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Novel Insights into the Pathogenesis and Prevention of Intradialytic Hypotension

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Abstract
Background: Intradialytic hypotension (IDH) is a common complication of haemodialysis (HD) and associated with adverse outcomes, especially when a nadir definition (systolic blood pressure <90 mm Hg) is used. The pathogenesis of IDH is directly linked to the discontinuous nature of the HD treatment, in combination with patient-related factors such as age, diabetes mellitus and cardiac failure. ***Summary:*** Although the decline in blood volume due to removal of fluid by ultrafiltration is the prime mover, thermally induced reflex vasodilation compromises the haemodynamic response to hypovolemia. Recent studies have stressed the relevance of changes in tissue perfusion during HD, which may translate in long-term organ damage. Monitoring changes in tissue perfusion, for which emerging evidence becomes available, appears to have great promise in the fine-tuning of the dialysis procedure. ***Key Messages:*** While it is unlikely that IDH can be completely prevented, reduction in inter-dialytic weight gain, prevention of an increase in core temperature by adjusting the dialysate temperature and more frequent or prolonged dialysis treatment remain cornerstones in providing a more comfortable and safe treatment.

Introduction

Intradialytic hypotension (IDH) is a frequent complication of haemodialysis (HD) sessions. Depending on the definitions, IDH is reported to occur between 5and 30% also based on different definitions in varying patient populations [1]. In a recent study assessing 44,801 treatments in 1,137 patients, in which IDH was defined as a decrease in systolic blood pressure (SBP) by more than 30 mm Hg to a level of less than 90 mm Hg, the incidence was 17.2% [2]. In a study in the HEMO population, the incidence of IDH was 9.6% when the Kidney Disease Outcomes Quality Initiative definition (decline in SBP >20 mm Hg including symptoms) was applied, and 11.3% when a nadir (SBP <90 mm Hg) was used [3]. Next to patient discomfort, IDH is also associated with adverse outcomes [2, 3]. Therefore, insight in its mechanisms and consequences of IDH has emerged. The aim of this paper is to project novel insights on the pathogenesis of IDH (Fig. 1) in the perspective of established literature.

Pathophysiology of IDH: Patient-Related Factors

The discontinuous nature of HD, in which fluid that accumulates during one week is generally removed in 12 h, yields a significant burden on the cardiovascular system of

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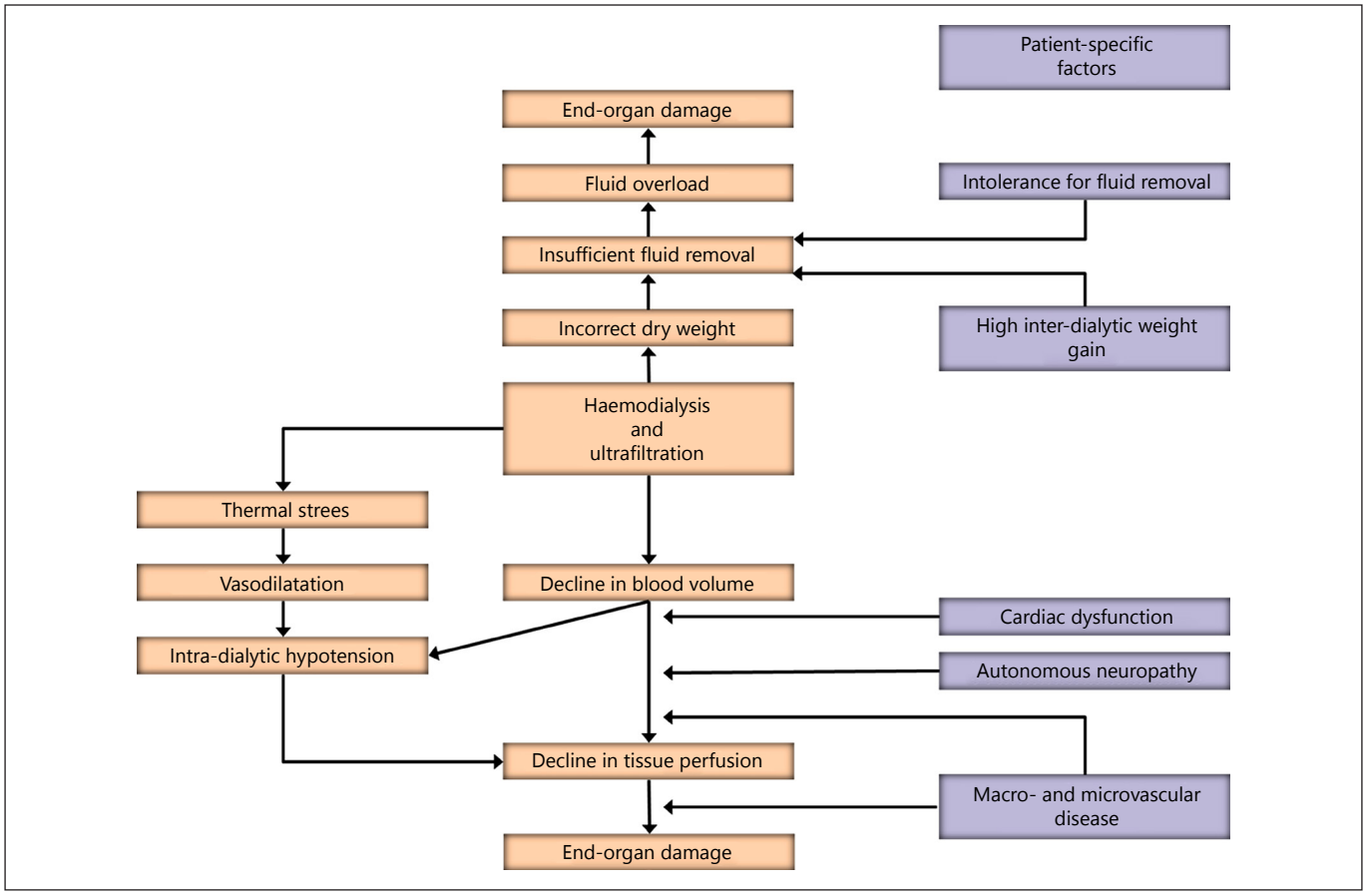

