Ventricular arrhythmia in chronic kidney disease patients
Arritmia ventricular em pacientes com doença renal crônica

ABSTRACT
Patients with chronic kidney disease (CKD) are susceptible to the occurrence of ventricular arrhythmias. The leading cause of death in dialysis patients is cardiac arrhythmias. The pathophysiology of arrhythmias in this population is complex and seems to be related to structural cardiac abnormalities caused by CKD, associated with several triggers, such as water and electrolyte disorders, hormonal conditions, arrhythmogenic drugs, and the dialysis procedure itself. Little is known about the clinical outcomes in CKD patients with asymptomatic ventricular arrhythmias. The results of treatments with anti-arrhythmic drugs and invasive devices are controversial in these patients, according to the available literature. The aim of this study was to review this often-neglected topic, which is of special importance in the CKD population.

Keywords: arrhythmias, cardiac; epidemiology; renal insufficiency, chronic.

INTRODUCTION
The association between chronic kidney disease (CKD) and high cardiovascular morbidity and mortality is well known. Uremic cardiac disease progresses rapidly and is usually severe, following a different pattern from that of cardiac disease in the general population. According to the United States Renal Data System (USRDS), the leading cause of death among CKD patients undergoing dialysis is related to cardiac arrhythmias (Figure 1). Although this is a topic of particular relevance, little is known about the impact and management of ventricular arrhythmias in the CKD population. The aim of this study was to review the literature related to ventricular arrhythmias in CKD patients.

DEFINITIONS
Ventricular extrasystole is a premature ectopic heartbeat originating in the ventricles. An episode of three or more consecutive ventricular complexes, associated with a heart rate higher than 100 bpm and lasting less than 30 seconds, is referred to as nonsustained ventricular tachycardia (VT). Sustained VT is defined as VT that lasts more than 30 seconds, leads to syncope or cardiac arrest, or requires electric cardioversion or shock delivery by an implantable cardioverter-defibrillator (ICD).
When the VT is polymorphic, there are different QRS patterns, suggesting several focal ventricular activations. In this case, myocardial ischemia is an important cause. Monomorphic VT has the same QRS configuration in each beat. In general, it is caused by reentry and originates from a single focus or an anatomical substrate (infarct scar, cardiomyopathy, heart surgery, etc.).

Ventricular fibrillation is identified by the absence of a P wave with abnormal QRS complexes, with markedly different morphologies, varying its amplitudes and axes. The rhythm is irregular, usually greater than 300 beats per minute, leading to cardiac arrest.

Sudden death is defined as “unexpected death that occurs suddenly, in less than an hour from the beginning of the symptoms”; or “unwitnessed and unexpected death, in the absence of a known non-cardiac cause, which occurs in patients who were well the last 24 hours”. In the general population, about 50% of cases of sudden death are due to sustained VT and ventricular fibrillation. In CKD patients, the electrocardiographic rhythm that causes cardiac arrest is unknown. However, it seems that tachyarrhythmia plays an important role.

Epidemiology

Few studies have investigated the occurrence of ventricular arrhythmia in CKD patients in different stages of disease. Studies using 24h electrocardiographic monitoring (Holter monitor) in dialysis patients confirm the high prevalence of ventricular arrhythmias in this population, ranging from 19-72%. Data from our group have shown that ventricular arrhythmia was present in 35% of non-dialyzed patients, 45% of patients underwent peritoneal dialysis, and 30% of patients underwent hemodialysis and 30% of patients underwent renal transplantation.

Little is known about the impact of the presence of asymptomatic ventricular arrhythmia on clinical outcomes in the CKD population, especially in relation to the risk of sudden death. Our group recently showed that the presence of complex ventricular arrhythmia was associated with an increased risk of cardiovascular events, hospitalization, and death in this population.

In a retrospective study including 75 hemodialysis patients with ICDs, ventricular tachyarrhythmias were responsible for 79% of cardiac arrests, suggesting that ventricular arrhythmias are the most important final event in this population. On the other hand, an Australian study of predominantly elderly CKD patients pointed out that bradycardia or asystolia were the major contributors to sudden death in hemodialysis patients. These conflicting results suggest that the type of arrhythmia and terminal event may differ according to patient age, severity of cardiac disease, and length of time on dialysis.

