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Review Article

Chronic kidney disease and risk factors responsible for sudden cardiac death: a whiff of hope?

Márcio G. Kiuchi, Decio Mion Jr.*

Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

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Abstract

Several studies have shown a strong independent association between chronic kidney disease (CKD) and cardiovascular events, including death, heart failure, and myocardial infarction. Recent clinical trials extend this range of adverse cardiovascular events, also including ventricular arrhythmias and sudden cardiac death. Furthermore, other studies suggest structural remodeling of the heart and electrophysiological alterations in this population. These processes may explain the increased risk of arrhythmia in kidney disease and help to identify patients who are at increased risk of sudden cardiac death. Sympathetic hyperactivity is well known to increase cardiovascular risk in CKD patients and is a hallmark of essential hypertensive state that occurs early in the clinical course of the disease. In CKD, the sympathetic hyperactivity seems to be expressed at the earliest clinical stage of the disease, showing a direct relationship with the severity of the condition of renal failure, being more pronounced in the terminal stage of CKD. The sympathetic efferent and afferent neural activity in kidney failure is a key mediator for the maintenance and progression of the disease. The aim of this review was to show that the feedback loop of this cycle, due to adrenergic hyperactivity, also aggravates many of the risk factors responsible for causing sudden cardiac death and may be a potential target modifiable by percutaneous renal sympathetic denervation. If it is feasible and effective in end-stage renal disease, little is known.

Introduction

Chronic kidney disease (CKD) is a major public health problem worldwide. The main consequences of CKD include loss of renal function leading to end-stage renal disease (ESRD), accelerated cardiovascular disease (CVD) and death. In 2011, the number of patients receiving treatment for ESRD in the United States of America (USA) reached a new milestone, 615,899 cases. The prevalence of dialysis population (including peritoneal dialysis and other modalities) reached 430,273 at December 31, and the prevalence of the number of kidney transplants reached 185,626 [1].

Analyses of developed countries have shown that 2–3% of health expenditures are used to provide treatment for patients with ESRD, although they represented only 0.02–0.03% of total population [2]. ESRD expenses were estimated at 6.4% of the entire budget of the US health care system in 2006, 4.1% of the total health budget in Japan, and 3.24% of the expenditure of the national health system in other countries as South Korea. As the costs of the national American health care system for the

* Corresponding author. Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, Rua Dr. Ovídio Pires de Campos, 05403 010 São Paulo, Brazil.
E-mail address: deciomion@uol.com.br (D Mion).

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treatment of ESRD reached 34.4 billion dollars and the costs of treating ESRD who were not from the health system reached 14.9 billion dollars, the total cost of the ESRD reached 49.3 billion dollars in the USA. The health care system spending per person per year an average of $75,000, ranging from $32,922 for the patient transplanted to $87,945 for those receiving hemodialysis [1].

Diabetes is the disease that most contributes to CKD and ESRD worldwide, accounting for 30–50% of all cases [3]. Because diabetic nephropathy is already the most common cause of CKD, a significant increase in the burden of this disease can be expected. Hypertension is both a common cause, as well as one of the main consequences of CKD. In 2000, it was estimated that more than a quarter of the world's adult population had hypertension, two thirds of them in developing countries. It is projected that this number will increase ~60% to 1.56 billion in 2025 [4]. Hypertension control is weak in the presence of CKD as referred to "Kidney Early Evaluation Program", in which only 13.2% achieved good blood pressure control [5]. The high risk of cardiovascular morbidity and mortality in people with these diseases, as well as in the elderly and obese is well established and often precedes progression to ESRD and dialysis [6–9]. Historically, cardiovascular death associated with CKD was attributed to complications of atherosclerotic disease [10]. A substantial proportion of deaths from heart disease, however, is not directly linked to myocardial infarction (MI), stroke, or heart failure (HF), suggesting the presence of other processes that contribute to cardiovascular mortality [11–13]. Recently, renal dysfunction was assessed as an independent risk factor for sudden cardiac death (SCD), which has been considered as a distinct end point in several cohort studies and clinical trials.

