cycles of a given cluster. The square root value (i.e. standard deviation) is reported and expressed in microvolt. T-wave amplitude variability (TAV in μV) was defined as the median standard deviation value obtained from every segment of repolarization among all available clusters.

Statistical analysis

Kolmogorov-Smirnov test was used to verify the normality of distribution. Data concerning continuous variables were expressed as means ± standard deviation, whereas data obtained from non-normally distributed variables as absolute numbers and percentages. For comparisons, we used paired and unpaired Student's t-test, Wilcoxon matched-pair test, Mann-Whitney U test and exact Fisher test, according to variable type and distribution. Correlations were assessed by Spearman's rank correlation method. For all tests, a P value of <0.05 was considered statistically significant. Data were analyzed using NCSS version 9 (NCSS Statistical Software, Kaysville, Utah, USA).

Results

Study population characteristics

Holter recordings were collected from 97 patients. Twenty of them were excluded from the study because of extremely noised recordings, mainly due to low- or high-frequency artefacts disturbances or frequent ventricular ectopies, which did not permit TAV analysis. The remaining 77 patients sample consisted predominantly by male (58 patients, 75.3%) with a mean age of 68 ± 12.2 years. Median LVEF was 54 ± 10.9%. All patients received optimal medical therapy, when tolerated: aspirin (76 patients, 98.7%), clopidogrel (65 patients, 84.4%), angiotensin-converting enzyme inhibitors (59 patients, 76.6%), beta-blockers (65 patients, 84.4%) and statin (77 patients, 100%). Four patients (5.2%) were on amiodarone at the time of admission. Other baseline characteristics of the study population including heart rate, QT and QTc interval are shown in Table 1.

Due to the finding of a hemodynamically significant stenosis during coronary angiography, 49 patients (63.6%) underwent percutaneous transluminal coronary angioplasty (PTCA), with intracoronary stenting. The treated infarct-related artery (IRA) was respectively: left anterior descending artery (LAD) in 36.7%, left circumflex artery (CX) in 30.6% and right coronary artery (RC) in 32.7%. The remaining 28 patients did not undergo coronary revascularization procedure either for the absence of a hemodynamically significant stenosis or for an indication for surgical revascularization. Two separate groups of revascularized and non-revascularized subjects were therefore considered. There were no significant differences between the two groups when considering heart rate, QT and QTc interval, systolic arterial pressure, left ventricular ejection fraction and clinical characteristics, except for gender, active smoking and diabetes mellitus (Table 1).

T-wave amplitude variability

At admission, mean TAV measured in the entire study population was 20.5 ± 7.1μV. No significant changes were observed after coronary angiography (mean TAV 23.2 ± 8.8μV, P = 0.84). When the study population was analyzed in term of performing effective revascularization, no significant differences were detectable in the two groups when considering admission recordings before coronary angiography (20.4 ± 6.7μV vs 20.6 ± 7.7μV, P = 0.88). On the contrary, TAV significantly increased in revascularized patients (from 20.4 ± 6.7μV to 23.2 ± 9.4μV, P = 0.02); this
Table 1 Clinical characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>All subjects (n = 77)</th>
<th>Revascularized (n = 49)</th>
<th>Non-Revascularized (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.1 ± 12.2</td>
<td>67.2 ± 12.7</td>
<td>69.8 ± 11.3</td>
<td>0.37</td>
</tr>
<tr>
<td>Male gender</td>
<td>58 (75.3)</td>
<td>42 (85.7)</td>
<td>16 (57.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Active smoking</td>
<td>44 (57.1)</td>
<td>33 (67.3)</td>
<td>11 (39.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>46 (59.7)</td>
<td>30 (61.2)</td>
<td>16 (57.1)</td>
<td>0.81</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>39 (50.6)</td>
<td>25 (51)</td>
<td>14 (50)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>23 (29.9)</td>
<td>19 (38.8)</td>
<td>4 (14.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Prior MI</td>
<td>22 (28.6)</td>
<td>17 (34.7)</td>
<td>5 (17.9)</td>
<td>0.18</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>54 ± 11</td>
<td>56 ± 9</td>
<td>51 ± 10</td>
<td>0.44</td>
</tr>
<tr>
<td>Aspirin</td>
<td>76 (99)</td>
<td>48 (98)</td>
<td>28 (100)</td>
<td>1.00</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>65 (84)</td>
<td>46 (94)</td>
<td>19 (68)</td>
<td>0.24</td>
</tr>
<tr>
<td>β-blocker</td>
<td>65 (84)</td>
<td>42 (86)</td>
<td>21 (75)</td>
<td>0.35</td>
</tr>
<tr>
<td>ACE-inhibitor</td>
<td>59 (77)</td>
<td>48 (98)</td>
<td>19 (68)</td>
<td>0.26</td>
</tr>
<tr>
<td>Statin</td>
<td>77 (100)</td>
<td>49 (100)</td>
<td>28 (100)</td>
<td>1.00</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>4 (5.2)</td>
<td>2 (4.1)</td>
<td>2 (7.1)</td>
<td>0.61</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before CAG</td>
<td>67 ± 14</td>
<td>66 ± 11</td>
<td>70 ± 20</td>
<td>0.87</td>
</tr>
<tr>
<td>After CAG</td>
<td>68 ± 12</td>
<td>67 ± 11</td>
<td>69 ± 14</td>
<td>0.70</td>
</tr>
<tr>
<td>QT (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before CAG</td>
<td>398 ± 48</td>
<td>400 ± 39</td>
<td>394 ± 63</td>
<td>0.74</td>
</tr>
<tr>
<td>After CAG</td>
<td>399 ± 45</td>
<td>402 ± 35</td>
<td>394 ± 62</td>
<td>0.71</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before CAG</td>
<td>415 ± 37</td>
<td>415 ± 36</td>
<td>414 ± 40</td>
<td>0.62</td>
</tr>
<tr>
<td>After CAG</td>
<td>420 ± 40</td>
<td>423 ± 38</td>
<td>415 ± 44</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Abbreviations: MI = myocardial infarction; LVEF = left ventricular ejection fraction; ACE-inhibitors = angiotensin-converting enzyme inhibitor; CAG = coronary angiography; QTc = QT interval corrected for heart rate by Bazett’s formula. Data expressed as mean ± SD or absolute numbers (percentage). P value of comparison between revascularized and non-revascularized are presented.

