

# Beware Intradialytic Hypotension

## How Low Is Too Low?

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Intradialytic hypotension (IDH) is a long-recognized complication of the hemodialysis procedure. Although numerous definitions exist to define IDH, the 2005 National Kidney Foundation Kidney Disease Outcomes Quality Initiative definition (a decrease in systolic BP [SBP] by  $\geq 20$  mm Hg or a decrease in mean arterial pressure by  $\geq 10$  mm Hg with associated symptoms) has not consistently been associated with adverse clinical outcomes (1–4). This lack of association is likely related to the relative insensitivity of these small falls in BP in truly identifying those “at risk” as well as the difficulty in capturing symptoms of IDH in database analyses. Importantly, recent studies have identified IDH defined as a nadir intradialytic SBP of  $< 90$  mm Hg as consistently being associated with adverse clinical outcomes, primarily all-cause mortality.

Flythe *et al.* (3) recently investigated the relationship between varying definitions of IDH and all-cause mortality among both 10,392 patients on prevalent dialysis cared for within a large dialysis organization (LDO) and 1409 Hemodialysis Study cohort patients. In their analysis, nadir intradialytic SBP  $< 90$  mm Hg was associated with a 30%–56% higher adjusted mortality risk. Intradialytic drops in SBP, other than those combined with low nadir intradialytic SBP, failed to correlate with higher mortality. In one of our recent analyses of a large LDO database, we investigated the relationship between intradialytic SBP and all-cause mortality among 112,013 patients on incident hemodialysis (4). We identified a nadir intradialytic SBP of  $< 90$  mm Hg to be associated with a 57% higher 5-year mortality risk. Nadir intradialytic SBP of  $< 100$  mm Hg was associated with a 25% higher adjusted 5-year mortality risk, and clinically, it may be an earlier BP threshold to consider, particularly if in combination with a large decline in SBP. In our study, intradialytic declines in SBP  $> 50$  mm Hg were associated with 30% higher 5-year mortality risk.

In this issue of the *Clinical Journal of the American Society of Nephrology*, Eun Young *et al.* (5) performed a patient controlled study to describe the relationship between IDH and hospitalized mesenteric ischemia. They hypothesized that patients with a hospitalized mesenteric ischemic event (patients) would be more likely to have had IDH in the 30 days before hospitalization than matched patients without mesenteric ischemia (controls). The authors used data from the US Renal

Data System merged with electronic health records from an LDO to create a 1:4 patient-control cohort of 3052 patients on hemodialysis with and without mesenteric ischemia matched on demographics and comorbidities. Mesenteric ischemia was identified by the International Classification of Diseases Ninth Revision (ICD-9) codes combined with abdominal imaging during an individual hospitalization stay. IDH was assessed for 30 days before the index hospitalization stay, and it was defined in a number of different ways, including nadir intradialytic SBP  $< 90$  and  $< 100$  mm Hg, declines in SBP  $> 20$  and  $> 30$  mm Hg, and combinations of both. Because the patients were matched on comorbidities, patients with and without mesenteric ischemia both had a high prevalence of coronary artery disease, diabetes, and heart failure, and they were relatively similar overall. Additionally, treatment times and ultrafiltration rates were similar between patients and controls.

The proportion of patients with IDH varied depending on the definition of IDH. Patients and controls both had frequent occurrences of a 20- or 30-mm Hg decline in SBP in the month before the index date for mesenteric ischemia, and this was not a meaningful delineator. When IDH was defined using a nadir intradialytic SBP of  $< 90$  or  $< 100$  mm Hg (with or without a 20- or 30-mm Hg fall in SBP), there was a nearly twofold higher odds of IDH occurring in patients versus controls. The authors also identified a dose-response association between the frequency of IDH and mesenteric ischemia; those with  $> 30\%$  of sessions with nadir intradialytic SBP  $< 90$  mm Hg had  $> 60\%$  adjusted odds of being patients with mesenteric ischemia. The results were consistent with a number of sensitivity analyses performed, including assessing antihypertensive agent use.

