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Bursts of reperfusion arrhythmias occur independently of area at risk size and are the first marker of reperfusion injury

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ABSTRACT

Background: The presence of reperfusion ventricular arrhythmias (VA) has been shown to correlate with larger infarct size (IS). However it is unclear whether the initial area at risk (AAR), also a determining factor for IS, is responsible for this correlation. We hypothesized that IS would be significantly larger in the presence of VA, while AAR would not differ.

Methods: 68 STEMI patients from the MAST study with 24-hour, continuous, 12 lead Holter monitoring initiated prior to primary percutaneous coronary intervention (PCI) resulting in TIMI 3 flow post PCI were included. VA bursts were identified against subject-specific background VA rates using a previously validated statistical outlier method. IS, and infarct endocardial surface area (ESA) were obtained using CMR at mean 4.9 days after admission. Holter and CMR results were determined in core laboratories blinded to all other data.

Results: VA bursts were present in 69% (45/65) of patients. No significant differences were found for demographic characteristics, comorbidities, infarct location, number of diseased coronary vessels, or duration of ischemia between groups with and without VA burst. IS was significantly smaller in the group without VA bursts (median 9.3% vs 17.0%; $p = 0.025$). Infarct ESA did not significantly differ between the population with and without VA burst; median 24.3% vs 20.0%; $p = 0.15$.

Conclusion: VA bursts are a marker for larger IS independent of AAR, assessed by surrogate markers. These findings support the hypothesis that VA bursts are a marker of reperfusion damage occurring downstream at myocellular level.

1. Introduction

Historically ventricular arrhythmias (VA) after thrombolytic therapy were considered a favorable non-invasive marker of reperfusion [1]. More recent studies in the era of primary percutaneous intervention (PCI) have shown that reperfusion VA bursts are related to larger infarct size (IS) and worse left ventricular function (Fig. 1) [2–8]. Such VA bursts include mostly ventricular premature beats with long coupling intervals and accelerated idioventricular rhythms. They are usually transient, hemodynamically well tolerated and occur closely related to the time of reopening of the infarct vessel [9].

Our group developed a quantitative method to distinguish reperfusion VA bursts from background arrhythmias during STEMI and reperfusion [2]. VA bursts correlates significantly with larger IS even in the absence of microvascular obstruction (MVO) or with optimal myocardial blush grade [6,8], consistently suggesting they are a signal of injury occurring further downstream at myocellular level [3]. It has been suggested that the initial area at risk (AAR) is related to the occurrence of VA bursts and therefore the correlation with larger infarct size.

AAR is a known determinant for final infarct size, in combination with factors such as the duration of infarction, the extent of collateral flow and the success of revascularization attempt [10–12]. Because AAR is an important prognostic marker, its accurate measurement has been pursued using various imaging modalities, including SPECT imaging and, more

Abbreviations: AAR, area at risk; DE-CMR, delayed enhancement cardiovascular magnetic resonance imaging; ECG, electrocardiogram; ESA, infarct endocardial surface area; IS, infarct size; LV, left ventricle; MVO, microvascular obstruction; PCI, percutaneous coronary intervention; SPECT, single-photon emission computed tomography; STEMI, ST elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; VA, ventricular arrhythmias; VPC, ventricular premature complex.

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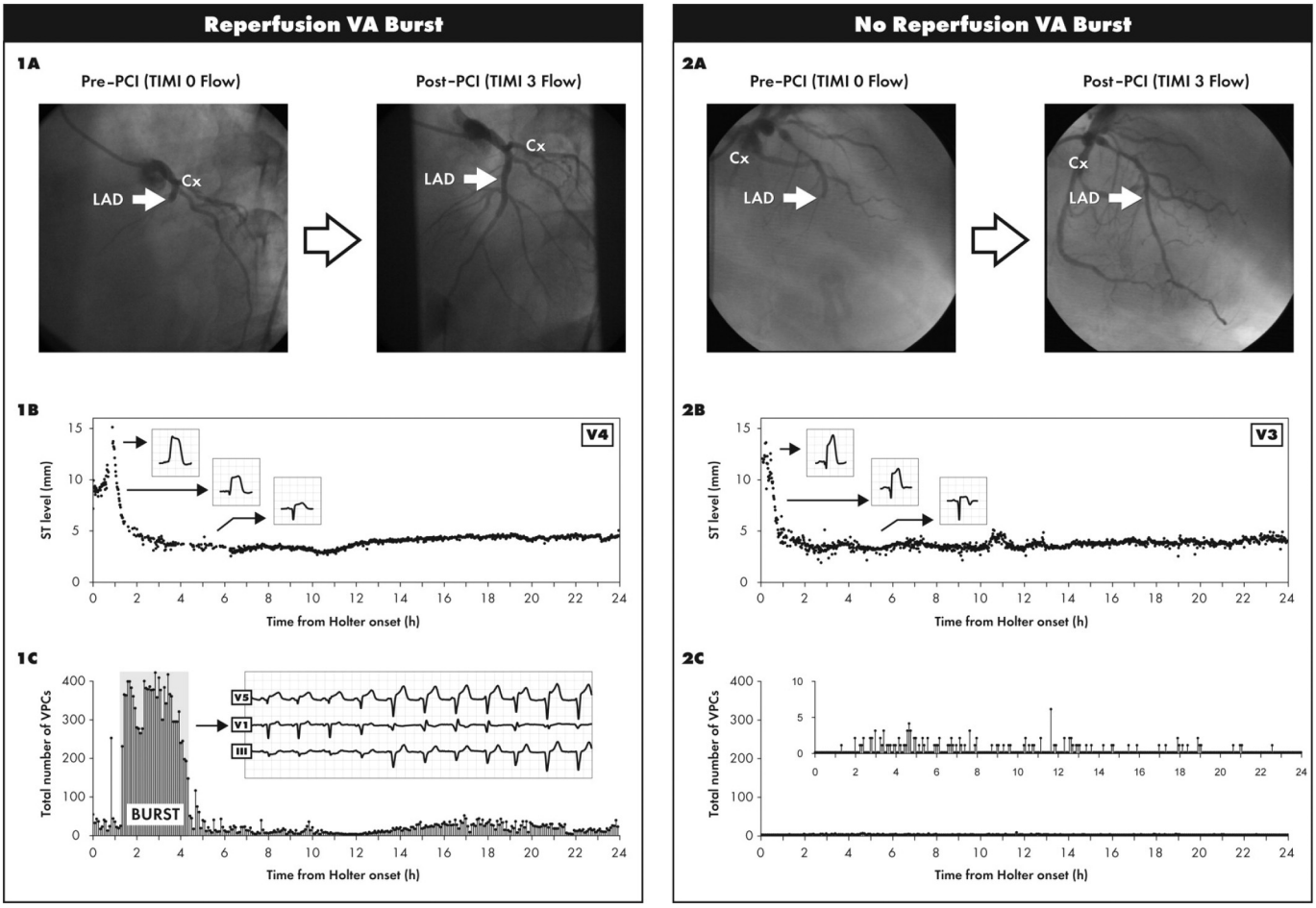