Fig. 1. Novel insights into the pathogenesis of intra-dialytic hypotension.

the patient. Dialysis patients may be more sensitive to a decline in blood volume as compared to a healthy population, in whom a decline in SBP is usually associated with a fall in blood volume of 20% or more [4, 5]. Both patient- as well as treatment-related factors play a role in the pathogenesis of IDH. A recent multicentre study found an association between IDH with factors such as age, female gender, diabetes mellitus, Hispanic origin, longer dialysis vintage, higher body mass index and lower pre-dialytic SBP [2]. Also, the presence of cardiac dysfunction [6] and autonomous neuropathy [7] can increase the vulnerability for the haemodynamic effects of HD [1, 8].

Pathophysiology of IDH: Treatment-Related Factors

Next to unmodifiable patient-related factors, treatment-related factors also play a major role in the pathogenesis of IDH. The decline in blood volume, induced by ultrafiltration, is the prime mover. In a study in hypotension-prone patients, the mean decline in relative blood volume (RBV) before the occurrence of IDH was 12.3% [4], although changes in RBV may underestimate changes in absolute blood volume due to the refill of blood with a lower haematocrit from the microcirculation [9, 10]. While a high ultrafiltration rate is a major risk factor for IDH [2], its effect on changes in RBV is highly variable between patients, likely depending on the refill of plasma volume from the interstitial compartment [10, 11].

Ultrafiltration can lead to a decline in blood pressure because of a reduction in central blood volume and cardiac output [12]. In a recent study, we observed a fall in cardiac output of –1.4 ± 1.5 L/min during 4 h of HD with a decline in RBV of 8.1 ± 1.5%. [13]. However, even despite a fall in cardiac output, blood pressure can still be maintained if systemic vascular resistance rises appropriately. In previous years, we and others have extensively studied the relation between the extracorporeal energy balance and the haemodynamic response during dialysis [14–16]. In short, an increase in core temperature during

conventionally used dialysate temperatures (such as 37–37.5 °C) may lead to the redistribution of blood volume to the vasodilated skin vessels and counteracts the normal response to hypovolemia. Although the exact magnitude of this redistribution has not been precisely calculated, under severe heat stress skin blood flow can increase up to 7.5 till 8 L/min [17, 18]. In addition to this, dilation of the cutaneous veins can lead to the pooling of "unstressed" blood volume, impairing the redistribution to the central blood volume compartment [12, 19]. These observations have direct therapeutic consequences as the fall in RBV can be mitigated by longer dialysis sessions [13], thereby improving vascular reactivity and blood pressure response by reducing the temperature of the dialysate [16, 20].

