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Autonomic dysfunction in kidney diseases

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Abstract. – Kidney diseases are associated with many cardiovascular risk factors, such as anaemia, inflammation and chronic volume overload. Changes in the sympathovagal balance are common findings in patients with end-stage renal disease (ESRD). In particular, sympathetic hyperactivity is linked with an increase in resting heart rate leading to myocardial hypertrophy and fibrosis. The latter increases the risk of sudden cardiac death from fatal arrythmias and therefore assessment of both sympathetic and parasympathetic tones could be clinically relevant in ESRD patients.

Heart rate variability and other indices are currently used to evaluate the functionality of the autonomic nervous system. Some of these have emerged as potential diagnostic tools that can support clinical decision-making processes and therapeutic strategies in patients with renal disease, including those who are on dialysis replacement therapy.

In this review, we summarize the impact and the relationships between sympathovagal disturbances and kidney diseases, replacement therapies and transplantation.

Key Words:
Kidney disease, Autonomic dysfunction, Heart rate variability, Dialysis, Renal transplantation.

Introduction

The autonomic nervous system (ANS) regulates the cardiovascular system by controlling the heart rate, conduction velocity and force of contraction through the balanced involvement of both the sympathetic and parasympathetic (also known as vagal) divisions. This sympathovagal balance reflects the effect of the ANS on heart rate variability (HRV) and disruptions to this equilibrium result in autonomic dysfunction (AD) (Figure 1). The resultant increase in sympathetic activity might have deleterious effects on cardiac electrophysiology, putting patient at high risk for ventricular arrhythmias and major cardiac events[1]. Hyperactivation of the sympathetic system not only leads to an increased basal heart rate, but also promotes myocardial hypertrophy and fibrosis which are associated with increased risk for sudden cardiac death (SCD)[2].

HRV is an indirect measure of the sympathovagal interaction at the sinoatrial node (SA node) and an index of cardiac neural control. HRV is defined as the variation of time intervals between consecutive heart beats over a period of observation. It is evaluated by measurement methods grouped under the time-domain and frequency-domain using spectral signal analysis (generally in the course of an Electrocardiographic Holter recording)[3]. Measurements under the time-domain are statistically derived from beat-to-beat intervals with sinus rhythm and are quantified using units of time (milli-seconds, ms). The most important parameter is the SDNN (ms) which refers to the standard deviation of the "normal to normal" (NN) beat intervals. The evaluation of the frequency-domain is based on the identification and quantification of the main oscillatory rhythms that are characteristic of a sequence of RR intervals.

In short-term recordings (5-10 minutes) two different frequency bands are evaluated: a low frequency (LF) band [range of 0.04-0.15 Hz] and a high frequency (HF) band [range of 0.15-0.4 Hz]. The LF band is a reflection of both the sympathetic tone, as well as baroreflex activity to an extent[4], while the HF band is mainly influenced by parasympathetic activity. The LF/HF ratio reflects the sympathovagal balance. Predominance of the sympathetic tone is indicated by a reduction in the SDNN and/or an increase in the LF/HF ratio to more than 6 (normal range: 3-6).

