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Influencing factors and prognosis of blood pressure variability in maintenance hemodialysis patients

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Abstract: *The fluctuation of Blood pressure within a certain period of time is called Blood pressure variability (BPV). Recent studies have confirmed its value in predicting cardiovascular events and death. However, large changes in hemodynamics and internal environment in dialysis patients due to dialysis treatment in a short period of time, often face more complex blood pressure variability. At present, there are a variety of research on BPV, and the pathogenesis and influencing factors of BPV are numerous. In this paper, the variability of blood pressure in maintenance hemodialysis patients and its influencing factors were reviewed to provide reference for the management of hypertension in dialysis patients.*

Keywords: *Hemodialysis, Blood pressure variability, Influencing factors, Prognosis*

1. Introduction

In recent years, the concept of blood pressure variability (BPV) has received wide attention. Clinical studies have found that abnormal blood pressure fluctuations are closely related to the structural and functional impairment of target organs, cardiovascular and cerebrovascular events, and mortality, and this effect does not depend on the exact value of blood pressure. It may become a new risk predictor and therapeutic target. In patients on long-term hemodialysis, the mechanism of blood pressure variability is more complex and diverse, and the mechanism and influencing factors of BPV are still unclear. This article reviews the definition, classification, measurement methods, influencing factors, significance and clinical application of BPV in maintenance dialysis patients.

2. Definition and measurement methods of blood pressure variability

The fluctuation of blood pressure over a certain period of time is called blood pressure variability. BPV can be divided into long-term BPV and short-term BPV according to the length of time. Long-term BPV is usually calculated on measured blood pressure in days, weeks or months, in a dialysis population, long-term BPV is usually calculated as a blood pressure measurement at each start of dialysis over a period of time. Short-term BPV is usually measured by ambulatory blood pressure monitoring at 24 h or specified short intervals, in a dialysis population, short-term BPV refers to blood pressure variability during dialysis. According to the pre- and post-dialysis periods, it can be divided into inter-dialysis BPV and intra-dialysis BPV. According to systolic blood pressure and diastolic blood pressure, it can also be divided into systolic blood pressure variability and diastolic blood pressure variability.

A number of indices have been proposed to assess and quantify BPV: (1) BP change is the absolute value of blood pressure change before and after dialysis, which is easy to calculate, but does not reflect the fluctuation of blood pressure during dialysis. (2) Standard deviation (SD) is a measure of the average absolute distance between an observed measurement and its mean, which only reflects the dispersion of the measured BP near the mean, regardless of the order of measurement, and is highly dependent on the mean BP. (3) The coefficient of variation (CV) is another widely used parameter of BPV, the standard deviation divided by the corresponding mean, as it is independent of the mean blood pressure level, so data with different mean values can be compared. (4) The average real variability (ARV) is the average of the absolute difference between successive BP measurements, which takes into account the order of BP measurements and is relatively insensitive to low sampling frequencies[1]. (5) The variation independent of mean (VIM) was used to exclude the influence of mean BP in BPV by

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applying nonlinear regression analysis. (6) The logarithmic transformation of BP was carried out to establish a linear mixed-effect model with time variation. The SD of the residuals (BP residual) derived from the model (the difference between the true BP and the predicted BP) can also assess BPV. This measurement method is independent of the fluctuation of the mean blood pressure, considers the effect of dialysis on blood pressure, can reflect the true error with the expected blood pressure, and is applicable to describe the BPV of patients during dialysis. However, due to the complexity of the method, it is rarely used in clinical practice, but this index is a promising method for assessing blood pressure variability considering the change trend of blood pressure.

3. Influencing factors of blood pressure variability in maintenance hemodialysis patients

The mechanism of blood pressure variability in dialysis patients is very complex. Not only to consider the circadian rhythm of the general population, but also consider the long-term capacity overload, autonomic dysfunction, vascular compliance and other factors, especially the rapid clearance of water in the dialysis process, rapid changes of plasma concentration, electrolyte and acid base balance, the clearance of vasoactive transmitter and part of the antihypertensive drugs in dialysis. Therefore, the impact of intra-dialysis BPV cannot be ignored.