Coronary artery disease (CAD) or congestive HF significantly increases the risk of SCD in the general population [14,15]. Both the left ventricular dysfunction as the functional class (New York Heart Association) are important risk factors for SCD and were incorporated as clinical and diagnostics parameters that guide the implant of automatic implantable cardioverter-defibrillator (ICD) for primary prevention of SCD [16]. Most patients who experienced a cardiac arrest, however, does not have a left ventricular ejection fraction (LVEF) documented <35% before the SCD and therefore would not fulfill criteria for ICD implantation [17,18].

SCD, CKD, and epidemiology

Initial studies demonstrate an increased risk of SCD in patients with kidney disease from clinical trial subgroup analyses to assess the effectiveness of ICDs. The "Multicenter Automatic Defibrillator Implantation Trial II", which evaluated the benefit of therapy with implantation of prophylactic ICD in patients with prior MI and a LVEF $\leq$ 35% [19], investigated the risk of SCD among patients with CKD. Among the participants submitted only to optimized drug therapy, the risk of SCD was 17% higher for every 10 mL/min/1.73 m^2 of decrease in estimated glomerular filtration rate (eGFR) [20]. Likewise, in "Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure Trial" [21], which demonstrated the benefit of cardiac resynchronization therapy in reducing death or hospitalization in patients with advanced HF and cardiac electrical conduction disease, renal dysfunction was associated with a 67% higher risk for SCD during the 16-month follow-up period [22]. Similar studies carried out in populations of most intermediate risk with CAD and without HF also demonstrate an independent association between renal dysfunction and SCD [23,24]. Despite these findings, the presence of HF, systolic and/or CAD that were necessary for the entry into such studies prevented an understanding of renal dysfunction was a marker of severity of heart disease or an independent risk factor for SCD.

Population studies have tried to understand the risk of SCD among participants with kidney disease, minimizing the effects of confounding prevalent CVD. Among 4,465 participants in a community of "Cardiovascular Health Study," without a history of HF or MI, the incidence of SCD was 2.5 times higher with lower levels of kidney function [22]. A more detailed analysis of this study also used measurements, creatinine and cystatin C, to identify a predefined subgroup with renal disease as a GFR based on creatinine $\geq$ 60 mL/min/1.73 m^2 and cystatin C $\geq$ 1.0 mg/L. After multivariate adjustment, the risk of SCD was twice as high in the group with preclinical kidney disease compared with the group who had normal renal function (eGFR based on creatinine $\geq$ 60 mL/min/1.73 m^2 and cystatin C < 1.0 mg/L). These results suggest that reduction, although soft, in renal function, increases the risk of SCD, especially in susceptible populations such as the elderly [25].

Most cardiovascular deaths reported in the ESRD are assigned to SCD events [26]. Some data suggest that the arrhythmic deaths and heart attack in patients with ESRD, combined, account for 22% of all deaths in this population [27]. Dialysis prospective cohort studies have corroborated these findings. In "Choices for Healthy Outcomes in Caring for ESRD trial," 658 deaths occurred in 1,041 participants on dialysis along 8-year follow-up. Among these 658 deaths, 146 were because of SCD (SCD rate of 1.8% per year) [28]. In addition, a high incidence of SCD during 5 years of longitudinal follow-up (SCD rate of 4.9% per year) was observed in a prospective cohort study in Chinese patients undergoing chronic peritoneal dialysis [29]. Despite the slight variations in the annual rates of SCD, about 20–25% of all causes of death were attributed to the SCD. This relative risk is almost identical to that reported by "US Renal Data System", in which 25% of all causes of death among patients on peritoneal dialysis and 27% of all causes of death among patients on hemodialysis, in the USA, were attributed to cardiac arrest (National Institute of Diabetes and Digestive and Kidney Diseases, 2006).

Finally, the strong association between ESRD and SCD also extends to the pediatric population. In a retrospective analysis of almost 1,400 deaths among patients with ESRD and aged 0–30 years (US Renal Data System data), cardiac arrest and arrhythmia made up most deaths related to cardiac causes, which occurred at a rate of > 2% per year [30]. These findings suggest that other mechanisms not related to CAD and/or HF are responsible for triggering fatal arrhythmias in people with ESRD.

