

Recent Advances in the Prevention and Management of Intradialytic Hypotension

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ABSTRACT

Intradialytic hypotension continues to play a significant role in the morbidity and in some cases the mortality associated with maintenance hemodialysis. Greater precision in the determination of dry weight using bioimpedance technology and biofeedback systems designed to prevent rapid fluctuations in blood volume have recently been shown to decrease the frequency of this complication. Pharmacologic strategies designed to maintain peripheral vascular resistance in patients with insufficient release of endogenous vasoconstrictors continue to be explored. The sudden development of intradialytic hypotension may respond to specific antagonists to hypotensive mediators.

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A symptomatic reduction in BP during or immediately after dialysis occurs in approximately 20 to 30% of dialysis sessions. The treatment includes stopping or slowing the rate of ultrafiltration, placing the patient in the Trendelenburg position, decreasing the blood flow rate, and restoring intravascular volume. Such episodes predispose the patient to leave the dialysis unit volume overloaded and if repetitive can lead to inadequate clearance. Intradialytic hypotension and orthostatic hypotension after the procedure are significant and independent risk factors affecting mortality in dialysis patients.¹ This clinical commentary focuses on recent advances in the prevention and management of intradialytic hypotension.

Dialysis hypotension is the result of an inadequate cardiovascular response to the reduction in blood volume that occurs when a large volume of water is removed during a short period of time. In a typical dialysis procedure, an ultrafiltrate volume that is equal to or greater than the entire plasma volume is often removed.

Despite the large ultrafiltrate volume, plasma volume typically decreases by only approximately 10 to 20%. This ability to maintain plasma volume during ultrafiltration requires mobilization of fluid from the interstitial into the intravascular space. Vascular refilling is influenced by both patient-specific and treatment-related factors that dictate the distribution of water between the body fluid compartments.

The amount of interstitial fluid available for vascular refilling is influenced by the dry weight set for the patient. When the volume of interstitial fluid is small, any ultrafiltrate volume will more likely be associated with hemodynamic instability. This explains the development of hypotension when patients undergo dialysis below their true dry weight. By contrast, increased amounts of interstitial fluid will expand the volume of fluid accessible for refilling of the intravascular space and, therefore, decrease the likelihood of hypotension. In most patients, a dry weight that minimizes the

amount of interstitial fluid present is selected because chronic volume overload has long-term deleterious effects on the cardiovascular system.

The determination of dry weight is largely assessed empirically by trial and error. The dry weight is set at the weight below which unacceptable symptoms, such as cramping, nausea, and vomiting, or hypotension occur. The dry weight is highly variable in many patients and can fluctuate with intercurrent illnesses (*e.g.*, diarrhea, infection) and with changes in hematocrit (as with erythropoietin). A number of methods have been proposed to define more objectively the dry weight of the patient (Table 1). Comparative studies have generally favored methods based on bioimpedance measurements, which provide an assessment of extracellular and intracellular volume and total body water.^{2–4} A variant of this technique in which continuous intradialytic measurements are confined to the calf shows particular promise because the relative volume of excess extracellular fluid is greatest in the lower extremities.⁵ During dialysis, plasma

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Table 1. Objective tools to determine dry weight in hemodialysis patients^a

Blood volume monitoring
relative change during treatment
blood volume with ultrafiltration pulse (to assess increment of vascular refill)
Ultrasound assessment of IVC
IVC diameter
IVC collapsibility index (fractional decrease of diameter during breathing cycle)
BNP, N-terminal pro-BNP, atrial natriuretic peptide levels
Bioimpedance method
whole body (wrist to ankle)
segmental
continuous intradialytic calf measurements ⁵
Extravascular lung water index (invasive) ²⁶

^aBNP, brain natriuretic peptide; IVC, inferior vena cava.

refilling is more dynamic from the leg in comparison with the trunk or arms, suggesting that the calf could be used as a window to monitor intradialytic changes in whole-body extracellular fluid volume.⁶

The use of a higher dialysate sodium concentration (>140 mEq/L) is an effective means to ensure adequate vascular refilling and has proved to be among the most efficacious and best tolerated therapies for episodic hypotension. Sodium modeling is a technique in which the dialysate sodium concentration is varied during the course of the procedure. Most common, a high dialysate sodium concentration is used initially with a progressive reduction toward isotonic or even hypotonic levels by the end of the procedure. This method of sodium control allows for a diffusive Na influx early in the session to prevent the rapid decline in plasma osmolality as a result of the efflux of urea and other small molecular weight solutes. During the remainder of the procedure, when the reduction in osmolality accompanying urea removal is less abrupt, the dialysate sodium level is set at a lower level. Higher dialysate sodium concentrations, whether fixed or modeled, carry the risk for sodium accumulation, leading to stimulation of thirst, increased fluid gain, and hypertension in the interdialytic period.

