

Intradialytic Hypotension: Mechanisms and Outcome

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Keywords

Dialysis · Hemodialysis · Intradialytic hypotension · Pathophysiology

Abstract

Intradialytic hypotension (IDH) occurs in approximately 10–12% of treatments. Whereas several definitions for IDH are available, a nadir systolic blood pressure carries the strongest relation with outcome. Whereas the relation between IDH may partly be based on patient characteristics, it is likely that also impaired organ perfusion leading to permanent damage, plays a role in this relationship. The pathogenesis of IDH is multifactorial and is based on a combination of a decline in blood volume (BV) and impaired vascular resistance at a background of a reduced cardiovascular reserve. Measurements of absolute BV based on an on-line dilution method appear more promising than relative BV measurements in the prediction of IDH. Also, feedback treatments in which ultrafiltration rate is automatically adjusted based on changes in relative BV have not yet resulted in improvement. Frequent assessment of dry weight, attempting to reduce interdialytic weight gain and prescribing more frequent or longer dialysis treatments may aid in preventing IDH. The impaired vascular response can be improved using isothermic or cool dialysis treatment which has also been associated with a reduction in end organ damage, although their effect on mortality has not yet been assessed. For the future, identification of vulnerable patients based on artificial intel-

ligence and on-line assessment of markers of organ perfusion may aid in individualizing treatment prescription, which will always remain dependent on the clinical context of the patient.

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Published by S. Karger AG, Basel

Introduction

Intradialytic hypotension (IDH) is associated with disabling symptoms, underdialysis, vascular access thrombosis, accelerated loss of renal function, cardiovascular events, and mortality [1–3]. The prevalence of IDH depends on the definitions that are used. Defining IDH is difficult because there is no accepted “safe” blood pressure (BP) range for dialysis patients; therefore, many different definitions are used. Most definitions use at least one of these components: (1) occurrence of low BP below a certain threshold/nadir, (2) intradialytic BP decline, (3) patient-reported intradialytic symptoms, and (4) medical intervention during dialysis aimed at restoring blood volume (BV) [4]. Flythe et al. [1] investigated outcomes with 8 existing IDH definitions. This study showed that an absolute intradialytic nadir systolic BP <90 mm Hg is most strongly associated with mortality, whereas more common definitions such as those of K-DOQI, which define IDH as a decline in systolic BP >20 mm Hg with accompanying symptoms, were not [1]. A recent meta-analysis estimated the prevalence of dialysis sessions complicated

by IDH to be 11.6% when the nadir <90 definition was used; and 10.1% when IDH was defined as a >20 mm Hg decrease in systolic BP in combination with clinical events and interventions [2]. Therefore, IDH remains a highly relevant problem in dialysis patients. This short review serves to discuss the relation between IDH and outcome and will also focus on selected pathophysiological mechanisms with their possible implications for prevention. No attempt is made to discuss all potential preventive interventions, for which recent reviews are available [5].

Why Is IDH Related to Outcome?

IDH is associated with cardiovascular mortality and all-cause mortality [1, 6]. One explanation is that reduced tolerance to fluid removal may occur more often in patients with multiple comorbidities [7]. However, there is substantial evidence that the HD procedure on itself leads to end-organ ischemia and thus causally related to outcome [8]. The best-known example is cardiac myocardial stunning (transient regional wall motion abnormalities of the myocardium) induced by the dialysis procedure, which is related to persistent systolic dysfunction and increased mortality [9]. Although cardiac stunning can also be induced by the dialysis procedure independent of ultrafiltration (UF) [10], an important risk factor for myocardial stunning is a decline in systolic BP [11]. However, in critically ill patients, cardiac stunning also occurred during continuous renal replacement therapy despite stable hemodynamics [12]. In addition, intradialytic cerebral ischemia, defined as a 15% decline in base-line cerebral oxygen saturation, occurs in about one-quarter of hemodialysis sessions and is related to mean arterial pressure [13]. In the long term, cumulative exposure to frequent IDH is associated with an increased 5 years risk of new-onset dementia [14]. Next to this, also a relation between IDH and mesenteric ischemia was observed in dialysis patients [15].