Pathophysiology

The SCD pathophysiology is complex, and it is thought that it requires interaction between a transient event and a pre-existing substrate. This process induces electrical instability and ventricular arrhythmias, followed by hemodynamic collapse. Understanding the mechanisms that incite these events can help clarify when the interaction between a triggering event and an existing substrate proves to be harmful.

The structural and electrophysiological remodeling of the heart, vascular calcification and fibrosis, autonomic dysregulation, and volume changes and electrolytes are bandied about some of the mechanisms to explain the high predisposition to SCD in patients with CKD. Although some of the studies that support the proposed mechanisms have previously been conducted in patients with CKD who were not on renal replacement therapy, most of the data come from patients with ESRD.

Kidney disease induces cardiac remodeling including left ventricular hypertrophy (LVH) and heart fibrosis. Several clinical studies, including those who recruited participants with mild-to-moderate reduction in eGFR, showed an independent association between CKD and LVH [31–34]. Specifically, there is a progressive increase in the prevalence of LVH, and left ventricular mass increased when the eGFR decreases. In addition, among participants with more advanced kidney disease on dialysis, magnetic resonance imaging (MRI) with contrast demonstrates a diffuse pattern image with gadolinium uptake suggestive of fibrosis and nonischemic cardiomyopathy [35]. The pathogenesis of these conditions is considered multifactorial, and the presence of commonly associated comorbidities, such as hypertension, diabetes mellitus, and anemia, explain only part of the left ventricular remodeling [36–38]. The molecular basis for these changes includes activation of growth factors, proto-oncogenes, plasma norepinephrine, cytokines, and angiotensin II. These factors regulate intracellular processes that accelerate cardiac hypertrophy, myocardial fibrosis, and apoptosis [39,40]. Any LVH and cardiac fibrosis has been linked to increased risk of sustained ventricular arrhythmias and predisposition to SCD [41–45].

Kidney disease is also associated with vascular disease, including calcification and hardening of the blood vessels [46–49]. The decreases in eGFR and endothelial dysfunction are inter-related processes that reduce the vascular elasticity and subsequently increase ischemic events. Studies in humans have shown that a deficient vasodilator response that is endothelium dependent is associated with mild renal impairment [50,51]. If untreated, these conditions progress independently and establish a cyclical relationship that results in vascular and kidney damage. Subsequent remodeling and sclerosis of the vessels can compromise the perfusion reserve and increase the risk of ischemic events [52], which are common triggering factors for the onset of arrhythmias. In the scenario of ESRD, vascular remodeling is even more pronounced because the calcium phosphate deposition may further exacerbate vascular integrity [53]. High concentrations of phosphate and an increase in calcium phosphate product contribute to calcification of vessels and the myocardium, as well as for plaque instability, increasing the risk of SCD in 20–30% [54].

Structural changes can alter the electrophysiological properties of the myocardium. The myocardial fibrosis disrupts the normal architecture and results in a decrease in conduction velocity through the diseased tissue [55]. This condition can form heterogeneous areas of conduction and depolarization that can sustain a re-entrant arrhythmia, such as ventricular tachycardia [43,45,56]. These structural changes in cardiac conduction delay ventricular activation and create late potentials in the terminal portion of the QRS complex. Furthermore, these low amplitude signals, which may be detected using a high-resolution electrocardiogram, were identified in 25% of patients on dialysis [57]. Several studies also evaluated QT dispersion, reflecting the nonhomogeneous recovery of ventricular excitability, and is calculated as the difference between the highest and lowest QT interval in a standard 12-lead electrocardiogram. The QT interval dispersion is maximally elevated in the postdialysis period [58–60] and reflects a greater susceptibility to arrhythmias.

The ventricular arrhythmias and SCD in patients with ESRD may be related to the duration of dialysis. A failure to maintain homeostasis predisposes such patients to adverse events, especially after a long interdialytic interval. Cardiac arrhythmias and SCD are more common on Mondays and Tuesdays after without-hemodialysis weekends and in the 12 hours after the start of a hemodialysis session [61–64]. These findings suggest that major changes in blood pressure, electrolyte, and volume can induce triggers that trigger arrhythmias.

