

Hypotension in renal failure patients undergoing dialysis therapy

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Abstract: In this paper we present the current views on the causes, symptoms, prevalence and clinical importance of hypotension in chronic renal failure patients undergoing dialysis therapy. The results of clinical studies indicate that persistent hypotension in dialysis patients is associated with increased mortality.

Key words: hemodialysis, hypotension, peritoneal dialysis, renal failure

INTRODUCTION

Hypotension, called also low blood pressure, can be described as such blood pressure values which do not guarantee the minimal blood flow in the vascular system, indispensable for the correct functioning of the organism. An accurate specification of blood pressure values, which enable the diagnosis of hypotension, is practically impossible as they may markedly differ in each person. Apart from that, a physiological blood pressure day-nocturnal rhythm is found in healthy individuals, as well as an individual pressure diversification, induced by common stimuli such as the vertical position, physical exercise, emotional stress and others [1].

Owens and O'Brien [2] assessed hypotension prevalence from a 24-hour blood pressure measurement in healthy individuals, the diagnostic criterion being the systolic blood pressure <115 mmHg at daytime and <70 mmHg at night, and the diastolic blood pressure <97 mmHg at daytime and <56 mmHg at night in males, and respectively lower in females: 105 mmHg and 65 mmHg, and 92 mmHg and 52 mmHg. There is no data in the bibliography on similar studies in dialyzed patients.

In conventional blood pressure measurement methods the value of <120/80 mmHg [3-5] is considered optimal. It has also been shown that the arterial blood pressure >115/75 mmHg correlates with a higher risk of cardio-vascular complications [5]. It should therefore be accepted that maintaining the arterial blood pressure below <115/75 mmHg is related to health benefits. In comparison with results obtained earlier by Owens and O'Brien [2] such blood pressure values border on hypotension, which may be an indication for a 24-hour blood

pressure measurement and cardiologic diagnosis, especially with such clinical symptoms as dizziness, orthostatic collapse in blood pressure, or syncope. These are typical symptoms caused by hypotension.

The blood pressure being too low even for a short period induces complex blood pressure control mechanisms bound to guarantee an appropriate organ perfusion [2]. With the efficiency of those mechanisms and with the discontinuation of stimuli causing a significant arterial blood pressure fall, the normalization of blood pressure is quickly obtained. A typical example would be the faint of a healthy individual who has been in an upright position for a long time which is gone immediately with the change of position to horizontal with uplifted legs. The disruption, however, of the blood pressure fall compensation mechanisms, or their exhaustion as a result of an extended duration stimulus causing a significant blood pressure drop, results in serious health consequences.

At a very low arterial blood pressure, the organ blood flow auto regulation mechanisms, leading to compensation of a commonly nonsignificant change in perfusion pressure through the change in vascular resistance in order to maintain the blood perfusion on a relatively constant level [2], fail. A fall of systolic blood pressure in the systemic circulation below 65 mmHg results in the drop of central nervous system blood perfusion. The drop in central nervous system blood perfusion causes hypoxia, especially of the very sensitive cortex leading to a mental block in a short time. A predominant response to the drop of blood pressure, from the heart, is a reflex rise of sympathetic nervous system discharges in the noradrenergic nerves, which guarantees the maintenance of the coronary blood flow, and is caused by metabolism alterations taking place in the myocardium at this time. At the same time the constriction of the cutaneous vessels, renal vessels and the gastrointestinal tract vessels is observed. Thanks to this, the cardiac circulation (as of the central nervous system) is maintained while the blood flow in other organs is restricted. The prolonging excessively low blood pressure results in a shock which is a serious life threat. With the insufficiency of the

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organism's compensation mechanisms, a rapid fall in a readily risen blood pressure, even only up to normal values, is related to a similar threat.

Intradialytic hypotension and chronic hypotension in hemodialysed patients

It is necessary to distinguish 2 main types of hypotension in hemodialysed patients: the episodes of hypotension closely related to the dialysis therapy, namely the dialysis hypotension, and a chronic hypotension not directly related to the dialysis therapy.