It is important to recognize that the main driving parameter for any causal relation between IDH and outcome is likely dependent upon tissue ischemia. Tissue blood flow is dependent not only on systemic BP but also on the vascular resistance relative to other body regions, as well as on the capillary function and density [16]. Vascular resistance is regulated by both central (baroreceptor) as well as locally mediated mechanisms. These can be divided into responses based on local metabolic activity, myogenic autoregulatory responses (which are especially prominent in brain and kidney), and flow-mediated dilatation, which is dependent upon an intact endothelium [16]. End-stage re-

nal disease may further complicate the relation between BP and tissue perfusion because of the possible presence of upstream vascular stenosis, endothelial dysfunction, and capillary rarefaction [17–20]. Exemplary of this complexity are the highly variable levels of the lower limits of cerebral autoregulation in dialysis patients. Whereas it is generally assumed that these are reached when mean arterial pressure falls below 60 mm Hg, in a recent study in dialysis, the mean limit was 74 mm Hg with a wide range (39–103 mm Hg) [13]. From a theoretical point of view, derivatives of the relation between cardiac output and local metabolic needs, such as central venous oxygen saturation may be more precise predictors of outcome as compared to systemic BP [21]. However, this hypothesis needs to be tested in future clinical trials. Interestingly, impaired tissue ischemia may also further aggravate hypotension by release of the endogenous vasodilator adenosine [22].

Predicting IDH

Although preexistent patient characteristics such as older age, comorbidities such as diabetes and longer dialysis vintage are more frequently observed in patients prone to IDH [7, 23], its occurrence remains difficult to predict. Recently, it has been attempted by machine learning techniques to create models to predict IDH. Using a least absolute shrinkage and selection operator algorithm including a relatively limited number of parameters such as body and dialysate temperature, UF rate and patient characteristics, a model was created which predicted IDH defined as a nadir systolic BP below 90 mm Hg with sensitivity of 86% and specificity of 81% [24]. In addition, Barbieri et al. [25] presented an artificial neural network that predicted nadir systolic BP with a mean absolute error of 9.3 mm Hg, which appears promising for potential clinical use [25]. As the available models used a relatively limited number of predictors, future models with a higher level of granularity may show a further improvement in performance.

Pathophysiologic Mechanisms of IDH

As dialysis is usually accompanied by UF, a logical mechanism behind the decline in BP is a decline in cardiac output due to reduced venous return. This will be more pronounced in patients who are, due to underlying cardiac disease, not able to increase myocardial contractility and/or heart rate. This will at least partly explain why many dialysis patients do not tolerate a decline in BV which is easily tolerated by

