CHAPTER V

Incremental Prognostic Value of an Abnormal Baseline Spatial QRS-T Angle in Chronic Dialysis Patients

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ABSTRACT

Aims: In order to improve the abysmal outcome of dialysis patients, it is critical to identify patients with a high mortality risk. The spatial QRS-T angle, which can be easily calculated from the 12 lead electrocardiogram (ECG), might be useful in the prognostication in dialysis patients. The objective of this study was to establish the prognostic value of the spatial QRS-T angle.

Methods and results: All patients who initiated dialysis therapy between 2002 and 2009 in the hospitals of Leiden (LUMC) and Amsterdam (AMC) at least 3 months on dialysis were included. The spatial QRS-T angle was calculated, from a routinely acquired ECG, and its relationship with mortality was assessed. An abnormal spatial QRS-T angle was defined as ≥130° in men and ≥116° in women. In total, 277 consecutive patients (172 male, mean age 56.3 ± 17.0) were included. An abnormal spatial QRS-T angle was associated with a higher risk of death from all causes [hazard ratio (HR) 2.33; 95% confidence interval (CI) 1.46–3.70] and especially a higher risk of sudden cardiac death (HR 2.99; 95% CI 1.04–8.60). Furthermore, an abnormal spatial QRS-T angle was of incremental prognostic value, when added to a risk model consisting of known risk factors.

Conclusion: In chronic dialysis patients the spatial QRS-T angle is a significant and independent predictor of all-cause and especially sudden cardiac death. It implies that this parameter can be used to identify high risk patients.

INTRODUCTION

With an annual mortality of ~20%, the prognosis of dialysis patients remains poor, despite numerous interventions that have been studied in the past decade.[1–5] In particular, sudden cardiac death (SCD) has been put forward as an important contributor to all-cause mortality.6 It has been reported, in both large observational registries and prospective trials with adjudicated end points, that SCD accounts for ~25% of all-cause mortality.[2] Identification of dialysis patients at risk for increased mortality, especially SCD, therefore is essential to design new therapeutic strategies.[7–10]

For the identification of patients at risk for mortality, in particular at risk for SCD, the spatial QRS-T angle has recently gained renewed interest. This vectorcardiographic parameter, which can be easily synthesized from a standard 12 lead electrocardiogram (ECG),[11] describes cardiac repolarization and its relation to the preceding depolarization[12] and has proven to have predictive value for (cardiovascular) mortality. For instance, in the general population as well in some clinical settings, such as post-infarction patients, it has been reported that larger values of the spatial QRS-T angle are associated with all-cause mortality and cardiac events.[13–16]

In dialysis patients currently little is known regarding the clinical value of the spatial QRS-T angle. However, a recent exploratory study published by Jaroszynski et al.[17] documents that in a small group of 57 selected peritoneal dialysis (PD) patients spatial QRS-T angle was larger compared with a group of control patients and could be associated to coronary artery calcium burden.

The objective of the current study is to test whether in a consecutive cohort of dialysis patients the spatial QRS-T angle was associated with mortality, especially SCD.

METHODS

Subjects

For this study patients were included from the university hospitals of Leiden (Leiden University Medical Center) and Amsterdam (Academical Medical Center). All consecutive patients who initiated haemodialysis (HD) or PD therapy between January 2000 and December 2009 and who remained >3 months on dialysis therapy were included.

Electrocardiograms

Routine acquisition of ECGs is common practice in dialysis patients. For the current analysis the first routinely acquired ECG, after a patient became dependent on dialysis therapy, was used. Electrocardiograms related to cardiac hospitalization were not considered routinely acquired. If the ECG was not suitable for analysis due to poor technical quality of the ECG (electrode displacement, missing leads, or signal noise) the next available ECG was used. If there was no ECG available for analysis, within the first 18 months after initiation of the

dialysis therapy, the patient was excluded. Electrocardiograms showing pacemaker rhythm were also considered not suitable for analysis.

