International Journal of Cardiology 237 (2017) 19–21

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Short communication

Identifying high-risk post-infarction patients by autonomic testing — Below the tip of the iceberg

Axel Bauer *

Medizinische Klinik und Poliklinik I, Munich University Clinic, Munich, Germany
German Center for Cardiovascular Research (DZHK), Germany

ARTICLE INFO

Article history:
Received 8 March 2017
Accepted 13 March 2017
Available online 18 March 2017

Keywords:
Cardiac autonomic function
ECG
Heart rate variability
Implantable defibrillator myocardial infarction
Sudden cardiac death

ABSTRACT

Despite major advances in medical therapies late mortality after myocardial infarction (MI) is still high. A substantial proportion of post-MI patients die from sudden cardiac death. Prophylactic implantable-cardioverter defibrillator (ICD) therapy has been established for post-MI patients with reduced left ventricular ejection fraction (LVEF ≤35%). However, most patients who die after MI have an LVEF >35%. For this large group of patients, no specific prophylactic strategies exist. There is strong evidence that measures of cardiac autonomic dysfunction after MI provide important prognostic information in post-MI patients with preserved LVEF. Combinations of autonomic markers can identify high-risk patients after MI with LVEF >35% whose prognosis is equally worse than that of patients with LVEF ≤35%. The ongoing REFINE-ICD (NCT00673842) and SMART-MI trials (NCT02594488) test different preventive strategies in high-risk post-MI patients with cardiac autonomic dysfunction and LVEF 36–50%. While REFINE-ICD follows the traditional concept of ICD-implantation, SMART-MI uses implantable cardiac monitors with remote monitoring capabilities to sensitively detect asymptomatic, but prognostically relevant arrhythmias that could trigger specific diagnostic and therapeutic interventions.

1. The clinical problem

Sudden cardiac death (SCD) is the most common single cause of death in the industrialized world, claiming more than 4 million victims per year in Europe [1,2]. Most events occur in patients with structural heart disease, especially coronary artery disease (CAD) and after myocardial infarction (MI). It is assumed that up to 50% of cardiovascular deaths after MI occur suddenly and are thus potentially preventable by prophylactic implantation of a cardioverter-defibrillator (ICD).

Although the principle of prophylactic ICD-therapy has been invented by Michel Mirowski almost five decades ago [3], it was ignored for longtime by the medical community for various reasons. The publication of the successful MADIT-II study by Arthur Moss in 2002 could be seen as a milestone that paved the way towards the broad clinical adoption of prophylactic ICD-implantation [4]. The reason was not the efficacy of prophylactic ICD-implantation in terms of a 31%-mortality reduction *per se*, it was the simplicity of the study design that was convincing: patients after MI basically needed to fulfill only one criterion, by which they qualified for prophylactic ICD-implantation, namely that of a reduced left ventricular ejection fraction (LVEF ≤30%). Later, further trials confirmed the efficacy of prophylactic ICD-implantation in patients with reduced LVEF (≤35%) [5], leading to a class I recommendation by current guidelines [1].

From an epidemiological point of view, the impact of these trials on SCD-prevention is only moderate, since patients with a reduced LVEF (≤35%) represent just the tip of the SCD population iceberg. LVEF and SCD-incidence are inversely related, with the vast majority of SCD victims having only a moderately impaired or normal LVEF [6]. This is also true for post-infarction patients, where sensitivities of around 30% for the low-LVEF criterion have been reported [7]. Hence, in order to address the SCD problem after MI effectively, we need to develop prophylactic strategies in patients with preserved LVEF. However, this patient group is large and generally at low risk, making risk-stratification challenging. However, accurate identification of high-risk patients after MI with preserved LVEF is the most crucial step and considered as an unsolvable problem by many [1].

This article focuses on measures of cardiac autonomic function to predict risk after MI and describes traditional as well as novel strategies to prevent SCD in post-MI patients with preserved LVEF.

