T wave alternans in experimental myocardial infarction: Time course and predictive value for the assessment of myocardial damage

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Abstract

Background: T-wave alternans (TWA) is associated with prognosis after myocardial infarction (MI), however its link to the extent of ischemic injury has not been clarified. We analyzed the course of TWA and its relation to myocardial damage in experimental myocardial infarction.

Methods: In 21 pigs, infarction was induced by 40-minute long balloon inflation in LAD under continuous 12-lead ECG monitoring. TWA was assessed in a 32-beat sliding window, using periodic component analysis and the Laplacian Likelihood Ratio method. Myocardium at risk (MaR) and infarct size (IS) were evaluated by SPECT and magnetic resonance imaging respectively.

Results: TWA appeared at 7.2 ± 4.5 minutes of occlusion, reached its maximum at 12.7 ± 6.3 and lasted until 26.5 ± 9.2 minutes. The maximal level of TWA was associated with both MaR ($r = 0.499$, $p = 0.035$) and IS ($r = 0.65$, $p = 0.004$).

Conclusion: TWA magnitude is associated with both MaR and IS in experiment, which encourages further studies in clinical settings.

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Keywords: T wave alternans; Myocardial infarction; ST-elevation myocardial infarction

Background

T-wave alternans (TWA), an ECG phenomenon reflecting spatiotemporal heterogeneity of repolarization, is known to be associated with the ventricular vulnerability and risk of death in different categories of patients, particularly in post-myocardial infarction (MI) patients.[1–3] The negative association between the presence of TWA and ejection fraction has been reported in post MI patients.[4] It was supposed that larger infarcts resulted in low ejection fraction and discordant alternans due to considerable extension of abnormal tissue.[4] Infarct size (IS) is one of the most important factors related to mortality in ST-elevation myocardial infarction (STEMI).[5,6] However, the link between TWA and the size of ischemic damage has not

been clarified yet. We analyzed the course of T wave alternans (TWA) during coronary artery occlusion and its relation to myocardial damage in experimental myocardial infarction (MI).

Methods

Experimental protocol

A porcine model of myocardial infarction was used in this work. The experimental preparation, study protocol and imaging technique were previously described in detail.[7] In brief, in pigs weighing 40–50 kg, anaesthetised with fentanyl and thiopental, an angioplasty balloon was positioned in the mid portion of the left anterior descending coronary artery (LAD), immediately distal to the first diagonal branch. Twelve-lead ECG monitoring (("Kardiotechnica-04-8 m", Incart, St. Petersburg, Russia) with a sampling rate of 1024 Hz and an amplitude resolution of

1.4 μV) was initiated before starting the occlusion and lasted throughout all the period of occlusion.

Ischemia was induced by inflation of an angioplasty balloon for 40 minutes. An angiogram was performed after balloon inflation and before balloon deflation in order to verify total occlusion of the coronary vessel and correct balloon positioning. ^{99m}Tc-tetrofosmin was administered intravenously at the 20th minute of occlusion for subsequent single photon emission computed tomography (SPECT). After 40 minutes of occlusion the balloon was deflated and a subsequent angiogram was performed to verify restoration of blood flow in the previously occluded artery. TIMI-3 flow upon balloon deflation was achieved in all animals. Experiment was terminated after 4 hours of reperfusion. Gadolinium-based contrast agent was administered intravenously 30 minutes prior to removal of the heart for subsequent magnetic resonance imaging (MRI). After 4 hours of reperfusion the hearts were explanted and ex-vivo SPECT for assessment of area at risk (MaR) and MRI for assessment of IS was performed.

The study conforms to the Guide for the Care and Use of Laboratory Animals, US National Institute of Health (NIH Publication No. 85-23, revised 1996) and was approved by the local animal research ethics committee.