Pathophysiology

A vulnerable diseased myocardium and a transient trigger are required for the occurrence of ventricular arrhythmias. In patients with normal renal function, ischemia due to atheromatous plaque rupture, focal myocardial scars, or systolic dysfunction are the most common substrates for the occurrence of fatal arrhythmias.

In CKD patients, this process is more complex, and the increased susceptibility to ventricular arrhythmias in this population seems to be related to metabolic disturbances and cardiac structural disorders caused directly by renal disfunction (Figure 2).

Experimental electrophysiological studies have shown that mice with CKD have peculiarities predisposing to arrhythmogenic cardiac events, such as action potential prolongation, increased electrical instability, frequent early depolarization, and greater sensitivity to induction of ventricular fibrillation. There are also changes in intracellular calcium homeostasis, with reduction of calcium content in the sarcoplasmic reticulum.
A recent study showed that indoxyl sulfate has an arrhythmogenic effect in cardiomyocytes in vitro and indicated an independent association between levels of this uremic toxin and QT interval prolongation in CKD patients not on dialysis.21

Another uremic toxin that has been the subject of many recent studies is FGF23, which is a cause of left ventricular hypertrophy and an independent predictor of cardiovascular events, CKD progression, and death from all causes in CKD patients.24 Deo et al.25 showed that this phosphatonin is not independently associated with fatal arrhythmias in the CKD population.5

On the other hand, a recent post hoc analysis of the EVOLVE (Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events) study showed that reduction of FGF23 with cinacalcet can decrease the risk of sudden death.24 In this study, it was not possible to discriminate whether the beneficial effect was directly related to the reduction of FGF23 or was an indirect effect of the actions of other drugs.

In the context of mineral and bone disorders, parathormone (PTH) also plays an important role. Its elevation is independently associated with the occurrence of sudden death in CKD population, especially when the level is above 495 pg/mL.26 The risk may increase in the case of association with vitamin D deficiency.27 Vitamin D deficiency is also an independent risk factor for sudden cardiac death in diabetic hemodialysis patients.24 The physiopathology of this association may be related to left ventricular hypertrophy and coronary artery calcification, which make the myocardium vulnerable to the occurrence of arrhythmias.

In the general population, patients with electrocardiographic evidence of left ventricular hypertrophy (LVH) have higher prevalence, complexity, and severity of ventricular arrhythmias.29 LVH is the most common cardiovascular complication in CKD patients.30 Its physiopathology encompasses hemodynamic factors, such as hypertension, hypervolemia, sympathetic hyperactivity and inappropriate activation of endothelin and renin-angiotensin systems. In addition, non-hemodynamic factors are involved, such as anemia, inflammation, and mineral and bone disorders.30

Elevated levels of phosphorus, PTH and FGF23 contribute not only to hypertrophy but also to myocardial fibrosis. The fibrosis is aggravated by non-atherosclerotic ischemia caused by the disproportion between the number of cardiac muscle fibers and the capillary density.31 The consequence of fibrosis is left ventricular diastolic dysfunction. The increase in the number of cardiomyocytes, the appearance of fibrotic bands and the disorganization of muscle fibers

**Figure 2.** Pathophysiology of ventricular arrhythmias in chronic kidney disease (CKD) patients. Muscle and vascular cardiac abnormalities secondary to CKD lead to myocardial electrical instability and make these patients susceptible to trigger arrhythmias after internal or external stimuli. HD: hemodialysis.
increase the electrical instability of the myocardium and predispose to the occurrence of arrhythmias.\textsuperscript{15,16,32}

An association between low ejection fraction and sudden death has also been demonstrated in CKD patients.\textsuperscript{11,32} A Chinese cohort of peritoneal dialysis patients has shown that systolic dysfunction is the most important predictor of sudden death in this population. The prolonged increase in preload and afterload, excessive oxygen demand and the consequent death of cardiomyocytes lead to the adaptive process known as cardiac remodeling, with dilatation of the chambers and reduction of their contractility.\textsuperscript{33} Systolic dysfunction seems to predispose to electrical instability and ventricular arrhythmia, because of sympathetic neurohumoral activation, which would explain the pathophysiological mechanism of the association between systolic dysfunction and ventricular arrhythmias.\textsuperscript{32}