Hypovolemia resulting from ultrafiltration during hemodialysis is the main factor to induce the episodes of a rapid arterial blood pressure drop in patients undergoing this type dialysis therapy [6]. Additional factors inducing the hemodynamic instability during hemodialysis are: the rise of body temperature and the dialysis solution composition (the type of buffer used, water quality, electrolyte composition) [6-8]. In new studies the term intradialytic morbid event IME has been introduced to describe such a fall in systolic blood pressure or the occurrence of a typical symptom (i.e. cramps, dizziness, vomits, loss of consciousness), which due to its intensity requires a medical intervention (the discontinuation of ultrafiltration, changing the patient's body position, an intravenous infusion of a 0.9% NaCl) [7].

It is worth mentioning that the definition of an intradialytic morbid event IME does not determine a strict border in a blood pressure drop. Patients, in whom such episodes occurred 4 times in 4 weeks, are considered to be at a high risk of such an event [9]. A detailed description of such patients allowed to determine that in most of them there is an individual critical relative blood volume (expressed in percent of volume at the beginning of dialysis) under which intradialytic morbid events occur [9]. A greater percent of critical relative blood volume (RBVcrit) demands increased cautiousness with ultrafiltration volume modeling. Factors substantially contributing to a greater percent of the RBVcrit appear to be: advanced patient age, low diastolic blood pressure at the beginning of dialysis and at its end (suggesting there being a reduced vascular compliance as a result of calcification and rigidity), coexistence of heart failure (NYHA class I–IV) and of arrhythmias, a high body mass index and a decreased body mass gain between procedures (which determines the planned ultrafiltration volume during the procedure). Taking the above into account, the authors proposed a formula which with great likelihood allows to determine the RBVcrit limit [9]. According to authors, using this formula in practice may limit the risk of intradialytic morbid events. In addition, the modern hemodialytic equipment with a computerized sodium concentration, dialysis solution temperature and ultrafiltration volume monitoring system during hemodialysis, allows for a better control of additional factors influencing the risk for intradialytic morbid events [10-13].

The drop in the incidence of intradialytic morbid events has a great significance, as it has been estimated that intradialytic hypotension occurs in 30–40% of patients on long term hemodialysis [9]. The occurrence of intradialytic hypotension or intradialytic morbid events worsens the patient's life quality, decreases the treatment efficacy, and increases the patient's morbidity and therapeutic costs. The recurring symptomatic dialysis hypotension episodes may cause important brain and myocardium damage and correlate with cardiovascular complications, and are an independent death risk factor in prospective observation [9].

The immediate intervention in dialytic hypotension includes, as earlier mentioned, the discontinuation of ultrafiltration, changing the body position to a horizontal one with legs uplifted, and an intravenous infusion of a 0.9% NaCl solution. As many clinical study results have shown, a substantial drop of hypotension incidence in hemodialysed patients can be reached by designing the dialysis solution sodium concentration and the ultrafiltration volume at the same time. A greater concentration of sodium in the dialysis solution at the beginning of dialysis results in a greater sodium serum concentration in the first hour of dialysis, and protects against the drop in the RBVcrit [14-16].

Prevention of frequent intradialytic hypotension episodes is more difficult in patients who do not respect preventive indications, or when episodes occur despite the implementation of earlier mentioned prevention methods. A procedure is proposed which aims at increasing the systemic vascular resistance, increasing the venous return to the heart and cardiac output. Sympathomimetics such as midodrine, and in some patients the use of compressive support orthosis tights for lower extremities are also suggested. The efficacy of such procedures is, however, limited and requires further studies [17].

