DOI: 10.1111/sdi.12781

EDITORIAL FOCUS: INTRADIALYTIC HEMODYNAMICS—A CLOSER LOOK

WILEY Seminars in Dialysis

Intradialytic hypotension and splanchnic shifting: Integrating an overlooked mechanism with the detection of ischemia-related signals during hemodialysis

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Abstract

In the most simple analysis, a patient's hematocrit during hemodialysis will rise when the rate of ultrafiltration exceeds the rate at which the fluid is mobilized from extravascular spaces; the greater the rise in hematocrit, the lower blood volume is and the more likely intradialytic hypotension (IDH) is to occur. A secondary mechanism of IDH may be due to sudden shift of blood volume away from the heart under conditions of borderline cardiac filling. A substantial portion of blood volume resides in the splanchnic venous system. During the early part of dialysis, a centripetal shift of red cells from this anatomical region to the central circulation has been documented to occur. The magnitude of this shift is unpredictable, and it may depend on the level of splanchnic vasoconstriction predialysis. The amount of splanchnic shift may also be reduced in patients with autonomic dysfunction. Once this central shift in blood volume has occurred, it can be reversed during further ultrafiltration due to ischemia-induced release of vasodilatory molecules that cause dilation of upstream splanchnic arterioles; this causes increased transmission of arterial pressure to the splanchnic veins, acutely increasing their capacity. The increased splanchnic venous capacity may cause a sudden shift of blood away from the central circulation to fill these veins under conditions where cardiac filling has already been reduced. The result can be severe IDH due to insufficient cardiac filling and cardiac output. One fruitful preventive approach might be to continuously monitor the blood or dialysate for the sudden appearance of such ischemia-related molecules or other signals which may herald not only dialysis hypotension but tissue stunning, warning that the fluid removal rate should be immediately reduced.

1 | INTRODUCTION

Intradialytic hypotension (IDH) has been a concern for the dialysis community for many years. Fluid overload is associated with congestive heart failure and poor outcomes, but excessive removal of fluid can lead to complications as well, including an increased risk of IDH, access thrombosis, accelerated loss of renal function, and markedly increases post dialysis recovery times.[1] IDH is associated with stunning of the heart, brain, and gut as well as poor survival,[2] and so is best avoided. One approach to trying to prevent IDH has been to monitor changes in hematocrit; the hematocrit typically rises over the course of a dialysis session as the rate of ultrafiltration exceeds the rate at which the fluid is mobilized from extravascular spaces, with a lower blood volume reflected by a greater rise in hematocrit. One idea has been that IDH tends to be preceded by a rapid increase in hematocrit, evidence of a rapid decrease in blood volume, as vascular refilling is temporarily overwhelmed. It has also been

suggested that IDH may occur when a certain, reproducible level of low blood volume has been reached and that IDH might be anticipated based on a patient-specific level of "crash crit." However, despite the fact that hematocrit monitoring has been available for a number of years, its usefulness in warning of impending IDH has been questioned.[3,4]

In some patients, IDH can occur suddenly, with little antecedent change in the hematocrit. When I began my career as a nephrologist, I studied the hemodynamic response to fluid depletion in an animal model, in both nephric and anephric dogs. In this model, fluid was removed until there was a 20% fall in predialysis blood pressure.[5] During ultrafiltration, cardiac output and blood pressure would fall in a predictable manner, and the hematocrit would indeed increase in response to ultrafiltration. However, at the endpoint of fluid removal, there would be a sudden decrease in blood pressure as well as cardiac output without any immediate antecedent rapid increase in the hematocrit (unpublished data). These responses were observed in animals that had been splenectomized to make blood volume measurement easier (dogs have markedly contractile spleens) and similar responses were observed in both nonuremic and nephrectomized animals. The responses also were similar with isolated ultrafiltration and ultrafiltration during dialysis (reviewed in[6]). In these studies, blood volumes (measured using I^{125}-albumin) at the point of hypotension were similar, but the variability was such that it was doubtful that this value could be used to predict hypotensive episodes.