Electrocardiographic analysis

In both institutions all ECGs are electronically stored in an ECG database management system. For the spatial QRS-T angle measurement ECGs were exported from this storage system and analysed with the MATLAB-based (The MathWorks, Natick, MA, USA) computer program LEADS (Leiden ECG Analysis and Decomposition Software). Details on the technical background of LEADS have been reported previously.[18,19] In short, in a largely automatic process, the software averages the standard 10 s ECG into one single beat and then subsequently converts this beat into a vectorcardiographic beat. The software calculates this vectorcardiographic beat by multiplying the 12-lead ECGs by the inverse Dower matrix.[20] In addition to heart rate, QRS duration, and QT interval, the software also calculates the magnitude and orientation of the mean QRS and T vectors on the vectorcardiogram and consequently calculates the angle between these vectors. An abnormal spatial QRS-T angle was, based on the normal limits derived by Scherptong et al.,[19] defined as a spatial QRS-T angle >116° for females and a spatial QRS-T angle >130° in male subjects.

Left ventricular hypertrophy (LVH) was defined according to the Sokolow–Lyon criterium (S in V1 + R in V5 or V6 >34 mm or R in aVL ≥ 11 mm).

Definitions

Mortality was adjudicated, by two reviewers, unaware of the patients' spatial angle, using both hospital and general practitioner records. Cardiovascular mortality was defined as SCD, death due to acute myocardial infarction (MI) or death due to congestive heart failure. Death was considered sudden when (i) a subject apparently well, is observed to have died within a few minutes from the onset of symptoms and if the cause of death cannot reasonably be attributed to some potentially lethal disease; (ii) if the patient was found dead after an unwitnessed event with no other cause of death identifiable and if the patient had been in his or her usual state of health without any symptoms when last observed.[21] Death due to MI was based on criteria of typical chest pain, elevated cardiac enzyme levels, and typical changes on the ECG.[22] Death following new onset, or worsening heart failure was defined as death due to congestive heart failure. Death due to any other reason was considered non-cardiovascular.

Statistical analysis

Continuous data were expressed as mean ± SD and compared with the two-tailed Student's t-test for unpaired data. Categorical data were compared using the χ^2 test. A survival analysis comprising all-cause mortality and SCD was performed. Cumulative event rates were assessed using the method of Kaplan–Meier and log rank test. Relationships between

baseline parameters and endpoints were analysed with Cox proportional hazard regression analysis. Patients were censored on the day of their last dialysis if they underwent renal transplantation. All statistical analyses were performed in SPSS version 16.0.

RESULTS

Patients and follow-up

A total of 353 patients with end-stage renal disease that initiated dialysis therapy and remained > 3 months on dialysis therapy were identified. In this group, 299 had a routine ECG made available within 18 months after initiating dialysis therapy. A total of 22 patients had to be excluded because their ECG was not suitable for analysis (16 due to poor ECG quality, 6 due to pacemaker rhythm). The remaining 277 were included in this analysis. During a mean follow-up of 2.1 ± 1.7 years 91 of the 277 patients died (15.5/100 patient-years). Cause of death was cardiovascular in 25 [4.3/100 patient-years; with SCD accounting for 18 out of 25 (68%) deaths], infection in 28 (4.8/100 patient-years), malignancy in 11 (1.9/100 patient-years), refusal of therapy in 11 (1.9/100 patient-years), and other in 16 patients (2.7/100 patient-years).

Baseline characteristics

An abnormal spatial QRS-T angle was documented in 96 (34.7%) of all patients. As summarized in Table 1, patients with an abnormal spatial QRS-T angle were older (60.2 ± 14.8 vs. 54.3 ± 17.8 years), more likely to have a history of hypertension (82.3 vs. 68.5%), diabetes mellitus (43.8 vs. 26.0%), coronary artery disease (42.7 vs. 14.9%), and to have severe heart failure (documented ejection fraction of <35%, 12.1 vs. 1.7%). Patients with an abnormal spatial QRS-T angle were also more likely to be on β-blocker therapy (61.5 vs. 43.1%). With regard to other ECG variables, in patients with an abnormal spatial QRS-T angle, heart rate was significantly higher (81.8 ± 19.5 vs. 75.1 ± 13.8 b.p.m.) and both QRS duration and QTc interval were significantly longer (104.9 ± 21.7 vs. 95.7 ± 14.4 ms and 437.2 ± 33.7 vs. 423.0 ± 30.3 ms respectively) compared with patients with a normal spatial QRS-T angle. Furthermore, patients with an abnormal spatial QRS-T angle were more likely not to be in sinus rhythm, to have Q-waves and LVH (8.3 vs. 2.7%, 20 vs. 5%, and 30 vs. 14%, respectively). With regard to the timing of acquisition of the ECG there was no difference between the two groups (142 ± 128 vs. 130 ± 138 days, P = 0.49).