TWA analysis

The ECG signals were preprocessed, including QRS detection, normal beat labelling and baseline wander attenuation by cubic-spline interpolation. In each normal beat, ST segment amplitude was measured at J point + 40 ms. In each beat, an interval of 300 ms was selected for TWA analysis (including the ST-T complex). Then, TWA analysis was performed automatically on every ECG recording, as explained in the next paragraphs. The person performing the TWA analysis (AMY) was blinded to the rest of the data.

TWA analysis was performed using a sliding 32-beat signal window, applying a multilead processing scheme which makes use of the technique of periodic component analysis (πCA) for multilead ECG processing combined with the Laplacian Likelihood Ratio method (LLR) to detect and quantify TWA.[8]

The πCA technique searches for the linear combination of the available leads which maximizes the desired periodicity in the combined lead. For TWA analysis, we were interested in combining the leads in such a way that the 2-beat periodicity was maximized in the resulting signal. As shown previously,[8] the optimal combination is obtained by solving a generalized eigenvalue problem involving the spatial correlation matrix of the segment as well as the spatial correlation matrix of the non-periodic components. Using this technique we defined a linear transformation, from the 8 original independent leads (V1–V6, I, II) to 8 transformed leads (T1...T8), where T1 is the lead which maximizes the 2-beat periodicity in the ST-T segment. Note that to allow a good tracking of the TWA, the optimal combination was obtained for each 32-beat segment, as it depends on how the alternant components and noise are distributed within the ECG leads.
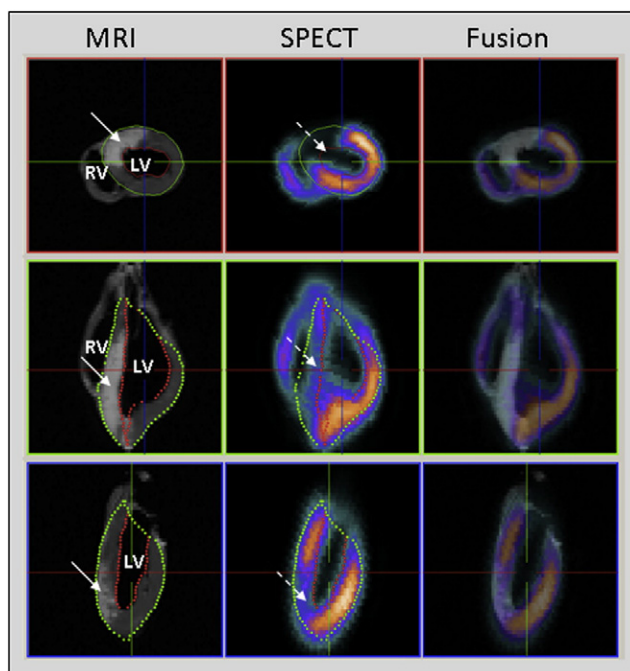

Fig. 1. Imaging of myocardium at risk and final infarct size after experimentally induced ischemia by occluding the left anterior descending coronary artery. Left column: Magnetic resonance imaging (MRI) performed for visualization of the anteroseptal infarction (solid arrows). Dark gray myocardium indicates viable myocardium and white indicates infarction. Middle column: Single photon emission computed tomography (SPECT) used to assess the myocardium at risk by visualization of the anteroseptal perfusion defect (dashed arrows). Warm colors indicate adequate perfusion and cold/absent colors indicate decreased/lack of perfusion. Right column: Fusion of MRI and SPECT images. The upper panel shows a mid-ventricular short-axis slice and the lower two panels show two long-axis slices. Endocardial and epicardial borders of the left ventricle were manually delineated in the MR images and fused with the co-registered SPECT images. LV = left ventricle, RV = right ventricle. (From Demidova et al. J Electrocardiol 2011; 44 (1):74-81).