Chronic hypotension in hemodialysed patients

Chronic hypotension in hemodialysed patients, not immediately related to dialytic therapy, is a major problem related to poor prognosis. According to Barth et al. [9] chronic hypotension in hemodialysed patients can be found with the systolic blood pressure below 100 mmHg. These authors diagnosed chronic hypotension in 5.1% of 60 hemodialyzed patients from the intradialytic morbidity events higher risk group, and interestingly only in males (13% of 23 patients) [9]. Cases and Coll [17] assessed the occurrence of chronic hypotension as 5–10% of patients undergoing long lasting hemodialysis. The pathophysiology of hypotension in chronically hemodialysed patients is complex, and the potential mechanisms influencing chronic hypotension are: disorders of the autonomic nervous system, reduced reactivity of blood vessels to pressure factors such as noradrenaline and angiotensin II, the overproduction of vasodilators, such as adrenomedullin or nitric oxide, or advanced heart failure.

Autonomic nervous system neuropathy accompanying renal failure is an important factor which influences the occurrence of chronic hypotension in dialysed patients. As shown in multi-center studies, the dysfunction of the autonomic nervous system is more pronounced in dialysed patients with chronic hypotension than it is in patients with a normal arterial blood pressure [18]. Moreover, it has been proved that with the duration of the hemodialytic treatment, the arterial blood pressure drops, which may be an indicator of a worsening of the autonomic neuropathy, and also of the increasing heart failure in the course of a long-lasting dialysis therapy. In the assessment of the functioning of the autonomic nervous system, the analysis of sinus rhythm variability and the assessment of autonomic nervous system reflex activity is employed. Takahashi et al. [19] through spectral analysis of the variability of sinus rhythm in dialysed patients with chronic hypotension, observed the decrease of high frequency amplitude and the decrease in low to high frequency ratio. According to these data the authors drew a conclusion that the activity of the parasympathetic and sympathetic nervous systems in patients with chronic hypotension is diminished. This phenomenon however does not occur in dialysed patients with a normal blood pressure. According to Cases et al. [20], the reaction to the Valsalva maneuver in dialysed patients with chronic hypotension is weaker, at the same time being normal in patients with a normal blood pressure. Similar reactions were observed by authors during the assessment of the parasympathetic and sympathetic efferent pathways.

In dialysed patients the serum catecholamine concentration increases, being an indirect indicator of the increased activity of the sympathetic nervous system [21]. The results of the microneurographic examinations of Converse et al. [22] confirmed the increased sympathetic nervous system activity in patients with chronic renal failure. It has been proved that there is a postsynaptic nonsensitivity of the vascular system to stimuli from the sympathetic nervous system, which is explained by Esforzado et al. [18] and Carretta et al. [23] by the reduced number of the α_2 -adrenergic vascular receptors and by their dysfunction. In patients with chronic hypotension, the beta-adrenergic reaction is also weakened as a result of the limitation of number of β_2 -adrenergic receptors, which has been documented in studies performed on lymphocytes. The data of the mentioned authors [18,23] given above show that in dialysed patients with chronic hypotension and with an increased angiotensin serum concentration, the reaction of the circulatory system to angiotensin is weaker. This phenomenon can be explained by the diminished concentration of the angiotensin II receptors as demonstrated in the studies with trombocytes; similarly to the reaction of the β_2 -adrenergic receptors, as documented in studies on lymphocytes. It therefore seems that one of the accepted reasons for chronic hypotension in dialyzed patients is the reduced sensitivity of the cardiovascular system to adrenergic stimuli and to angiotensin II, with coexisting increased activity of the sympathetic system and the renin-angiotensin system.

Other factors that could contribute to the development of a chronic hypotension in dialysed patients would be a higher production of vasodilators such as adrenomedullin and nitric oxide, compared to patients with normal blood pressure [24]. Comparing the serum concentration of adrenomedullin and nitric oxide in hemodialysed normotensive, hypertensive and hypotensive patients, Cases et al. [20], found that patients with hypotension would have the greatest concentration of adrenomedullin, while the nitric oxide concentration in the 3 studied groups remained within similar ranges. The role of adrenomedullin in the occurrence of chronic hypotension in hemodialysed patients is widely accepted with the mechanism of its increased release not yet being fully explained. The analysis of correlations between adrenomedullin concentration and the sympathetic system activity parameters indicates that there is an association between an excessive activity of the sympathetic system and an increased adrenomedullin production in patients with hypotension. The current hypothesis states that an increased synthesis of at least one of the known vasodilating factors is related to an altered vascular response to pressure factors, while the sympathetic nervous system and the renin-angiotensin-aldosterone RAA system increased activity is a compensation mechanism, not sufficiently effective due to the earlier described vascular receptors dysfunction.