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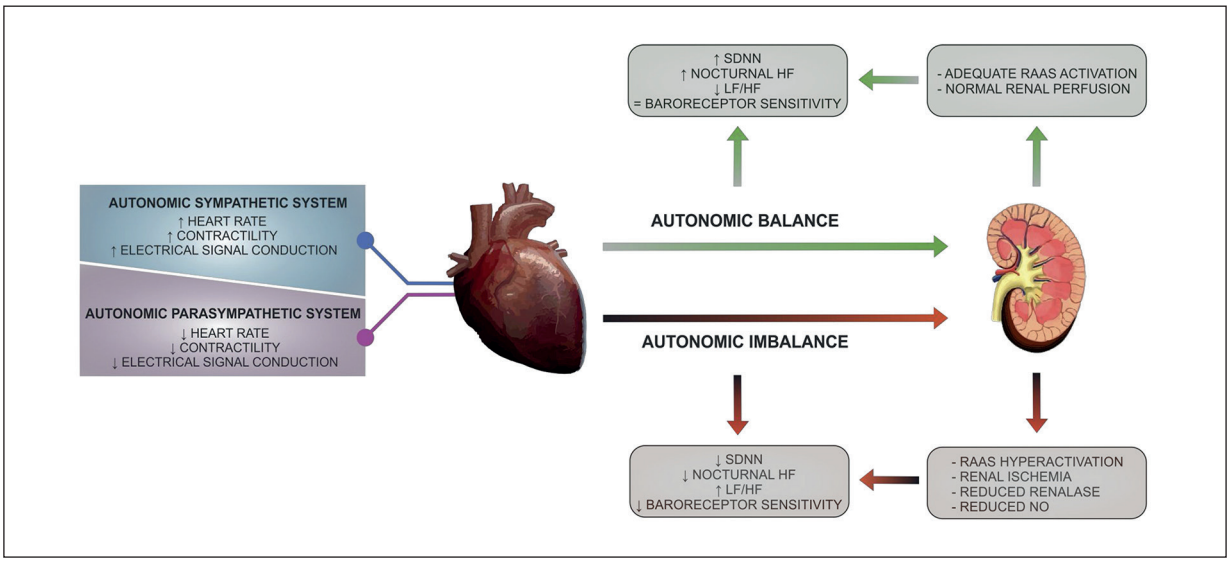

Figure 1. Role of the Autonomic balance and Its Modulation in Cardiorenal connections. Abbreviations: SDNN: standard deviation of the normal-to-normal heart beat intervals; HF: high frequency; LF/HF: low-frequency/high frequency; NO: nitric oxide; RAAS, renin angiotensin aldosterone system.

In some settings, a very low frequency (VLF) band [range of 0.01-0.04 Hz] is considered. For example, in patients with chronic heart failure, this frequency band is associated with the increased respiratory drive, activated cardio-pulmonary reflexes, and changes in intrathoracic pressure as part of the respiratory cycle[5].

Modifications of the sympathetic impulse carried to the SA node influence the low-frequency HRV while the parasympathetic stimulus influences the high-frequency HRV. Assessing the variability of the cardio-respiratory cycle, both quantitatively and qualitatively, can provide accurate information about the pathophysiological mechanisms involved in the reduction of the normal cyclical frequency of the heart rate. For this reason, HRV can also be considered an indicator of risk for the development of cardiovascular diseases (CVD).

Additionally, recent evidence shows that HRV is a risk predictor of arrhythmic events in patients with a history of myocardial infarction. Kleiger et al[6] first showed that patients with SDNN of <50 ms had an increased risk of mortality compared to those with a SDNN value of >100 ms.

The ATRAMI study (Autonomic Tone and Reflexes After Myocardial dysfunction) demonstrated that altered sympathetic-parasympathetic balance (where SDNN is <70 ms) is a significant predictor risk of having increased number of ectopic beats per hour, reduced left ventricular function, and cardiac-associated mortality[7].

Based on these considerations, the Task Force of the European Society of Cardiology has proposed the assessment of autonomic balance (indication Class I, Level of evidence A) as part of a risk stratification for SCD[8].

With respect to non-cardiac conditions, AD with altered HRV is observed in patients with neurological disorders and especially in those affected by diabetes[9]. Several autonomic disturbances are linked with diabetes, such as decreased sweating, intestinal motility alterations, and bladder dysfunction[10]. In particular, orthostatic hypotension (OH) is commonly observed in the early stages of type 2 diabetes before clinical manifestations of the disease appear[11]. OH is defined as a "sustained reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg within 3 minutes of standing or head-up tilt to at least 60° on a tilt table"[12]. Although many tests have been proposed to assess this condition, the head-up tilt and supine-to-standing tests remain the gold standard in clinical practice[13].

In addition, diabetic patients are characterized by impaired HRV parameters, which are related with the progression of disease and with unfavourable prognosis[14]. Diabetes-associated cardiac autonomic neuropathy (CAN) causes a decrease in VLF, LF, HF, and LF/HF ratio[15]. These impairments are frequently observed nocturnally, leading to the loss of HRV physiological circadian rhythm.