3.1 Traditional factors

3.1.1 Age

Most of the potential mechanisms of blood pressure variability, such as hemodynamic instability, autonomic dysfunction[2], arterial remodeling, arteriosclerosis[3, 4], hypobarreflexia, endothelial dysfunction[5] and chronic inflammation[3, 6, 7], are associated with aging, and the aging of organ and system function reduces the ability to regulate stress.

3.1.2 Sex

Sarafidis et al.[8] found that men were a risk factor for a higher short-term ARV in CKD patients, while K.-I. Kim et al.[9] suggested that women had a higher BPV compared to men. This may because estrogen may have a protective effect on atherosclerosis in female patients, but the effect of estrogen decreases with age, and there are sex differences in atherosclerosis and vascular inflammation, and the differences change with age[10].

3.1.3 Obesity

Excessive ectopic adipose tissue leads to dysfunction, secreted cytokines and chemokines mediate endocrine effects, to increase vasoactive mediators (angiotensin II, aldosterone, renin)[11], change the dynamic homeostasis environment, and induce local or systemic inflammation. Increased oxidative stress leads to insulin resistance, abnormal glycemia[12]. Endothelial dysfunction due to dyslipidemia increases vascular stiffness thus increasing blood pressure variability.

3.1.4 Habits

Smoking, tobacco components induce oxidative stress and inflammation, induce endothelial dysfunction and atherosclerosis formation to increase blood pressure variability[13, 14]. High-sugar and high-fat diets increase vascular inflammation, insulin resistance[12] and the lack of exercise contribute to obesity[15].

3.2 Hemodialysis related factors

3.2.1 Frequency and duration of dialysis

It has been reported that increasing the frequency of dialysis may reduce the variability of blood pressure during dialysis and shorten the time to recovery after dialysis[16], possibly due to the reduced need for active ultrafiltration, and reduced duration of dialysis. Fagugli RM et al.[17] suggested that, compared with dialysis three times a week, dialysis once a day for a shorter duration of dialysis could better control blood pressure and even stop antihypertensive medications. Rapid changes in blood volume, electrolyte levels, and osmotic pressure can be reduced in the shorter duration but more frequent HD treatment. Blood pressure fluctuations can be better controlled by increasing treatment duration and reducing ultrafiltration (UF)/h[18]. However, Kraus MA et al.[19] suggested that intensification of HD increases the risk of vascular access complications and infection, and Increases

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the burden on patients and caregivers. The development of dialysis protocols should consider the potential benefits and risks of treatment.

3.2.2 Vascular access

Studies have shown that venous catheters have a more significant effect on hemodynamics than internal arteriovenous fistulas, and patients using catheters have higher blood pressure variability[20]. In addition, central catheters may lead to associated infections and thrombosis, and increased blood pressure variability may also raise the risk of thrombotic events in pathways[21]. Therefore, it is necessary to choose the time of fistula reasonably and encourage the use of arteriovenous fistula for hemodialysis.

3.2.3 Ultrafiltration quantity and rate

Flythe et al.[22] believed that ultrafiltration volume was positively correlated with the variability of SPB in dialysis, which might be due to the rapid changes in blood volume, electrolyte level and osmotic pressure in a short period of time and increased the variability of blood pressure. Low ultrafiltration volume and/or ultrafiltration rate can reduce the variability of blood pressure in dialysis[16], Shafi et al.[23] suggested that higher ultrafiltration volume can reduce long-term BPV, reduce the volume load of dialysis interval by maintaining dry weight, and help control blood pressure.

3.2.4 Interdialytic weight gain (IDWG)

The interdialytic weight gain is generally due to the accumulation of excess fluid from renal failure. Volume overload, rapid clearance of accumulated fluid, decreased blood volume after dialysis, and decreased renal perfusion may overactivate the angiotensin-aldosterone system and increase blood pressure variability. IDWG may be associated with high salt intake, blood pressure is salt-sensitive, and high salt intake reduces the sensitivity of baroreceptors, thus affecting BPV[24]. A large volume load leads to an increase in ultrafiltration, which also increases blood pressure variability. In order to minimize the volume change during each course of treatment, patients should be required to control the growth rate of interdialysis body mass < 5%, take low sodium diet and limit water intake.