2. Measures of cardiac autonomic function to predict risk after MI

There is compelling evidence that important prognostic information after MI can be derived from the cardiac autonomic nervous system. Both, loss of vagal activity and sympathetic overactivity after MI have been linked to poor prognosis. Over the last decades various non-

* Medizinische Klinik und Poliklinik I, Munich University Clinic, Ziemssenstr. 1, 80336 München, Germany.
E-mail address: axel.bauer@med.uni-muenchen.de.

http://dx.doi.org/10.1016/j.ijcard.2017.03.087
0167-5273/

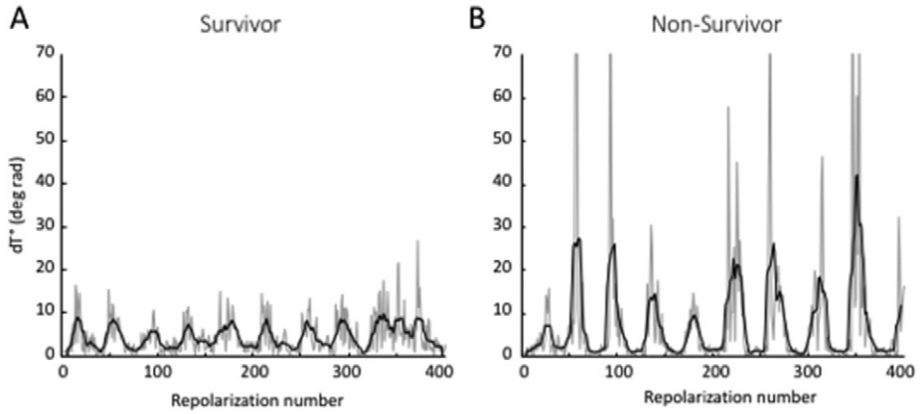

Fig. 1. Low-frequency (<0.1 Hz) oscillations of cardiac repolarization instability in a surviving post-infarction patient (A) and a post-infarction patient who suddenly died during follow-up (B). For assessment of repolarization instability, the spatio-temporal information of each T-wave is condensed into a three-dimensional vector and the angle between two successive vectors ($dT°$) is calculated. Thin gray lines show the pattern of $dT°$. Bold black lines show low-pass filtered signals.
Adapted from [11].

invasive and invasive measures including heart rate variability (HRV) [8], heart rate turbulence (HRT) [9] and baroreflex sensitivity (BRS) [10] have been proposed to quantify autonomic function and to predict risk. It is far beyond the scope of this article to review all methods in detail and to provide comparisons regarding their predictive values. All these measures consider changes of beat-to-beat (RR) intervals, either globally (HRV) or in response to specific triggering events (HRT, BRS), as read-out of autonomic activity. It might be a limitation that established measures assess autonomic activity at the level of the sinus node and not at the left ventricular myocardium where malignant arrhythmias arise.

Periodic Repolarization Dynamics (PRD) is a novel autonomic marker that substantially differs from the above-mentioned methods [11]. PRD refers to previously unknown oscillations of cardiac repolarization in the low-frequency range (<0.1 Hz, Fig. 1) and therefore does not rely on the analysis of RR-interval changes. Indeed, it could be shown by use of fixed atrial stimulation that PRD-oscillations occur independently from underlying heart rate variability [11]. Although the exact underlying physiological mechanisms need to be elucidated, existing data suggest that PRD reflects the ventricular response to phasic sympathetic activation which is known to take place in the low-frequency range [12]. This hypothesis is supported by pharmacological studies which showed that PRD is suppressed by blockade of beta-1 adrenergic receptors. Conversely, PRD is enhanced by physiological provocations that lead to sympathetic activation. In post-infarction patients and patients with stable CAD, increased PRD is associated with poor outcomes, independently from established risk factors including LVEF, HRV or T-wave alternans [11]. However, future studies are needed to test whether PRD might be a more specific marker of arrhythmic events (or mortality *per se*) than other markers of autonomic function.

Although single autonomic markers have been shown to provide strong and independent prognostic information in many studies, risk prediction can be optimized by combining measures that capture different facets of autonomic function. Strong combinations result from combinations of tonic and reflex-based measures, including *Severe Autonomic Failure* (combination of deceleration capacity [13] and heart rate turbulence) [7] and *Tonic and Reflex Vagal Activity* (combination of HRV and baroreflex sensitivity) [14]. Such combinations are very capable of identifying high-risk post-MI patients with preserved LVEF. Fig. 2 exemplarily shows risk prediction by the combination of deceleration capacity [13] and PRD [11], reflecting vagal and sympathetic function, that is also being used in the ongoing SMART-MI trial (see below).

