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Prospective evaluation of where reperfusion ventricular arrhythmia "bursts" fit into optimal reperfusion in STEMI

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ABSTRACT

Background: Early reperfusion of ischemic myocytes is essential for optimal salvage in acute myocardial infarction. VA (ventricular arrhythmia) bursts after recanalization of the culprit vessel have been found to be related to larger infarct size (IS), using SPECT.
Objective: The hypothesis was tested that this finding could be confirmed in an independent cohort using a more accurate technique, i.e. delayed-enhancement cardiovascular magnetic resonance imaging (DE-CMR).
Methods: All 196 patients from the PREPARE and MAST studies who had 24-hour, continuous, 12-lead Holter, started before primary percutaneous coronary intervention resulting in brisk TIMI (thrombolysis in myocardial infarction) 3 flow and stable ST-recovery were included. VA bursts were identified against subject-specific background VA rates using a previously published statistical outlier method. IS was assessed using DE-CMR. Angiography, Holter and DE-CMR results were assessed in core laboratories, blinded to all other data.
Results: VA bursts were present in 154/196 (79%) of patients. Baseline characteristics between the groups with and without bursts were similar. VA burst was associated with significantly larger infarct size in the population as a whole (median 11.3% vs 5.3%; $p = 0.001$) and also when divided in non-anterior (median 9.9% vs 4.9%; $p = 0.003$) and anterior myocardial infarction (median 21.4% vs 12.0%; $p = 0.48$), the latter not reaching statistical significance due to the small subset of patients.
Conclusion: Beyond the classical markers of "optimal" reperfusion such as TIMI 3 flow and stable ST-segment recovery, VA bursts occurring during the reperfusion phase are an early electrobiomarker of larger IS. Clinical trial registration: PREPARE: ISRCTN71104460 http://www.controlled-trials.com/ISRCTN71104460.

1. Introduction

Ventricular arrhythmias (VAs) upon reperfusion are recognized as a typical phenomenon since the advent of recanalization techniques in acute ST-elevation myocardial infarction (STEMI). However, not much is known about their pathophysiological and prognostic significance [1]. Morphologically, these reperfusion VAs include ventricular premature beats with long coupling intervals and accelerated idioventricular rhythms. They occur (almost) directly at the moment of reperfusion, are hemodynamically well tolerated and originate within the reperfusion zone (Fig. 1) [2]. In conjunction with thrombolytic therapy, reperfusion VAs were considered a positive event as a non-invasive marker of infarct artery recanalization [2]. In the more contemporary era of direct percutaneous coronary intervention (PCI), where TIMI 3 epicardial flow is restored in >90% of STEMIs and mortality has been reduced to less than 5% [3], the hypothesis that VA "bursts" are associated with larger infarct size (IS) and worsened outcomes in the setting of anterior MI has been proposed by our group, based on retrospective modeling [4–7].

Over the last years, it has become clear that clinically beneficial reperfusion in STEMI is dependent on both the clinical context and on a series of key mechanistic steps defining "optimal" reperfusion per se. Clinically, the timing of presentation relative to the ongoing irreversible injury or "wavefront" of cell death has been addressed with emphasis on early diagnosis and time to intervention and results in smaller IS and lower morbidity [8–10]. IS as an endpoint was traditionally measured with SPECT imaging, but can now be measured with greater precision using delayed enhancement cardiovascular magnetic resonance imaging (DE-CMR) [11].

Abbreviations: DE-CMR, delayed enhancement cardiovascular magnetic resonance imaging; ECG, electrocardiogram; IS, infarct size; PCI, percutaneous coronary intervention; SPECT, single-photon emission computed tomography; STEMI, ST elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; VA, ventricular arrhythmias.

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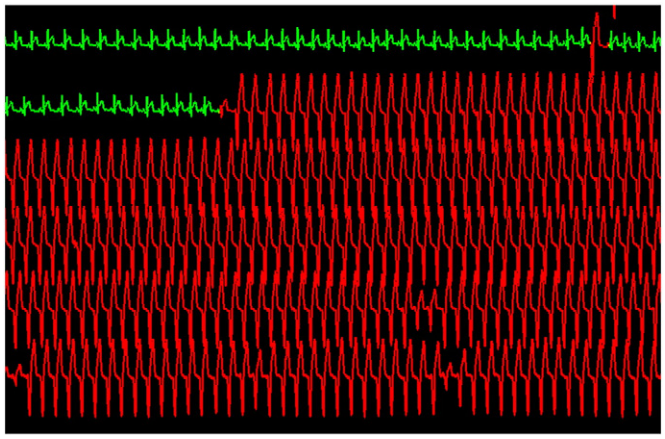

Fig. 1. Full disclosure format of a 24 hour ambulatory recording illustrating the onset and perpetuation of a reperfusion ventricular arrhythmia burst. Green waveforms: Sinus beats still showing some ST segment elevation. Red waveforms: accelerated idioventricular rhythm interrupting the sinus rhythm.