We have previously shown that the analysis of the πCA-transformed leads allows the detection of TWA episodes embedded in noise, which remain undetectable when they are analyzed in the original leads.[8] Thus, we used the LLR method explained in Martinez and Olmos[9] to detect and estimate TWA in each of the πCA transformed leads. TWA was considered to be present at the analyzed segment if it was detected in any of the transformed leads. To avoid spurious detections, only stable episodes, with duration longer than 64 beats were considered. For segments where TWA was detected, the TWA waveform (i.e, the median difference between even and odd beats) was estimated in all πCA transformed leads using the maximum likelihood estimate for Laplacian noise.[9] The multilead TWA amplitude was then defined as the sum of the root mean squared (RMS) values in all transformed leads. When no TWA was detected, the TWA amplitude was considered to be zero. To quantify TWA in the standard leads, we applied the inverse πCA transformation, after setting to zero all transformed leads where TWA was not found. In this way, we obtained a reconstructed version of the original signal, which kept essentially unaltered the TWA content and its lead distribution while discarding other non-alternant

components.[8] The RMS value of the TWA amplitude was then estimated in each standard lead using the LLR Method.

Imaging

The imaging technique has previously been described in detail.[10–12] Magnetic resonance and SPECT images were analyzed using freely available software (Segment v1.700, Medviso, Lund, Sweden, http://segment.heiberg.se).[13] In brief, SPECT was used to assess the MaR as a percent of the left ventricular myocardium. The endocardial and epicardial borders of the left ventricle that were manually delineated in the MR images were copied to the co-registered SPECT images (Fig. 1). A SPECT defect was defined as a region within the MRI-determined myocardium with counts lower than 55% of the maximum counts in the myocardium and expressed as a percentage of left ventricle as previously described.[14]

For MRI assessment, after removal, the heart was immediately rinsed in cold saline and the ventricles were filled with balloons containing deuterated water. MRI was performed using a 1.5 T MR scanner (Intera, Philips, Best, the Netherlands). The infarcted myocardium was defined as the myocardium with a signal intensity >8SD above the average intensity of the non-affected remote myocardium.[12] The infarcted myocardium was then quantified as the product of the slice thickness and the area of hyperenhanced myocardium. The IS was expressed as percent of left ventricular myocardium.

Statistical methods

Data are presented as mean values ± standard deviations. Pearson's correlation was used for assessment of relationships between repolarization indices and MaR/IS. Statistical analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Twenty three experimental animals comprised the study group. One pig was lost due to unsuccessful resuscitation after ventricular fibrillation during the occlusion period. In one more animal, TWA could not been assessed due to a poor signal quality. TWA was therefore calculated in 21 pigs. Indexes of myocardial damage could not be measured in three more pigs, which had died during reperfusion period from resistant VF or electromechanical dissociation. Thus data on MaR, IS and TWA were available for 18 of 23 pigs.