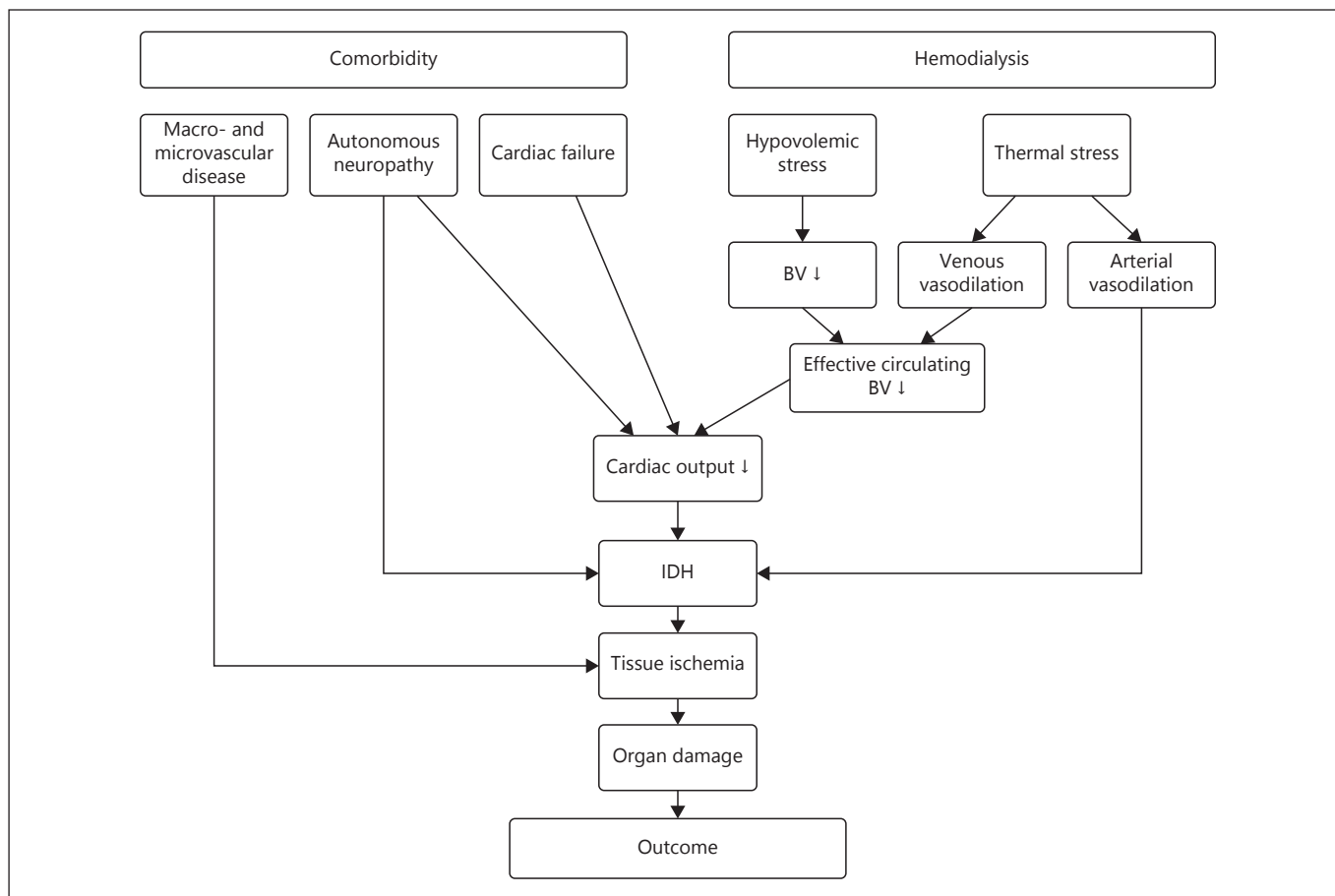


Fig. 1. Mechanisms behind intradialytic hypotension and its relation to outcome. BV, blood volume; IDH, intradialytic hypotension.

healthy individuals [26, 27]. However, this does not appear to be the sole mechanism, as hypotensive episodes may also be accompanied by peripheral vasodilation, which is clearly not a physiological response to hypovolemia [26, 28–30] (Fig. 1). The following paragraphs with the focus on the interaction between changes in BV and vascular resistance.

Decline in BV

The first driver in the pathophysiology of IDH is the decline in BV due to UF. In the absence of UF, the occurrence of IDH is rare although studies on intradialytic BP behavior showed that the largest BP drop occurred in the first 20–25% of the dialysis treatment [31]. This suggests that other factors beyond volume, such as rapid osmolar and electrolyte shifts or neurohumoral and inflammatory pathways may also affect the intradialytic BP response. However, BP measured at the start of dialysis may not be representative due to the stress accompanying the start of the dialysis procedure [32].

A decline in BV occurs when the rate of fluid withdrawal exceeds the rate of refilling from the interstitium into the vascular space, in which the latter appear relatively independent on the rapidity of fluid removal [33]. UF rates are related to a decline in cardiac output [6, 34, 35] and are incrementally related to IDH [6]. UF rates above 13 mL/kg/h are associated with both an increased risk of IDH as well as mortality [8]. In addition, increased UF may result in symptoms that inappropriately can result in shorter dialysis treatments, missed treatments, adjustments in target weight, or use of saline infusion [8]. Therefore, it has been suggested to limit UF rate to 13 mL/kg/h and to introduce it as a quality measure [36]. Indeed, the use of so-called “intensive dialysis” with prolonged weekly treatment hours is associated with a significant decline in IDH [37]. Another study showed that lowering UF rates below 13 mL/kg/h resulted at a facility level reduction in IDH [38]. On the other hand, reducing UF rate without increasing time and/or frequency evidently car-

ries the risk of worsening fluid overload, if attempts to reduce interdialytic weight gain are not successful [39].