A number of years ago, there was some controversy whether IDH was primarily caused by a decrease in total peripheral vascular resistance (TPR) or a fall in cardiac output. The careful work by Chen and colleagues using echocardiography definitively established that the latter, a fall in cardiac output due to decreased filling, is the most important mechanism, although those studies were done when acetate, which has vasodilatory properties,[7,8] was used as the primary buffer base.[9,10] With bicarbonate dialysis solution, TPR normally rises, and cardiac output falls appropriately[11] and the fall in cardiac output is related to the change in blood volume.[12] However, a fall in cardiac output associated with changes in venous compliance has also been documented.[13] This hemodynamic event may manifest as sudden hypotension, a consequence, perhaps, of an abrupt reduction in cardiac filling due to venodilatation.[6,14]

A decrease in TPR may lead to a fall in cardiac output.[6,15,16] To understand how this can occur, one needs to appreciate that a substantial portion of the blood volume is located in the splanchnic venous system. The splanchnic vein capacity is thought to depend largely on upstream filling pressure, which depends on the pressure drop across the upstream resistance arterioles. A reduction of upstream arteriolar resistance will cause the pressure in the splanchnic veins to increase, markedly increasing their capacity. The relation between arterial resistance and downstream venous capacity is called the De Jager-Krogh effect (Figure 1), and was highlighted in a review manuscript by Rothe et al.[17]

To see if splanchnic venous capacity might be involved in the hemodynamic response to fluid removal,[6,18] we looked to the nuclear medicine literature. There we found evidence that, when the

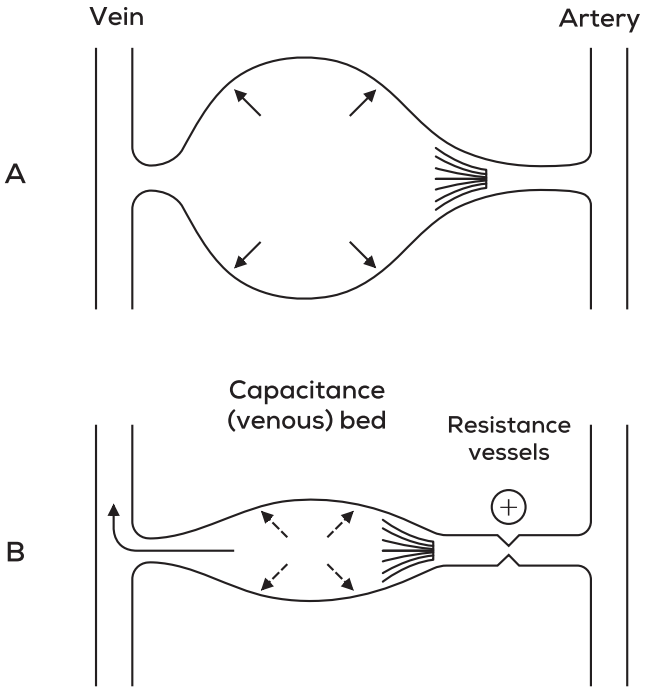

FIGURE 1 The De Jager-Krogh phenomenon, illustrated, is applicable to the splanchnic vasculature. In the upper panel (A), resistance vessel tone is low, and this increases the distending pressure in the downstream splanchnic veins, increasing their capacity. In the lower panel (B), the resistance level at the arterioles (plus sign) is increased. This lowers the downstream pressure in the veins, resulting in a reduction of splanchnic venous capacity (due to passive recoil). As a result, blood previously stored in the dilated splanchnic veins is translocated into the central circulation. Reprinted with permission from Daugirdas et al[6]

red blood cell pool is tagged with radiolabelled technetium, counts over the abdomen decrease markedly on shifting from the supine to upright position, consistent with a volume shift of red blood cells from the abdomen to (presumably) the central circulation.[19] To determine if a similar splanchnic shift occurs during dialysis, we tagged the erythrocytes of eight ESRD patients on two separate occasions. On one occasion, the patients were subjected to diffusion dialysis without fluid removal for the initial 2 hours of a dialysis treatment while on the other occasion, dialysis during the initial 2 hours was accompanied by a relatively high rate of ultrafiltration.[20]

As shown in Figure 2, when fluid was not removed, there was no change in splanchnic abdominal radioactivity from the technetium-tagged erythrocytes. However, when the fluid was removed, there was a prompt reduction in the splanchnic erythrocyte radioactivity (of about 10%). This occurred within the first 30 minutes of fluid removal, and was established before there was any change in blood pressure or heart rate. The results suggested that this central shift of splanchnic blood occurs very early during ultrafiltration, without any major change in hematocrit. The presence of this compensatory mechanism to volume depletion may well increase the ability to remove fluid from a patient.