TWA appeared at 7.2 ± 4.5 (IQ range 3.9–9.6) minutes after occlusion onset, reached its maximum at 12.7 ± 6.3 (IQ range 8.8–17.5) minutes after occlusion onset and lasted until 26.5 ± 9.2 (range 21.2–32.9) minutes (Figs. 2 and 3). The amplitude of TWA was maximal in leads with maximal ST elevation most often in $V_2, -V_4$ (Fig. 4). The correlation between maximal ST deviation and maximal TWA amplitude measured in each individual lead was significant for leads $V_2 - V_6$, I and II. However, we did not observe in any lead a significant correlation between maximal T wave
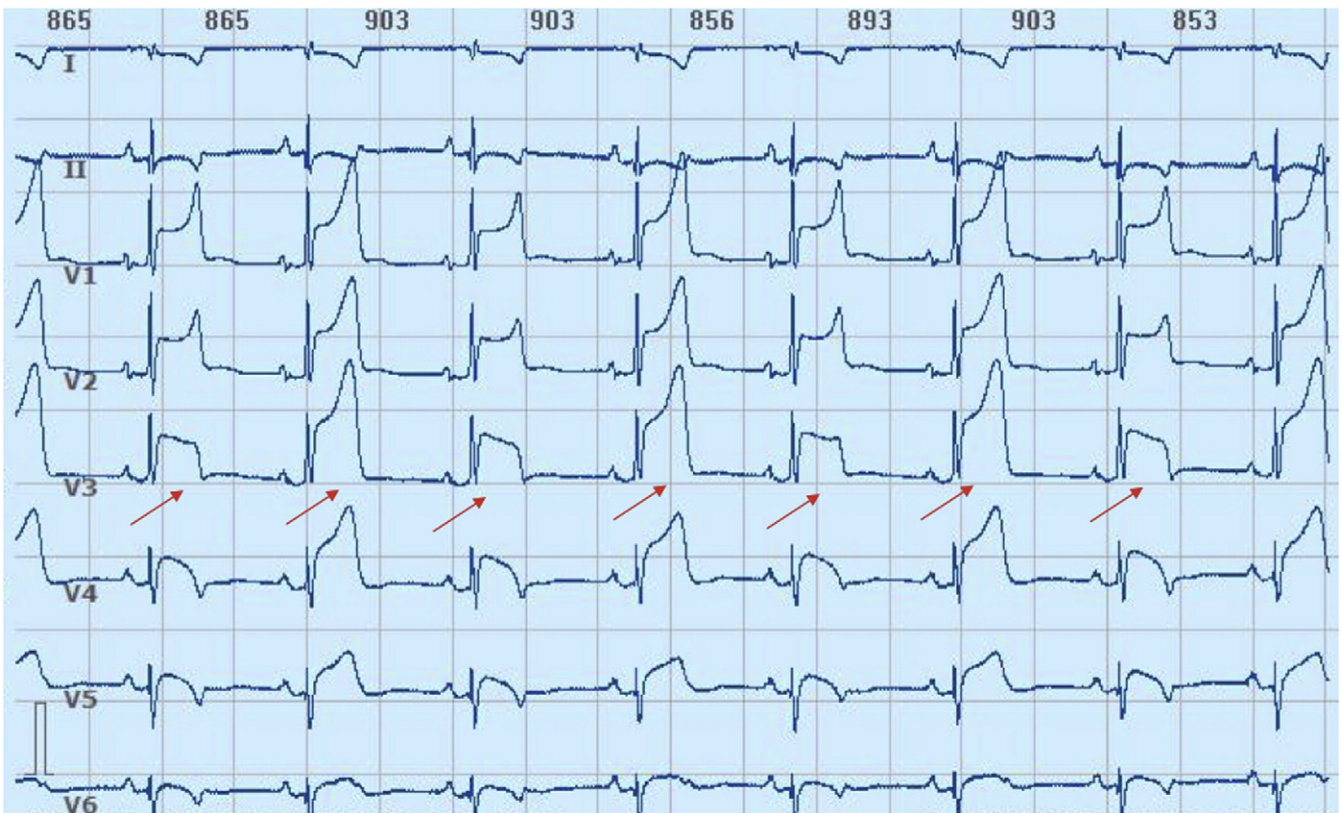