In humans, the circadian rhythm controls sleep-wakefulness cycle, metabolism, endocrine function and cardiovascular and motor activity[16]. A "biological clock" which is related to changes in light intensity and temperature, interacts with cyclic clock-genes that are regulated by environmental and hormonal status. This interaction allows dynamic homeostasis and the adaptation to internal and external changes[17-20]. The central nervous system and the ANS act as a hub where all the information coming from the external environment and from several organs systems are integrated[16,21,22]. HRV reflects the interplay between the brain and the cardiovascular system[23-25]. Notably, variations in HRV occur in a circadian (24-hour) pattern, showing a peak during the second half of the night[26].

In a similar way, hormonal production is widely influenced by the circadian cycle. Catecholamine, insulin, growth hormone, cortisol, prolactin, and other hormone levels are known to fluctuate during the day, controlled by extrinsic and intrinsic stimuli[27]. In particular, altered catecholamines serum levels and urinary excretion are known to be associated with worse outcomes in CVD[28] and a higher risk of mortality and functional decline in older patients[29]. Increased serum levels of this group of hormones are linked with worse outcomes in heart failure[30], justifying the use of β-blockers in these settings[31].

In addition to catecholamines serum levels, other cyclic physiological parameters influence cardiovascular function, such as blood pressure, cardiac output, as well as the renin-angiotensin axis activity[32-35].

Nevertheless, there are major limitations to the use of noradrenaline (or adrenaline) serum levels as a marker of deranged sympathovagal balance. Firstly, catecholamine levels give a "snap shot" of the simpathoexcitation and represent the net balance of neural reuptake, neural release and other forms of clearance (unless serial evaluations are performed)[36]. Secondly, there are cases (i.e., hypoxia) in which increased sympathetic neural activity is present in spite of normal serum levels of noradrenaline[37].

Considering the impact that AD has on the cardiovascular system, evaluating cardiac ANS functionality is becoming increasingly relevant. To date, non-invasive molecular imaging techniques are available for global and regional investigation of the myocardial nervous system. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are used to evaluate myocardial nerve function by using catecholamine analogue radiotracers (CART). These devices are employed to assess abnormalities on a cellular level, with the aim of early detecting heart failure.

CART commonly used to evaluate cardiac sympathetic nerve integrity are ^{123}I-meta-iodobenzylguanidine (^{123}I-mIBG), ^{11}C-hydroxyephedrine (^{11}C-HED), N-[3-Bromo-4-(3-[^{18}F]fluoropropoxy)-benzyl]-guanidine (^{18}F-LMI1195), and ^{18}F-fluoro-3-hydroxyphenethylguanidine (^{18}F-4F-MPHG)[38]. In particular, ^{123}I-mIBG scintigraphy is reliable in predicting cardiac adverse events in patients with coronary artery diseases, myocardial infarction and heart failure. Analogs of norepinephrine are used in myocardial imaging to stratify the risk for SCD in patients with heart failure[39].

Comparable results have been obtained using the analogous PET agent ^{11}C-meta-hydroxyephedrine. On the other hand, PET provides better accuracy for cardiac regional analysis due to the capacity for dynamic quantification and higher spatial resolution[40]. However, continuous studies on different radiotracers and subcellular biology will improve sympathetic imaging and will individualize patient care and therapies.

Sympathovagal disturbances affect the functionality of several organs and tissues, involving systemic pathways, e.g., phlogosis. In fact, sympathetic hyperactivity might also be associated with microalbuminuria and activation of proinflammatory/profibrotic markers[41] and consequent impaired renal filtration. In patients with chronic renal failure, one of the main causes of SCD is related to arrhythmias induced by disruption of the sympathovagal balance[42].

The aim of this review is to assess how AD interferes with chronic and acute kidney disease and with their courses. Furthermore, we analysed the reciprocal effects between sympathovagal imbalance and renal replacement therapy (RRT) and transplantation.

Chronic Kidney Disease (CKD) and AD

In patients with CKD, AD is a leading cause of cardiovascular morbidity and mortality[43]. In these patients, an increased sympathetic activity is observed and is associated with a reduction in the parasympathetic tone. Decreased parasympathetic tone has a significant clinical impact, including delayed gastric emptying, intestinal and erectile dysfunction, as well as immune system dysregulation among others[44-46].

Cardiovascular manifestations of AD, such as elevated blood pressure, altered HRV and compromised baroreflex sensitivity (BRS), may lead to an increased risk for developing fatal arrhythmias and SCD[42].