Relative BV monitoring, based on on-line monitoring of changes in hematocrit or protein, is an easy and widely used method in estimating decline in BV and subsequent risk of IDH. However, relative BV is a composite parameter of fluid status and UF rate and thus the interpretation in an individual patient may not be straightforward. Besides, this method may underestimate changes in absolute BV due to the refill of blood from the microcirculation with a relatively low hematocrit [40], although the importance of changes in so-called F cell ratio during HD with moderate UF rates has been questioned [41]. A large decline in relative BV is associated with IDH, but large interindividual variation exists [27]. On the other hand, “flat” curves in relative BV are also unfavorable because of their association with increased mortality [42, 43]. Thus, high UF rates, which are related to IHD, result in a sharper decline in relative BV [44], whereas predominantly the flat curves are related to mortality. A possible explanation for this apparent paradox is that the combination of fluid overload and an impaired cardiovascular reserve, which are independently related mortality, are also related to a reduced fall in relative BV during dialysis, whereas patients with a good cardiovascular reserve are able to tolerate high UF rates and a large decline in relative BV.

Studies in which relative BV monitoring was used to guide fluid removal have not yet yielded consistently positive results. In one study, adjustment of UF based on relative BV monitoring was associated with an increase in mortality [45], whereas in another study, no positive effects on IDH were observed [46]. At present, we feel that the use of relative BV can be a valuable add-on parameter in the decision process but is at this moment not ready for automated prescriptions in clinical practice outside a clinical trial.

Recently, the measurement of absolute BV that can be assessed by measuring the change in RBV after on-line infusion of 240 mL ultrapure dialysate. It was observed that an absolute BV below 65 mL/kg had a good predictive value (positive predictive value = 0.79; negative predictive value = 1) for predicting IDH, greatly surpassing that of relative BV. Adjustment of IDH based on absolute V resulted in a reduction in IDH. However, the experience with this method is yet based on relatively small patient populations [47, 48].

Lastly, bioimpedance spectroscopy (BIS) has been introduced in recent years on a wider scale to monitoring fluid status and to attempt to reduce extracellular fluid overload as well as fluid depletion. Whereas predialytic

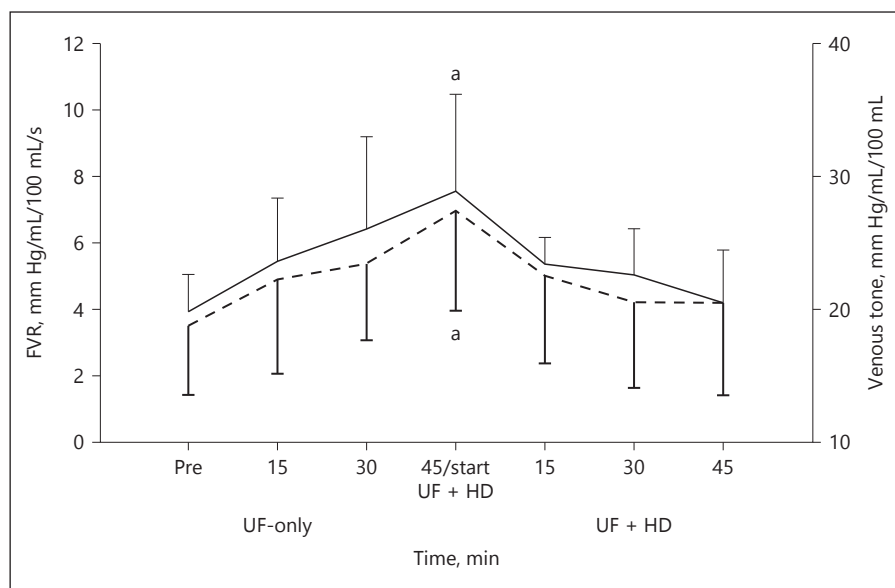
extracellular fluid overload, and to a lesser extent, fluid depletion were found to be powerful predictors of mortality at a population level [49–51], evidence from interventional studies is only available from relatively small studies which showed that BIS-guided treatment can potentially improve predialytic fluid overload and hemodynamic tolerance [52, 53]. However, the interpretation of BIS values can be complicated in elderly and malnourished patients [54]. More research is needed because BIS can be used as a tool to guide treatment. However, given its excellent properties in risk stratification, we feel that BIS can be of relevance in the treatment decision process, given that it is interpreted in the clinical context of the patient. Importantly, notwithstanding the usefulness of technological aid, the single factor that was found to be significantly related to a reduced incidence of IDH at a facility level was the presence of a protocol for dry weight assessment [55], stressing the importance of individualized attention for the patient in a clinical care setting.