Macrovascular disease has a more rapid progression in CKD patients and works as a substrate and a trigger for arrhythmias in this population.\textsuperscript{34} The inflammatory environment in CKD patients accelerates endothelial dysfunction and the atherosclerotic process,\textsuperscript{35,36} particularly in dialysis patients.\textsuperscript{37} High phosphorus contributes to intima calcification and media calcification, promoting an accelerated vascular aging. Patients with PO4 greater than 6.5 mg/dl present a 20\% higher risk of sudden death when compared to those with PO4 between 2.4-6.5mg/dl, which may be related to calcification of the cardiac conduction system and to vascular calcification.\textsuperscript{26}

Our group and other researchers\textsuperscript{38-40} have documented the relationship between coronary artery calcification and increased cardiovascular mortality in CKD patients. Vascular calcification may also play a role in the pathophysiology of ventricular arrhythmias in this population. Di Iorio \textit{et al.}\textsuperscript{41} demonstrated that in CKD stage 4 and 5D patients, coronary artery calcification progression was a predictor of QT interval prolongation, which is a known risk factor for fatal ventricular arrhythmias. Other mechanisms that could be involved include the loss of coronary artery dilation and the increased afterload due to aortic calcification,\textsuperscript{40,42,43} which is a cause of spontaneous ventricular depolarization (mechano-electrical feedback).\textsuperscript{44}

In the presence of such a number of anatomical substrates in CKD patients, electrolyte disturbances become important triggers for the occurrence of arrhythmias. In experimental and clinical models, imbalances between intracellular and extracellular ionic concentrations of potassium, calcium, and magnesium were able to trigger arrhythmias.\textsuperscript{45}

In CKD patients, potassium disorders are frequent and have particular importance. Hyperkalemia has been associated with successive electrocardiographic changes, such as high and peaked T waves, short QT interval, prolonged PR interval, QRS widening, P wave disappearance, and, finally, idioventricular rhythm with sinusoidal pattern.

Excessive reduction in the duration of action potentials may promote reentrant arrhythmias in conditions of slow electric conduction. Hyperkalemia in combination with hypocalcemia, hyperphosphatemia, and hypomagnesemia or hypermagnesemia may have adjuvant effects in triggering arrhythmias in this population.\textsuperscript{46}

It has been observed that, in dialysis patients, ventricular arrhythmias often occur after the longer interdialytic period (Mondays and Tuesdays). Dialysis sessions may trigger the arrhythmic process due to blood pressure instability, fluid and electrolyte imbalances, and acid-basic disequilibrium.\textsuperscript{47}

Adrenergic hyperactivity may also be important in the pathophysiology of arrhythmias in dialysis patients. Studies in humans show that CKD increases the adrenergic discharge of the sympathetic nervous system, mediated by renal afferent nerve pathways.\textsuperscript{47} The increase in autonomic tone results in a predisposition to a higher frequency of extrasystoles and is associated with increases in mortality, risk of cardiovascular events, and sudden death in CKD patients.\textsuperscript{11,48}

\section*{Diagnosis and risk assessment}

Ventricular arrhythmias may manifest clinically as palpitations, presyncope, syncope, or chest pain.\textsuperscript{4} The majority of individuals with cardiac arrhythmias have structural heart disease. Frequently, the underlying disease is not recognized, and sudden cardiac death is the first manifestation. For this reason, assessment of the risk of ventricular arrhythmia should be performed on the basis of clinical data and complementary tests.
ELECTROCARDIOGRAM (EKG) AND 24H EKG MONITORING (HOLTER MONITOR)

The electrocardiogram (EKG) is an important cardiac screening method and is more valuable during active symptom manifestation. In asymptomatic patients, this exam may indicate underlying structural cardiac disease that can act as a substrate for the occurrence of ventricular arrhythmia.