In CKD patients, an overproduction of inflammatory mediators is observed leading to activation of the vagal inflammatory reflex. Sympathetic/parasympathetic imbalance is strongly associated with a low glomerular filtration rate (GFR) and replacement therapies fail to adequately bring the ANS back into a balanced state. At present, only the removal of native kidneys or renal denervation can improve the sympathovagal balance, slowing the deterioration of renal function[42].

The exact pathogenetic mechanism behind AD in CKD is not entirely clear. It is however known that AD can be seen in early stages of CKD to different extents of severity, depending on the degree of renal failure. Thio et al[47] observed that only SDNN values had a negative correlation with the estimated GFR when adjusted for other factors, such as sex, age, obesity, diabetes and other comorbidities.

Many pathological conditions underlying renal damage (e.g., diabetes, autoimmune disease, etc.) induce uraemia-associated neuronal toxicity and hence affect normal ANS function[48].

In a recent study of 326 patients with different stages of CKD, the authors found a significant degree of AD in stage 5, especially when assessing the frequency domain with abnormal values of LF, HF, LF/HF ratio in 69.5%, 52.8% and 50% of patients, respectively. Furthermore, the authors observed that AD is more prevalent in patients with diabetes mellitus and CKD stage 5 compared to other stages of CKD[49].

LF values and the LF/HF ratio show an important correlation between associated clinical manifestations of CKD and AD and could therefore be used as predictors of clinical outcomes in patients with CKD[50].

Haemodialysis (HD), Peritoneal Dialysis (PD) and AD

Patients with end-stage renal disease (ESRD) receiving renal replacement therapy are at high risk for development of new and exacerbation of existing CVD[51]. The question of whether one form of RRT or another is more beneficial in this group of patients, remains largely unanswered. HD and PD are associated with similar long-term mortality among patients who are eligible for both modalities[52]. Nevertheless, several studies[53-55] show that PD patients are at greater risk of developing cardiovascular risk factors. Conversely, left ventricular hypertrophy is more prevalent in HD patients than in those receiving PD[56].

The ANS plays a key role in maintaining hemodynamic stability. The uremic CAN observed in patients having chronic HD is characterized by sympathetic hyperactivity with parasympathetic deterioration.

Only a few studies however, evaluated the variations in HRV in patients undergoing PD, reporting a common observation in which altered sympathovagal balance is a feature in this cohort of patients. Tang et al[57] studied autonomic balance in three PD patients' groups: those with a stable, lowered or absent residual renal function (RRF). They observed that all HRV parameters (lower SDNN, SDSD, RMSSD, pNN50, LF, HF, TP and higher LF/HF) negatively correlated with RRF decline. HRV changes may have a negative impact on the survival of the nephropathic patient receiving PD. In particular, a decreased LF/HF ratio (expressing blunting in the sympathetic activity) was identified as an independent prognostic factor for death[58,59]. Furthermore, the evaluation of non-linear HRV parameters appears to be very precise in predicting the risk of arrhythmias and SCD[60].

A large number of tests have shown that a lower HRV is an indicator of poor prognosis in patients on chronic HD. Fluid overload can worsen autonomic imbalance probably due to heart structure remodelling[61-63]. Therefore, several authors suggested that HD could improve HRV parameters and reduce cardiovascular-associated mortality in this cohort of patients.

Chan et al[63] compared HRV in two patient cohorts: those undergoing daily HD and a second group where patients underwent HD three times a week. This study showed that daily HD can have an important effect on the sympathovagal balance with an overall increase in HRV. In a prospective study reported by Park et al[64], 40 patients were divided into two groups. The first group included those receiving regular high flux HD, while a second group was composed of patients undergoing online hemodiafiltration (OL-HDF). Although no change in HRV was observed in the first group, an increase in the frequency domain HRV parameters was observed in the OL-HDF cohort.

Not all patients seem to benefit from HD with respect to improvement in HRV[65]. For example, patients with a history of stroke do not seem to

have a benefit in autonomic balance[66]. Kida et al[67] assessed HRV variations in 90 patients before and after HD as a risk factor of major adverse cardiac and cerebrovascular events (MACCE). The lack of variation in HRV seems to be useful in predicting MACCE in HD patients apart from those with diabetes. HD patients with a history of MACCE have the worst prognosis because they cannot benefit from HRV improvement following dialysis.

