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Electrocardiographic predictors of mortality and sudden cardiac death in patients with end stage renal disease on hemodialysis ☆

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Abstract Patients with end stage renal disease (ESRD) on hemodialysis experience a high incidence of cardiovascular mortality, and sudden cardiac death (SCD) accounts for approximately 25% of all deaths in this patient population. Despite this high risk of SCD, many non-invasive SCD risk stratification tools that are frequently applied to other patient populations (such as those with prior myocardial infarction and reduced left ventricular systolic function) may be less useful markers of increased SCD risk in ESRD. Improved SCD risk stratification tools for use specifically in patients on hemodialysis are therefore necessary to optimally target use of primary prevention interventions aimed at decreasing SCD incidence. Electrocardiography is an effective, non-invasive SCD risk stratification tool in hemodialysis patients. This article reviews data supporting the association between various ECG parameters (QT interval, spatial QRS-T angle, signal averaged ECG, heart rate variability, and T-wave alternans) and mortality/SCD in the dialysis population. Despite the association between abnormal ECG parameters and SCD, it remains unclear if these abnormal parameters (such as prolonged QT interval) are mechanistically related to SCD and/or ventricular arrhythmias, or if they are simply markers for more severe cardiac disease, such as left ventricular hypertrophy, that may independently predispose to SCD. Current obstacles that impair widespread implementation of ECG risk stratification in the hemodialysis population are also discussed.

Keywords: Electrocardiogram; Hemodialysis; End stage renal disease; Sudden cardiac death; Arrhythmia; Conduction abnormality; Cardiovascular disease

Sudden cardiac death (SCD) accounts for approximately 25% of deaths in patients with end stage renal disease (ESRD), with an incidence of approximately 50 events per 1000 person-years [1]. Although chronic kidney disease is an independent risk factor for cardiovascular disease, factors beyond coronary atherosclerosis contribute to this disproportionately elevated SCD risk, as treatment of cardiovascular risk factors and coronary revascularization in ESRD patients have not resulted in reduced rates of cardiovascular mortality or SCD [2,3]. The majority of dialysis patients have preserved left ventricular systolic function [4], and left ventricular ejection fraction (LVEF), which is the foundation of SCD risk stratification in patients with prior myocardial infarction or non-ischemic cardiomyopathy, has poor sensitivity for SCD in ESRD patients. Chronic uremia in ESRD patients results in diffuse myocardial fibrosis, coronary calcification, left ventricular hypertrophy (LVH), endothelial dysfunction [5], and autonomic dysfunction [6], all of which increase the risk of ventricular arrhythmia independent of LVEF.

SCD is frequently the result of lethal ventricular arrhythmias secondary to abnormalities in ventricular conduction or repolarization. The electrocardiogram (ECG), which can identify some of these arrhythmogenic electrical abnormalities (Fig. 1), is therefore a potentially useful SCD risk stratification tool [7]. This review will summarize data supporting use of the ECG as a SCD risk stratification tool in patients with ESRD on hemodialysis, and will discuss future challenges related to widespread deployment of ECG risk stratification in this population.

QT interval

The QT interval (or heart rate corrected QT interval (QTc)) reflects the total duration of ventricular depolarization and repolarization. Since the duration of ventricular depolarization (as reflected by QRS duration) is usually relatively fixed,