Ultrafiltration profiling is the deliberate use of a high rate of ultrafiltration in the initial part of the treatment, when the volume of interstitial fluid available for vascular refilling is maximal, and then sequentially decreasing the rate so as to parallel the anticipated fall in interstitial fluid volume. Recent studies suggest this approach is particularly effective when combined with sodium modeling.^{7,8}

Devices to monitor intradialytic changes in blood volume have been advocated as a tool to minimize intradialytic hypotension on the basis of the concept that the likelihood of developing hypotension will always occur at roughly the same reduction of blood volume. Unfortunately, most studies have not found a close relationship between individual changes in blood volume and occurrence of hypotension.⁹ In a prospective, randomized trial,¹⁰ use of an intradialytic blood volume monitoring device was associated with greater non-vascular- and vascular access-related hospitalizations and mortality as compared with standard monitoring.

The lack of benefit noted with blood volume monitoring as typically used may in part be explained by its tendency to underestimate the actual amount of volume removed. The technique is based on measuring the degree of hemoconcentration that occurs with ultrafiltration and assumes uniform mixing of plasma and red blood cells throughout the circulation. Recent observations suggest that this assumption is incorrect.¹¹ Whole-body hematocrit is lower than arterial or venous blood as a result of a dynamic reduction in hematocrit in the capillary beds, a phenomenon known as the Fahraeus effect. During ultrafiltration, there is presumably a compensatory mobilization of hematocrit-poor blood from the microvasculature into the central circulation. This dilution effect minimizes the degree of hemoconcentration, leading to a potential underestimation of the total ultrafiltrate volume.

Blood volume monitoring has been shown to be an effective tool when incorporated into a biofeedback system

in which dialysate conductivity and ultrafiltration rate are constantly adjusted through the procedure on the basis of input from the measured change in blood volume. The system is designed to guide the reduction in blood volume along a preset individual trajectory so as to avoid the acute and sudden reductions that can precipitate hypotension. This technique has been found to reduce the frequency of hypotensive episodes and provide greater stability of BP both during and after the procedure.^{12,13} In hypertensive dialysis patients, this technique can lead to better BP control through optimization of volume status and at the same time reduce the frequency of hypotensive episodes when compared with standard treatment.¹⁴

The frequency of intradialytic hypotension has also been reduced using a biofeedback system in which the ultrafiltration rate is adjusted according to changes in BP measured every 5 min during the dialysis procedure.¹⁵ This method uses a fuzzy logic control system that adjusts ultrafiltration according to instantaneous changes in BP in the context of historical data concerning the individual's BP behavior during previous treatments.

In response to ultrafiltration, increased activity of the sympathetic nervous system leads to vasoconstriction of the dermal circulation. As a result, heat dissipation is impaired and core body temperature tends to increase. In addition to impaired heat dissipation, increased central heat production accompanies the dialysis procedure. At some point, the increase in core body temperature can overcome peripheral vasoconstriction and precipitate acute hypotension. Cooling the dialysate reduces the rate of intradialytic hypotension by 7.1 times when compared with conventional therapy.¹⁶ Most studies have used a fixed reduction in dialysis temperature from 37 to 35°C. A beneficial effect has also been shown using a biofeedback system in which the dialysate temperature is adjusted on an ongoing basis to keep body temperature constant (isothermic dialysis).¹⁷

A reduction of plasma volume will not necessarily result in symptomatic hypotension as long as the circulatory system is able to respond by compensatory vasoconstriction. Venoconstriction leads to a shift of blood into the central circulation, helping to maintain cardiac output. Impaired sympathetic nerve activity or abnormalities in venous compliance can limit this response. In a study of 25 patients with intractable postdialytic orthostatic hypotension, application of an inflatable abdominal band was found to be an effective means to attenuate the fall in BP immediately after the treatment.¹⁸ This device improved venous return to the heart as evidenced by an increase in ejection fraction and fall in atrial natriuretic peptide concentration.