It is important to notice that other electrocardiographic abnormalities often occur in course of CKD, such as changes in T wave, QRS amplitude and QT interval. In fact, ESRD patients undergoing HD often experience fluid overload, hyperparathyroidism, metabolic acidosis, hyperkalaemia, as well as serum calcium, phosphate and magnesium disorders. All these conditions might be involved in the pathogenesis of arrhythmogenic cardiomyopathy[68]. Although it is known that ESRD patients show prolonged baseline QT interval, the influence of HD on this parameter is still not clear[69].

Acute Kidney Injury/Disease and ANS Disorders

In recent years, the term "acute kidney/renal injury" (AKI) has replaced the historically used term "acute renal failure" (ARF). AKI represents the loss of renal function which occurs within a time frame of hours or days. As a result, this leads to metabolic and biochemical derangements with altered fluid, acid-base and electrolyte balance. In contrast to ARF (which implies a state where complete or almost-complete loss of kidney function exists[70,71]), AKI takes into account cases with only a slight decrease in renal function. AKI is a major concern in surgical patients and those admitted to Intensive Care Units (ICU) for various reasons. For instance, 30% of patients undergoing cardiac surgery are affected by AKI in peri-operative or post-operative periods, leading to an increase in short-term and long-term mortality rates[72]. The aetiology of kidney disorders related to surgery is multifactorial. Indeed, a combination of pathological processes, such as oxidative stress, ischemia/reperfusion time, and inflammation are probably involved in the development of this clinical condition[73]. Moreover, the ANS plays an important role in modulating renal function[74] and its potential effect on post-operative AKI has not been completely investigated. Ranucci et al[73] analysed BRS during pre-operative and post-operative periods in patients undergoing cardiac surgery. The authors reported that BRS, computed by spectral domain in the low frequency domain (BRSαLF), represents an independent predictor of AKI. In this study, AKI was defined as any increase in serum creatinine value from baseline within 48 hours following surgery. Nevertheless, no correlation between BRSαLF and AKI stage 1 was found, probably because of the low number of AKI events observed in the study (n=7). Considering all the factors causing post-operative renal dysfunction, inflammation plays a major role. Several studies[75,76] focused on the role of the vagus nerve in modulating the crosstalk between immune system and inflammation, through the "cholinergic anti-inflammatory pathway". Inoue et al[77] demonstrated a positive effect of vagal stimulation in an ischemia/reperfusion model of AKI. Data regarding the correlation between AKI and ANS disorders are limited. Likely, this is due to the complex clinical settings of ICU or post-operative patients and the poor reliability of *in vivo* and *in vitro* models. For these reasons, extensive prospective studies are needed to better understand the link between acute kidney dysfunction and ANS alterations. Improving our knowledge would give better tools to categorize patients by probability of developing kidney diseases in critical settings.

Renal Transplantation (RT) and ANS Disorders

RT is the gold standard treatment for CKD and is associated with a reduction in cardiovascular risk in CKD patients[78-81]. In kidney recipients (KR), despite the amelioration of renal function and mineral metabolism, cardiovascular and autonomic modifications may persist. These include increased aortic stiffness, reduced left ventricular function, increased left ventricular afterload and higher risk for cardiovascular events[82]. CVD are the principal cause of death in patients with a functioning graft and consequently, graft loss[82,83]. It is also known that KR can be affected by various psychological disorders such as depression and anxiety[84]. Moreover, they can present with reduction in quantity and quality of sleep[85]. These conditions greatly influence the quality of life in these patients and may also produce or maintain, if already present, cardiovascular impairment and autonomic modifications (i.e., reduction in HRV). In fact, CKD patients are often affected by ANS impairments, which represent an independent factor associated with worse prognosis and SCD. Nevertheless, amelioration of left ven-

tricular ejection fraction and restoration of a good balance between the sympathetic and parasympathetic cardiac tones are known to have a positive effect on cardiac ANS and renal function[86-88].