Impaired Vascular Resistance and Venous Tone: A Tale of 2 Stressors

In a healthy subject, loss of intravascular volume leads to a compensatory cardiovascular response to maintain BP and organ perfusion. In HD patients, these normal responses are often impaired because of comorbidities such as cardiac dysfunction and autonomous neuropathy [26, 30]. In addition, the HD procedure itself can impair the normal vascular response to hypovolemia, by acting as a thermal stressor. During HD with dialysate temperatures of 37.0 °C or higher, core temperature usually increases, although an increase can also be observed with lower dialysate temperatures depending on the predialytic body temperature of the patient. Increases in core temperature above 0.5 °C are not uncommon [56, 57], which is likely to be of relevance given the fact that differences in core temperature between 0.3 and 0.8 °C separate the threshold for the skin from shivering to vasodilation [57]. An increase in core temperature above the setpoint evokes powerful homeostatic mechanisms, for example, in the form of dilatation of the skin vasculature, counteracting the vascular response to hypovolemia and contributing to IDH [26, 57]. This appears to be at least partly mediated through nitric oxide [58]. Although the mechanism behind the increase in core temperature during dialysis differs, this response is conceptually comparable to experimental conditions where passive heating and lower body negative pressure are combined [59, 60].

The reduced response of the peripheral vasculature during “standard temperature” HD has been observed

Fig. 2. Forearm vascular resistance and venous tone during isolated UF and hemodialysis. UF-only = isolated UF. UF rate was equal between UF-only and UF = HD. Dialysate temperature was 37.5 °C. Measurements were performed by strain gauge plethysmography. From [32], with permission. FVR, forearm vascular resistance; UF, ultrafiltration.



both in the arterial as well as in the venous compartments [32]. The observation that isolated UF usually is associated with a better hemodynamic tolerance as compared to hemodialysis [61] is likely due to a more physiological increase in the vascular response [32] (Fig. 2). Indeed, difference in the hemodynamic response between HD and isolated UF appears to be fully explained by differences in energy transfer between both techniques [62]. Moreover, differences in the hemodynamic response between HD and hemo(dia)filtration, which also can have a cooling effect by loss of thermal energy through the infusion line, disappeared after matching for thermal differences [63–66]. Reduced temperature dialysis increases hemodynamics stability, is easy to deliver and usually well tolerated. Based on 11 trials, the pooled effect of cool dialysis is a 70% reduction in the rate of IDH [67]. In addition, cool dialysis reduced the progression of HD-associated cardiomyopathy and HD-associated white matter brain injury [68, 69]. Also positive effects have been observed with the use of a feedback controlled treatment in which core temperature is kept stable (isothermic), which has the advantage above cool dialysis that the risk of shivering appears reduced [67]. In a small study, lowering core temperature appeared to have some additional benefit above isothermic treatments, as in a controlled nadir systolic BP was found to be significantly higher during treatments in which the core temperature was experimentally cooled by 0.5 °C versus isothermic treatments (98 ± 27 vs. 113 ± 30 mm Hg), but at the cost of an increased incidence of shivering [70]. Therefore, the best balance between hemodynamic tolerance and patient comfort is likely reached when (near) iso-

thermic treatments are prescribed. Still, despite its hemodynamic benefits and apparent benefits on organ damage, the effects of cool or isothermic dialysis on mortality have still not been adequately studied [71].

The Role of the Venous System in the Hemodynamic Response

The venous return (preload) together with cardiac function determines cardiac output [72]. The venous system, which holds approximately 65–70% of total BV [73], can conceptually be divided into an unstressed and a stressed part. The stressed part generates distending (or elastic recoil) pressure, which serves as the pressure gradient between the small veins/venules and the right atrium, thus determining mean systemic filling pressure, the driving force for venous return [74, 75] (Fig. 3). The unstressed part is the (theoretical) volume remaining in the circulation at zero distending pressure and serves as a reservoir than can partly be mobilized under conditions of hemodynamic stress (Fig. 3). Stressed volume, which can only be measured during circulatory arrest, was measured during hypothermic cardioplegia and found to be 30% ± 17 of the predicted total BV (1,290 ± 296 mL) [76].