The spatial QRS-T angle and all-cause mortality

The cumulative survival for patients with a normal spatial QRS-T angle, 92.7% [95% confidence interval (CI) 88.8—96.6%] at 1 year and 57.5% (95% CI 45.1–69.9%) at 5 years follow-up, respectively, was significantly higher compared with the cumulative survival in patients with an abnormal spatial QRS-T angle, 66.8% (95% CI 56.8–76.8%) at 1 year and 29.3% (95% CI 16.2–42.4%) at 5 years follow-up, respectively (P < 0.001). See Figure 1.

Table 1: *Baseline characteristics*

	All (n=277)	Normal angle (n=181)	Abnormal angle (n=96)	P-value
Age, years	56.3±17.0	54.3±17.8	60.2±14.8	0.006
Male Gender	172(62.1%)	112(61.9%)	60(62.5%)	0.92
Hemodialysis at initiation†	174(62.8%)	110(60.8%)	64(66.7%)	0.334
Dialysis vintage, days	139±131	142±128	130±138	0.49
Hypertension	203(73.3%)	124(68.5%)	79(82.3%)	0.014
Diabetes mellitus	89 (32.1%)	47(26%)	42(43.8%)	0.003
Coronary artery disease	68 (24.5%)	27 (14.9%)	41 (42.7%)	<0.001
History of severe heart failure*	14(5.1%)	3(1.7%)	11(12.1%)	<0.001
History of smoking	65(23.5%)	36(19.9%)	29(30.2%)	0.054
Medication				
β-Blocker	137(49.5%)	78(43.1%)	59(61.5%)	0.004
ACEi/ARB	161(58.1%)	100(55.2%)	61(63.5%)	0.18
Calcium channel-antagonist	115(41.5%)	72(39.8%)	43(44.8%)	0.42
Statin	141(50.9%)	84(46.4%)	57(59.4%)	0.04
Not in sinus rhythm	13 (4.7%)	5 (2.7%)	8 (8.3%)	0.037
Heart rate (bpm)	77.4±16.3	75.1±13.8	81.8±19.5	0.001
QRS duration (ms)	98.9±17.8	95.7±14.4	104.9±21.7	<0.001
QTc interval (ms)	427.9±32.2	423.0±30.3	437.2±33.7	0.001
Q-waves	28 (10.1%)	9 (5.0%)	19 (19.8%)	<0.001
LVH	54 (19.5%)	25 (13.8%)	29 (30.2%)	0.001
Spatial angle (°)	103.5±41.2	79.4±28.1	149.1±14.9	<0.001

†Remaining patients initiated with peritoneal dialysis; * Documented ejection fraction <35%; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; HD = hemodialysis; LVH = left ventricular hypertrophy;

Absolute incidence of death was 10.0 per 100 patient-years in patients with a normal spatial QRS-T angle compared with 28.4 per 100 patient-years in patients with an abnormal spatial QRS-T angle.

In order to control for possible confounders multivariate analysis was performed using a model consisting of univariate predictors of mortality. As shown in Table 2, age, type of dialysis, coronary artery disease, diabetes mellitus, not in sinus rhythm, heart rate, QRS duration, and presence of Q-waves were univariate predictors of mortality. After multivariate analysis, age [hazard ratio (HR) 1.04, $P < 0.01$], heart rate (HR 1.16 per 10 b.p.m. increase; $P < 0.01$) and an abnormal spatial QRS-T angle (HR 2.33, $P < 0.01$) remained significant predictors of all-cause mortality. Furthermore, an abnormal spatial QRS-T angle added incremental value to the prognostic stratification achieved with a model consisting of baseline clinical parameters (age, type of dialysis, coronary artery disease, diabetes mellitus,

not in sinus rhythm, heart rate, QRS duration, and presence of Q-waves). When added to the model the global χ^2 increased from 59.1 to 71.7 ($P < 0.001$).

