Feedback Control in Hemodialysis—Much Ado about Nothing?

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In this issue of the *Clinical Journal of the American Society of Nephrology*, Leung *et al.* (1) present the negative results of their randomized, controlled trial testing the efficacy of relative blood volume–controlled ultrafiltration to reduce symptomatic intradialytic hypotension. In brief, the authors thoroughly executed their well designed study protocol, but the findings are disappointing for those who have spent time and effort developing blood volume monitoring technology and/or putting it into practice. For the silent majority not regularly using this technology in patients on hemodialysis, we provide a brief introduction.

Absolute (= total) blood volume (*i.e.*, the volume in liters of all components contained within the cardiovascular system) cannot be measured directly, but several technical devices can be integrated within the tubing of the dialysis machine to continuously measure the concentration of blood constituents, such as hemoglobin, hematocrit, or total protein, during hemodialysis. Blood volume changes in percentage can thus be inferred relative to hemodialysis start under a single-pool assumption. The term "blood volume monitoring" has become most widely used, although only relative blood volume changes are measured and used for control.

The relative blood volume curve has been postulated to be useful as a readout for overall blood volume status (2). If the curve steeply falls during ultrafiltration, because intravascular fluid volume decreases, the patient may be close to experiencing intradialytic hypotension, whereas flatter relative blood volume curves may result from adequate compensation by sufficient fluid entering the bloodstream from extravascular pools (vascular refilling), indicating that (often excessive) fluid is present in the interstitial space. Interpreting the relative blood volume curve is particularly appealing in patients with acute kidney injury for achieving an adequate ultrafiltration volume in unstable situations.

The confusion starts when relative blood volume–controlled feedback of the ultrafiltration rate (the term "bio"-feedback refers to psychophysiology and was erroneously introduced by one of the feedback developers) is loosely entitled "blood volume monitoring" (the measuring or diagnostic process itself). The logic of that feedback control is to maximize vascular refilling by starting treatments with a high ultrafiltration rate and subsequently decreasing and adjusting the ultrafiltration rate. Controlling blood volume by continuously adjusting the ultrafiltration rate to prevent hypovolemia rather than waiting for patient symptoms or arterial hypotension that necessitate immediate countermeasures certainly seems compelling.

Leung *et al.* included patients who had >30% hemodialysis sessions complicated by symptomatic intradialytic hypotension 8 weeks before eligibility assessment, and the authors prespecified definitions of the symptoms (3). This approach necessitated screening 12 times more patients than were included. Despite rescreening, the expected sample size of 35 patients could not be achieved, but those 24 participants completing the study would still have provided >80% power to detect a 30% reduction in the primary outcome. Unfortunately, at a rate of 0.10/h symptomatic intradialytic hypotension events with feedback-controlled versus 0.07/h during constant ultrafiltration (1), the study was clearly negative. All included patients had residual urine volume <250 ml/d at baseline, 75% were patients with diabetes, and 63% had a central venous catheter. Fluid overload assessed by whole-body bioimpedance measurements was around 25% of extracellular volume throughout the study and increased slightly during controlled ultrafiltration but did not decrease during the run-in period, where the authors had actually intended to lower dry weight using a "modified version" of the Dry-Weight Reduction in Hypertensive Hemodialysis Patients Study protocol Together, these results indicate that Leung *et al.* (1) rightfully targeted patients on hemodialysis with severe fluid removal problems who all would have benefitted from improved intradialytic stability.

The principal strength of the analysis by Leung *et al.* (1) is that the straightforward, detailed, peer-reviewed study protocol (3) left little to no interpretative freedom compared with other trials, such as the Crit-Line Intradialytic Monitoring Benefit (CLIMB) Study (4). The CLIMB Study tested the hypothesis that mere blood volume monitoring availability would decrease morbidity by encouraging, but not enforcing, an interventional algorithm to control ultrafiltration rate on the basis of relative blood volume curves. Blood volume monitoring availability in the CLIMB Study was associated with higher nonvascular access– and vascular access–related hospitalizations and mortality, which

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were disturbing, despite atypically low hospitalization and mortality rates in the control group. By contrast, Leung *et al.* (3) carefully defined the intervention that they were testing: they allowed no dialysate conductivity adjustments and used a system that provided automatic feedback control of ultrafiltration on the basis of a "critical" relative blood volume change. This critical threshold has to be entered at the beginning of the hemodialysis session for each individual patient, feeding the machine's software. Reasonably, the authors' identified the critical threshold as the minimum relative blood volume change recorded immediately before the most recent episode of symptomatic intradialytic hypotension, and they weekly reassessed this threshold. Unfortunately, the variation of this threshold within study subjects and throughout the study period is not provided. Altogether, the study design was elegant, with blinding of patients to their assignment and a crossover component to conventional, best clinical practice hemodialysis that applied constant ultrafiltration rates after a phase of feedback-controlled ultrafiltration or *vice versa*.