Fig. 2. ECG example of visible T-wave alternans during coronary occlusion. ECG at the 12th minute of occlusion. Heart Rate – 68 b.p.m. Arrows show the apparent beat to beat alternation of T-wave morphology. The scale (1 mV) could be seen in the lower left corner. TWA amplitude is maximal in leads V_2 (302 μV), V_3 (550 μV) and V_4 (446 μV).
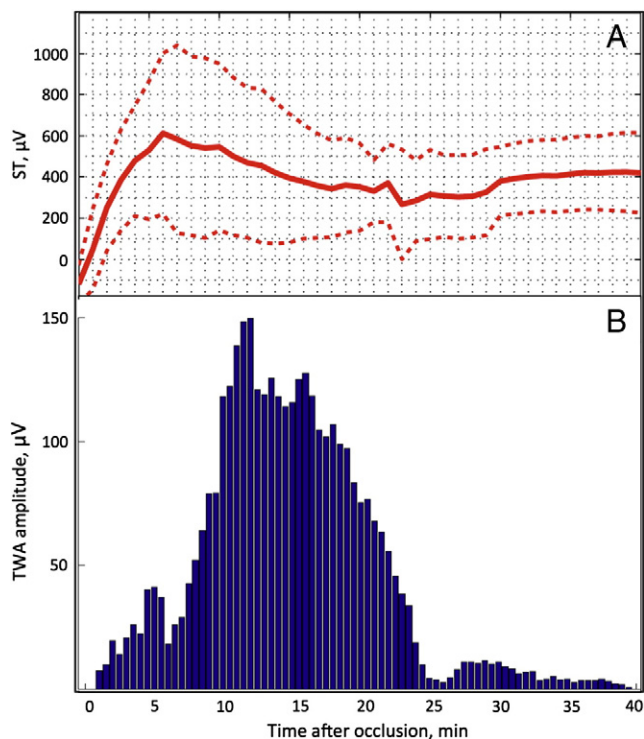
Fig. 3. ST dynamics and the time-course of TWA amplitude during occlusion. A. ST dynamics in one lead with most prominent ST elevation during the occlusion period (V$_3$), group-averaged (Mean (heavy line) ± standard deviation (dotted line)). B. TWA time course during the occlusion period, group-averaged. The standard lead with maximal TWA amplitude (usually V$_2$–V$_4$) was used to build the TWA time-course. For each animal, the RMS voltage of TWA was averaged every 30 seconds along the 40-minute occlusion. Then, the averaged time-course of all these 21 individual profiles was calculated. Abbreviations: TWA – T-wave alternans; RMS – root mean square.

amplitude and maximal TWA. Maximal TWA was not associated with any significant change in heart rate (75 ± 19 vs 76 ± 21 b.p.m., p = 0.575 for heart rate at baseline and during a minute preceding maximal TWA).

Twelve of 21 animals suffered from ventricular fibrillation during two distinct periods during LAD occlusion early (n = 5 at 2.0 ± 0.8 minutes) and late (n = 7 at 16.9 ± 5.8 minutes). All late VF episodes were preceded by TWA, but we did not observe any association between the peak amplitude of TWA and VF occurence.

The MaR was 40 ± 9% (range 28–57%) and the IS was 23 ± 7% (range 10–40%) of the left ventricle. The maximal level of TWA in a standard lead was associated with both MaR (r = 0.499, p = 0.035) and IS (r = 0.65, p = 0.004) (Fig. 5, top panel). When measuring the maximal level of multilead TWA as the sum of the amplitudes in the πCA transformed lead, correlations were stronger with MaR (r = 0.58, p = 0.012) and IS (r = 0.79, p < 0.001) (Fig. 5, bottom panel).

Discussion

We performed quantitative TWA-assessement in the settings of complete and prolonged coronary occlusion, resulting in acute ischemia followed by myocardial necrosis.