EKG monitoring performed over the course of a 24h period (Holter monitor) increases the chance of detection of an arrhythmic episode by more than 10 times. This test may also detect other noninvasive risk markers, such as nonsustained monomorphic VT, decreased heart rate variability, the presence of delayed action potentials, and T wave alternation.

Heart rate variability is a method to assess autonomic nervous system function. Decrease in heart rate variability is a predictor of adrenergic activation and increases the risk of sudden death in both the general and hemodialysis populations.

Detection of repolarization defects and QT interval abnormalities are also important. In dialysis patients, the acquired long QT interval syndrome is highly prevalent and may contribute to the occurrence of sudden death. On the other hand, hypercalcemia, hyperkalemia, and digitalis intoxication, common conditions in CKD patients, can shorten the QT interval. This alteration also increases the risk of polymorphic VT and sudden death.

The QT interval dispersion, characterized by heterogeneous QT duration among EKG leads, reflects regional differences in ventricular recovery time. This finding has been linked to the occurrence of malignant ventricular arrhythmias in different kinds of heart disease. Lorincz et al. showed that hemodialysis increases QT interval dispersion in CKD patients. It is possible that this phenomenon reflects a heterogeneous repolarization of different ventricular regions during hemodialysis, resulting in a predisposition to the occurrence of arrhythmias.

ECHOCARDIOGRAM AND CARDIAC MAGNETIC RESONANCE IMAGING (MRI)

Echocardiography helps to detect structural heart disease, mainly systolic dysfunction, which is considered the most important risk factor for arrhythmia in the general population. In dialysis patients, the test should preferably be performed preferably on a day without a hemodialysis session and with the patient at dry weight, since hemodynamic fluctuations may affect the echocardiographic findings.

Cardiac MRI is a good option to assess myocardial fibrosis and LVH. MR angiography may help to detect cardiac scars, which are the most common substrate for the occurrence of sustained monomorphic VT. In CKD patients, the MR angiography must be performed without gadolinium, due to the risk of nephrogenic systemic fibrosis. High costs restrict the routine use of this modality.

DOBUTAMINE STRESS ECHOCARDIOGRAPHY, MYOCARDIAL SCINTIGRAPHY, AND CORONARY ANGIOGRAPHY

Detection of coronary artery disease is also relevant, as it is highly prevalent in CKD patients. Both dobutamine stress echocardiography and myocardial scintigraphy have moderate sensitivity and specificity (75-90%) for the detection of obstructive coronary artery disease in CKD patients. Coronary angiography is the gold standard, but carries the risk of contrast-induced nephropathy in non-dialysis CKD patients. This modality should be reserved for patients at high risk of acute coronary syndrome and those who may benefit from revascularization therapy.

PREVENTION AND TREATMENT

Treatment of arrhythmias initially involves correction of modifiable factors, such as withdrawal of drugs causing QT prolongation (clarithromycin, chlorpromazine, haloperidol, amiodarone, procainamide, etc.), adjustment of metabolic and electrolyte imbalances, and interruption of drugs that stimulate the sympathetic nervous system (such as caffeine and amphetamine analogs).

In hemodialysis patients, one therapeutic option is modification of the dialysate composition. When serum potassium is less than 4.0 mg/dl, potassium replacement in the dialysate should be performed. Increasing potassium in the dialysate reduces ventricular ectopic beats and raises serum potassium levels in these patients, contributing to reductions in the QT interval and in QT dispersion during dialysis.

The use of dialysate with potassium < 2 mEq/l is associated with an increased risk of sudden death and should be avoided. Avoiding dialysate with calcium...
< 2,5 mEq/l also seems to reduce the risk of fatal arrhythmias. Other possible procedures include better control of interdialytic weight gain, reduction of the dialysate temperature, and, potentially, the use of intensive hemodialysis modalities.

Multiple trials have shown that frequent or prolonged (nocturnal) dialysis reduces left ventricular mass and improves heart rhythm. Observational studies also indicate that daily hemodialysis is associated with a lower risk of cardiovascular death and hospitalization. The explanation for these findings may be lower neurohumoral activation and lower electrolyte translocation, with greater myocardial stability.

