DYNAMICS OF HEART RATE VARIABILITY IN PATIENTS WITH CHRONIC KIDNEY DISEASE DURING BACKGROUND THERAPY (LITERATURE REVIEW)

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Abstract. *This review article examines the effect of various therapeutic interventions on autonomic dysfunction that characterizes chronic renal failure in CKD. It has been shown that drugs acting on the renin-angiotensin system, as well as central sympatholytics, improve autonomic cardiovascular control.*

Keywords: *autonomic nervous system, sympathetic activity, parasympathetic activity, chronic renal failure, heart rate variability.*

Chronic kidney disease (CKD) can be defined as persistent damage to the renal parenchyma resulting in chronic deterioration of renal function, which may progress gradually to terminal kidney disease (TKD). The term CKD recognizes that this condition exists on a continuum with varying degrees of renal function impairment, rather than as a separate condition of renal insult (acute kidney injury). The term CKD has replaced the previously used term "chronic renal failure".

CKD is defined as the presence of impaired renal structure or function persisting for more than 3 months [27]. This includes 1 or more of the following: 1) an FFR less than 60 mL/min/1.73 m2; 2) albuminuria (i.e., urinary albumin ≥30 mg in 24 hours or urinary albumin-to-creatinine ratio [ACR] ≥30 mg/g); 3) abnormalities in urine sediment, histology, or imaging suggestive of renal damage; 4) renal tubule abnormalities; or 5) a history of renal transplantation [9,27].

According to the literature, CKD affects 8% to 16% of the population worldwide and is often not recognized by patients and physicians [18,25]. The disease is more prevalent in low- and middle-income countries than in high-income countries [33].

CKD is most commonly associated with diabetes and/or hypertension, but there are other causes of onset such as glomerulonephritis, infections, and environmental exposures (e.g., air pollution, medicinal herbs, and pesticides) that are common in Asia, sub-Saharan Africa, and many developing countries [25]. Genetic factors may also contribute to the risk of CVD. For example, sickle cell trait and the presence of two APOL1 risk alleles, which are common in people of African but not European descent, may double the risk of developing CKD [20,25,34,36].

CKD impairs physiologic and biological mechanisms of the body, such as water-electrolyte and pH balance, blood pressure regulation, toxin and waste excretion, vitamin D metabolism, and hormonal regulation. Many patients with CPB are at risk for hyperkalemia, hyperphosphatemia, chronic metabolic acidosis, bone destruction, blood pressure abnormalities, and edema [22-24,26]. CPB often remains undiagnosed due to the lack of visible symptoms in the early stages. It is estimated by K.E. Adair et al, 94% of people with mild to moderate renal function decline and about 48% of people with severe renal dysfunction remain undiagnosed [5]. Early detection and treatment by primary care physicians is important because progression of CKD is associated with adverse clinical outcomes, including terminal kidney disease (TKD), cardiovascular disease, and

increased mortality [10,32]. For example, studies have found that the prevalence of cardiovascular disease is markedly higher among persons with CKD compared with persons without CKD. For example, in the 5% Medicare sample, 65% of 175,840 adults aged 66 years and older with CHBP had cardiovascular disease compared with 32% of 1,086,232 without CHBP. Moreover, the presence of CHBP was associated with worse cardiovascular outcomes. For example, in the same population, the presence of CBP was associated with poorer 2-year survival in people with coronary heart disease (77% vs 87%), acute myocardial infarction (69% vs 82%), heart failure (65% vs 76%), atrial fibrillation (70% vs 83%), and cerebrovascular disorder/transient ischemic attack (73% vs 83%) [43]. Thus, the main component of treatment of CKD is the reduction of cardiovascular risk. In patients aged 50 years and older with CKD, treatment with statins at low to moderate doses is recommended, regardless of low-density lipoprotein cholesterol levels [7,28,42].

In patients with CKD, drug dosage adjustments are often required. Common medications requiring dose reduction include most antibiotics, direct-acting oral anticoagulants, gabapentin and pregabalin, oral hypoglycemic agents, insulin, chemotherapeutic agents, and opiates, among others [19,27]. In general, the use of medications with a low likelihood of beneficial effects should be minimized because patients with CKD are at high risk of adverse drug effects [11,12]. In recent years, much attention has been paid to studies on the prognostic value of heart rate variability in determining the risk of sudden death and dangerous ventricular arrhythmias in patients with coronary heart disease [8,15]. At the same time, the issue of diagnostics of electrical instability of the heart in patients with CPB remains insufficiently studied.

Low level of heart rate variability (HRV) indicates monotonically regular heart rate (HR). Moreover, it is associated with impaired regulatory and homeostatic functions of the autonomic nervous system, which reduces the body's ability to cope with internal and external stressors. Thus, HRV is a noninvasive electrocardiographic method that can be used to measure the autonomic nervous system in various clinical situations [2,41]. The term "variability" means changeability. There is a change in the parameters of the heart work and rhythm - it is its reaction to certain causes. Thus, HRV serves as an indicator of the work of the CCC, as well as a mechanism for the subsequent regulation of the work of the body as a whole. Among other basic indicators of heart rate variability are the following:

- Heart rate (HR) - reflects the work of the heart in general.