In earlier studies on TWA caused by ischemia, TWA was observed during exercise stress-test,[15] accompanied ST elevation in patients with Prinzmetal's angina[16] and transitory occlusion of coronary artery during PCI.[17,18] In our study, TWA occurrence was markedly higher (93%) than in studies with even prolonged occlusion during PCI (52%),[19] that could be explained by more severe ischemia and development of necrosis. The 40 minute-duration of occlusion in our experiment corresponds to approximately 4–5-hour of human myocardial infarction because the rate of myocardial infarction progression in pigs is approximately 7-times faster than in humans, presumably due to a poor collateral blood flow.[20] To the best of our knowledge, TWA dynamics during acute long-time coronary artery occlusion has not been described in detail either in experimental or in clinical settings. In previous PCI studies, where the time of occlusion was short, the TWA magnitude increased continuously during all the period of occlusion.[18,19] The prolonged occlusion we could maintain in the experiments as compared
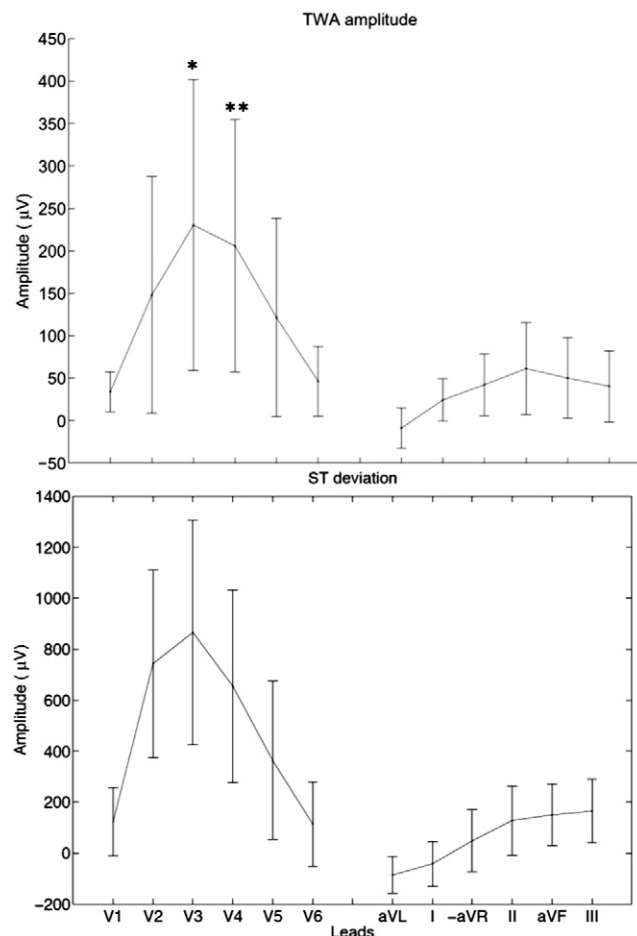