Table 2: *Uni- and multivariate predictors of all-cause mortality*

Parameter	Univariate HR	P	Multivariate HR	P
Age	1.04 (1.03 – 1.06)	<0.001	1.04 (1.03 – 1.06)	<0.01
Male Gender	1.00 (0.80 – 1.23)	0.96		
HD vs. PD	1.33 (0.85 – 2.08)	0.22	0.94 (0.58 – 1.52)	0.81
Diabetes Mellitus	1.32 (0.86 – 2.01)	0.20	0.94 (0.58 – 1.46)	0.72
Coronary artery disease	1.89 (1.22 – 2.93)	0.005	0.95 (0.57 – 1.59)	0.84
History of severe heart failure*	1.22 (0.53 – 2.76)	0.66		
Not in sinus rhythm	4.08 (2.10 – 7.93)	<0.001	1.92 (0.92 – 4.01)	0.09
Heart rate (10 bpm increase)	1.14 (1.01 – 1.27)	0.03	1.16 (1.04 – 1.29)	<0.01
QRS (10ms increase)	1.17 (1.06 – 1.29)	0.002	1.06 (0.94 – 1.19)	0.36
Q-waves on ECG	1.62 (0.90 – 2.91)	0.11	1.02 (0.55 – 1.92)	0.94
LVH on ECG	1.24 (0.77 – 1.99)	0.38		
Abnormal Spatial QRS-T angle	2.82 (1.86 – 4.26)	<0.001	2.33 (1.46 – 3.70)	<0.01

In the multivariate analyses, all parameters with a $p < 0.25$ were entered. * Documented ejection fraction <35%; HD = hemodialysis; LVH = left ventricular hypertrophy; MI = myocardial infarction; PD = peritoneal dialysis.

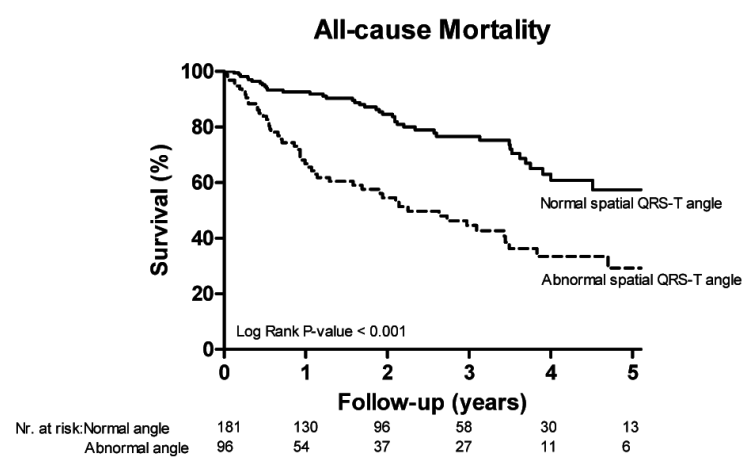

Figure 1: *Cumulative incidence of all-cause mortality*
Kaplan-Meier curve analysis showing the difference in survival between patients with a normal and an abnormal spatial QRS-T angle.

Sudden Cardiac death

Sub analyses were performed to assess the prognostic value of an abnormal spatial QRS-T angle with regard to cardiovascular mortality in particular. As shown in Figure 2 the cumulative incidence of SCD was significantly higher in patients with an abnormal spatial QRS-T angle. After 1 year the cumulative probability SCD was 9.6% (95% CI 2.7–16.5%) after 1 year and 26.9% ± (11.8–42.0%) after 5-year follow-up in patients with an abnormal spatial QRS-T angle, compared with 1.8% ± (95% CI 0–4.0%) and 6.5% (95% CI 0.3–12.7%) in patients with a normal spatial QRS-T angle ($P < 0.001$). See Figure 2. Absolute incidence of SCD was 1.5 per 100 patient-years in patients with a normal spatial QRS-T angle compared with 6.8 per 100 patient-years in patients with an abnormal spatial QRS-T angle. In order to control for possible confounders multivariate analysis was performed using a model consisting of univariate predictors of SCD. Table 3 shows both the univariate and multivariate analysis which demonstrated that age, coronary artery disease, not being in sinus rhythm, LVH on the ECG, and an abnormal spatial QRS-T angle were univariate predictors for SCD. After controlling for univariate predictors of SCD age (HR 1.04 $P < 0.05$), LVH on the ECG (HR 2.94; $P < 0.05$), and an abnormal spatial angle (HR 2.99; $P < 0.05$) were independent predictors of SCD. An abnormal spatial QRS-T angle was of incremental value to the prognostic stratification model for SCD consisting of baseline parameters (age, coronary artery disease, not being in sinus rhythm, and LVH on the ECG). When added to the model there was a significant increase in the global χ^2, from 26.2 to 30.3 ($P = 0.037$).

