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Defining intradialytic hypertension: the importance of measuring blood pressure accurately

Grégoire Wuerzner [1,2], Menno Pruijm [1] and Michel Burnier [1,2]

[1]Service of Nephrology and Hypertension, University Hospital, Lausanne, Switzerland and [2]Hypertension Research Foundation, St-Légier, Switzerland

Correspondence to: Michel Burnier; E-mail: michel.burnier@chuv.ch

The blood pressure (BP) profile of patients on maintenance hemodialysis (HD) is characterized by large fluctuations occurring within and between HD sessions. Indeed, during a typical HD session, BP decreases from pre- to postdialysis and generally increases gradually until the next dialysis session owing to salt and fluid retention. In observational studies, both intra- and interdialysis changes in BP have been associated with target-organ damage, cardiovascular events and mortality with a U-shape relationship, the incidence of clinical events increasing in patients with very low as well as very high BP values [1].

In 2004, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines proposed to consider hypertension in HD patients when pre-dialysis BP is >140/90 mmHg or when postdialysis BP is >130/80 mmHg [2]. In 2019, however, participants in the Kidney Disease: Improving Global Outcomes (KDIGO) Conference on Blood Pressure and Volume Management in Dialysis came to the conclusion that there are no accepted definitions of hypertension and BP treatment targets in the dialysis population since no population-specific evidence has established BP thresholds and targets for interdialytic BP in this population [3]. Thus nephrologists remain confronted with several unsolved issues regarding definitions, targets and management of dialysis-associated hypertension phenotypes. One good example is intradialytic hypertension.

When BP values are higher during or immediately after dialysis than before starting the HD session, patients are diagnosed with intradialytic hypertension. Clinically it appears that almost every patient develops at least one episode of intradialytic hypertension over a 6-month period. However, the reproducibility of the phenomenon is poor and persistent intradialytic hypertension is less frequent. Thus the phenomenon has a prevalence ranging from 5 to 25%, depending on its definition [4]. In fact, as for interdialytic hypertension, there is no consensus on the definition of intradialytic hypertension [3]. Some investigators define it as a BP increase of any degree during the second or third intradialytic hour; others as a systolic BP (SBP) increase >15 mmHg within or immediately after dialysis, or an SBP increase >5, 10 or 20 mmHg from pre- to postdialysis, or an increasing intradialytic BP that is unresponsive to volume removal. Considering the low reproducibility and the variability of BP, it has also been proposed to include in the definition the frequency at which the phenomenon occurs during a time period in the definition, for example, an increase in SBP in at least four of six consecutive dialysis treatments.

In a recent study published in *Hypertension,* Singh *et al* [5] investigated the association of different definitions of intradialytic hypertension with long-term mortality in a very large set of HD patients (n = 3198). In their analyses, the authors used three definitions of intradialytic hypertension: any increase in SBP from pre- to post-HD (Hyper0), any increase of >10 mmHg (Hyper10) and any increase of >20 mmHg (Hyper20). Patients had to experience intradialytic hypertension in ≥30% of HD sessions during the 90-days baseline exposure period. Those patients who did not meet this criterion formed the reference group. The main objective of these analyses was to describe the association between these definitions of intradialytic hypertension and long-term mortality.

The authors also assessed the demographic and clinical factors that could modify these associations. In this cohort, 1502 had intradialytic hypertension and 1696 were in the control group. During the baseline period, the percentages of patients fulfilling the three definitions were 47%, 21.2% and 6.8% for the first (Hyper0), second (Hyper10) and third definition (Hyper20), respectively. All three definitions were associated with an increased unadjusted risk of death with a hazard ratio (HR) ranging from 1.77 [95% confidence interval (CI) 1.49–2.10] for the Hyper0 definition to 1.49 (95% CI 1.11–2.00) for the Hyper20 definition. However, after full adjustment, only the Hyper0 definition was associated with a significantly higher risk of death [HR 1.32 (95% CI 1.05–1.66)].

Of note, patients meeting the Hyper0 definition had a higher prevalence of heart failure, lower ultrafiltration volume and lower ultrafiltration rates. The association of Hyper0 with mortality was most apparent in patients ages 45–70 years.