Coronary reperfusion, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), aldosterone antagonists, and beta-blockers reduce the risk of sudden death after acute myocardial infarction in the general population. The cardiovascular benefits of these drugs and procedures have also been studied in CKD patients with conflicting results, especially due to the high risk of hyperkalemia in this population. Of note, none of the studies specifically analyzed the impact of these drugs on the reduction of ventricular arrhythmias in CKD patients.

Many arrhythmias are caused or aggravated by sympathetic stimulation and respond favorably to beta-blockers. These drugs are considered first-line therapy for symptomatic ventricular arrhythmias, although they are less effective in treatment of arrhythmias associated with structural heart disease. In the CKD population, a randomized trial showed a survival benefit with carvedilol in hemodialysis patients with heart disease. There are also data showing increased survival after cardiac arrest in hemodialysis patients taking beta-blockers. However, a secondary analysis of the Hemodialysis (HEMO) study did not demonstrate that these drugs could reduce the risk of fatal arrhythmias.

The use of statins has been associated with a lower risk of cardiovascular events and death in non-dialyzed CKD patients. However, the benefits of these drugs are still controversial in the dialysis population and in transplant recipients.

Anti-arrhythmic drugs have an important role in reducing symptomatic arrhythmias and ICD shocks in the general population. Drugs that block membrane activation through cardiac ion channels (propafenone, sotalol, quinidine, etc.) have high toxicity and can aggravate arrhythmias, especially in CKD patients. In patients using propafenone, a reduction in renal function contributes to accumulation of N-acetylprocainamide, a potentially arrhythmogenic toxic metabolite.

Doses of the following drugs should be adjusted according to renal function (Table 1): digoxin, procainamide, atenolol, and sotalol. Carvedilol does not require adjustment; however, slow and cautious dose progression should be considered, especially in elderly patients. Other agents (amiodarone, flecainide, and metoprolol) can be used at normal doses in CKD patients. Caution should be used with amiodarone in relation to thyroid, lung, liver, and nervous system toxicity. This drug is contraindicated in patients with left ventricular ejection fraction < 35% due to increased mortality, especially in patients with New York Heart Association (NYHA) heart failure functional class III or greater.

Digoxin is excreted in the urine and has a narrow therapeutic window. Therefore, dose reduction is crucial in CKD patients. The accumulation and toxicity of digoxin may lead to the same arrhythmia that the drug is intended to treat or avoid. Regular EKG and digoxin concentration monitoring are highly recommended in these patients.

ICDs are used for primary and secondary prevention in the general high-risk population with preserved renal function. Criteria for ICD insertion include good functional status and life expectancy of at least one year. ICDs are effective in reversing VT and ventricular fibrillation, resulting in decreased mortality in these patients. In CKD patients, the role of ICDs in the prevention of sudden death is controversial.

