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Ventricular tachycardia-inducibility predicts arrhythmic events in post-myocardial infarction patients with low ejection fraction. A systematic review and meta-analysis

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ABSTRACT

Background: Inducibility of ventricular arrhythmias at electrophysiological study (EPS) has long been suggested as predictive for subsequent arrhythmic events. Nevertheless, the usefulness of EPS in the clinical practice is still unclear. We performed a systematic review and meta-analysis to assess the predictive power of EPS in primary prevention of ventricular arrhythmias in post-myocardial infarction (MI) patients with left ventricular dysfunction.
Methods: MEDLINE and the Cochrane Library databases were systematically searched to identify studies, which analyzed EPS predictive value in post-MI patients with mean EF < 40% for the composite arrhythmic endpoint defined by: sudden cardiac death (SCD), aborted SCD, ventricular tachycardia (VT), ventricular fibrillation (VF), appropriate implantable cardioverter-defibrillator (ICD) interventions.
Results: Nine studies, evaluating 3959 patients with 647 arrhythmic events, were included in the meta-analyses. EPS showed a strong predictive power for the arrhythmic endpoint with a pooled odds ratio (OR) of 4.00 (95% confidence interval [CI]: 2.30–6.96) in the whole set of studies, albeit a high level of heterogeneity among studies. EPS predictive power was higher in studies where VT-inducibility was tested (OR 6.52; 95% CI: 2.30–18.44; sensitivity 0.65, specificity 0.78, and negative predictive value 0.94), versus those assessing VT/VF-inducibility (OR 2.09; 95% CI: 1.34–3.26). VT-inducibility was predictive even when assessed within one month after MI (OR 7.85; 95% CI: 3.67–16.80).
Conclusions: Inducibility of ventricular arrhythmias at EPS is a strong predictor of the arrhythmic endpoint in post-MI patients with impaired EF, particularly when VT-inducibility is tested. EPS could help selecting the patients who can mostly benefit from ICD therapy.

1. Introduction

The current guidelines recommend implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death (SCD) in patients with ischemic cardiomyopathy, based on the values of the left ventricular ejection fraction (EF) [1, 2]. However, EF lacks both sensitivity and specificity for prediction of arrhythmic events. Contemporary real-world data indicate that the majority of patients addressed to ICD therapy by the current guidelines do not have life-saving therapies, while being exposed to ICD side effects [3, 4]. By contrast, several patients who are at risk of SCD are not identified by the EF value, because the main part of SCD patients exhibits just mildly depressed EF [5]. Thanks to the modern pharmacological therapies and wide spread of primary percutaneous coronary interventions (PCIs), a reduction in the risk of SCD has been observed in post-myocardial infarction (MI) patients with impaired EF [6]. This makes particularly urgent to improve, beyond the EF criterion, the selection of patients who can most benefit from an ICD.

In recent years, a great effort has been made to identify additional methods for SCD risk stratification to improve the appropriateness of ICD implantation [5, 7–10]. After MI, a ventricular scar is generally formed, which can act as a predisposing factor to ventricular arrhythmias [11]. The assessment of total scar and border zone extent by late gadolinium enhancement - cardiac magnetic resonance (LGE-CMR) has been demonstrated a promising non-invasive risk marker for arrhythmic events [8]. However, while scar presence is a predisposing factor, arrhythmia inducibility by programmed ventricular stimulation during

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an electrophysiological study (EPS) directly tests the functionality of scar-related circuits, adding significant information to the stratification of arrhythmic risk in post-MI patients. Although some studies have highlighted the predictive power of EPS for arrhythmic events [12, 13], the test is poorly utilized in the current clinical practice and its usefulness is still controversial [1, 14]. To address this question, we performed a systematic review and meta-analysis aiming to assess the predictive power of EPS in post-MI patients with reduced EF.

2. Methods

The systematic review and meta-analysis were conducted following the guidelines of the PRISMA Statement [15].

2.1. Eligibility criteria

The literature search was performed to identify studies assessing ventricular arrhythmias inducibility by programmed ventricular stimulation during an EPS, in the primary prognostic stratification of ventricular tachyarrhythmias in post-MI patients with mean EF < 40%. Studies presenting endpoints related to ventricular arrhythmic events, such as sudden cardiac death (SCD), aborted SCD, sustained ventricular tachycardia (VT), ventricular fibrillation (VF), appropriate ICD therapy with the inclusion of antitachycardia pacing (ATP), were selected. Additional inclusion criteria were a sample size >50, and a follow-up of at least 1 year. The search was restricted to articles published in English in peer-reviewed journals. Abstracts and session presentations were excluded.

