Ventricular Arrhythmias in Dialysis Patients

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The occurrence of ventricular arrhythmias is common in renal failure patients who are receiving long-term hemodialysis. Associated ventricular arrhythmias may account for a major component of the cardiovascular mortality in hemodialysis patients. In the literature, a number of factors have been implicated in the genesis of these arrhythmias. Postulated theories range from hemodynamic alterations induced by dialysis, to metabolic alterations and derangements, to the molecular level of the current alterations in the L-type calcium channels of the heart. Studies have been conducted to ascertain whether testing, with signal-averaged electrocardiograms or electrophysiologic studies, can help to predict whether certain patients with renal failure might be more at risk for developing the complex arrhythmias noted in a large proportion of renal failure patients undergoing dialysis. This article examines the literature with regard to possible predictors in terms of patient characteristics, risk factors, electrophysiologic variables, and even dialysis method, all of which may play a part in determining the likelihood of a patient developing a ventricular arrhythmia.

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Ventricular arrhythmias are common in renal failure patients treated with long-term hemodialysis[1-6] and the risk for arrhythmia is known to increase during the course of hemodialysis therapy.[3,4] This significant proportion of patients with renal failure who are affected by ventricular arrhythmias may account for a major component of the cardiovascular mortality in hemodialysis patients. Identifying and stratifying the factors contributing to this increased incidence of arrhythmia in dialysis patients is central to decreasing their cardiovascular morbidity and mortality.

A number of factors have been implicated in the literature for the genesis of these arrhythmias. The theories postulated have ranged from hemodynamic alterations induced by dialysis, to metabolic alterations and derangements, to even the molecular level of current alterations in the L-type calcium channels in the heart during dialysis. Arterial hypertension, which can frequently occur in renal failure patients secondary to volume overload, has been known to be a risk factor for the development of complex arrhythmias. Along with hypertension, the presence of left ventricular hypertrophy has also been implicated in the development of arrhythmias.

Studies have been conducted to ascertain whether testing, with signal averaged electrocardiograms or possibly electrophysiologic studies, can help predict whether certain patients with renal failure might be at greater risk to develop the complex arrhythmias noted in a large proportion of those undergoing dialysis. QT dispersion and left ventricular end diastolic diameter are two other factors in predicting the risk of arrhythmia development. Focusing on these patients and noting trends and clues regarding increased cardiovascular morbidity and mortality secondary to ventricular arrhythmias has become important to their proper evaluation and medical care.

Scope of the Problem

Complex ventricular arrhythmias in renal failure patients are common. The combination of ventricular arrhythmias and other cardiac risk factors serve to make cardiac disease the most common cause of death in hemodialysis patients.[7,8] Sforzini and associates noted, in a group of randomly selected dialysis patients, that 76% of those who underwent 48-hour Holter monitoring were found to have ventricular arrhythmias.[9] De Lima and colleagues noted that about 50% of their hemodialysis patients developed complex ventricular arrhythmias.[10] In a substudy, De Lima and associates noted that complex arrhythmias were twice as likely in dialysis patients when compared with non-dialysis renal patients.[11] In yet another study, Narula and coworkers found that about 29% of studied patients actually developed ventricular arrhythmias during dialysis and that, in this group, there was a significantly greater proportion of patients with clinical ischemic heart disease. Silent myocardial ischemia as identified by ST-segment depression and ventricular arrhythmias was noted most frequently during the last hour of hemodialysis.[12]

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Though ventricular arrhythmias appear to play a major role in cardiac mortality in hemodialysis patients, in a follow-up to their initial multicenter study, Sforzini and associates noted that the presence of ventricular arrhythmias in dialyzed patients did not correlate independently with 4-year mortality. Only age and the presence of ischemic heart disease correlated significantly with mortality.[13]

Determinants for the Development of Complex Ventricular Arrhythmias

The development of complex ventricular arrhythmias as described above is known to be a common and major occurrence in patients on hemodialysis. The direct causes, however, have only been theorized and still remain in dispute (Table 1).

Table 1
Possible Determinants of the Development of Complex Ventricular Arrhythmias in Dialysis Patients

Metabolic Derangements
Myocardial Injury
Hemodynamic Alterations
Patient Age
Molecular Determinants
Dialysis Method

Metabolic Derangements

One of the original and oldest theories regarding hemodialysis and arrhythmias involves the question of metabolic derangements of cardioactive metabolites like potassium, phosphorus, and calcium, and the change, the rate of change, and/or correction of these metabolic levels with dialysis. Rombola and colleagues[14] have hypothesized that hemodialysis patients with arrhythmias have decreased intraerythrocytic potassium content in comparison with other patients and that this finding constitutes a predisposing factor for arrhythmias. Even though these metabolic shifts during dialysis would be expected to affect the arrhythmogenicity of the myocardium, numerous studies using QT dispersion as a marker of homogeneity, in terms of ventricular depolarization, have failed to reveal a direct correlation between alterations in pre- vs. post-dialysis potassium, phosphorous, bicarbonate, or calcium levels.[15-17]