Besides dependent re-entrant arrhythmias scar forming heterogeneous areas of electrical conduction, renal dysfunction also increases the risk of arrhythmias, automatic or triggered by other trigger spots [65]. These rhythms are sensitive to adrenergic activity. Studies in humans show that ESRD increases the discharge rate of the sympathetic nervous system, which is mediated by afferent signals from kidney patients [66]. This autonomic tone increased in the setting of electrophysiological remodeling, which explains the basis for an increased frequency of premature ventricular complexes that occur in over 75% of patients with ESRD, during and after the dialysis sessions [67]. Sympathetic activity in these patients probably reflects more serious pathophysiological state because it correlates with an increased risk of death and general cardiovascular events [68].

Sympathetic nervous system and renal sympathetic denervation

Sympathetic hyperactivity is well known to increase cardiovascular risk in CKD patients and is a hallmark of essential hypertensive state that occurs early in the clinical course of the disease [69–71]. In both conditions, hypertension and kidney failure, the mechanisms of hyperadrenergic state are varied and include reflex and neurohumoral pathways [69,70,72]. In CKD, the sympathetic hyperactivity seems to be expressed at the earliest clinical stage of the disease, showing a direct relationship with the severity of the condition of renal impairment [72–75]. The increased sympathetic tone alters renal function because of the retention volume of sodium reabsorption, decrease in renal blood flow, and activation of the renin–angiotensin–aldosterone system [76]. Meta-analyses have shown that impaired renal function is an independent cardiovascular risk factor [77], and other studies reported that adrenergic activation exhibits an adverse impact on cardiovascular morbidity and, in the case of kidney failure, also on cardiovascular mortality [68–70,75]. Consequently, prevention of further damage of renal function is a therapeutic target by itself [78]. Tinucci et al evaluated basal muscle sympathetic nerve activity (MSNA) and the sympathetic hyperactivity mechanisms in mild chronic renal failure caused by hypertension. The baseline MSNA was significantly higher in hypertensive patients with mild renal impairment (34 bursts/min) compared to hypertensive patients with normal renal function (24 bursts/min, $P < 0.05$) and compared to normotensive patients (16 bursts/min, $P < 0.05$). This finding demonstrated that the high sympathetic activity can be detected early in renal

insufficiency [79]. Recently, Hering et al reported that the renal sympathetic denervation (RSD) in refractory patients with hypertension caused a significant reduction in blood pressure associated with substantial and quick reduction in the individual firing properties of sympathetic vasoconstrictor fibers, using the method of MSNA, compared resistant hypertension patients who were not submitted for the RSD, after 3 months of follow-up [80]. The interruption of sympathetic hyperactivity and feedback of the renin–angiotensin–aldosterone system cycle can at least partly be beneficial for this population. The RSD as well as being safe, can be considered a promising new therapeutic strategy for patients with hypertension and CKD [81–84], reducing the level of renin activity, aldosterone, and angiotensin II in humans [85]. Another recent study [86], in patients with ESRD and uncontrolled blood pressure, showed that the RSD is feasible in these patients, and to promote a sustained reduction in systolic blood pressure over 12 months and significantly decrease MSNA.

In 2012, Brandt et al showed for the first time that beyond the known effects on reducing blood pressure, RSD significantly reduced LV mass and improved diastolic function assessed by echocardiography, which may have important implications for prognosis in patients with resistant hypertension at high cardiovascular risk [87]. Subsequently, Mahfoud et al [88] submitted 72 hypertensive patients refractory to cardiac MRI (55 patients underwent RSD and 17 served as controls) before and 6 months after the procedure. Clinical data and the results of cardiac MRI were analyzed blindly. The RSD significantly reduced systolic and diastolic blood pressure, about 22/8 mmHg, and indexed left ventricular mass (ILVM) about 7.1% (46.3 ± 13.6 g/m$^{1.7}$ vs. 43.0 ± 12.6 g/m$^{1.7}$, $P < 0.001$), unchanged in the control group (41.9 ± 10.8 g/m$^{1.7}$ vs. 42.0 ± 9.7 g/m$^{1.7}$, $P = 0.653$). The LVEF in patients in whom this parameter was reduced before the procedure (< 50%), it significantly increased after the RSD (43% vs. 50%; $P < 0.001$). Left ventricular circumferential strain as a surrogate of diastolic function in the subgroup of patients with reduced strain at baseline increased by 21% only in the RSD group (−14.8 vs. −17.9; $P = 0.001$) and not in control patients (−15.5 vs. −16.4, $P = 0.508$). In 15 of 18 (83%) nonresponders to the RSD (responsiveness to the RSD was set to drop in systolic blood pressure ≥10 mmHg), the ILVM was significantly reduced from 52.1 ± 14.9 to 47.8 ± 14.4 g/m^2 ($P = 0.001$). Interestingly, the structural and functional cardiac changes were partly independent of blood pressure, pointing to a direct interference modulating the activity of the sympathetic nervous system.