The natural question then arises: Is this splanchnic shifting response present in all dialysis patients? We did study one additional

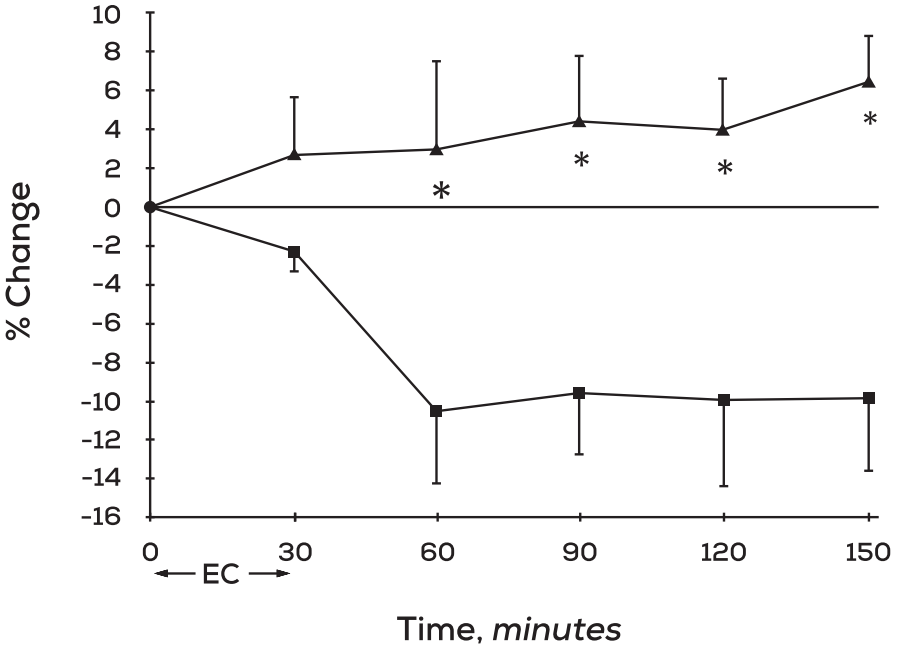

FIGURE 2 Changes from baseline in abdominal radioactivity (emanating from radiolabelled technetium-tagged red blood cells) during the initial 150 min study period. The triangles (top trace) represent dialysis without fluid removal while the bottom trace shows results in the same patients during another dialysis session when dialysis was combined with ultrafiltration. Both treatments began with a 30-min initial extracorporeal circulation (EC) period. Asterisks represent a *P* value <0.05 comparing the two treatments at each time point. Redrawn from Yu et al[20]

patient in whom autonomic neuropathy was documented by failure of the R-R interval to change substantially on either Valsalva or deep breathing. In that one patient there was no change in abdominal radioactivity counts during fluid removal, and this patient developed hypotension at an early stage of fluid removal. We never pursued our original intention to study a larger group of patients with diabetes, separating them out into those with, and those without autonomic neuropathy. We also planned to evaluate postural changes in abdominal radioactivity counts after technetium tagging of erythrocytes, as well as to compare splanchnic shifting during fluid removal, in patients with vs without autonomic neuropathy.

In the 1990s, Maeda et al[14,21] proposed that there were several varieties of IDH, one of which was sudden IDH. Maeda's group measured hemodynamic parameters in nine patients who habitually developed sudden onset hypotension during acetate dialysis and found that the hypotension was not preceded by falls in either blood volume or peripheral vascular resistance, but was heralded by a decreased cardiac output. They theorized that the decrease in cardiac output was due to decreased filling secondary to a peripheral shift in blood volume (possibly due to venodilatation). Maeda's group also found that IDH was preceded by a decrease in sympathetic activity,[22] results later confirmed by Converse et al.[23]

What could be the cause of the withdrawal of sympathetic tone, after sympathetic nerve activity had increased in response to volume removal? Maeda's group theorized that one mechanism might be the release of adenosine, a vasodilator. They proposed that ischemia accelerates conversion of adenosine triphosphate in tissues to the di- and monophosphates, which are further metabolized to adenosine as well as inosine and other purine metabolites. Indeed, Maeda's group found increased levels of adenosine metabolites in blood prior to a sudden hypotensive episode.[21] Consistent with this hypothesis, when they gave caffeine (an adenosine blocker), prior to dialysis in an attempt to prevent adenosine-mediated vasodilatation, they did find some protective effect.[21]