The results of this recent observational study confirm the association between intradialytic hypertension and the risk of death reported in several previous analyses and reviews [4, 6, 7] and also the association of more frequently occurring intradialytic hypertension with an increased morbidity and mortality risk [8]. The major strength of this article is the direct comparison of different definitions and their impact on hard endpoints. Their results suggest that intradialytic hypertension should be defined as any increase in BP occurring at the end or immediately after a dialysis session, provided the phenomenon is not sporadic and occurs in >30% of HD sessions. This is a straightforward definition that can be easily integrated in clinical practice. Hence nephrologists should be concerned whenever BP is not reduced at the end of the dialysis session.

However, the data presented by Singh *et al.* [5] deserve at least two comments. The first is the surprising inverse association between the degree of elevation of BP postdialysis and the risk of death. Indeed, the HR for the risk of death was lower in the Hyper20 than in the Hyper0 group. Yet, in the global-adjusted analysis, each 10 mmHg higher pre-SBP to post-SBP was associated with an 18% lower risk of all-cause mortality. In previous studies, the morbidity and mortality risks were clearly higher when the increase in postdialysis BP was greater. Thus in the analysis of 1748 HD patients participating in the US Renal Data System Dialysis Morbidity and Mortality Wave II Study published by Inrig *et al.* [6], every 10-mmHg increase in SBP during HD was associated independently with a 6% increased hazard of death. As long as the precise underlying mechanisms of intradialytic hypertension remain incompletely understood [4], it is difficult to explain differences between observations.

The second and most important issue concerns the methodology used to measure BP during dialysis sessions. This is a crucial point if one should consider any increase in BP in the definition of intradialytic hypertension. Singh *et al.* [5] mention that BP was collected in the setting of standard clinical practice, thus reflecting a real-world situation, and they admit that their procedure lacked the robustness and reproducibility of protocolized measurements. The problems associated with the quality of BP measurements during HD sessions are well known and have been reviewed in the consensus paper published by the European Renal Association and the European Society of Hypertension in 2017 [1]. Briefly, BP measurements during HD are not made for diagnostic purposes but rather to monitor patients' vital signs. Several factors may lead to inaccurate BP readings in HD, including the white coat effect due to the environment, limited time for relaxation, fear or anxiety about correct arteriovenous fistula puncture. Moreover, most BP measuring devices attached to commercially available hemodialysis machines have not been validated clinically. A survey assessing adherence to BP measurement recommendations in dialysis centers and comparing physicians' with patients' experiences has confirmed the limits of BP measurements in dialysis centers [9]. Indeed, in dialysis, standard recommendations for measuring BP appear to be poorly followed according to physicians themselves, and even less so according to patients. Of note, 74% of physicians indicate that BP measuring devices of HD machines had been properly validated when they were not. In the future, dialysis centers should consider using only validated devices in order to remove inaccuracy bias [1].

As with any BP measurements, focusing on one timed measurement only gives a punctual estimation of the patient's true BP profile. In recent years, ambulatory blood pressure monitoring (ABPM), over 24 h or 48 h, has been strongly recommended as the preferred way to assess interdialytic BP in hemodialyzed patients. However, as with traditional BP devices, many ABPM devices have not been validated in the specific population of dialysis patients, who have an advanced vascular phenotype. Moreover, they may not be suitable for every patient (multiple fistulas) and their tolerance is rather low. The ability of new technologies, such as cuffless devices, to continuously record intra- and interdialysis BP might provide an interesting new approach on how to define and interpret intradialytic in regard to interdialytic hypertension. This latter aspect may be of importance, as it remains unknown today whether interdialytic hypertension, rather than intradialytic hypertension, is the factor actually responsible for the increased risk of hospitalizations and mortality associated with intradialytic hypertension [10]. Hence, over the next few years there will be new opportunities to improve the diagnosis of intra- and interdialysis hypertension that should not be missed. HD often belongs to the forgotten study groups. Let us hope that this time dialysis patients will not be forgotten and that new technologies will be validated correctly in all subgroups of nephrology patients.

CONFLICT OF INTEREST STATEMENT

M.B. and M.P. have no conflicts of interest to declare. G.W. has received research grants from Aktiia.

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