change was particularly evident in the first five segments (T1-T5) of repolarization, which correspond to ST-segment and ascendant phase of T-wave (Figure 1). No changes were instead detectable when comparing admission and post angiography recordings in non-revascularized patients (from 20.6 ± 7.7 to 23.1 ± 7.7 μV, P = 0.17) (Figure 2).

Figure 1 T-wave amplitude variability measured before and after coronary angioplasty in revascularized subjects. TAV measured on each of the eight 50 ms-segments (T1-T8) in which repolarization is divided by the software. A statistically significant (P < 0.05) increase of TAV values in first five segments of repolarization is detectable after the revascularization procedure, regardless of the treated vessel.

Abbreviations: CAG = coronary angiography; PTCA = percutaneous transluminal coronary angioplasty; TAV = T-wave amplitude variability.

Figure 2 T-wave amplitude variability measured before and after coronary angiography in non-revascularized subjects. No significant (P ≥ 0.05) increase of TAV values in all repolarization segments were detectable in this subset of patients after the diagnostic procedure.

Abbreviations: CAG = coronary angiography; TAV = T-wave amplitude variability.
When considering the effects of reperfusion in relation to the treated vessel, we observed a significant increase of TAV in the first five segments of repolarization in patients treated on LAD coronary artery (from 19.2 ± 7.4µV to 24.3 ± 10.2µV, P = 0.01) (Figure 3), whereas no differences were detectable in patients who underwent revascularization of CX or RC artery (from 21.1 ± 6.4 to 22.6 ± 9.1µV, P = 0.34).

Ischemia and myocardial infarction are the most common substrates for the occurrence of malignant ventricular arrhythmias [24-26]. During ischemia several alterations of normal myocardial environment, particularly in beat-to-beat intracellular calcium homeostasis [27-30] and cell-to-cell coupling [27, 31, 32] can create an electrophysiological substrate prone to generate repolarization heterogeneity, conduction blocks and reentry, the latter considered as the major mechanism responsible for ischemia-induced arrhythmias [26]. Paradoxically, in addition to ischemia, reperfusion of the ischemic myocardium seems to be equally arrhythmogenic. In the clinical setting, this phenomenon is commonly referred as “reperfusion arrhythmias”, which frequently occur early after blood flow restoration and is considered an index of successful reperfusion [8, 25, 33-35].

Among the various available methods for detecting alteration of ventricular repolarization, mTWA, which detect a repeating ABABAB pattern in T-wave morphology and amplitude [8], has been considered the most sensitive and promising methodology to evaluate the risk for ventricular arrhythmic events [3, 4, 7, 36]. However, the spectral method, the most validated technique to detect mTWA, needs to increase patient’s heart rate to 100-110 beats for few minutes by a sub-maximal exercise [8, 37]. Such target is not always achievable, particularly in heart failure, recent acute myocardial infarction or optimal beta-blocking therapy. In addition, indeterminate results are obtained in almost 12-47% of published studies [8, 31, 37], thus making the interpretation of the mTWA test disputable.