In this report, we pursued to prospectively test the hypothesis generated by observations from Majidi et al. [4,5,19] to a unique patient population with not only anterior STEMI but also non-anterior STEMI and the use of DE-CMR, the current gold standard, for IS measurement. In this population we examined whether it could be confirmed that VA burst adds significantly to IS in patients with optimal reperfusion, as indicated by TIMI 3 epicardial flow and complete and stable ST-segment recovery.

2. Methods

2.1. Study population

Patients included in the Maastricht ST-Elevation Myocardial Infarction (MAST) cohort [12] and the Proximal embolic protection study in patients undergoing primary angioplasty for acute myocardial infarction (PREPARE) cohort were included for analyses. The protocols of both studies, specifically including Holter recording and CMR imaging, were prospectively designed to answer the questions of the study at hand. Since the PROXIS device used in the PREPARE trial did not influence the final infarct size, all patients from that study were included in this analysis [13]. Approval of both studies was granted by the Medical Ethical Committee of corresponding hospitals (MAST p06.0032L and PREPARE ISRCTN71104460) and written informed consent was obtained from all patients included.

Both studies included patients enrolled between August 2006 and June 2008. Inclusion criteria for both studies were as follows: (1) symptoms consistent with an acute STEMI lasting for more than 30 min but less than 6 h and (2) ST-elevation of more than 1 mm in anatomically adjacent leads in the initial electrocardiogram (ECG), and (3) primary PCI. Exclusion criteria were as follows: (1) age below 18 years, (2) cardiogenic shock, (3) pregnancy, (4) inability to obtain informed consent, (5) any contraindications to the use of glycoprotein IIb/IIIa receptor antagonists, (6) a co-existent condition associated with a limited life expectancy, (7) prior coronary artery bypass grafting or fibrinolytics, and (8) standard contra-indications for CMR.

In both studies, 24-hour, continuous, digital 12-lead ECG-Holter monitoring was started at the time of admission, and CMR imaging was scheduled 3 months after the acute event for analyses of final infarct size after remodeling [9]. Technical exclusion criteria for this VA burst study were as follows: (1) poor quality ECG-Holter recording, (2) previous myocardial infarction (MI), and (3) poor quality CMR imaging. Clinical exclusion criteria for the current study were (1) absence of successful epicardial flow restoration defined as TIMI flow ≤ 2, (2) failure to achieve complete and stable ST recovery within 240 min or (3) late ST re-elevation on continuous ECG-Holter. These exclusion criteria were formed because we were interested in the additional value of VA burst in patients with optimal epicardial reperfusion and brisk ST-recovery. Therefore, we did not perform statistical analyses of the groups excluded.

2.2. Angiographic TIMI flow assessment

TIMI flow grade assessment was performed by the angiographic core laboratories (Academic Medical Center, Amsterdam, The Netherlands and Maastricht University Medical Center, Maastricht, The Netherlands) blinded to all patient and other core laboratory data. TIMI flow was graded according to the TIMI trial classification [14].

2.3. ECG data acquisition

Continuous, high fidelity, digital, 12-lead ECG-Holter recording (NEMON 180+, Northeast Monitoring, Maynard, MA, USA) was started at the time of admission prior to 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 analysis. Quantitative ST-segment recovery analysis was performed on 60 second median beat 12-lead ECGs. Quantitative ventricular arrhythmia (VA) 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 (Duke Clinical Research Institute/Maastricht University Medical Center eECG Core, Durham, North Carolina, USA and Maastricht, The Netherlands), using NEMON Holter for Windows software.

2.4. Continuous ST recovery analysis

Methods and criteria for continuous 12-lead ST-segment recovery analysis and reperfusion of the culprit lesion have been described in detail previously [15]. In short, peak ST-segment deviation is determined based on the lead with the greatest baseline deviation taken from the most abnormal ECG recorded during monitoring. Stable and complete ST-segment recovery is defined as ≥50% recovery from previous peak ST-segment levels in the most deviated lead within 240 min, lasting >4 h without further ST-segment evolution (>100 μV). Late ST (re-)elevation defining epicardial vessel reocclusion (>150 μV re-elevation in the most abnormal lead evolving in <60 min) or microvascular insufficiency (>50% peak ST levels persisting >6 h in the most abnormal lead) were used to exclude patients from the "optimal reperfusion biosignature" group included in the current analysis.

2.5. Quantitative rhythm analysis and defining VA burst

For beat-to-beat quantitative rhythm analysis on all digital 3-lead Holter recordings, Holter 5 software (Northeast Monitoring, Maynard, MA, USA) was used [4]. All automatically assigned waveform labels were manually verified for each cardiac cycle from each subject to ensure accurate VA capture according to predefined criteria for ECG interpretation of VAs [4,5]. To generate quantitative VA rates over a 24 hour period, total VPC counts, for which no distinction between the types of VPC was made, were bundled into 5 minute blocks for temporal correlation with stable ST-segment recovery and angiographic observations (Fig. 2). Quantitative VA rates over the course of Holter recordings were incorporated in a statistical outlier detection method to automatically separate outlier events of VA rates (VA burst), if present, from patient-specific baseline VA counts. VA bursts were defined as "reperfusion VA bursts" if concomitant with or subsequent to angiographic documentation of re-established TIMI 3 flow in the infarct related