3.2.5 Hemodialysis mode

Nowadays, the mode of hemodialysis treatment has changed from ordinary dialysis mode to heterozygous dialysis mode. Heterozygous dialysis mode can improve dialysis interval (long) and intra (short) BPV in patients. The reason may be that BPV is associated with microinflammation in CKD patients, and the heterozygous dialysis modality can remove medium and macromolecular toxins to a greater extent and improve the microinflammatory state in patients, thus reducing BPV.

3.3 Disease-related factors

3.3.1 Primary disease

Hypertension, diabetes, hyperlipidemia, cardio-cerebrovascular disease, peripheral vascular disease, inflammation and other diseases can increase blood pressure variability, mainly related to inflammation, vascular endothelial damage, arterial plaque formation, arterial stiffness, renin-angiotensin-aldosterone (RAS) system activation, reduced baroreflex sensitivity and so on. Abnormal glycemia can lead to the disturbance of autonomic nervous function, but also aggravate vascular calcification, arterial wall hardening, microvascular disease, destroy vascular compliance, and thus increase BPV.

3.3.2 Abnormal calcium and phosphorus metabolism

Long-term hemodialysis patients are often accompanied by secondary hyperparathyroidism and abnormal calcium and phosphorus metabolism. Concistrè A et al.[25] suggested that serum calcium and PTH were positively correlated with blood pressure variability and cardiovascular morbidity and mortality, which may be related to cardiometabolic disorders, such as metabolic syndrome, increased carotid artery thickness in the intima, vascular calcification[26] and coronary microvascular dysfunction[27]. Secondary hyperparathyroidism and calcium and phosphorus metabolism disorders may activate the sympathetic nervous system and RAAS system, impair vascular endothelial function, increase vascular hardness, and thus increase blood pressure variability. Parathyroidectomy in patients with hyperparathyroidism is associated with reduced systolic blood pressure variability[25], and a higher risk of hypoparathyroidism, low bone remodeling, hyperphosphatemia, hypercalcemia and cardiovascular calcification[27].

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3.3.3 Nutritional status

Serum albumin level is the most commonly used nutritional marker in hemodialysis patients, and protein energy consumption is very common in elderly hemodialysis patients[28]. Studies have shown that[29] albumin level is closely related to the variability of blood pressure in dialysis patients, possibly because patients with good nutritional status have lower microinflammatory state and oxidative stress level in the body[30], therefore, blood vessel damage is light and blood pressure is relatively stable. Nutritional interventions and treatment of underlying inflammation may reduce BPV variability.

3.3.4 Antihypertensive drugs

Whether antihypertensive drugs are related to blood pressure variability in dialysis patients is still controversial. It has been reported that calcium channel blockers (CCB) antihypertensive drugs can effectively reduce short-term BPV[20, 31]. The reasons why CCB can reduce BPV may be as follows:

(1) Dislike β -blockers and RAS system inhibitors, CCB can relax peripheral arteries and increase arterial compliance; 2) CCB is mainly metabolized by the liver and is not easy to be cleared by hemodialysis, which can achieve long-term antihypertensive effect and reduce blood pressure fluctuations. The pathogenesis of renal hypertension is complex, and often requires the combination of drugs. β -blockers can be added when patients got rapid arrhythmia, increased sympathetic activity, coronary heart disease, cardiac dysfunction. While Shafi et al.[23] suggested that the number of antihypertensive drug was related to BPV, that patients receiving more than two antihypertensive drugs had higher BPV, and that individuals using non-beta-blocker and non-RAS (renin-angiotensin system) antihypertensive regiments had lower BPV than those using a regimen containing beta blockers. For dialysis patients, the blood pressure reduction regimen may be different on dialysis and non-dialysis days, and they may be asked to suspend medication before dialysis, which can also increase blood pressure instability.