In this context, T-wave amplitude variability was recently proposed as a new methodology for measuring repolarization variability on electrocardiographic recordings collected during resting conditions [14]. An increase in TAV was visible in MADIT II patients with appropriate ICD therapy [14] and in long-QT syndrome patients compared with normal subjects [17]. Higher TAV values were observed in Olympic athletes compared to healthy young adults and in subjects with a history of ventricular arrhythmias in absence of structural heart disease [19, 23]. Moreover, this methodology has proved to predict an increased arrhythmic risk in patients with dilated cardiomyopathy, in subjects undergoing cardiac resynchronization therapy and in Chagas disease [15, 16, 18, 19].

In the present study, TAV was tested in the particular electrophysiological environment represented by an ischemic myocardium, acutely subjected to blood flow restoration. We found an increase of TAV after myocardial revascularization following an acute subendocardial infarction. The increase was evident in subjects who underwent PTCA of LAD artery, a finding likely to be related to the extensive portion of myocardial muscle served by this vessel. Conversely, patients who were not revascularized
did not show any significant change in TAV before and after angiography, as a likely result of both lack of effective mechanical revascularization and sudden restoration of coronary blood flow. The apparently paradoxical result of an increase in TAV after restoration of coronary blood flow can be considered as an indirect evidence of the so-called reperfusion injury: restoration of blood flow may lead to the development of reactive oxygen species and to the worsening in intracellular calcium overload [38], thus exacerbating ischemia-induced cellular injury, known to affect the repolarization process, either in its mechanical and electromechanical characteristics [39]. This interpretation is supported by the results of a previous study, which reported a transient increase in mTWA during ballooning inflation and a subsequent decrease of this parameter 24hrs after the interventional procedure. In our study, we compared the admission recording with that performed within 24hrs from coronary revascularization, thus focusing on an earlier stage, in which abrupt blood flow restoration on peri-infarct zone generates a transient paradoxical effect [40]. Decrease in mTWA 24hrs after revascularization, as evidenced by the Batur et al. [41], would not be surprising or inconsistent with our results, being an expression of the progressive return to normal cellular metabolism of the ischemic zone, after successful restoration of blood flow. Interestingly, the same study reported more pronounced differences in mTWA after LAD angioplasty compared to other coronary vessels, similarly to what we observed [41]. Afterward, the Occluded Artery Trial – Electrophysiological Mechanism (OAT-EP) reported a decrease in TAV after coronary revascularization, but the after-procedure recording was obtained at 1 year from index event [42].

As to the values of TAV observed in the present study, it must be recalled that their averaged values did not differ notably from those measured in healthy subjects or in patients with minimal heart disease [17, 23]. In our opinion, this was due to the characteristics of our study population with normal QTc and, especially, preserved LVEF. Available literature established different cut-offs to identify patients at high risk for arrhythmic events, all characterized by TAV values ranging from 30 to 60 μV [14-16, 18], likely to reflect the enrollment of patients with more severe cardiac conditions such as, for example, the MADIT II population or a previous history of sudden cardiac death [14-16, 18]. It may pertinent to recall that none of our patients presented sustained ventricular arrhythmias after coronary revascularization.

Finally, it is interesting to note that, also in our study population, the segments T4 and T5 of the repolarization phase, which correspond to the T wave, were the most significant and sensitive in detecting variations in repolarization process, thus confirming the capability of this methodology to detect changes in the final part of repolarization process [14-19, 23].

**Limitations**

Our study has several limitations: the small sample size is the principal one. This was partially due to the fact that, in order to avoid any delay in the appropriate treatment, we were unable to repeat another recording if an excessive noise made impossible the computation of TAV. This was the reason for which 20% of patients were excluded from data analysis. In addition, recordings were obtained at different time of the day but not during the night, thus limiting, but not excluding, the possible effects of circadian pattern of variations in autonomic control mechanisms [17]. The two subset of patients were not fully balanced: there was a relative greater number of diabetic patients in the revascularized group, but mean heart rate interval, QT and QTc interval, systolic arterial pressure and left ventricular ejection fraction were not different among groups, thus making unlikely that these factors might have affected our measurements [43].

**Conclusions**

Percutaneous myocardial reperfusion in NSTE-MI patients causes alterations in the ventricular repolarization that can be detected with this noninvasive electrocardiographic technique. The increase of TAV was evident in patients with LAD revascularization, as a likely result of the amount of myocardial tissue served by this vessel. TAV segments corresponding to the ascending and descending part of the T-wave appear to be the most appropriate to detect the reperfusion-induced repolarization changes. This approach, which deserves further clinical validation, seems therefore suitable to noninvasively detect transient alterations in the repolarization process.

**Conflicts of interest**

Authors declare no conflicts of interest.

**References**


