Redefining the Burden of Intradialytic Hypotension in the Modern Era of Hemodialysis

Peter Noel Van Buren^{a, b}

^aDallas Veterans Affairs Medical Center, Dallas, TX, USA; ^bUniversity of Texas Southwestern Medical Center, Dallas, TX, USA

Blood pressure (BP) management in hemodialysis patients remains challenging, in part due to the BP changes during and between dialysis treatments. Although a modest reduction in BP from pre to postdialysis occurs in most patients, other patients experience either increases or large decreases in BP that are now known to be associated with increased mortality. The immediate goal of avoiding hypotension during dialysis is to ensure patient safety and limit unpleasant symptoms. Long-term goals are to avoid recurrent hypoperfusion of vital organs and avoid interruptions in ultrafiltration that can result in chronic extracellular volume overload, an independent mortality risk factor. Traditional definitions of intradialytic hypotension (IDH) have been stated in clinical practice guidelines (reduction in systolic BP >20 mm Hg with corresponding symptoms), but a more recent study validated the mortality risk associated with the definition of nadir systolic BP <90 mm Hg in at least 30% of exposure treatments [1]. In this issue of *American Journal of Nephrology*, Kuipers et al. [2] acknowledge that the demographic of hemodialysis patients has changed over time as have the interventions used to minimize IDH. They aimed to quantify the updated prevalence of the traditional and novel definitions of IDH.

In this meta-analysis, the authors reviewed studies from the past 28 years (final analysis included 23 studies out of >3,000 screened) that addressed IDH prevalence using a variety of definitions but focusing mostly on a decrease in systolic BP >20 mm Hg with clinical symptoms or intervention or a nadir systolic BP <90 mm Hg. Using the former definition, they found the prevalence of IDH to range from 5 to 31% with a mean prevalence of 9.7%. The prevalence ranged from 4 to 17% when the systolic BP nadir <90 mm Hg was used with a mean prevalence of 4.7% in the final analysis. They found the proportion of patients that experienced IDH to range from 6 to 77 and 10 to 75% for the respective definitions, but they did not conduct a meta-analysis of these outcomes due to differences in the qualifying frequency of IDH (1 treatment to 30% of treatments). Not surprisingly, the presence of diabetes and large interdialytic weight gain were frequently reported in the individual studies as risk factors for IDH. Further conclusions were that the absolute decrease and symptoms definition of IDH was consistently reported as 10% other than in studies where multiple episodes in a single treatment were included, but the systolic nadir <90 mm Hg was more heterogeneous across different studies. The authors acknowledged that limitations of

their analysis were the differences in observation period or standardized approach to how intradialytic symptoms were ascertained.

One interpretation of this current meta-analysis is that most of the time nephrologists are providing adequate protection against the negative consequences of IDH (90–95% on average), but there are further points worth considering. The first is that on a patient level, IDH still occurs at least intermittently in a large percentage of patients (up to 75% per this analysis). The second is that, while mortality is obviously a critically important endpoint to validate a definition of IDH, there are other consequences of less extreme reductions in BP that compromise the general well-being of the patient.

Despite the lower IDH prevalence identified in this study, it confirmed that these BP reductions occur in most patients at least occasionally. Some of the individual studies analyzed indicate that even intermittent IDH can be consequential. The Flythe study [1] primarily investigated mortality risk when IDH occurred in $\geq 30\%$ of treatments, but it also found an incremental increase in mortality risk for frequencies (of nadir systolic BP < 90 mm Hg) $> 5\%$ [1]. This graded increase in mortality was also found in the largest study included in this analysis where Chou et al. [3] specifically looked at incident hemodialysis patients. Unfortunately, IDH still occurs in the context of several novel tools to help assess ECV or intravascular volume. A recent study found that higher percentage of relative blood volume at each hour of dialysis (compared to baseline) was associated with increased mortality [4], but the authors were unable to find any association between percentage of relative blood volume at any point in time with the occurrence of IDH. One clinical trial using bioimpedance spectroscopy to guide ultrafiltration found favorable effects on pulse wave velocity and mortality in the intervention arm, but between-group differences in intradialytic symptoms were similar [5]. IDH is a multifactorial phenomenon related as much to failure to appropriately vasoconstrict as it is to intravascular volume depletion, so it is not surprising that it continues to occur even though these tools are available. While it remains unclear what the target BP pressure should be before or after dialysis, randomized trials clearly show that interventions which lowering BP in hemodialysis patients through either dry weight reduction and/or more intensive antihypertensive therapy result in increased episodes of IDH [6, 7]. If the BP in dialysis ultimately shows a benefit for more intensive lowering of predialysis BP, we should expect IDH to become more common.

The other consideration is that there are other clinically relevant consequences of organ hypoperfusion that might occur at higher BP thresholds than used in this meta-analysis. For example, one recent study demonstrated an incremental decrease in cerebral perfusion as mean arterial pressure decreased during dialysis [8]. While a mean arterial pressure of 60 mm Hg was specific for hypoperfusion, it had poor sensitivity with much higher mean arterial pressures failing to protect against hypoperfusion in individual patients. Unlike the Flythe study that found no independent association between BP change and mortality, this study found absolute reduction in mean arterial pressure to be associated with cerebral hypoperfusion. Another study found that the mean intradialytic arterial pressure extrema point frequency based on beat by beat digital arterial pressure measurements was associated with cerebral white matter changes on brain MRI, while IDH was not [9]. Finally, there is evidence that myocardial perfusion decreases early in dialysis prior to any significant ultrafiltration and in the absence of IDH [10]. Cumulatively, these studies highlight that organ perfusion can be compromised even when patients don't overtly experience IDH. While cognitive impairment or heart failure is not synonymous with mortality, we should still aim to avoid predisposing factors for these outcomes which likely start with intradialytic hypoperfusion.

In conclusion, a hazardous threshold of intradialytic BP nadir has been identified. Because of its association with increased mortality, a systolic BP < 90 mm Hg should be avoided. This analysis establishes that this definition of IDH occurs less frequently than other definitions. Having a validated definition for IDH provides guidance for what to avoid, but this must not come at the expense of ignoring other important yet less extreme changes in intradialytic BP. Furthermore, it remains to be determined whether there are other metrics of tissue perfusion or injury that are superior to nadir systolic BP at predicting mortality or even other nonfatal but highly morbid outcomes. The clinical practice of managing hemodialysis should continue to integrate important findings that have been generated by epidemiologic studies to minimize morbidity and mortality, but further research should continue to investigate the nature and significance of many other intradialytic BP patterns that might carry clinical relevance in patients on an individual level. This should include assessments of how to optimize patient well-being and limitation of hospitalizations and other metrics of nonfatal morbidity.

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