- Standard deviation of the average length of the RR interval (sdRR) and the coefficient of variation (VAR) - indicates the total activity of adaptation-regulatory mechanisms. - Difference indices (sdRR, RMSSD and pNN50) - reflect the activity of the parasympathetic nervous system (PN).

- Low frequency wave spectrum power (LF) - show the activity of the center that regulates vascular tone.

- Very Low Frequency (VLF) - show the activity of the center that regulates cardiac activity in the subcortical area of the brain.

- Mode, mode amplitude - indirectly reflect the degree of activation of sympathetic NS.

- Difference between min and max duration of intervals between contractions (MxDMn) - activity of parasympathetic NS.

- Stress index (SI) - stress level of adaptation and defense systems.

Patients with CKD are predisposed to cardiac rhythm disorders including atrial fibrillation (AF)/atrial flutter, supraventricular tachycardias, ventricular arrhythmias and sudden cardiac death (SCD). FP is the most common sustained arrhythmia [4,13]. The prevalence of FP is high, with estimates ranging from 16% to 21% in non-dialysis-dependent patients with CKD and 15% to 40% in patients on dialysis [3,6]. CKD and FP share many common risk factors, making it difficult to determine the contribution of individual factors to the condition or related outcomes.

For non-dialysis CKD, there appears to be an independent association between CKD and risk of FP [1,39]. It is bidirectional, with CKD increasing the incidence of PD and the presence of PD exacerbating renal impairment [17,31,37]. Drugs currently used in the treatment of CPB patients are aimed at providing direct and indirect (i.e., blood pressure-lowering dependent) nephroprotective effects to limit the progression of renal dysfunction and control the elevated BP values that almost always accompany progressive renal failure [30,45]. However, they also aim to have a favorable effect on autonomic function. Regarding parasympathetic changes, evidence has been provided that some drugs can improve vagal control of heart rate (HR), as assessed by spectral analysis of the heart rate signal. This includes beta-blockers, angiotensin II receptor antagonists and, although not always homogeneously, angiotensin-converting enzyme (ACE) inhibitors [38]. In contrast to the effects on the sympathetic cardiovascular system, statins have not demonstrated any potentiating effect on cardiac vagal control, assessed by heart rate variability, in patients with chronic renal failure [35]. It should be emphasized that statins may play an important role in determining this effect, since the use of these drugs has been reported to reduce elevated values of sympathetic nerve activity even when administered to patients without concomitant administration of any other sympathomodulatory drugs [40,46].

A significant reduction in cardiovascular sympathetic activity, as assessed by norepinephrine assay in venous plasma or more directly by microneurographic method, has been reported in patients with chronic renal failure when treated with central sympatholytics such as clonidine and moxonidine, the latter drug being evaluated when administered in addition to conventional treatment with pharmacological compounds acting on the renin-angiotensin system [41]. It should be emphasized that the mechanisms responsible for the sympathomodulatory properties of the above classes of drugs appear to be multiple and heterogeneous, including (1) reduction of the excitatory action of angiotensin II on peripheral and central adrenergic nerve impulses, (2) partial or complete restoration of the sympathoinhibitory properties exerted by the arterial baroreflex, and (3) direct effects of drugs (particularly but not exclusively central sympathoinhibitory drugs) on the central nervous system [21].

When discussing autonomic response to available therapeutic interventions for the treatment of CPB, several questions still remain unanswered. Three of them deserve special mention. First, neurohumoral interactions between heart and kidney may be an important target in the near future for therapeutic interventions aimed at exerting neuromodulatory effects.

Second, future studies will allow us to investigate whether previously described pharmacologic, nonpharmacologic, or device interventions can restore normal autonomic function in patients with nephropathy. Although the available data are limited, an in-depth analysis of the results obtained with the various treatments mentioned above may suggest that combination treatment with several drugs, including compounds acting on the renin-angiotensin system and central sympatholytic agents, may restore "normal" sympathetic function in patients with chronic kidney disease comparable to that described in healthy subjects. Similar conclusions were reached

when analyzing the results of a 43-month follow-up that R. Dell'oro et al. conducted in patients with congestive heart failure after baroreflex activation therapy [16].

A final question concerns the magnitude of the sympathoinhibitory effects that should result during treatment. Although there is currently no answer to this question, it should not be forgotten that excessive sympathoinhibitory effects of therapeutic interventions have a deleterious effect on morbidity and mortality. This was demonstrated in the MOXonidine in Congestive Heart Failure (MOXCON) trial in advanced heart failure using excessively high daily doses of moxonidine [14]. This was also demonstrated in hypertensive patients included in the International VERapamil SR-Trandolapril STudy (INVEST) study, in which achieving clinical heart rate values below 55 heart beats per minute during treatment with beta-blockers contributed to a paradoxical increase in side effects [29]. Thus, future studies in patients with chronic renal failure are needed to clarify the unresolved issues outlined above and to gather more information on the autonomic effects of the therapeutic procedures currently used in the treatment of chronic kidney disease.

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