Risk stratification after myocardial infarction: it is time for intervention

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This editorial refers to ‘Non-invasive risk stratification for sudden cardiac death by heart rate turbulence and microvolt T-wave alternans in patients after myocardial infarction’ by V. Sulimov et al., on page 1786

Despite significant advances in interventional and pharmacological therapies, late mortality after acute myocardial infarction (MI) is still high. Approximately 50% of cardiovascular deaths after MI occur suddenly and are potentially preventable by prophylactic implantation of a cardioverter-defibrillator (ICD). In recent decades, substantial efforts have been made to identify high-risk patients who may benefit from prophylactic therapy. While initial risk stratification strategies guiding ICD therapy were based on the comprehensive electrophysiological testing in highly selected subgroups of patients, a revolutionary concept was proposed in 2002, when Moss et al.1 presented the results of MADIT-2 (Multicentre Automatic Defibrillator Implantation Trial). In contrast with all previous attempts, MADIT-2 used the finding of a reduced left ventricular ejection fraction (LVEF) as the single selection criterion for prophylactic ICD-implantation. In terms of efficacy and effectiveness, the MADIT-2 criterion was a great success. Subsequent trials confirmed the concept of prophylactic ICD-implantation in patients with impaired LVEF, and later economic analyses verified the cost-effectiveness of this approach.

However, when looking from an epidemiological point of view at the global impact of ICD on the disease burden of sudden cardiac death (SCD) after MI, there is a growing sense of disillusionment. The vast majority of post-MI patients prone to SCD are not captured by the MADIT-2 criterion, and die despite exercising preserved or only moderately impaired LVEF.2 Identifying high-risk individuals after MI by reduced LVEF is therefore like looking at the tip of an iceberg with a telescope. Several studies have documented that the sensitivity of impaired LVEF in predicting death after MI is as poor as 30%; it is unlikely that a diagnostic test with such a low sensitivity would be accepted in many other fields of modern medicine.

But what are the alternatives? In the current issue of the Journal, Sulimov et al.3 report on the usefulness of the combination of two electrocardiogram (ECG)-based risk predictors, heart rate turbulence (HRT), and microvolt T-wave alternans (TWA), for the prediction of SCD after MI. Heart rate turbulence quantifies the baroreflex-mediated short-term oscillation of cardiac cycle lengths following spontaneous ventricular premature complexes.4 T-wave alternans refers to the beat-to-beat fluctuation in the morphology and amplitude of the ST segment and/or T-wave related to instabilities in membrane voltage and disruptions in intracellular calcium cycling dynamics.5 The combination of both markers makes sense from a pathophysiological point of view, as they capture different pathologies involved in the genesis of SCD. The main finding of the study was that both HRT and TWA were strong and independent predictors of SCD, yielding relative risks of 12.4 and 5.0, respectively. However, the study is limited in several respects. First, the study is underpowered; a sample size of 111 patients (out of whom 15 reached the primary endpoint of SCD) is too small by orders of magnitude to address the question of interest. Second, cumulative 1-year event rates of SCD were surprisingly high (13.5%). For comparison, in the 14 609 participants in the VALLIANT (VALsartan In Acute myocardial iNfarcTion) study, this figure was as low as 5.1%.6 Third, several technical and statistical issues remain, as the authors used a non-standard ECG lead configuration and defined new cut-off values for TWA that require prospective validation.

Nevertheless, the limitations of the study by Sulimov et al. do not necessarily imply that the conclusions are wrong. There is a huge body of evidence from retrospective and prospective studies (together including more than 10 000 patients) that both HRT and TWA are powerful predictors of risk after MI (Figure 1). The combination of HRT and TWA was also tested in the REFINE (Risk Estimation Following Infarction Noninvasive Evaluation) study.7 Of particular importance, both predictors are useful for the identification of high-risk patients otherwise classified as low-risk, making both markers suitable for combination...
with established criteria.4,5 The positive predictive values and specificities of both markers are in the range of that provided by impaired LVEF, suggesting that ICD may be equally effective.8,9 As is the case with many other methods, HRT and TWA have several shortcomings that are beyond the scope of this editorial but do not affect the risk-predictive power of both methods. Given this information, why have none of these markers been tested in a randomized, interventional ICD trial?

Although several reasons could be cited here, the central question remains: who is going to pay for such a trial? The costs of a prospective, multicentre ICD trial are enormous, and probably could only be covered by large ICD companies. However, these companies need to follow the rules of economy, balancing the potential benefits of widened ICD indications against the associated costs and, importantly, the risks of a negative outcome. In this respect, the DINAMIT (Defibrillation in Acute Myocardial Infarction Trial)10 and IRIS (Immediate Risk-Stratification Improves Survival)8 studies, which addressed questions different from those proposed here, were painful experiences for St Jude Medical and Medtronic. While discussing expansions of ICD indications to fight SCD, it is important to note that ICD therapy is still significantly underused in most, if not all, European countries according to already approved criteria.9 Nonetheless, as scientists we should promote the prospective validation of sound concepts. We strongly believe that prophylactic ICD in high-risk post-MI patients characterized by abnormal HRT and/or TWA belongs to this category of concepts.

Conflicts of interest: none.

References
Phrenic nerve (PN) injury is the most frequently observed complication of cryoballoon pulmonary vein (PV) ablation.\(^1,2\) We recently described a novel approach involving the use of diaphragmatic electromyography to reduce PN injury whereby a reproducible supramaximal diaphragmatic compound motor action potential (CMAP) can be reliably recorded on a surface electrode during continuous PN pacing.\(^3\) The figure demonstrates a tracing during cryoballoon ablation of the right inferior pulmonary vein (RIPV). The 28 mm cryoballoon catheter is positioned at the RIPV ostium. A 20 mm Achieve circular mapping catheter (CMC) is positioned distally in the RIPV to ensure catheter stability and optimize PV ostium–cryoballoon contact. During ablation the PN was continuously stimulated from a quadripolar catheter positioned in the superior vena cava (1000 ms; 10 mA; 1 ms) resulting in the recording of a surface diaphragmatic CMAP (PHREN2). A signal associated with, yet distinct from, the pacing artefact was recorded on the CMC (PV 1,2 to 8,1; *). This signal was dissociated from the far-field atrial (α) and ventricular electrograms (β) yet simultaneous to the surface CMAP. Although PV potentials were recorded proximally at the PV ostium there were no pulmonary vein potential (PVPs) recorded in this very distal position. While mimicking the appearance of a PVP this signal is intrathoracic representation of the diaphragmatic CMAP as elicited by PN pacing. It is important to recognize that the possibility for recording diaphragmatic potentials with very distal CMC positions exists. Differentiation of diaphragmatic CMAPs from PVPs is important in the avoidance of unnecessary right-sided cryoapplications and PN injury.