The intensification of the mentioned above changes in patients undergoing hemodialysis therapy contributes to the development of chronic hypotension, at the same time being the cause of the increasing risk for intradialytic hypotension occurrence induced by hypovolemia resulting from ultrafiltration in the course of hemodialysis.

At the same time other clinical symptoms and ultrasound features of chronic heart failure increase in dialyzed patients, 50–60% in the form of diastolic heart failure, and systo-diastolic or systolic in the rest of the patients with accompanying left ventricle dilation [25–27]. The complex reasons and mechanisms leading to the left ventricle hypertrophy, the disruption of its systolic function at first, and then to left ventricle dilation with a gradual deterioration of its systolic function, have been described in numerous studies [25–31]. It has been shown that with the development of left ventricle dilation its contractility and ejection fraction diminishes. In the event of a significant exacerbation of the left ventricle systolic insufficiency, and with the coexistence of the earlier described disruptions of compensation mechanisms, an autonomic neuropathy and an altered vascular reactivity to pressure stimuli, chronic hypotension develops in hemodialysed patients. These patients are especially sensitive to hypovolemia which induces a critical drop in blood pressure. The management of such cases requires a special ultrafiltration supervision during hemodialysis, sometimes the administration of medications (dopamine, dobutamine), and sometimes a resignation from hemodialysis and an attempt to replace it by peritoneal dialysis. Chronic left ventricle systolic insufficiency, left ventricle dilation and heart failure correlate with a higher death risk in hemodialysed patients [32].

This risk is even higher with intradialytic hypotension episodes and chronic hypotension [33,34]. Treatment in such cases is usually ineffective.

Hypotension in peritoneal dialysis patients

All the mentioned above factors influencing the development of chronic hypotension in hemodialysed patients take part in the development of chronic hypotension in patients undergoing continuous ambulatory peritoneal dialysis (CAPD).

In studies by Shetty et al. [35] and Malliary et al. [36] hypotension occurs in about 12% of patients, while studies of patients undergoing CAPD performed by Kann et al. [37], indicate that its incidence is 25%. The mentioned authors suggest that the main reason for hypotension is hipovolemia, which results from the increased ultrafiltration and excessive sodium losses as a result of the use of hiperosmic dialysis solutions, a low sodium diet and the overuse of diuretics. As imply mentioned authors' studies, hypotension occurs usually in the first 6 months of the CAPD treatment. Hipovolemia being the cause for hypotension in the CAPD treated patients has a good prognosis due to the possibility of a quick restoration of the normal vascular bed filling. Hipoproteinemia is a frequent complication of the CAPD. As a reason for peripheral edema, it diminishes the liquid volume in the vascular bed and increases hipovolemia. Aldosterone deficiency, which reduced concentration in the CAPD treated patients may result from reduced small intestine sodium absorption, low suprarenal secretion, and an increased peritoneal clearance, play an important role in the development of hipovolemia [38]. In 6 CAPD treated patients with accompanying hypotension, Marquez-Julio et al. [35] found a significantly lower aldosterone concentration in a horizontal position than in an upright one – it was respectively: 105 ± 10.9 pg/ml and 762.7 ± 99.0 pg/ml. In all the mentioned above patients the serum potassium concentration was low (<3 mEq/l), as was the aldosterone concentration. It has to be stressed that hypotension was not a constant symptom in these patients in comparison with hypotension in hipovolemia patients. Nor has it been observed that cortisone therapy resulted in an increase of blood pressure. However, with a high sodium level diet the blood pressure would raise, but this was related to the state of overhydration which resulted in edema increase. The factor determining the sodium loss in the CAPD is the degree of ultrafiltration. Nolph et al. [39] and Canaud et al. [40] found that the use of a hiperosmic dialysis solution increases the sodium loss. For example: with the serum sodium concentration equaling the one of the dialyzate, the patient loses 140 mEq, sodium per 1 liter of daily ultrafiltration a day. This will happen if the patient's body mass does not alter with the improvement of the patient's nourishment. According to authors the ultrafiltration can be lowered with the use of a hypotonic dialysis solution which can sometimes result in patient's overhydration. With the maintenance of the dose of diuretics, or even with its limitation in patients with