Myocardial Injury

In these studies, it was, however, noted that QT dispersion is higher in hemodialysis patients compared with control patients, and rises to even greater levels postdialysis, leaving these patients at increased risk for potentially fatal ventricular arrhythmias. The increased QT dispersion reflects nonhomogenous recovery of ventricular excitability, thus raising arrhythmia risk in the immediate postdialysis period. This dyssynchrony has been postulated as the reason patients with known ischemic disease have been noted to have an increased likelihood of developing arrhythmias. Ventricular wall fibrosis, scar, and ischemia all predispose to variations in the mechano-electrical current within the myocardium, thus predisposing to nonhomogenous ventricular contraction and an increase in the QT dispersion. At the same time, ventricular hypertrophy also induces these changes in the myocardium, which predispose to the same alterations in normal conduction.[16-18]

Hemodynamic Alterations

The influence of blood pressure alteration on the development of ventricular arrhythmias in hemodialysis patients was studied by De Lima and colleagues.[10] They studied a group of relatively young (mean age 49.9) hemodialysis patients in stable clinical condition and found that only systolic blood pressure and age were determinant of complex ventricular arrhythmias. They postulate that the arrhythmogenic effect of hypertension possibly involves the promotion of myocardial ischemia aggravated by concomitant left ventricular hypertrophy.[10,18] In support, they found that myocardial ischemia and LV hypertrophy were more common in their patients with complex ventricular arrhythmias.[10]

Age

Numerous studies have attempted to correlate different variables with ventricular arrhythmias. Most agree on the importance of age as a promoter of ventricular arrhythmias not only in hemodialysis patients, but also in healthy individuals.[13,19-21] Not only does age appear to be a causative agent, it also directly affects mortality in these patients. [13]

Cardiac Substrate

As with patients not on hemodialysis, the dialysis patient's underlying cardiac substrate plays a major role in the development of ventricular arrhythmias. Patients with a history of myocardial infarction and resultant ventricular scarring develop reentrant circuits that typically include the border zone between electrically inactive scar tissue and electrically active myocardial tissue. One way to identify patients with ventricular scarring is through their ejection fraction (EF). An EF less than 30% is generally believed to put a patient at greater risk when it comes to the development of ventricular arrhythmias. In the same vein, patients with long-standing hypertension, which leads to left ventricular hypertrophy, are also at increased risk for ventricular arrhythmias, due to remodeling of the ventricle and development of re-entrant circuits causing ventricular arrhythmias.[18]

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Molecular Determinants

Perhaps future studies and advances will allow us to better comprehend the intricate interplay between the visible clinical characteristics in these patients and the not-so-obvious molecular biochemical changes that take place during dialysis. Wu and associates[22] studied rabbit ventricular myocytes, which received prolonged stimulation with an early afterdepolarization-containing action potential clamp, to illustrate the role of calcium calmodulin-dependent protein kinase II on L-type calcium current during repolarization. The current was initially augmented and was dependent on calcium from the sarcoplasmic reticulum and its reaction with the protein kinase, which was affected by dialysis, based on the type of dialysis bath utilized.[22]

The effect of free oxygen radicals has also been studied, especially in the development of reperfusion-induced arrhythmias. Ravingerova and coworkers[23] studied the rat heart and noted the development of post-ischemia, reperfusion-induced ventricular tachycardia and ventricular fibrillation, which gradually ceased over a period of five minutes in isolated rat hearts.[23] This same production of free radicals is thought to occur in uremic patients who require chronic hemodialysis and may be yet another factor in the development of complex ventricular arrhythmias.

Dialysis Method

Canziani and colleagues[24] compared hemodialysis and continuous ambulatory peritoneal dialysis (CAPD) in terms of their effect on the heart. They noted that the presence of hypertension and left ventricular hypertrophy was lower in the CAPD group than in the hemodialysis

group. Severe cardiac arrhythmias occurred in only 4% of CAPD patients, as compared with 33% in the hemodialysis group. They hypothesized that the lower incidence of arrhythmias in the CAPD group may have been due to the lower frequency of left ventricular hypertrophy in these patients.[24]

Beyond the actual dialysis method used, the type of dialysis membrane and dialysate also affect the development of arrhythmias. Munger and associates[25] noted more frequent events, including hypoxemia and ectopy, with the use of the combination of acetate dialysis and cuprammonium membranes. Intrahemodialysis potassium removal through reduction in the plasma/dialysate/potassium concentration gradient was noted, by Redaelli and coworkers,[26] to significantly decrease the arrhythmogenic effect on patients undergoing regular hemodialysis treatment, especially during the first 2 hours of dialysis treatment.[26] Nappi and colleagues[27] noted that using a low calcium dialysate (dCa^{++}1.25 HD) increased QT_c dispersion, putting these patients at increased risk for ventricular arrhythmias.[27] It is, in fact, the increase in plasma ionized Ca^{++} during hemodialysis that has been cited as the cause for improved left ventricular contractility during hemodialysis.[28]

Identification of Determinants for the Development of Complex Ventricular Arrhythmias

The use of electrocardiography (ECG), particularly signal-averaged ECG (SAECG), has generally been applied to predict the development of arrhythmias. SAECG is utilized in patients on hemodialysis to assess their risk for ventricular arrhythmia development. Girgis and coworkers[29] found that abnormal SAECG parameters were detected in a significant proportion of patients undergoing hemodialysis for chronic renal failure. It was also noted that hemodialysis tends to improve some of these parameters (especially decreasing late potentials), which they postulated might be a result of the decrease in fluid load achieved through ultrafiltration.[29] Morales and colleagues[30] made similar findings in their study of SAECG pre- and postdialysis in 48 patients with chronic renal failure.