A recent meta-analysis of CKD patients not undergoing dialysis showed that the impact of ICD implantation on primary prevention of sudden death depends on the baseline renal function, with the benefit observed to decrease to the same extent that the glomerular filtration rate declined. In dialysis patients, several authors have shown high mortality and a higher risk of complications with ICD implantation. Although these patients have a higher incidence of ventricular fibrillation and a higher frequency of shocks administered by the device, survival outcomes by primary prevention are disappointing. In secondary prevention, there may be...
Table 1: Dosage Adjustment According to Renal Impairment of Digoxin and Anti-Arrhythmic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Creatinine Clearance (CrCl)</th>
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<tbody>
<tr>
<td>Digoxin</td>
<td>&gt; 50 mL/minute: No dosage adjustment necessary.</td>
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<tr>
<td></td>
<td>10 to 50 mL/minute: 0.0625 mg every 24 to 36 hours</td>
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<tr>
<td></td>
<td>&lt; 10 mL/minute: 0.0625 mg every 48 hours</td>
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<tr>
<td></td>
<td>Hemodialysis: Non-dialyzable. 0.0625 mg every 48 hours</td>
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<tr>
<td></td>
<td>Peritoneal dialysis: 0.0625 mg every 48 hours</td>
</tr>
<tr>
<td>Procainamide</td>
<td>&gt; 50 mL/minute: No dosage adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>10 to 50 mL/minute: Reduce initial daily dose by 25% to 50%</td>
</tr>
<tr>
<td></td>
<td>&lt; 10 mL/minute: Reduce initial daily dose by 50% to 75%; Monitor procainamide concentrations closely.</td>
</tr>
<tr>
<td></td>
<td>Hemodialysis: Moderately hemodialyzable (20% to 50%); monitor procainamide concentrations; supplementation may be necessary.</td>
</tr>
<tr>
<td></td>
<td>Peritoneal dialysis: Not peritoneal dialyzable.</td>
</tr>
<tr>
<td>Atenolol</td>
<td>&gt; 35 mL/minute: No dosage adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>15 to 35 mL/minute: Maximum dose: 50 mg daily</td>
</tr>
<tr>
<td></td>
<td>&lt; 15 mL/minute: Maximum dose: 25 mg daily</td>
</tr>
<tr>
<td></td>
<td>Hemodialysis: Moderately dialyzable (20% to 50%); administer dose post-dialysis or administer 25 to 50 mg supplemental dose.</td>
</tr>
<tr>
<td></td>
<td>Peritoneal dialysis: Elimination is not enhanced; supplemental dose is not necessary.</td>
</tr>
<tr>
<td>Sotalol</td>
<td>&gt; 60 mL/minute: Administer every 12 hours.</td>
</tr>
<tr>
<td></td>
<td>40 to 60 mL/minute: Administer every 24 hours.</td>
</tr>
<tr>
<td></td>
<td>&lt; 40 mL/minute: Use is contraindicated.</td>
</tr>
<tr>
<td></td>
<td>Hemodialysis: Use is contraindicated.</td>
</tr>
<tr>
<td></td>
<td>Peritoneal dialysis: Use is contraindicated.</td>
</tr>
</tbody>
</table>

CrCl = Creatinine Clearance.

some benefit, but there are no guidelines indicating this therapy in CKD patients.

Of note, the annual mortality in dialysis patients with an ICD between 1994 and 2006 was as high as 44.8% in the United States, and most of the deaths were attributed to cardiovascular causes. The post-implant infection rates were high, especially in the first year (988 events/1000 patient-years), although the majority of infections were not ICD-related. The insertion of transvenous cardiac devices may also lead to central vein stenosis, which adversely affects the maturation and preservation of arteriovenous fistulas for hemodialysis.

Catheter ablation efficacy and risks depend on the origin of VT, associated heart disease, and operator skill. Complications include tamponade, stroke, heart block, and, frequently, vascular access complication. In CKD patients, there is limited experience with ablation for treating ventricular arrhythmia. We found no studies that evaluated the success rate and complications of ablation in this population.

Perspectives and Conclusion

Further studies with emphasis on the clinical management of arrhythmias in CKD patients are needed, because the currently available data regarding cardioprotective medication, anti-arrhythmic drugs, and invasive therapy are lacking. There are drugs under investigation, such as carvedilol analogs, which have shown encouraging results in hypercalcemia-induced arrhythmia, catecholaminergic tachycardia, and arrhythmia related to heart failure.

Modern subcutaneous and external cardiac defibrillators, with improved efficacy and safety, are in the development phase. Such strategies could avoid vascular complications and minimize the risk of infection, which are desirable outcomes in the CKD population in particular. In the future, there will be devices capable of measuring intracardiac pressure, and these may assist in the earlier detection of cardiac function deterioration. Such advances would allow therapy based on the hemodynamic effects of arrhythmia, avoiding shocks in well-tolerated arrhythmias.

While such technologies are not available, the management of ventricular arrhythmia in CKD patients should focus initially on risk stratification and prevention. Physician should be attentive to modifiable risk factors and to the treatment of comorbidities that cause structural cardiac abnormalities, such as hypertension, fluid overload, bone mineral disorders,
and anemia. The most important aim with all these actions is to reduce the risk of arrhythmias and sudden death, the leading cause of death in this population.

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