Table 3: *Uni- and multivariate predictors of Sudden Cardiac Death*

Parameter	Univariate HR	P	Multivariate HR	P
Age	1.04 (1.01 – 1.09)	<0.01	1.04 (1.00 – 1.08)	<0.05
Male Gender	1.88 (0.62 – 5.74)	0.27		
HD vs. PD	1.95 (0.64 – 5.92)	0.24		
Diabetes Mellitus	0.59 (0.19 – 1.78)	0.35		
Coronary Artery Disease	2.75 (1.08 – 7.00)	0.03	1.14 (0.40 – 3.25)	0.80
History of severe heart failure*	1.02 (0.14 – 7.67)	0.99		
Not in sinus rhythm	6.40 (1.82 – 22.48)	<0.01	2.75 (0.68 – 11.18)	0.16
Heart rate (10 bpm increase)	1.20 (0.94 – 1.53)	0.14		
QRS (10ms increase)	1.15 (0.91 – 1.44)	0.24		
Q-waves on ECG	1.18 (0.27 – 5.11)	0.83		
LVH on ECG	3.62 (1.43 – 9.14)	<0.01	2.94 (1.12 – 7.75)	0.03
Abnormal Spatial QRS-T angle	4.51 (1.69 – 12.02)	<0.01	2.99 (1.04 – 8.60)	0.04

In the multivariate analyses, all parameters with a $p < 0.25$ were entered. * Documented ejection fraction <35%; HD = hemodialysis; LVH = left ventricular hypertrophy; MI = myocardial infarction; PD = peritoneal dialysis.

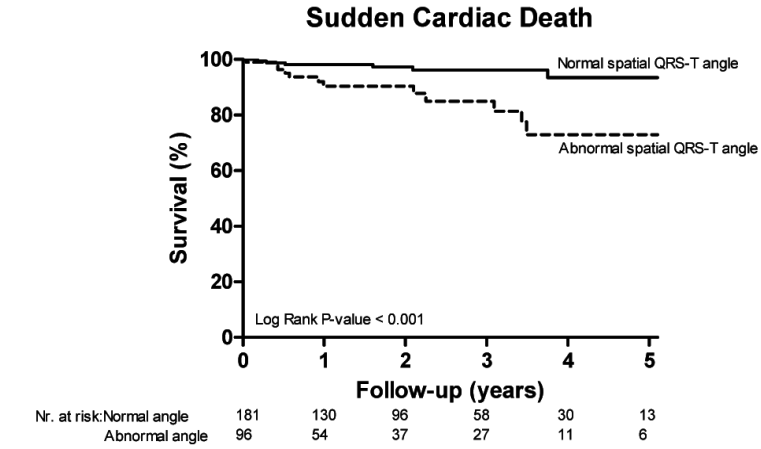

Figure 2: *Cumulative incidence of Sudden Cardiac Death*
Kaplan-Meier curve analysis showing the difference in the cumulative incidence of Sudden Cardiac Death between patients with a normal and an abnormal spatial QRS-T angle.

DISCUSSION

This study demonstrates that impairment in cardiac conduction, reflected by an abnormal spatial angle, is associated with poor outcome in dialysis. The spatial QRS-T angle, (semi-) automatically calculated from the first routinely acquired ECG, can be considered a strong and independent risk factor for all-cause mortality and in particular for SCD in chronic dialysis patients. Furthermore, the spatial QRS-T angle is of incremental value to the prognostication in dialysis patients, when added to other known risk factors for all-cause mortality and SCD such as not being in sinus rhythm and LVH.[23]

Acquisition of the spatial QRS-T angle

Although classical acquisition of vectorcardiograms is not common practice anymore, vectorcardiograms can be easily and automatically reconstructed using the standard 12-lead ECG. Most current electrocardiographs are probably capable of automatically calculating the spatial QRS-T angle. Therefore, this parameter is an inexpensive, easily available and non-invasive screening tool to identify dialysis patients at increased risk for mortality and especially for SCD.

Previous reports used slightly different cut-offs for the QRS-T angle compared with the cut-offs used in the current paper.[14,16] These cut-offs based on normal values were previously established in a study that included 510 patients that were hospitalized for reasons other than cardiovascular disease.[24] More recently Scherptong et al.[19] however conducted a study in a group of 660 healthy students (male and female) and they found that the previously established normal values might be too strict and more importantly that significant differences exist between males and females. Especially to also take into account the

differences between males and females, these more recently proposed cut-offs were used in this study.