From an anatomical point of view, the venous system can generally speaking be subdivided into the splanchnic part and the peripheral veins, the splanchnic showing slow transit times and peripheral veins a higher transit time of blood [77]. A main reservoir for unstressed volume is the splanchnic system that has very compliant vessels [72]. Centralization of blood from the venous system can occur by active venoconstriction flowing stimulation of α1-

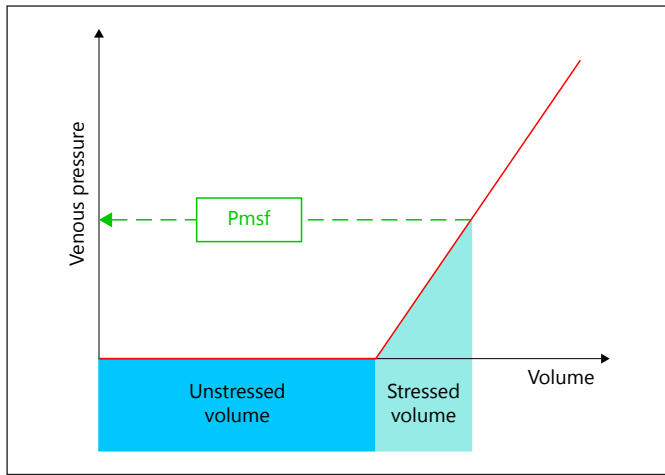


Fig. 3. Representation of the concepts of stressed and unstressed BV. Pmsf is mean systemic filling pressure. The unstressed volume is the volume which fills the vasculature without a change in transmural pressure. The stressed volume is the volume that leads to an increase in transmural pressure. From [75], with permission.

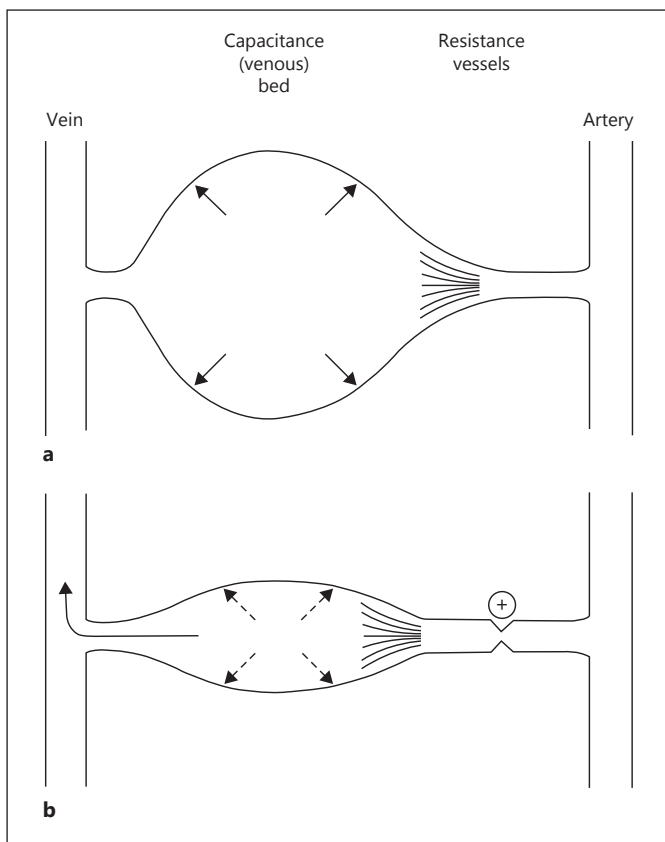


Fig. 4. a, b De Jager-Kroch phenomenon. During a reduction in arterial inflow, pressure in the venous bed is reduced and due to passive recoil of the venous wall, BV is mobilized. From [80], with permission.