Fig. 1. Example of a patient with and a patient without VA burst Concomitantly acquired coronary angiography assessments of pre- and post-primary percutaneous coronary intervention TIMI flow grades in two study subjects (1A and 2A) with a total occlusion in the proximal left anterior descending artery proximal (LAD); continuous digital 12-lead electrocardiography monitoring for ST-segment recovery analysis with both subjects having ≥50% stable ST-segment recovery (1B and 2B); and complete beat-to-beat Holter monitoring for quantitative rhythm analysis identifying (1C) or not identifying (2C) patient-specific ventricular arrhythmia 'bursts' by using independent statistical outlier detection methodology. Cx, circumflex artery; LMA, left marginal artery. (Majidi et al. Eur. Heart J 2009; 30: 757–764).

recently, cardiovascular magnetic resonance imaging (CMR). One such method is the endocardial surface area (ESA), the percentage of infarcted endocardial border of the left ventricle measured on delayed enhancement (DE-)CMR images. DE-CMR allows accurate measurement of irreversible myocardial injury [13]. ESA is based on the principle that the lateral extent of irreversible injury is completed within 40 min after coronary occlusion and therefore matches the lateral boundaries of the AAR [10]. Longer duration of ischemia will only result in progression of irreversible injury towards the epicardium as a transmural wave front, while ESA won't change [14,15].

We sought to investigate whether VA burst is related to larger AAR. If not, VA burst might be a marker of injury on a cellular level after reperfusion i.e. reperfusion injury.

2. Methods

2.1. Study population

Consecutive patients included in the Maastricht ST-Elevation Myocardial Infarction (MAST) database were studied, presenting with a first acute STEMI at Maastricht University Medical Centre from August 2006 to March 2008. STEMI was defined according to ECG and enzymatic criteria according to active consensus document [16]. As an enzymatic marker we used the cardiac troponin *t*-test of Roche Diagnostics (Basel, Switzerland) which is elevated if ≥0.05 ng/ml.

As previously described [17], inclusion criteria were: (1) symptoms consistent with an acute STEMI lasting for >30 min but <6 h, (2) ST-elevation of >1 mm in anatomically adjacent leads in the initial ECG, (3) primary PCI, (4) availability of CMR images. Exclusion criteria were: (1) age below 18 years, (2) cardiogenic shock, (3) pregnancy, (4) inability to obtain informed consent, (5) standard contra-indications for CMR, (6) absence or poor quality ECG-Holter recording, (7) previous myocardial infarction, (8) absence of or poor quality CMR images unreliable for infarct determination, (9) absence of successful epicardial flow restoration defined as TIMI flow ≤ 2, (10) inability to obtain stable ST recovery within 240 min, and (11) late ST re-elevation.

Approval of the study was granted by the Medical Ethical Committee of corresponding hospital (MAST, MEC 05-199) and written informed consent was obtained from all patients included.

2.2. Angiographic TIMI flow assessment

TIMI flow grade assessment was performed by the angiographic core laboratories (Academic Medical Centre, Amsterdam, The Netherlands and Maastricht University Medical Centre, Maastricht, The Netherlands) post-procedural and blinded to all other data. TIMI flow was graded according to the TIMI trial classification [18].

2.3. ECG data acquisition

Continuous, high-fidelity, digital, 12 lead ECG Holter recording (NEMON 180+, Northeast Monitoring, Maynard, MA, USA) was started before PCI and continued for an average of 24 h. This system provided the source data for both continuous ST-segment recovery and ventricular arrhythmia burst analyses on a single time track. Quantitative ST-segment recovery analysis was performed on median beat 12 lead ECGs every 60 s. Quantitative ventricular arrhythmia analysis was performed on 3 lead beat-to-beat Holter. ST and VA analyses were performed by independent experts blinded to all other patient and core laboratory data through the collaborative eECG core laboratory program (ST-analyses Duke Clinical Research Institute core lab Durham, North Carolina, USA/VA analyses Maastricht University Medical Centre eECG Core lab Maastricht, The Netherlands) using NEMON Holter for Windows software (NorthEast Monitoring, Inc. Maynard, Massachusetts, USA).

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