How might the adenosine hypothesis tie in with splanchnic shifting? One can postulate a subgrouping of IDH according to the baseline status of the splanchnic veins as well as the ability of the splanchnic veins to passively contract in response to fluid removal (Table 1). Group 1 might be those patients with intact autonomic reflexes; they would be expected to come into dialysis with dilated splanchnic veins and their veins should passively reduce their capacity in response to upstream arteriolar constriction as fluid is removed, augmenting venous return. Such patients, however, would still be susceptible to sudden IDH because if ultrafiltration were pushed to the

TABLE 1 Postulated relationship between the state of splanchnic veins (dilated or passively constricted), upstream resistance vessel contractility, and potential clinical consequences

Clinical condition	Splanchnic veins predialysis	Ability of upstream resistance vessels to contract	Splanchnic shift	Ease of fluid removal	Susceptibility to sudden hypotension
Normal	Dilated	Yes	Yes	Good	++
Diabetes? Heart failure?	(Passively) constricted	Yes	Reduced (veins already partially constricted at baseline)	Poor	+++
Autonomic neuropathy?	Dilated	No	Minimal (arterioles cannot contract)	Poor	0-+

point of causing tissue ischemia, sudden splanchnic venodilatation might occur. Group 2 might be patients in whom the splanchnic veins are partially constricted predialysis (eg, due to increased sympathetic one). Such patients would also be susceptible to sudden splanchnic vasodilatation from release of ischemia-mediated vasodilatory molecules. The splanchnic venous capacity in this group would be reduced predialysis, and such patients would be expected to tolerate fluid removal poorly because the normal splanchnic shifting mechanism in response to hypovolemia would not be fully functional. Group 3 might be patients in whom the splanchnic vessels are dilated predialysis and unreactive to volume removal stimuli (eg, due to autonomic neuropathy). Such patients might be susceptible to hypotension during hemodialysis because the splanchnic shifting mechanism would not be operative, but sudden ischemia-mediated IDH episodes might be less frequent, as further splanchnic vasodilatation in response to ischemia would be minimal.

There is some additional evidence suggesting splanchnic shifting during fluid removal. One study by Ribitsch and colleagues measured hepatic-splanchnic perfusion during fluid removal by dialysis. They confirmed that, with fluid removal, the hepato-splanchnic perfusion index fell, indicating vasoconstriction. They also found that the baseline hepato-splanchnic resistance was increased in dialysis patients with diabetes compared to those without diabetes.[24]

What about the effects of cool temperature dialysis solution? Of all the maneuvers to reduce the incidence of IDH, the use of low temperature dialysis solution has been the most reliably successful. Previous studies have focused on the effects of dialysis solution cooling on peripheral vascular resistance, but the effect on splanchnic shifting has not been measured. Use of cool temperature dialysate might, in theory, augment splanchnic vasoconstriction during fluid removal. Other treatments that reduce the incidence of IDH, such as the use of sympathetic agonists like midodrine, or vasopressin (which has a known splanchnic vasoconstrictive effect), might work partially by constricting splanchnic veins and shifting blood volume centrally.

Of the different types of IDH that are encountered clinically, it might be argued that sudden IDH may be especially worrisome, as its onset is typically unpredictable. If sudden splanchnic vasodilatation is caused by release of vasodilatory molecules by ischemic tissue, the ability to detect the release of ischemia-related molecules prior to a hypotensive episode might be very useful. This ability would allow ultrafiltration to immediately cease on detecting the release of these molecules and potentially avoid further tissue injury.

Some dialysis machines have a device that monitors spent dialysate for low molecular weight plasma solutes normally removed by dialysis[25]; this method has been used to monitor the adequacy of dialysis in real time. Perhaps, such a dialysate detection system could be modified to scan for an increase in ischemia-related molecules such as adenosine metabolites or other compounds. Another approach might be to look at mixed venous oxygen saturation. It is possible that, when a particular tissue bed becomes ischemic, the oxygen saturation in the veins draining this tissue might be sufficiently low to cause mixed venous O_2, (continuously monitored by some devices in the course of dialysis) to drop by a measurable amount.[26] Ideally, a dialysis machine-based device would detect the early release of ischemia-related molecules, and then automatically back off from aggressive fluid removal until release of such molecules is no longer observed. IDH has long been a thorn in the side of nephrologists as well as a vital threat to hemodialysis patients. Efforts to ameliorate this problem warrant our ongoing attention and efforts.

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How to cite this article: Daugirdas JT. Intradialytic hypotension and splanchnic shifting: Integrating an overlooked mechanism with the detection of ischemia-related signals during hemodialysis. *Semin Dial*. 2019;00:1–5. https://doi.org/10.1111/sdi.12781