3. Asymptomatic cardiac arrhythmias as precursors of life-threatening complications

The CARISMA study fundamentally expanded our knowledge of post-infarction arrhythmias [15] which may have important implications for future preventive strategies. CARISMA used implantable cardiac monitors (ICM) in 297 post-MI patients with LVEF ≤40% which

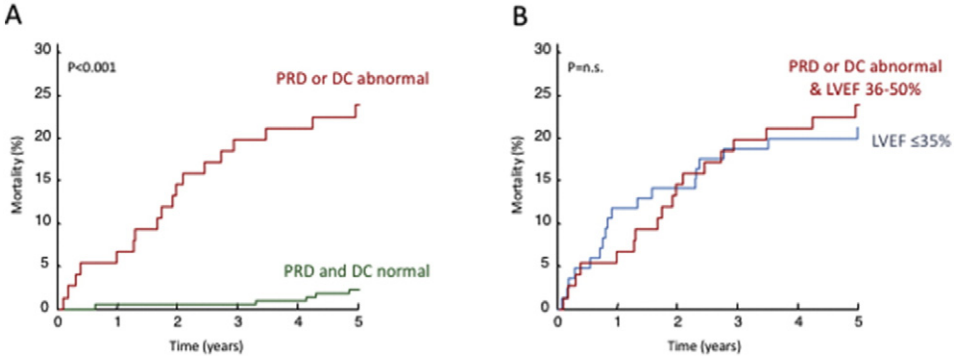

Fig. 2. Panel A: Risk stratification by means of Periodic Repolarization Dynamics (PRD ≥5.75 deg^2) and Deceleration Capacity (DC ≤2.5 ms) in post-infarction patients with low normal left ventricular ejection fraction (LVEF 36–50%). Panel B: Comparison of high-risk groups. Red curve shows mortality rate of patients with LVEF 36–50% and abnormal PRD or DC (same curve as in panel A). Blue curve shows mortality rate of patients with LVEF ≤35%.
Data from [11].

allowed to systematically document post-MI arrhythmias. Within two years of follow-up, predefined brady- and tachyarrhythmias were recorded in almost half (46%) of the patients. Almost one third of the patients (28%) developed new-onset atrial fibrillation and 10% experienced high-degree AV-block. The incidence of malignant tachyarrhythmias was lower (3%). Although most arrhythmias (86%) were asymptomatic, they had important prognostic implications, with bradyarrhythmias being the most important predictors of death [15]. New onset atrial fibrillation was associated with an increased risk of developing brady- and tachyarrhythmias [16]. Interestingly, cardiac autonomic dysfunction at baseline predicted both, new onset atrial fibrillation [17] and high degree AV-block [18].

4. Preventive strategies — traditional and novel concepts

Implanting ICDs in post-infarction patients at high risk for SCD appears to be the most logical approach. The REFINE-ICD trial (NCT00673842) follows that concept. Post-infarction patients (2–60 months after MI) with LVEF 36–50% are screened by Holter monitoring for the presence of cardiac autonomic dysfunction. 1000 patients with abnormal HRT [9] and abnormal T-wave alternans [19] are randomized to ICD-implantation or conventional follow-up.

In contrast, the ongoing multicenter, randomized SMART-MI trial (NCT02594488) follows a novel holistic approach. Survivors of MI may suffer from various complications in the years after MI that ultimately lead to death, including re-infarction, progression of heart failure, thromboembolic complications and arrhythmias. Although the final rhythm may be VT/VF in many cases, malignant arrhythmias are often sequelae of preceding complications. As learned from CARISMA [15], those complications are often preceded by asymptomatic arrhythmias, detectable by an ICM, which could serve as warning signals and open a time frame for preemptive interventions. In SMART-MI survivors of acute MI and LVEF of 36–50% are screened for the presence of cardiac autonomic dysfunction by means of abnormal deceleration capacity [13] or abnormal PRD [11] (see also Fig. 2). 400 high-risk patients are randomized to ICM-based remote monitoring or conventional follow-up. In case of predefined arrhythmias patients undergo immediate diagnostic evaluation. Predefined arrhythmias include arrhythmias that have either been shown to be associated with adverse outcomes (stroke, death) or fulfill established criteria for ICD-therapies (shock or ATP). Treatment paths have been developed for different kinds of arrhythmias and may include optimization of medical therapy, oral anticoagulation (in case of atrial fibrillation), revascularization or device therapy.

5. Conclusion

In conclusion, autonomic testing can identify high-risk post-infarction patients with preserved LVEF who have the same poor prognosis as patients with reduced LVEF. REFINE-ICD and SMART-MI are ongoing interventional trials that test different preventive strategies in these patients.

Conflicts of interests

Partial funding of the SMART-MI study is managed by Medtronic.