3.4 Environmental factors

The environment with industrial pollution, different latitudes, different altitudes and seasonal temperatures will also affect BPV.

4. Blood pressure variability and prognosis of patients on maintenance hemodialysis

The main mechanisms of target organ damage by BPV are as follows:(1) inflammatory reaction[20] :When BPV increases, the abnormal longitudinal shear force and ring tension on the blood vessel wall and platelets increase, then promotes the endothelial injury and platelet activation, increases the synthesis and release of inflammatory factors, especially IL-6, promotes the occurrence of inflammatory reaction, and finally accelerates the occurrence and development of atherosclerosis；(2) The activation of renin-angiotensin-aldosterone (RAS) system damages cardiomyocytes[32]: increased blood pressure variability can cause the activation of RAS system, promote cardiomyocyte protein synthesis, DNA synthesis and cell apoptosis in myocardial fibroblasts and other mechanisms lead to ventricular remodeling and left ventricular function change; (3)Direct damage to endothelial cells[33]: either too high or too low blood pressure has adverse effects on the body, and the rapid decrease in blood pressure may lead to obvious or subclinical ischemic injury to the target organs, while the sudden increase in blood pressure can lead to capillary endothelial shear stress injury.

Blood pressure variability is considered an independent predictor of early renal impairment[34], also a poor prognostic factor for the occurrence, progression, and severity of renal outcomes in patients undergoing CKD and hemodialysis[35]. Chronic kidney disease is also an important risk factor for cardiovascular disease, infection, and cognitive impairment[36]. Cardiovascular disease is a leading cause of morbidity and mortality in patients with end-stage renal disease undergoing hemodialysis, which may be due to hypertension, diabetes mellitus, dyslipidemia, and other aspects such as chronic volume overload, anemia, inflammation[37]. BPV is also one of the risk factors, and numerous studies have shown that blood pressure variability in hemodialysis patients is independently associated with cardiovascular events and death[23, 38]. As BPV increases, it increases the risk of cardiovascular disease and deterioration of kidney function11. The occurrence of cardiovascular events is usually the result of long-term exposure to hypertension and other risk factors, and often precedes asymptomatic functional and structural abnormalities called target organ injury, particularly left ventricular hypertrophy, BPV is associated with left ventricular hypertrophy in dialysis patients. Left ventricular hypertrophy (LVH) is a very common cardiac manifestation in dialysis patients.

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Heart failure is a common complication in the patients with hemodialysis. Fluid excess, left ventricular diastolic dysfunction, arterial stiffness, left ventricular systolic dysfunction often induce heart failure, because the nerve fluid factor is activated in the body, early heart failure presents a certain degree of blood pressure and heart rate, the decline with the heart function, heart output gradually reduced, lead to the occurrence of hypotension. Patients with advanced heart failure have more significant blood pressure fluctuations, which are more prone to hypotension, resulting in insufficient blood perfusion in target organs, resulting in increased blood pressure fluctuations and increased blood pressure variability (BPV).

Elevated systolic BPV is an independent risk factor for stroke. Elevated BPV is an independent predictor of cerebrovascular disease and cognitive decline and is associated with cognitive impairment and dementia[39]. Vascular dysfunction, increased risk of cerebrovascular disease and decreased cerebral perfusion may play a role in the development of Alzheimer's disease and vascular dementia, it may because that blood pressure fluctuations cause ischemic damage in white matter through cerebral hypoperfusion[40].

5. Conclusion and prospect

Blood pressure variability is important for cardiovascular health in maintenance hemodialysis patients. Although current clinical guidelines do not consider blood pressure variability as a target for the management of hypertension or heart failure, given its potential benefit in reducing the risk of cardiovascular disease, controlling blood pressure variability should be included as a therapeutic goal to help assess patient outcomes and predict cardiovascular events and all-cause mortality in maintenance dialysis patients. Future research should aim to establish a recognized and reliable measure of blood pressure variability and manage it through standardized practices and appropriate assessment indicators. In addition, the investigation and intervene of adverse factors affecting blood pressure variability is also an important research direction.

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