2.2. Search strategy, study selection and data collection

MEDLINE and the Cochrane Library electronic databases were systematically searched to identify primary references from January 2000 to December 2017. Studies published before 2000 were not considered to avoid that differences in MI treatment in older studies with respect to the current therapy could introduce bias in the analysis. The search terms used are outlined in the Supplementary material. The database search was followed by a review of the citations from eligible studies by two independent reviewers (MD and MM). Studies were selected based on title and abstract. Selected studies were read thoroughly to identify those suitable for the qualitative and/or quantitative analysis (meta-analysis). The two reviewers independently extracted the demographic and clinical outcome data from the selected studies. When disagreement occurred, they reviewed the papers together to reach joint conclusions. The methodological quality of the studies was evaluated by applying the Newcastle-Ottawa Score (NOS) checklist for non-randomized studies [16], and the Cochrane Risk of Bias Tool for Randomized Controlled Trials for randomized studies [17].

2.3. Statistical analyses

Patients' characteristics were conveniently expressed as numbers, percentages, mean ± standard deviation, median (interquartile range), or median [range]. In each study data for the assessed outcomes in patients with positive (EPS+) and negative test (EPS−) were summarized using simple counts. When raw data were not reported, proportions of positive cases, risk ratios, odd ratios (ORs), sensitivity, specificity, positive (PPV) and negative predictive values (NPVs) were used to calculate raw numbers. In one study [18], raw data were estimated from outcome probabilities reported in Kaplan-Meier survival curves at mean follow-up. Binary outcomes were combined by a random effects model using the method by DerSimonian and Laird [19], which estimated pooled ORs with 95% confidence intervals. Pooled ORs were computed for the arrhythmic endpoint, and, where available, for the total mortality endpoint. Where present into the primary studies, adjusted hazard ratios (HR) from Cox multivariate regression models were extracted and meta-analyzed.

Heterogeneity among studies was assessed by chi-squared test, quantified by I^2 statistics, and explored by sensitivity analysis, subgroup meta-analyses, and meta-regression.

Statistical measures of performance of a binary classification test, such as annualized event rate (AER) in EPS+ and EPS−, pooled sensitivity, specificity, positive and negative likelihood ratios, PPVs and NPVs were calculated for the overall group of studies and for relevant subgroups [20, 21]. Further details on heterogeneity analyses and computation of diagnostic indices are reported in Supplementary material.

Publication bias was assessed by funnel plot visual inspection and Harbord modified test [22].

All analyses were performed using the Cochrane Collaboration Software Review Manager 5 (version 5.2), and STATA 13.1 Statistics/Data analysis (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA). The 2-tailed statistical significance level was established at 0.05.

3. Results

3.1. Study selection

The search of Medline and the Cochrane Library databases identified 1125 relevant studies after duplicate removal, which were complemented by seven from the studies' references (Fig. 1S in Supplementary material). 1086 studies were excluded after reading title and abstract, and 46 were retrieved for further evaluation. Of these, 37 studies were excluded, because they did not fulfill all the inclusion criteria. Nine studies, enrolling 3959 patients, were included in the systematic review and meta-analyses. Of these, two were randomized trials (MUSTT (Multicenter Unsustained Tachycardia Trial) [13] and BEST + ICD (BEta-blocker STrategy plus ICD) [23]), one was a post-hoc analysis of a previous randomized trial (MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II)) [18], and six were prospective non-randomized trials [7, 24–28]. The study by Zaman et al. [28] was included despite a partial overlapping (~40%) with that by Kumar et al. [27], given the application of different patients' selection criteria.

3.2. Study characteristics

The general characteristics of the nine selected studies are reported in Table 1, while details on the specific EPS protocols applied in each study are outlined in Table 1S in Supplementary material. The studies presented differences in the EPS protocol and timing. In three studies inducibility of sustained monomorphic VT was the main criterion to identify patients with positive test, while in four studies inducibility of either VT or VF was accepted as positive result. In the remaining two studies [18, 26] both criteria were tested and compared. Given these protocol differences, inducibility ranged between 12 and 39% for VT-inducibility and between 24 and 46% for VT/VF-inducibility (Table 1S in Supplementary material). In four studies EPS was performed early after MI (within one month). The quality of the selected studies was generally good, the non-randomized studies yielding NOS scores ranging between 7 and 9, and the randomized studies presenting low risk of bias (Table 1). Demographic and clinical characteristics of the 3959 patients included in the meta-analysis are reported in Table 2. The patients had a mean age of 65 years, and 3304 (83%) were men. In all the studies the mean EF value was ≤ 35%. The average follow-up period ranged from a minimum of 18 months to a maximum of 48 months with a weighted mean of 32 months.

3.3. Predictive power of EPS

In the overall group of studies, the patients developed 647 arrhythmic events (16.3%), with an AER of 7% (Table 4S in Supplementary material). The arrhythmic endpoint was reached in 23.4% of patients with positive EPS (AER 10.0%) versus 13.7% of patients with negative EPS (AER 5.8%), with a pooled OR of 4.00 (95% CI: 2.30–6.96,