References

[1] S.G. Priori, C. Blomstrom-Lundqvist, A. Mazzanti, N. Blom, M. Borggrefe, J. Camm, et al., 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), Eur. Heart J. 36 (2015) 2793–2867.
[2] H.V. Huikuri, A. Castellanos, R.J. Myerburg, Sudden death due to cardiac arrhythmias, N. Engl. J. Med. 345 (2001) 1473–1482.
[3] M. Mirowski, M.M. Mower, W.S. Staewen, B. Tabatznik, A.I. Mendeloff, Standby automatic defibrillator. An approach to prevention of sudden coronary death, Arch. Intern. Med. 126 (1970) 158–161.
[4] A.J. Moss, W. Zareba, W.J. Hall, H. Klein, D.J. Wilber, D.S. Cannom, et al., Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction, N. Engl. J. Med. 346 (2002) 877–883.
[5] G.H. Bardy, K.L. Lee, D.B. Mark, J.E. Poole, D.L. Packer, R. Boineau, et al., Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure, N. Engl. J. Med. 352 (2005) 225–237.
[6] R.J. Myerburg, R. Mitrani, A. Interian Jr., A. Castellanos, Interpretation of outcomes of antiarrhythmic clinical trials: design features and population impact, Circulation 97 (1998) 1514–1521.
[7] A. Bauer, P. Barthel, R. Schneider, K. Ulm, A. Muller, A. Joeinig, et al., Improved Stratification of Autonomic Regulation for risk prediction in post-infarction patients with preserved left ventricular function (ISAR-Risk), Eur. Heart J. 30 (2009) 576–583.
[8] Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, Eur. Heart J. 17 (1996) 354–381.
[9] A. Bauer, M. Malik, G. Schmidt, P. Barthel, H. Bonnemeier, I. Cygankiewicz, et al., Heart rate turbulence: standards of measurement, physiological interpretation, and clinical use: International Society for Holter and Noninvasive Electrophysiology Consensus, J. Am. Coll. Cardiol. 52 (2008) 1353–1365.
[10] M.T. La Rovere, J.T. Bigger Jr., F.I. Marcus, A. Mortara, P.J. Schwartz, Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators, Lancet 351 (1998) 478–484.
[11] K.D. Rizas, T. Nieminen, P. Barthel, C.S. Zurn, M. Kahonen, J. Viik, et al., Sympathetic activity-associated periodic repolarization dynamics predict mortality following myocardial infarction, J. Clin. Invest. 124 (2014) 1770–1780.
[12] E. Pueyo, M. Orini, J.F. Rodriguez, P. Taggart, Interactive effect of beta-adrenergic stimulation and mechanical stretch on low-frequency oscillations of ventricular action potential duration in humans, J. Mol. Cell. Cardiol. 97 (2016) 93–105.
[13] A. Bauer, J.W. Kantelhardt, P. Barthel, R. Schneider, T. Makikallio, K. Ulm, et al., Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study, Lancet 367 (2006) 1674–1681.
[14] E. Vanoli, P.B. Adamson, S.S. Hull Jr., R.D. Foreman, P.J. Schwartz, Prediction of unexpected sudden death among healthy dogs by a novel marker of autonomic neural activity, Heart Rhythm. 5 (2008) 300–305.
[15] P.E. Bloch Thomsen, C. Jons, M.J. Raatikainen, R. Moerch Joergensen, J. Hartikainen, V. Virtanen, et al., Long-term recording of cardiac arrhythmias with an implantable cardiac monitor in patients with reduced ejection fraction after acute myocardial infarction: the Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) study, Circulation 122 (2010) 1258–1264.
[16] C. Jons, U.G. Jacobsen, R.M. Joergensen, N.T. Olsen, U. Dixen, A. Johannessen, et al., The incidence and prognostic significance of new-onset atrial fibrillation in patients with acute myocardial infarction and left ventricular systolic dysfunction: a CARISMA substudy, Heart Rhythm. 8 (2011) 342–348.
[17] C. Jons, P. Raatikainen, U.J. Gang, H.V. Huikuri, R.M. Joergensen, A. Johannesen, et al., Autonomic dysfunction and new-onset atrial fibrillation in patients with left ventricular systolic dysfunction after acute myocardial infarction: a CARISMA substudy, J. Cardiovasc. Electrophysiol. 21 (2010) 983–990.
[18] U.J. Gang, C. Jons, R.M. Jorgensen, S.Z. Abildstrom, M.D. Messier, J. Haarbo, et al., Risk markers of late high-degree atrioventricular block in patients with left ventricular dysfunction after an acute myocardial infarction: a CARISMA substudy, Europace 13 (2011) 1471–1477.
[19] R.L. Verrier, T. Klingenheben, M. Malik, N. El-Sherif, D.V. Exner, S.H. Hohnloser, et al., Microvolt T-wave alternans testing has a role in arrhythmia risk stratification, J. Am. Coll. Cardiol. 59 (2012) 1572–1573.