Some studies[89,90] demonstrated that baroreflex function is often re-established following RT. In 2013, in a prospective study on 23 ESRD patients, Kaur et al[91] reported improvement of arterial stiffness indices and blood pressure variability followed by normalization of BRS after 3 and 6 months after RT, respectively. Despite the predictive role of such parameters, it has been demonstrated that HRV-recording in the peri-operative period during RT procedure is not a reliable predictor of cardiac death risk *per se* in ESRD patients[92]. It is known that physical exercise, for a certain duration, intensity and specific type of training, has benefits on autonomic disorders and it has been studied in CKD patients[85,86] and in patients on HD[93]. In 2015 Dias et al[94] reported a higher HRV in the time domain and a greater vagal modulation in KR who underwent exercise training than those included in sedentary KR group after 8 weeks. Silva Filho et al[95] compared the effect of physical exercise on KR *vs.* patients undergoing HD. They found that exercising patients from both groups had improvement in cardiovascular autonomic modulation, biochemical markers, as well as in sleep quality, reduced anxiety, and depression levels. KR, however, had better results with respect to autonomic balance restoration as opposed to patients on HD. The latter, on the other hand, showed improvements in blood pressure, HDL, haemoglobin and phosphorus levels. According to these findings, they concluded that exercise training has the capacity to restore balanced autonomic control in patients who received RT. Furthermore, physical exercise should be also suggested to patients undergoing HD in order to similarly increase autonomic modulation and reduce cardiovascular risk factors.

Treatment

HRV is also known to be affected by certain medications or several invasive procedures.

Spironolactone has a favourable effect on cardiac autonomic function. In particular, Flevari et al[96] described how aldosterone antagonists improve AD in HD patients in the absence of heart failure. In the management of heart failure, as well as during progressive renal damage, the use of angiotensin converting enzyme inhibitors and angiotensin receptor blocking is associated with reduced mortality[97]. β-blockers and a-blockers are commonly used in patients with AD. In patients with CKD however, β-specific blockade has been linked with increased parasympathetic activity[98]. Moreover, the use of β-blockers reduces the risk of AD and SCD in several high-risk patient groups, such as those with arterial hypertension, chronic ischemic heart disease, heart failure, and left ventricular dysfunction[99].

HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase inhibitors reduce cardiovascular morbidity by improving endothelium function, inflammation and nitric oxide bioavailability[100,101]. One pleiotropic effect of statins is to induce a decrease in sympathetic activity. Statins seem to have a sympathetic inhibitory action which reduces the risk for arrhythmia and SCD, although further studies are needed to clarify the exact mechanisms behind their action and the associated clinical impact[102]. In diabetic patients, the use of icodextrin-based peritoneal dialysis reduces fluid overload which showed higher degree of recovered sympathetic function as opposed to glucose-based solution[103]. Antiarrhythmic treatment in nephropathic patients does not significantly differ from management strategies applied in the general population, at least according to general guidelines[104]. At the moment, amiodarone seems to be one of the most effective antiarrhythmic drugs used in the treatment of ventricular arrhythmias and atrial fibrillation, but specific trials are needed in patients with CKD[105-107].

Conclusions

Autonomic symptoms are non-specific and are not pathognomonic of AD in patients with acute or chronic renal disease. Nevertheless, they are a cause of morbidity and must be individually investigated in each patient in order to eliminate other differential diagnoses. The identification of sympathovagal imbalance is relatively straight forward in patients with renal impairment and it should be addressed relatively early, considering its negative impact on cardiovascular system. Therefore, it is necessary to confirm this as an underlying diagnosis which can be obtained by using relatively simple cardiovascular function tests, such as the most commonly used analysis of HRV.

Importantly, the evaluation of HRV in patients in chronic replacement therapy could be performed for CVD risk stratification. Patients with

a stable RRF in PD have the lowest risk due to a better autonomic function. Further advancements in dialysis methods may also provide an opportunity to prevent CVD complications of dialysis treatment.

The possibility of effective treatment for at least some aspects of AD underlies the need to identify comorbidities (i.e., diabetes) and associated cardiovascular risk factors. Thus, the HRV analysis could be a useful tool in the diagnostic workup, as well as in the follow up, of AD and could therefore guide toward appropriate therapeutic strategies.

When possible, the restoration of normal ANS function is imperative in order to minimize the chances of cardiovascular disturbances (such as arrhythmias) in a population with renal function impairment.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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