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PERSPECTIVES

Autonomic dysfunction in chronic kidney disease: An old problem in a new era

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Introduction

Chronic kidney disease (CKD) is a growing problem globally, affecting 11.9% of people in Taiwan.[1] Autonomic dysfunction is a common and important complication of CKD because it contributes to the high incidence of cardiovascular morbidity and mortality.[2] Autonomic dysfunction in CKD means increased sympathetic nervous system activity and depressed parasympathetic pathway. Its clinical findings include delayed gastric emptying, bowel dysfunction, impotence, sweating abnormality, etc. Cardiovascular autonomic dysfunction consisting of resistant hypertension, orthostatic and intradialytic hypotension, reduced heart rate variability (HRV), and impaired spontaneous baroreflex sensitivity poses an increased risk of sudden cardiac death.[2] However, the mechanisms are not thoroughly understood and most of the research included only a small population and focused on dialysis patients. The prevalence of autonomic dysfunction among nondialysis patients has also not been reported widely.

Pathogenesis of autonomic dysfunction in CKD

Although it has been reported that uremic toxins could directly damage small nerve fibers via hydroelectrolytic changes producing expansion or shrinkage of the endoneurial space, the exact pathogenesis is not completely elucidated.[3] One reason is that various underlying causes of CKD such as diabetes, autoimmune disease, or polycystic kidney disease could render the pathophysiology more complicated than uremic toxins do. Further experimental research should be done to clarify the effect of uremic toxins on autonomic function.

Some clinical studies have reported that CKD alters autonomic function indirectly through the following mechanism[2]: the renin–angiotensin–aldosterone system is activated and angiotensin II modulates regional sympathetic outflow and resets the baroreflex toward a higher blood pressure range. CKD also activates excitatory renal afferent fibers and impairs inhibitory renorenal reflex, contributing to increased peripheral sympathetic activity. Other factors such as salt retention, decreased nitric oxide bioavailability, cardiovascular remodeling, and increased endothelin and insulin production may also influence sympathetic and cardiovagal tone.

Assessment of autonomic dysfunction in CKD

More than 30 years ago, Ewing and Clarke[4] suggested a group of autonomic functions tests including heart rate variation in response to deep breathing, heart rate response to standing, postural changes in blood pressure, the Valsalva maneuver, and sustained handgrip. However, the Ewing test requires patient cooperation and is often not performed due to comorbidities in the patients.

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Tsai et al[5] demonstrated autonomic dysfunction in CKD patients with noninsulin-dependent diabetes mellitus by the Valsalva ratio or postural changes in systolic blood pressure. They found that the incidence of cardiovascular dysfunction increases as the renal functional reserve decreases. In recent years, although some advanced techniques have been used for autonomic function measurements, there remains significant limitations such as a small population and multiple heterogeneous causes of CKD. Therefore, cross-comparison between studies is difficult.

Nowadays, the most useful and convenient method should be identified to standardize the definition of autonomic dysfunction in CKD. This definition might also provide a useful classification with adequate prognostic information. HRV is an old method but it is a practical tool because it is noninvasive and easily applied. We can only record 5 minutes of electrocardiogram to analyze beat-to-beat R-R interval variability. These signals can be switched to frequency domain data. High-frequency (HF) power reflects parasympathetic modulation, while sympathetic function can be estimated by normalized low-frequency (LF) power and the ratio of LF power to HF power (LF/HF). Considerable studies support HRV indexes as good predictive factors for cardiovascular risk.[6] Thus, we believe that HRV measurement might be able to provide sufficient information and allow comparison of future research on a common platform.

Treatment of autonomic dysfunction in CKD

Angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, and renin inhibitors have been reported to have comparable sympathoinhibitory and antihypertensive effects. In addition, β-receptor blockade appears to improve HRV and cardiac autonomic balance in patients with end stage renal disease.[2] Some surgical interventions such as renal denervation have shown a beneficial blood pressure effect and better renal outcome in patients with CKD.[7]

In addition, a traditional Chinese exercise, breathing-coordinated exercise, could improve the quality of life for hemodialysis patients.[8] The exercise consists of end-inspiratory pause, slow diaphragmatic breathing, and Kegel's exercise. The exercise maneuvers closely resemble the autonomic function test. Such an exercise may exaggerate the effect of respiration on cardiac output and demonstrate a pulsatile increase of peripheral microcirculation. This exercise is gentle and requires only little effort. Patients who underwent this exercise also showed improvement of appetite, bowel movement, physical strength, and sexual function. These results may be related to the training of cardiovascular autonomic reflexes during the exercise.

Further perspectives

Autonomic dysfunction in CKD is complex and multifactorial. In order to improve treatment strategies, we should define autonomic dysfunction in CKD clearly by a powerful and convenient method first. Currently, HRV has the potential to be widely adopted in CKD patients. Future studies should validate the sensitivity and specificity of HRV indexes for the severity of autonomic dysfunction in CKD. To better understand the mechanism, more experimental research is necessary to delineate the nerve damage process by uremic toxins. Clinical studies should categorize patients according to various etiologies of CKD and include more nondialysis CKD patients.

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