Table 2
Techniques for the Identification and Risk Stratification of Dialysis Patients for the Development of Ventricular Tachyarrhythmias

- Electrocardiography
  - QRS duration
  - QT interval
  - QT dispersion
  - T-wave alternans
- Signal-averaged ECG
- Holter Monitor/Event Recorder
- Diagnostic electrophysiologic study

As discussed earlier, the focus on QT dispersion also represents a major development when assessing hemodialysis patients with ventricular arrhythmias. It is therefore helpful to measure QT dispersion using ECG and assess for the presence of LV hypertrophy using both electro- and echocardiography in these patients.

The various techniques and their uses can be seen in Tables 2 and 3.

Therapeutic Management

In patients with a history of nonsustained ventricular tachycardia, a diagnostic electrophysiologic study (EPS) is performed to test susceptibility to development of ventricular tachycardia. Patients with substrate for the development of reentrant ventricular tachycardia circuits (patients with a history of myocardial infarction and ejection fraction $< 30\%$) may undergo implantation of a cardioverter defibrillator without a prior EPS.[31] Studies to assess the efficacy of electrophysiology testing in these dialysis patients, as well as the further placement of cardioverter defibrillators in the subgroup without prior cardiac history, are still needed.

During acute ventricular arrhyth-

Table 3
Objectives for Electrophysiologic Testing in Dialysis Patients

Indication	Clinical Situation	Result
Diagnosis	Recurrent syncope in context of structural heart disease	EPS shows inducible VT requiring ICD implantation
Risk Stratification	Asymptomatic nonsustained VT in setting of significant left ventricular dysfunction and coronary artery disease	EPS showing inducible VT; non-inducibility suggests lower risk for sudden cardiac death
Therapy Selection	Sustained VT	EPS guides ICD programming; EPS may reveal a tachycardia that is curable by ablation

EPS, Electrophysiologic study; ICD, implantable cardioverter-defibrillator; VT, ventricular tachycardia.

mia, standard advanced cardiac life support therapies should be applied. In hemodynamically unstable patients, cardioversion should be performed with hemodynamic support. In patients with stable ventricular tachycardia, pharmacologic therapy with amiodarone (150 mg intravenously over 10 minutes) or lidocaine (1-1.5 mg/kg intravenous push followed by 0.5-0.75 mg/kg, intravenously, every 5-10 minutes to a maximum of 3 mg/kg) should be administered. The recent SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), a placebo-controlled, randomized clinical trial that studied the use of implantable cardioverter-defibrillators in heart failure patients with poor ejection fraction (≤ 35%) who have not experienced a previous ventricular arrhythmia, showed that amiodarone, when used as a primary preventive agent, does not improve survival in these patients.[32-33]

Summary and Conclusions

The development of complex ventricular arrhythmias in patients with chronic renal failure on dialysis has long been a known, studied complication and inducer of morbidity and mortality. Identifying the root causes or variables in these patients has become a focus of researchers in this field. As this survey of the literature depicts, further study is required in order to pinpoint a single, agreed-upon cause or group of causes to which ventricular arrhythmias in patients with chronic renal failure on hemodialysis can be attributed. ■

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Main Points

- A number of factors have been implicated in the literature for the genesis of ventricular arrhythmias in dialysis patients; they include hemodynamic alterations induced by dialysis, metabolic alterations and derangements, molecular-level current alterations in the L-type calcium channels in the heart, arterial hypertension, which can frequently occur in renal failure patients secondary to volume overload, and the presence of left ventricular hypertrophy.
- Signal-averaged electrocardiography is utilized in patients on hemodialysis to assess their risk for ventricular arrhythmia development.
- Canziani and colleagues compared hemodialysis and continuous ambulatory peritoneal dialysis (CAPD) in terms of their effect on the heart and noted that the presence of hypertension and left ventricular hypertrophy was lower in the CAPD group than in the hemodialysis group; severe cardiac arrhythmias occurred in only 4% of CAPD patients, as compared with 33% in the hemodialysis group.
- QT dispersion is higher in hemodialysis patients when compared with control patients, and it rises post-dialysis to even greater levels, leaving these patients at increased risk for potentially fatal ventricular arrhythmias.
- In patients with a history of nonsustained ventricular tachycardia, a diagnostic electrophysiologic study (EPS) is performed to test susceptibility to development of ventricular tachycardia, whereas patients with substrate for the development of reentrant ventricular tachycardia circuits (patients with a history of myocardial infarction and ejection fraction < 30%) may undergo implantation of a cardioverter defibrillator without a prior EPS.

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