Fig. 4. Averaged TWA lead distribution and average ST distribution profiles, illustrating that maximal TWA corresponds to the area of ischemic injury caused by LAD occlusion. Data from all animals calculated on a per ECG lead basis for each of the 12 standard ECG leads. For each lead, the mean ± standard deviation of the RMS values at the peak of TWA are presented. * - maximal TWA amplitude in V3 was significantly larger than TWA in any other lead excepting V4 (all p < 0.005), and ** - maximal TWA amplitude in V4 was significantly larger than TWA all the leads exept V2 and V3 (all p < 0.005). Abbreviations: TWA – T-wave alternans; LAD – left descending artery; RMS – root mean squared.
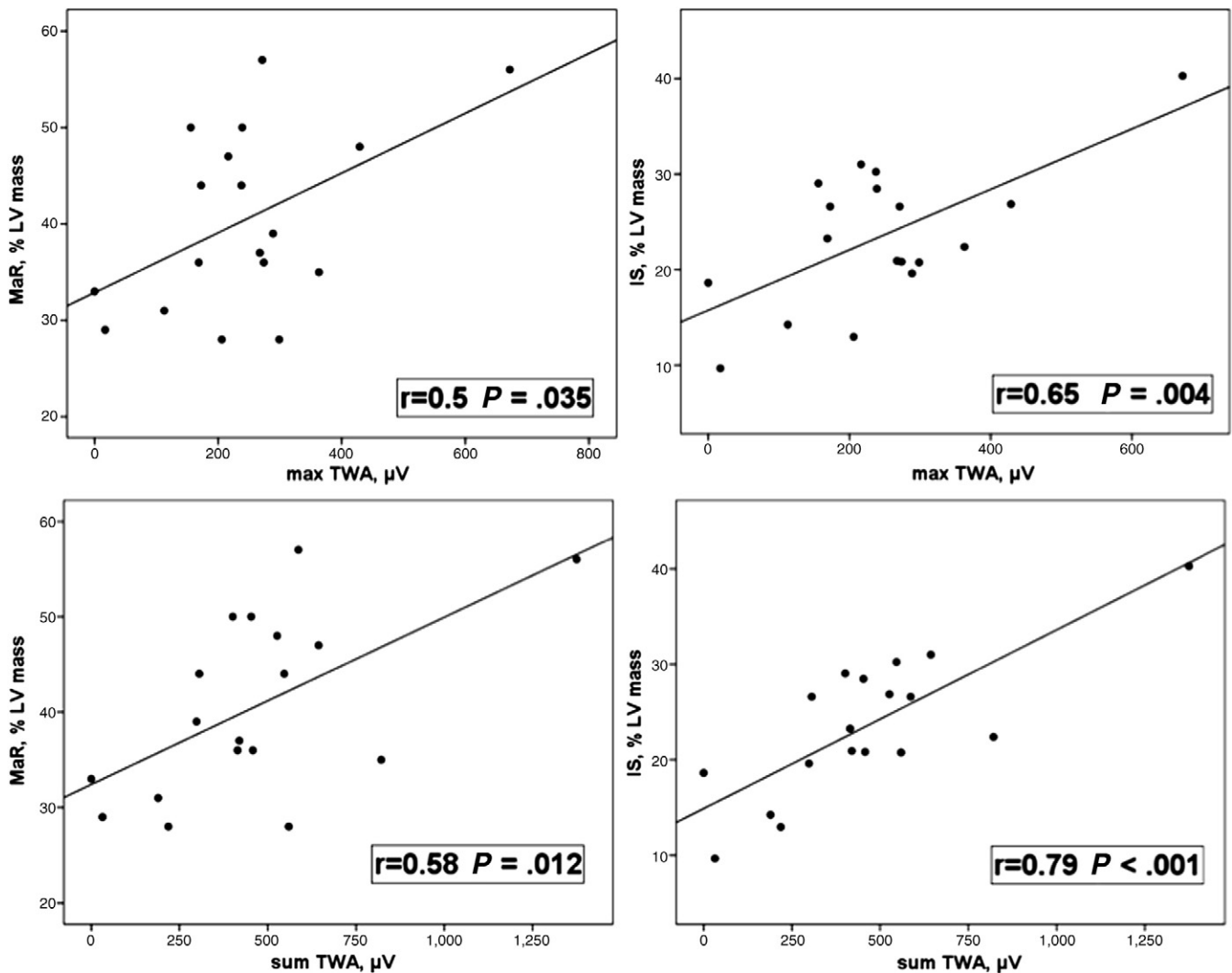
Fig. 5. The association between maximal TWA and the extent of myocardial injury. In the top panels, TWA amplitude is measured as the RMS value in the standard lead with maximal TWA amplitude. In the bottom panels TWA is given as the sum of the RMS amplitudes in the transformed leads. Abbreviations: MaR – myocardium at risk, IS – final infarct size, TWA – T-wave alternans; RMS – root mean squared.

to clinical settings allowed to detect late TWA episodes in some animals (which made the average onset time to delay until 7.2 ± 4.5 min), but the percentage of animals with TWA in the first minutes of occlusion (19% in the first two minutes, 38.1% in the first 5 minutes) as well as their onset times was comparable to those reported in PCI. [19]

In a dog model of ischemia, TWA had a tendency to decrease during the last two minutes of 10-minute long occlusion. [18] Extension of coronary artery occlusion beyond the 10-minute period, at least in the porcine model that was used in our study, leads to a rather abrupt decrease in TWA amplitude by 25th minute and becomes nearly negligible by the end of the 40-minute long occlusion. The reason for such reduction of TWA amplitude despite continued occlusion is not fully understood but may be explained by progressive loss of living myocytes and development of electrically inactive necrotic tissue in the infarcted area.