adrenoreceptors as well as passive recoil of the venous wall after reduced arterial inflow (de Jager-Kroch phenomenon) [72, 78–80] (Fig. 4). It is likely that the splanchnic venous system plays the largest role in the immediate response to hypovolemia under thermoneutral conditions. In healthy subjects, splanchnic BV decreased by 500 mL after 1 L of hemorrhage without a change in BP [78]. Also during HD combined with UF, a mobilization of labeled erythrocytes from the splanchnic system was observed using a gamma camera during dialysis [79, 81]. Interestingly, in a recent study, liver water assessed by magnetic resonance imaging even increased after UF [82]. Whereas this appears counterintuitive, one explanation could be that in this case active venoconstriction during hypovolemia involves also the hepatic veins [83], thus increasing the “resistance to venous return” in Guytonian terms. Whether changes in liver water by magnetic resonance imaging reflect the mobilization of blood from the splanchnic system during dialysis has to the best of our knowledge not been investigated.

The Role of the Vascular System in the Thermoregulatory Response

Whereas the splanchnic system is mainly involved in volume regulation by serving as an important reservoir, the cutaneous veins are involved mostly in thermoregulation and under thermoneutral circumstances; their relative contribution to the hemodynamic response to hypovolemia is likely limited. However, under maximal passive heating, a situation that is obviously not encountered during HD, skin blood flow can increase up from 300 mL/min to 7–8 L/min, which is accompanied by dilatation of the cutaneous veins, which have a high capacitance under these circumstances [84, 85]. This is accompanied by a reduction in blood flow to other organs, such as the brain, splanchnic system, and kidneys [86]. Splanchnic veins do not appear to be affected by the thermoregulatory response and can even mobilize blood under episodes of heat stress, likely due to a combination of active venoconstriction and passive recoil [74]. During maximal heat stress, total splanchnic volume decreased by 23% and unstressed BV by 38.5% [74]. Thus, the hemodynamic effects of the thermal changes during HD are likely related to dilatation of the cutaneous blood vessels, which leads to hemodynamic consequences when accompanied by UF-induced hypovolemia after the splanchnic reservoirs have been exhausted.

Mechanisms Behind the Increase in Core Temperature

The pathophysiology of the observed increase in core temperature during HD is complex and not fully understood. Interestingly, during isothermic treatments, ther-

mal energy needs to be removed from the patient in order to keep core temperature stable [87]. Possible mechanisms are changes in temperature setpoint due to cytokine production in reaction to the biocompatibility of the HD procedure [88], although the rise in core temperature was also observed in the absence of changes in interleukin-6. However, even with biocompatible membranes, there is evidence of complement activation during dialysis, which may also affect thermoregulation [89, 90].

Even, the effect of the circadian rhythm could be a contributing factor, although a circadian increase in core temperature is actually preceded by a decline in skin blood flow, which is opposite to which is observed during dialysis [32, 56, 91]. Another explanation is an initially peripheral vasoconstriction as a reaction to hypovolemia, leading to a “shell phenomenon” with initial accumulation of heat leading to an increase in core temperature, later followed by vasodilation [92]. However, whereas this hypothesis seems to be confirmed by the relation between UF volume and thermal energy that needed to be removed to keep core temperature stable [87], another study showed also a comparable increase in core temperature between isovolemic HD with ultrapure dialysate and HD combined with UF [93]. Therefore, the mechanisms behind the increase in core temperature remain still somewhat enigmatic and are likely multifactorial.

Conclusion

Despite advances in dialysis therapy, IDH still remains an important clinical problem that is related to end-organ damage and mortality, which is likely mediated through organ ischemia. Predominant in its pathogenesis are the combination of a decline in BV in combination with an inadequate vascular response, at a background of a re-

duced cardiovascular reserve. Whereas IDH can likely not be completely prevented given the intermittent nature of dialysis therapy several methods can be applied to reduce its incidence, including reducing intradialytic weight gain, increasing dialysis time and frequency, frequent assessment of dry weight, as well as prescribing cool or isothermic treatments. Whereas feedback methods based on relative BV monitoring have not yet fulfilled the expectation, future technologies basing UF thresholds on markers of organ perfusion would allow for a further individualization of dialysis therapy. In the opinion of the authors, the future for the prevention of IDH lies in the application of smart methodologies that are able to detect subclinical abnormalities in fluid status and tissue perfusion, in combination with individualized attention for the patient in all aspects of daily clinical practice.

Acknowledgment

None.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

There is no funding source to declare.

Author Contributions

The 3 authors jointly wrote the paper.

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