earlier hypotension the blood pressure may return to normal values. Shetty et al. [35] observed the influence of body mass increase on the improvement of hypotension in 14 from among 16 CAPD treated patients.

Shetty et al. [35] and other authors [36,37] believe that the CAPD treated patients' prognosis with hypotension symptoms resulting from systolic and diastolic heart insufficiency is worse than that of patients with hypotension and a circulatory sufficiency. In studies of mentioned authors heart insufficiency occurred rarer than in hemodialysed patients, it was noted in 20–25% of patients. In 40% of these patients the restriction of the body mass improved the prognosis and in the remaining patients in whom angiotensin converting enzyme inhibitor treatment was introduced, no improvement was obtained.

Another reason for hypotension in dialysed patients may be the use of hipotensive drugs. The analysis of the results of studies assessing the influence of the arterial hypertension pharmacological treatment, leads to a general conclusion: it is necessary to avoid rapid collapses in the arterial blood pressure during hipotensive therapy as they may lead to hypotension symptoms as a result of administration of an excessive medication dose or of short acting medications which reach their maximal serum concentration in a short time [41]. The administration of short acting dihydropiridine derivatives (nifedipine) is especially dangerous. A rapid fall of total peripheral resistance after medicine administration results in the arterial blood pressure drop and the activation of the sympathetic nervous system, which may be the cause for arrhythmias and in consequence, a sudden cardiac death. Neither as a result of long acting calcium antagonists' administration, nor after the administration of angiotensin converting enzyme inhibitors, do we encounter the activation of the sympathetic nervous system, despite the drop in arterial blood pressure. Hypotension resulting from an inappropriate hipotensive therapy in dialyzed patients is often a reversible disorder; it occurs in 10–18% of patients, and the discontinuation of medications, excessively lowering the blood pressure leads to the arterial blood pressure normalization.

When discussing the influence of drugs on arterial blood pressure in dialysed patients, it is also necessary to mention the potential role of aminoglycosides in hypotension development. This group of antibiotics is commonly used in dialysed patients for treatment of various infection complications. The results of experimental studies in spontaneously hypertensive rats (SHR) and in normotensive rats, performed by Boblewski et al. [42], have shown that intravenous gentamicin administration resulted in hypocalcemia, hypophosphaturia, and in the fall of the mean arterial blood pressure of as much as 15 mmHg in 35 minutes from drug administration. This observation confirms the hypothesis of McLarnon et al. [43] which assumes that aminoglycosides through their affinity to the calcium receptor may inhibit parathormone (PTH) and parathyroidal hypertensive factor (PHF) secretion, thus inducing hypotension.

SUMMARY

Results of numerous studies have shown that intradialytic hypotension is an independent risk factor for increased mortality in hemodialysed patients [33,34]. Chronic hypotension in hemodialysed patients as well as in patients treated with peritoneal dialysis, is an adverse phenomenon the basis for which are the usually coexisting various alterations in the cardiovascular system. In patients with clinical symptoms of hypotension, a strict supervision during hemodialysis and between treatments is necessary. Similar attention should be paid to patients undergoing peritoneal dialysis. Intradialytic hypotension prevention and counteracting to all factors influencing the development of chronic hypotension in dialysed patients ought to be a rule, as treatment attempts bring little effect.

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