In 2014, Doltra et al [89] underwent 23 refractory hypertensive patients to RSD and 5 patients served as controls, evaluated prospectively. Cardiac MRI, 1.5 T, was performed in all patients before and 6 months after the procedure. The ILVM, the extracellular volume fraction of the septa, and indexed absolute extracellular volume (a quantitative measure of extracellular matrix) were quantified. The RSD significantly decreased left ventricular mass, whereas the extracellular volume remained stable. The results suggest that the observed decrease in left ventricular mass was not only due exclusively to a reversal of myocyte hypertrophy but also due to a further reduction in the collagen content, indicating myocardial interstitial fibrosis. In 2015, McLellan et al [90] underwent 14 refractory hypertensive patients to ambulatory blood pressure monitoring (ABPM) for 24 hours, on echocardiography, cardiac MRI, and electrophysiological study before and 6 months after the RSD. The electrophysiological study included duration of measurements of the P wave, effective refractory periods, and driving times. The electroanatomic mapping of the right atrium was full to determine the local and regional conduction velocity and tissue voltage. After the procedure, the mean BP in 24-hour ABPM reduced, the global conduction velocity significantly increased, and the conduction time shortened. Changes in conduction velocity showed positive correlation changes in the mean systolic blood pressure of 24-hour ABPM. There was also a significant reduction in left ventricular mass and diffuse ventricular fibrosis to cardiac MRI. More recently, Dörr et al [91] studied 100 consecutive patients with refractory hypertension, and these were submitted to RSD. The therapeutic response was defined as a decrease in systolic blood pressure of office >10 mmHg (considered responsive patients), 6 months after the procedure. Venous blood samples were collected for measurement of amino-terminal propeptide (PINP, PIIINP) and a carboxyl terminal propeptide (PICP) before and 6 months after the RSD. This study evaluated the effect of renal denervation in increasing collagen absorption, reflected by these specific biomarkers for resorption of cardiac extracellular matrix and cardiovascular fibrosis. A significant reduction in office systolic blood pressure of 24.3 mmHg has been documented 6 months after the RSD, as well as serum levels of PICP, PINP, and PIIINP were significantly lower than baseline in patients with higher resorption of collagen, showing differences significant comparing responders and nonresponders regarding the drop in blood pressure. These results suggest a beneficial effect of RSD in cardiovascular fibrosis in hypertensive heart disease and target organ injury in high-risk patients.

For years, it is known that the control of blood pressure reduces the rate of progression of CKD. However, only recently, RSD emerged as a powerful tool for the control of resistant hypertension [92,93]. This procedure has also proved effective in controlling resistant hypertension even in patients with CKD. In 2 studies with a short follow-up period, the RSD was associated with increased eGFR [81,94,95] and the reduction of albuminuria [81,94,96].

Aim and conclusion

In patients with ESRD, probably there will be no recovery of renal function, as a recent study including patients with eGFR < 45 mL/min/1.73 m^2, did not improve this parameter 12 months after the procedure [82]. Recently, Kiuchi et al [97] reported for the first time the reduction in left ventricular mass and diameter, the improvement on systolic function, and correlation between the increase in eGFR and the reduction in LVM 6 months after RSD in CKD patients with resistant hypertension. This review aims to show that these results suggest that the renal artery ablation in this kind of patients seems to be effective in reducing lesions of target organs such as the heart and kidneys. However, many of the factors discussed previously that lead to SCD in patients with CKD in end-stage appear to be modifiable by the RSD according to the aforementioned studies, which would make use of this new tool to modify such factors risk, until now not modifiable.

Conflicts of interest

All authors have no conflicts of interest to declare.

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