The intensity of TWA was maximal in leads with maximal ST elevation, most often in V_2–V_4 corresponding the anterio-septal wall – the area supplied by the left anterior descending artery (LAD); SPECT and MRI showed

myocardial injury in the same area. The regional nature of TWA was in line with literature data. [18]

Not only the presence of post-infarction scar, but also the acute ischemia seems to be an important trigger of TWA as shown in another experiment, in which the presence of myocardial scar without acute ischemia was not associated with TWA at intrinsic heart rhythm but could be induced by rapid ventricular pacing. [21] In clinical practice, exercise tests are often used to reach acceleration of heart rate sufficient to enable detection of TWA in post MI patients. [22,23] In the acute STEMI experiment, we observed visible TWA at spontaneous heart rhythm.

TWA is conventionally considered a rate-dependent phenomenon that requires certain rate increase in order to induce measurable TWA. In this context, occurrence of TWA at lower heart rates has been associated with higher risk of ventricular arrhythmias in clinical settings. [24] In our series, mean heart rate was relatively low and TWA, including the visually apparent one, occurred without preceding heart rate acceleration. It is possible that the lack of rate increase can be attributed to the use of fentanyl-

induced general anesthesia in our model. However, the most likely explanation for the TWA that occurred independently of heart rate increase was severe acute ischemia that impairs cellular calcium cycling, which would permit alternans to be initiated at slower heart rates.[25,26] Clinical data on TWA occurrence in the acute phase of STEMI are scarce[27,28] while experimental data are limited to mostly the analyses of intracardiac electrograms and open-chest settings[18,29–31] not directly comparable to the closed chest model employed in our study.

Numerous clinical studies demonstrated role of TWA in sudden cardiac death prediction.[1,2,22,32] The majority of them have included patients with a specific substrate for ventricular tachyarrhythmia, such as infarct scar. It is plausible to suggest the existence of relationship between regional inhomogeneities of ventricular repolarization predisposing to ventricular arrhythmias and the size of myocardial damage. To clarify whether TWA is associated with the degree of myocardial injury we correlated TWA magnitude with MaR and final infarct size. To our knowledge, the relationship between repolarization variability and infarct size was previously studied in only one experimental study in a porcine model of subacute myocardial infarction, and no significant correlation between beat-to-beat variability of repolarization and infarct size was found.[21] In the present study, we have shown that the maximal level of TWA was associated with both MaR and IS. This finding suggests that TWA may be a potential marker of prognostic assessment in STEMI patients. SPECT and MRI – the "gold standard" – in evaluating of myocardial injury, are still far from being a routin clinical examination in patients with STEMI. TWA analysis is a non-invasive marker and can be relatively simply calculated using conventional holter ECG recording, but its value in clinical settings remains to be determined.

Limitations

The findings in the present study should be interpreted in the light of some limitations. In order to achieve reproducibility of myocardial lesion in the settings of a limited number of experimental animals, only LAD occlusions with uniformly 40-minutes duration of ischemia were induced, resulted in necrotic area, corresponding approximately 20–30% of left ventricle. Thereby, this experimental model corresponds in clinical settings to MI of high risk of adverse outcome.

Secondly, the experimental model of myocardial infarction produced by inflation and deflation of the balloon does not fully reflect the course of events during STEMI in humans that is characterized by progression through an inflammatory and coagulation cascade to a thrombotic occlusion and commonly occurring spontaneous recanalization or alternating occlusion of the infarct-related artery.

Thirdly, the direct histologic examination has not been performed in this study, but results of several previous studies have shown strong correlation between infarct size assessed by MR-study and histology.[33–35]

Finally, it would be of value to assess TWA in the chronic phase of the MI in this porcine model and evaluate its

relationship to the findings obtained in the acute phase. However, due to the acute study settings it could not be performed.

Conclusion

In experimental myocardial infarction induced by LAD occlusion, the maximal level of TWA during occlusion period was associated with both MaR and IS, which further supports the need for evaluation of TWA in clinical settings for assessment of its prognostic value in patients with acute coronary syndrome.

Acknowledgments

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