A Fall in Blood Pressure during Dialysis Is Not Always Detrimental

Blood pressure usually falls during HD. In the HEMO cohort, a decline of SBP of 20 mm Hg or more was observed in 68% of treatments, and a decline in SBP of 30 mm Hg or more in 51%. Although both were associated with increased mortality in unadjusted analysis, this relation lost statistical significance after correction for confounders, unless accompanied by a nadir SBP of 90 mm Hg or lower [3]. In contrast, an increase in blood pressure during dialysis is also associated with increased mortality [21].

The same type of apparently paradoxical relations was observed for changes in RBV. Higher ultrafiltration rates, both at thresholds of 10 or 13 mL/kg/h, are associated with increased mortality; however, low declines in RBV are also associated with adverse outcomes. A decline in RBV slope below the median of 1.35%/h was associated with an increased risk in mortality [22], which is likely related to the expansion of the interstitial fluid compartment, leading to increased refill of plasma volume. Moreover, higher slopes of RBV decline were associated with an increase in arterial oxygenation, suggesting a beneficial effect on pulmonary oxygen exchange due to fluid removal [10]. Therefore, it might be suggested that higher ultrafiltration rates may be associated with increased mortality because of impaired tissue perfusion, and because of the accompanied patient characteristics, a low decline in blood volume or a rise in SBP may be associated with adverse outcomes because of concomitant fluid overload in these patients [22, 23]. In a recent study, we noticed that the prognostic value of changes in SBP was related to the pre-dialytic blood pressure. While in patients with low SBP a decline was associated with an adverse outcome, the opposite was observed in patients with high pre-dialytic SBP, which appears in line with the pathophysiologic considerations. Therefore, most likely not the fall in blood pressure per se is detrimental but the associated changes in tissue perfusion.

Effects of Dialysis on Tissue Perfusion

Tissue perfusion is expressed at blood flow rates per 100 mL of tissue and is expressed by the formula Q = P/R (Q = flow, P = pressure, R = resistance). Therefore, a decline in tissue perfusion may occur when a decline in pressure is not accompanied by regional autoregulatory vasodilation or when the decline in pressure is too high. Moreover, in case of proximal stenosis or in case of microcirculatory alterations, which have been described in cardiac tissue of uremic patients and animals [24], even a relatively small decline in systemic blood pressure might lead to an impaired tissue perfusion. Alternatively, for example, in case of left ventricular hypertrophy, the increased oxygen demand may make the cardiac tissue more vulnerable for a decline in blood pressure [25]. Also, even in non-uremic subjects, changes in tissue perfusion may already occur when cardiac output declines before a change in blood pressure is already apparent [5].

These factors may explain why even in the presence of relatively small changes in blood pressure, HD is associated with a reduction in tissue perfusion in vital organs, such as the heart and brain, which is of importance, given the relation between temporary perfusion deficits and persistent end-organ damage [26–30]. However, the risk of myocardial stunning appears to be even greater when HD is accompanied by a significant decline in blood pressure [31]. Moreover, the splanchnic region, and especially the gut mucosa, is especially sensitive for tissue hypoperfusion because of high α-adrenergic activity [5]. In 9 patients with acute renal failure, despite a stable blood pressure, cardiac output declined from 3.0 to 2.7 mL/min/m^2 and was accompanied by a reduction in splanchnic but not femoral blood flow, as measured by dye dilution. These changes were also accompanied by an increase in tumor necrosis factor alfa [32], potentially indicating the translocation of bacterial fragments. As it is true for the blood pressure response, cooling or individualizing of dialysate has also been shown to reduce hypoperfusion-related complications such as cardiac stunning [33] and resulted

in less white matter lesions in the long term [29]. In addition, more frequent HD also resulted in a reduction in myocardial stunning [33]. Recent developments, notably Sidestream Dark Field imaging, a microscopic technique using polarised light to visualise erythrocytes passing through sublingual capillaries, have enabled the direct visualization of the microcirculation during HD and observed a decline in perfused vessel density during HD. This was not related to changes in blood pressure, showing that microcirculatory changes can occur, which are unnoticed by changes in macrovascular parameters [34].

Changes in Perfusion Are Important, But How Can They Be Measured Routinely?