Arteriolar vasoconstriction mediated by increased sympathetic nerve activity directly maintains BP by increasing peripheral vascular resistance. In some patients, this response is inadequate because of excessive production of vasodilators or an impaired sympathetic response to volume loss. Adenosine is an endogenous vasodilator released by endothelial cells and vascular myocytes implicated in the sudden development of hypotension during dialysis. It has been hypothesized that during ultrafiltration, localized areas of tissue ischemia may develop, leading to the release of adenosine, which in turn causes vasodilation and depresses myocardial contractility. This mechanism might explain the sudden development of hypotension in settings where blood volume is not significantly reduced. Caffeine, which is a nonselective A₁ and A₂ adenosine receptor antagonist, was previously found to reduce the frequency of sudden hypotension. In a prospective, double-blind, placebo-controlled trial in patients with frequent intradialytic hypotension, injection of a selective A₁ receptor blocker provided a significant but modest benefit in reducing the incidence of hypotension.¹⁹ Expression of the A_{2A} receptor is increased to a greater extent on peripheral blood mononuclear cells in dialysis patients with frequent hypotension compared with hemodynamically stable patients,

Table 2. Treatment of hemodynamic instability^a

Exclude non-dialysis-related cause (cardiac ischemia, pericardial effusion, infection)
Individualize the dialysis prescription
accurate setting of the dry weight
optimize dialysate composition
fixed Na ⁺ concentration >140 mEq/L
or Na ⁺ modeling
HCO ₃ buffer
avoid low Mg ²⁺ dialysate
avoid low Ca ²⁺ dialysate
optimize method of UF
UF modeling alone or with Na ⁺ modeling
sequential UF and isovolemic dialysis
cool temperature dialysate
Maximize cardiac performance
inflatable abdominal band to enhance venous return to heart
Avoidance of food
Avoid antihypertensive medicines on dialysis day
Pharmacologic interventions
midodrine
vasopressin
adenosine antagonists
others: sertraline, ephedrine, phenylephrine, carnitine

^aUF, ultrafiltration.

suggesting that A_{2A} receptor antagonism might also be of benefit.²⁰

An inadequate sympathetic response to volume removal is a common finding in patients with recurrent intradialytic hypotension. The postdialysis plasma concentration of chromogranin A (a protein co-released with catecholamines) increases to a lesser extent in patients with intradialytic hypotension compared with those with stable BP, consistent with a blunted response of sympathetic nerve activity to hypotension.²¹ The precise mechanism by which uremia leads to autonomic dysfunction is not known, but chronic hyperkalemic depolarization of nerves may play a contributory role.²²

The most common approach to overcome impaired sympathetic activity has been to administer other vasoconstrictors to increase peripheral vascular resistance. A systematic review of the literature²³ revealed that 2.5 to 10 mg of the selective α-1 adrenergic agonist mido-

drine was proved to be an effective treatment in some patients with frequent intradialytic hypotension. This drug may also have the additional benefit of better preserving cerebral blood flow in patients with orthostatic hypotension after hemodialysis.²⁴ Vasopressin was recently reported to be an effective agent to support BP during volume removal. Previous observations found that plasma vasopressin levels do not significantly increase during ultrafiltration dialysis despite an anticipated unloading of baroreceptors. In a randomized, double-blind, placebo-controlled trial, the continuous administration of subpressor doses of vasopressin provided for greater hemodynamic stability even when target fluid loss was set to be increased by 0.5 kg over the baseline prescription (Table 2).²⁵

In summary, a number of advances have been made in the prevention and management of intradialytic hypotension. Perhaps the greatest promise in minimizing this complication lies in technologies capable of adjusting the dialysate composition and rate of ultrafiltration continuously throughout the procedure on the basis of real-time changes in parameters that influence vascular refilling. The delivery of dialysis in this manner allows for adjustments to be made on the basis of minute-to-minute variations in the response of the cardiovascular system to ultrafiltration. As currently practiced, parameters are set before each treatment on the basis of the assumption the cardiovascular system will simply recapitulate what occurred in previous treatments. This assumption in many instances is incorrect because of the dynamic nature of factors that influence vascular refilling.

DISCLOSURES

None.

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