The spatial QRS-T angle and the relation with sudden cardiac death

The risk for SCD was significantly higher for patients with an abnormal baseline spatial QRS-T angle indicating that this parameter identifies dialysis patients prone for cardiac arrhythmic death. This relationship between the spatial QRS-T angle and arrhythmic events can be explained by the fact that the spatial QRS-T angle may reflect subclinical damaged areas of the myocardium. These damaged areas may influence the spread of electrical forces through the myocardial wall which could result in ventricular arrhythmias. Therefore, patients with an abnormal spatial QRS-T angle might be prone to the development of ventricular arrhythmias. This hypothesis was underscored by Kardys et al. who documented that in the general population, next to all-cause mortality, an abnormal spatial QRS-T angle is also a strong and independent predictor of SCD. They documented a 5.6-fold increased risk of sudden death in patients with an abnormal spatial QRS-T angle.[16] The findings of Borleffs et al. further underline the association between the spatial angle and arrhythmic events. In a population of implantable cardioverter defibrillator (ICD) recipients they documented that, after adjustment for several clinical parameters, patients with a wide spatial QRS-T angle had a seven-fold higher risk for the occurrence of appropriate ICD therapy.[15]

This relationship of the spatial QRS-T angle with arrhythmic events makes it of particular interest for the dialysis population given the proposed high incidence of SCD in this vulnerable patient population.[6] The mechanisms that underlie this high risk for SCD in dialysis patients are complex and not yet completely understood. However, next to the traditional risk factors associated with SCD in the general population, such as ischaemic heart disease,[25] there are several more dialysis specific risk factors and circumstances which have been proposed to be associated with SCD. These factors include: LVH, rapid electrolyte, and fluid shifts in HD patients, and abnormalities in myocardial ultrastructure and function, including endothelial dysfunction, interstitial fibrosis, and sympathethic overactivity.[2,26,27]

These risk factors are known to have considerable effects on cardiac cell excitability and it is therefore not surprising that it has been reported that dialysis patients have wider spatial QRS-T.[17]

Study limitations

There were several limitations for the current analysis. First, this was a retrospective study and thereby subject to possible biases associated with studies of this kind. Secondly, although routine acquisition of ECGs is common practice in dialysis patients, the time window between the initiation of dialysis and acquisition of the ECG might vary between patients. However, there were no differences with regard to this time window between

patients with and without an abnormal spatial QRS-T angle and therefore the impact of this drawback is probably limited. It can also be considered a limitation that there is no comparison with other important prognostic tools such as for instance echocardiography, myocardial perfusion imaging or even coronary angiography. Although these tools have also proven to give valuable information regarding prognosis and outcome it should be also taken into account that these tools are more expensive, more invasive, and less available. An ECG can be acquired in all patients, at any time, at virtually no cost, thereby making it a very feasible tool to rapidly screen for high risk patients. In our opinion, the results of this study do not make these kind of diagnostic tools obsolete but rather identify patients who could benefit most from these more invasive, expensive, and less available screening modalities. Finally, the sample size of the current study population is smaller than other non-dialysis patient populations in which the predictive value of the QRS-T angle was investigated. Nevertheless, the population was large enough to significantly demonstrate a predictive value for the spatial QRS-T angle. Furthermore, it should be taken into consideration that this study investigates a very specific patient population and is the first to demonstrate the clinical value of this parameter among this vulnerable patient group.

IMPLICATIONS AND CONCLUSIONS

The spatial QRS-T angle is a simple tool that allows baseline risk assessment of patients initiating dialysis therapy. Identification of vulnerable dialysis patients may help identify those patients that could benefit from further clinical evaluation using more advanced and invasive techniques (such as for instance coronary catheterization and modern imaging techniques) and furthermore could benefit from treatment options geared towards creating electric stability in the heart (e.g. anti-arrhythmic drugs and intensivation of dialysis treatment) or prevention of electric instability that leads to SCD (e.g. use of ICDs).
This study also confirms the high incidence of SCD among dialysis patients and moreover the association of the spatial QRS-T angle with SCD points towards an important role for cardiac arrhythmias in the poor prognosis of dialysis patients. This latter finding warrants future research in this area.
In conclusion, impaired cardiac conduction, reflected by an abnormal spatial QRS-T angle is an important risk factor for mortality in dialysis patients. Especially, there is an increased risk of SCD compared with patients with a normal spatial QRS-T angle at initiation of dialysis therapy.

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