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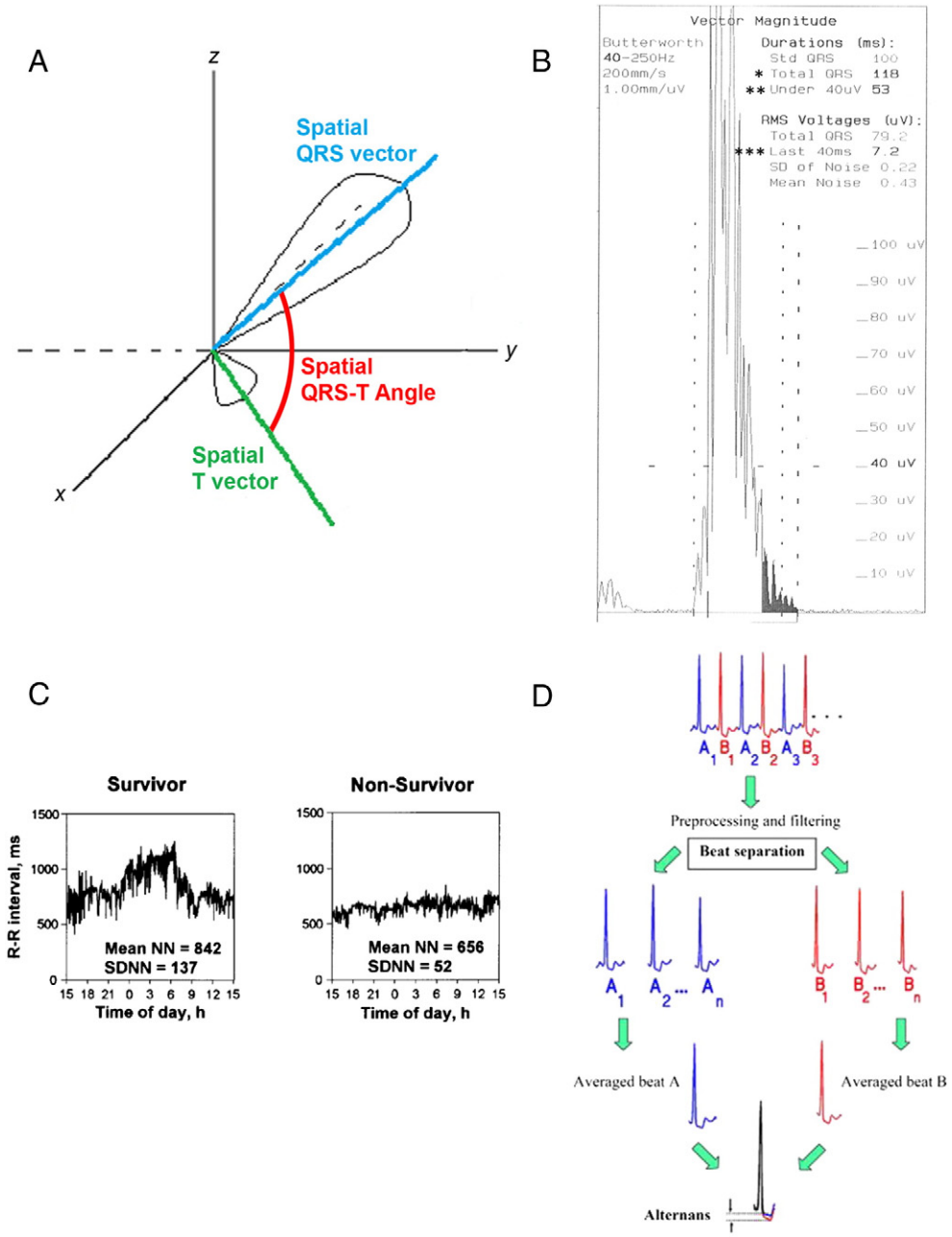

Fig. 1. Selected ECG parameters associated with total mortality and sudden death in hemodialysis patients. A: Spatial QRS-T angle is the 3-dimensional angle between the spatial QRS vector and the spatial T vector. Adapted with permission from Oehler et al. [19]. B: Example of an abnormal signal averaged ECG. The filtered QRS complex, which is the vector magnitude ($\sqrt{X^2 + Y^2 + Z^2}$) of orthogonally recorded X-, Y-, and Z- ECG leads after signal averaging over many cardiac cycles and filtering, is displayed. The duration of the filtered QRS complex (denoted by *) is abnormally prolonged at 118 ms (normal ≤114 ms). The duration of low amplitude signals in the terminal part of the filtered QRS complex that are less than 40 μV (denoted by **) is abnormally long at 53 ms (normal ≤38 ms). The root mean square (RMS) voltage in the terminal 40 ms of the filtered QRS complex (denoted by ***) is abnormally low at 7.2 μV (normal ≥20 μV). C: Heart rate variability: standard deviation of RR intervals (SDNN). The graphs represent plots of RR intervals over a 24-h period in 2 separate patients. SDNN is also displayed. The survivor has a larger SDNN (137 ms) than the patient who died of SCD (52 ms). Reproduced with permission from Fukuta et al. [50]. D: T wave alternans: signal averaging and filtering techniques are used on alternating QRS complexes (denoted by A beats and B beats) over many cardiac cycles. The average A beat and average B beat are then compared. T wave alternans is calculated as the difference between the ST-T segments in the average A beat and average B beat. Reproduced with permission from Verrier et al. [37].

short-term variations in QT interval therefore primarily reflect variations in the duration of ventricular repolarization. The QT interval is dynamic and highly variable; electrolyte shifts (especially potassium, calcium, and magnesium) [8], acidosis, various medications, co-existing cardiac disease (especially left ventricular hypertrophy [9]), changes in autonomic tone, and genetics all can influence QT interval. Women also tend to have slightly longer QT intervals than men. A prolonged QTc interval has been associated with SCD and ventricular arrhythmias in various populations [10]. The QT/QTc interval is readily available and easy to assess, and therefore is an attractive SCD risk stratification parameter.

Many patients with ESRD have a prolonged QT/QTc interval, and studies investigating changes in QTc associated