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Biosignal-guided personalized therapy

An application for cardiac risk stratification

Abstract: Sudden cardiac death (SCD) is the leading single cause of death in the industrialized world. Current guidelines recommend a prophylactic implantation of an implantable cardioverter-defibrillator (ICD) in patients with reduced left ventricular ejection fraction (LVEF ≤ 35%). However, most deaths after myocardial infarction (MI) occur in patients with normal or moderately reduced LVEF (>35%). There is a large body of evidence that cardiac autonomic dysfunction after MI is linked to increased susceptibility to malignant arrhythmias. Deceleration capacity of heart rate (DC) and periodic repolarization dynamics (PRD) are novel ECG-based risk markers, which capture different facets of cardiac autonomic dysfunction. Both parameters are strong and independent predictors of mortality and SCD after MI. Previous studies indicated that combined assessment of DC and PRD allows identification of a new high-risk group among post-infarction patients that is not addressed by current guidelines, thus opening new perspectives for biosignal-guided personalized therapies.

Keywords: sudden death - risk stratification - autonomic nervous system

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1 Introduction

Sudden cardiac death (SCD) is the leading single cause of death in the industrialized world [1], which is potentially preventable by prophylactic implantation of a cardioverter-defibrillator (ICD). Moss et al. [2] showed, that prophylactic ICD implantation in post-MI patients with reduced left ventricular pump function (left ventricular ejection fraction (LVEF) <30%) resulted in a 31% reduction of mortality. However, most deaths after MI occur in patients with normal or moderately reduced LVEF (>35%) [3], highlighting the need for refined risk stratification strategies.

Experimental and clinical trials showed, that dysfunction of the cardiac autonomic nervous system (ANS) has a major impact on the risk of SCD [4]. In general, increased sympathetic and/or depressed vagal activity are associated with a higher susceptibility to malignant arrhythmias.

The analysis of biological signals that are modulated by the ANS provides a non-invasive approach to diagnose cardiac autonomic dysfunction.

2 Measures of cardiac autonomic dysfunction

Over the last decades various ECG-based methods have been proposed to analyze the cardiac autonomic nervous system. Deceleration capacity (DC) and periodic repolarization dynamics (PRD) are novel ECG-based methods that are capable of separately assessing the vagal and sympathetic components of cardiac autonomic function [5] [6].

DC is an advanced measure of heart rate variability, thus basically analyzing autonomic innervation at the level of the sinus node. To obtain DC, the sequence of beat-to-beat (RR)-intervals is transformed into a new condensed signal, preserving deceleration-related oscillations of heart rate [7]. Figure 1 visualizes these oscillations for a low-risk (A) and a high-risk patient (B). DC is therefore predominantly a measure of tonic vagal activity.

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In contrast, PRD quantifies recently discovered low-frequency periodicities (<0.1Hz) of cardiac repolarization. It is known that efferent sympathetic nerve activity to the ventricles is organized in low-frequency bursts. These findings and recent results from computer-based models suggest that PRD most likely reflects the response of the ventricular cardiac myocytes to phasic sympathetic activity. For PRD-assessment, low-frequency beat-to-beat vector changes of cardiac repolarization are analyzed by means of wavelet-analysis. Figure 1 shows vector changes in a low-risk (C) and a high-risk patient (D), respectively. In the high-risk patient, low-frequency changes (black curve) are much more pronounced.

Both, DC and PRD, can be calculated from a 20-minute high-resolution resting surface ECG in frank lead configuration. Figure 2 shows risk stratification in post-infarction patients with moderately reduced left ventricular function by means of DC and PRD. Patients with abnormal DC and/or PRD but only moderately reduced LVEF have the same poor prognosis as patients with severely reduced LVEF. These patients therefore represent a new high-risk group of patients who might benefit from prophylactic treatments.

### 3 Personalized treatment strategies

The multicentre randomized “Implantable cardiac monitors in high-risk post-infarction patients with cardiac autonomic dysfunction and moderately reduced left ventricular ejection fraction” trial (SMART-MI) tests a novel personalized preventive strategy in high-risk patients identified by abnormal DC and/or PRD. The rationale of the trial is based on findings of the “Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction” trial (CARISMA, [8]) which showed by means of implantable cardiac monitors (ICM) that adverse events including death are preceded by mostly asymptomatic arrhythmic events, including paroxysmal atrial fibrillation, higher degree AV-block or non-sustained ventricular tachycardias. This possibly opens a “window of opportunity” for preventive interventions.

In SMART-MI (flow-chart shown by Figure 3), post-infarction patients with LVEF 36-50% are screened for presence of cardiac autonomic dysfunction by means of a 20-minute resting ECG. High-risk patients identified by abnormal DC and/or PRD are 1:1 randomized to implantation of an ICM. In the ICM arm possible arrhythmias are daily transmitted to an ICM-core lab. In case of predefined serious arrhythmic events the local study center is informed within 48 hours and can take care of the patient. Specific treatment paths have been developed for different kind of arrhythmias.

The study includes 16 centers across Germany. First results are expected in 2018.
SMART-MI will provide the basis for novel preventive strategies in high-risk patients based on remote monitoring. In many patients with heart failure devices are implanted that are capable of continuously recording intracardiac EGMs. This opens the perspective to implement diagnostic algorithms into the devices allowing continuous ANS assessment. We are currently working on a modification of the three-dimensional PRD algorithm that could be implemented in implanted CRT (cardiac resynchronization therapy) devices. First results suggest that PRD may also be obtained from the leads of a CRT device.

Author’s Statement
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References