While studies on regional changes in tissue perfusion, or change in microcirculation during dialysis have yielded highly important results for pathophysiologic understanding of the haemodynamic effects of HD, they are unsuitable for routine clinical applications on a treatment-to-treatment basis. For this purpose, changes in central venous oxygen saturation ($ScvO_2$), which can be assessed in patients treated with a central venous catheter, is an integrated parameter influenced by cardiac output, tissue oxygen delivery and oxygen extraction, predominantly of the upper body [35]. While $ScvO_2$ above 70% is considered optimal, most HD patients already start the dialysis treatment with substantially lower values [35, 36]. $ScvO_2$ is influenced by ultrafiltration rate [36], whereas the change may be different in patients prone to IDH. In a study in 11 hypotension-prone and 9 stable HD patients, $ScvO_2$ dropped by 7.7% ± 1.7 in hypotension prone patients, in contrast to a rise of 1.0 ± 1.3% in the stable group. It has also been suggested that continuous assessment of arterial oxygen saturation (SaO_2), in patients with arteriovenous fistulae, or $ScvO_2$ could both be useful in the early prediction of IDH [37]. Future studies should be performed to investigate whether treatment guided by changes in $ScvO_2$ would be of clinical benefit to the patient in preventing IDH. A drawback of $ScvO_2$ is that it is only available for patients with a central venous catheter. Easily applicable, non-invasive techniques assessing changes in tissue perfusion would therefore be a great asset for the fine-tuning of the HD treatment. Near infrared spectroscopy (NIRS) could be an interesting technique for this purpose. NIRS operates by the same principle as pulse oximetry with the difference that while the former measures only oxyhaemoglobin, NIRS measures the difference between oxyhaemoglobin and deoxygenated haemoglobin [38]. Recently, this method was applied in intensive care unit patients with acute renal failure [39], but to the best of our knowledge not yet in the haemodynamic monitoring of chronic HD patients. A recent study used an older tool, transcutaneous pO_2 ($TcpO_2$) monitoring, in the assessment of changes in tissue perfusion in the lower limb. While critical ischemia, defined as $TcpO_2$ <10 mm Hg, occurred only in patients with macrocirculatory abnormalities, 47% of the 50 patients experienced severe ischemia, defined as $TcpO_2$ <30 mm Hg, during a conventional HD procedure. Overall, $TcpO_2$ declined from 45.7 ± 15.5 vs. 33.5 ± 15.6 mm Hg. This tissue again shows that significant changes in tissue perfusion may accompany routine HD treatments [40].

Prevention

The fact that HD is an intermittent technique is makes it unlikely that IDH can be completely prevented. Therefore, it is of utmost importance to find an optimal balance between prevention of fluid overload on one hand and haemodynamic tolerance on the other, which can be very difficult to achieve using thrice weekly treatments. While prevention of interdialytic weight gain by sodium restriction is a cornerstone of treatment [41], the dilemma between too rapid fluid removal and persistent fluid overload may in some cases be solved only by increasing dialysis time and/or frequency [42]. As preventive methods have been discussed in detail both in older and more recent literature [8, 23], we will focus here on recently published trials. Antlanger et al. [43] randomized fluid overloaded patients, defined as an overhydration/extracellular water ratio above 15%, to a reduction in dry weight using conventional strategies, to ultrafiltration-dialysate conductivity controlled feedback modelling and to ultrafiltration-temperature controlled feedback. The latter strategy was associated with the lowest incidence of intradialytic morbid events (21%) as compared to conventional and ultrafiltration-conductivity feedback (34 and 39%) respectively. However, it also shows that dry weight reduction even in fluid overloaded patients may be associated with a significant percentage in intradialytic morbid events and should therefore be undertaken gradually. Also, online haemodiafiltration (HDF) was associated with a reduction in IDH [44], which is possibly related to its thermal effects [45]. However, the exact role of online HDF in the prevention of IDH has not been definitely established, as a recent study paradoxically observed an increase in IDH with online HDF as compared to high flux HD [46]. Until now, most solid evidence regarding

modifiable effects of the HD treatment in the prevention of IDH appears to be obtained from studies addressing time, frequency of treatments and temperature of dialysate.

Conclusion

IDH, due to the discontinuous nature of the HD procedure is a common complication, which is associated with adverse outcomes. Increasing evidence suggests that not the decline in blood pressure per se, but rather associated changes in tissue perfusion are related to short- or long-term complications in vital organs such as heart, gut and brain. Therefore, routine online measurement of tissue perfusion would be a great asset in the prevention of dialysis-associated morbidities. At present, reducing interdialytic weight gain, extending dialysis time and/or frequency, and preventing thermally induced reflex vasodilation are functions that remain cornerstones in the prevention of IDH.

Disclosure Statement

There is nothing to disclosure.

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