Of note, there are some important limitations to this study. Although the authors matched on available comorbidities, unmeasured confounders likely exist. Residual confounding from uncaptured or unconsidered variables that might make a patient more likely to have lower intradialytic BP within the month before mesenteric ischemia may exist. Furthermore, it is plausible that low intradialytic BP is a marker of the patient’s illness rather than a contributor to the occurrence of mesenteric ischemia. Additionally, utilization of ICD-9 codes without chart review to confirm

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that the patient's hospitalization included a diagnosis of acute mesenteric ischemia may lead to misclassification of patients and controls and dilution of the associations. The authors appropriately performed a sensitivity analysis isolated to an ICD-9 code only for acute mesenteric ischemia, and the results were more pronounced. Given the rarity of the condition and the inability to access actual hospital records, it is understandable that additional confirmation of diagnosis would not be feasible in this type of analysis.

The findings of Eun Young *et al.* (5) are informative and add another layer to our knowledge about the risks of extremes in BP during dialysis. As mentioned above, nadirs of intradialytic SBP <90 and even <100 mm Hg have been associated with higher mortality. Additionally, IDH occurring in >30% of dialysis sessions is also associated with higher mortality. However, mortality is not the only important event. Recurrent episodes of low systemic perfusion, particularly in combination with atherosclerotic disease, are likely to increase the patient's risks for other adverse ischemic events, such as myocardial ischemia and subsequent arrhythmias, heart failure, and cerebral ischemia. Additionally, recent studies have identified associations between IDH and adverse sequelae, including myocardial infarction, vascular access thrombosis, and ischemic brain injury (2,6–9). McIntyre *et al.* (10) identified a correlation between hypotension during dialysis and higher levels of gut-derived endotoxin levels. The analyses of Eun Young *et al.* (5) add support to the hypothesis and identified mesenteric ischemia as associated with recurrent episodes of IDH. Taken together, it seems relatively intuitive that there is a lower-limit BP (<90 and possibly, <100 mm Hg in some patients), below which the risk for ischemic events starts to increase.

What causes IDH? The initial stimulus for a decline in BP is a decrease in effective circulating intravascular volume. Intravascular volume will decrease if the ultrafiltration rate exceeds the capacity for the interstitium to refill the intravascular space or if there is a drop in the intravascular relative to the extracellular osmolality. To compensate for the decline in intravascular volume, cardiac output should increase, or vasoconstriction should occur. However, these compensatory mechanisms are impaired or inhibited in many patients on dialysis due to patient comorbidity (cardiovascular disease or autonomic insufficiency) and treatment factors, such as low dialysate sodium or calcium, use of antihypertensive medications, or inappropriate ultrafiltration. As a consequence, IDH occurs due to an insufficient physiologic compensation to the drop in effective intravascular volume.

Taken together, how should we better manage our patients to avoid increasing their risk for adverse hemodynamic complications during dialysis? There are no randomized trials to show that minimizing low BP can improve outcomes. However, there are observational studies and small trials that provide guidance for interventions that can reduce the frequency of IDH. These include individualized cool dialysate, extending dialysis sessions, more frequent dialysis sessions, holding BP medications before dialysis, and using midodrine selectively. Additionally, patient

education about minimizing sodium and fluid intake as well as encouraging adherence with their prescribed dialysis regimen are important. Hypertonic saline and sodium modeling should be used cautiously, because this may result in a positive sodium balance, which can lead to long-term volume overload. In the absence of published trials suggesting benefit or harm with the aforementioned interventions, treatments should be individualized to the patient, their risk profile, age, and life expectancy. As we continue to become aware of the risks associated with extremes in BP during dialysis, providers should add mesenteric ischemia to the growing list of cardiovascular complications to consider while trying to best optimize patient BP. Finally, education is a critical factor with patients, particularly when trying to optimize their dialysis regimen to minimize high ultrafiltration rates and the risks of IDH.

#### Disclosures

None.

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