Given the quality of this study, it is reasonable to conclude that relative blood volume–controlled ultrafiltration alone is not able to improve hemodynamic stability in patients on hemodialysis prone to intradialytic hypotension. If this is not to be the end of blood volume control, several questions need to be addressed.

(*1*) Are relative blood volume changes suitable? Apart from the single-pool assumption, which must be questioned when calculating relative blood volume changes, the futility to controlling intravascular volume using relative changes can be compared with a room thermostat controlling the temperature change rather than the absolute room temperature: the resulting temperature could be anything. Intravascular volume control, therefore, may require a measure for absolute blood volume. The importance of absolute values becomes evident from the recent success of bioimpedance analysis to control extracellular volume using the measurement of absolute fluid overload to set the dry weight. The measurement of absolute blood volume is not beyond reach, even with everyday dialysis (5), and a specific blood volume threshold of $<$65 ml/kg was recently identified as highly sensitive and specific to predict intradialytic morbidity (6). This information together with online relative blood volume tracking might provide better ability to control ultrafiltration.

(*2*) Which blood volume? Ventricular filling and stroke volume depend on central venous pressure, which varies with central blood volume (7). It, therefore, has been argued to focus on monitoring central blood volume and venous oxygenation rather than total blood volume when concerned about hypovolemia during hemodialysis. This approach is in line with the recent focus on lung ultrasound to detect volume excess (8). Thoracic electrical impedance is known to follow changes in central blood volume, and an excessive increase in thoracic electrical bioimpedance was predictive of intradialytic hypotension (9). Bioimpedance analysis has become a standard in volume assessment (mostly outside the United States), and thoracic electrical impedance technology is available as perhaps one of the most adequate predictors for intradialytic hypotension.

(*3*) What else can be adjusted other than ultrafiltration rate? The requirement to remove the prescribed ultrafiltration volume within a specified treatment time represents an unfortunate limitation, because the removal of fluid from peripheral compartments and equilibration throughout the whole body is a slow process and probably slower in intradialytic hypotension–prone patients on hemodialysis. As acknowledged by Leung *et al.* (1), additional options for feedback control in hemodialysis to increase hemodynamic stability include adjusting dialysate temperature and dialysate sodium concentration. (We are well aware of the controversy over the adequate dialysate sodium concentration [10] and do not mean to support an undifferentiated use of [often outdated] sodium profiles that might result in sodium loading.) The majority of feedback control studies reporting improved hemodynamic stability adjusted both ultrafiltration rate and dialysate sodium concentration on the basis of the assumption that an increase in effective osmotic pressure stimulates vascular refilling (11). The importance of osmotic refilling, however, must be questioned (12); hemodynamic stability from a rapid increase in dialysate sodium might better be explained by a completely different mechanism: the osmotic stimulation of arginine vasopressin (antidiuretic hormone) secretion and subsequent vasoconstriction (12,13). Strikingly improved hemodynamic stability can also be achieved using isolated ultrafiltration when the warm dialysate flow is turned off, providing a "cold-pressor" effect of extracorporeal blood exposed to the cool environment (14).

In summary, failure of simple relative blood volume control to reduce the frequency of symptomatic intradialytic hypotension in a selected group of extremely hypotension-prone patients is not really surprising given the limitations of this technique. Importantly, feedback control was not associated with significantly worse outcomes given previous discouragement (4,15). Only the options of prolonging treatment time, adjusting dialysate composition and/or temperature, and providing isolated ultrafiltration may currently be suited to help the most vulnerable patients. Determining absolute values for dry weight using bioimpedance and absolute blood volume may be required to set ultrafiltration goals and control ultrafiltration rates. Continuous surveillance of thoracic electrical impedance may be an additional tool to recognize impending hypotensive episodes in patients at risk. Thus, the negative trial result by Leung *et al.* (1) should not discourage further work in this area, because not all feedback control systems are created equal.

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References

1. Leung KC, Quinn RR, Ravani P, Dunn H, MacRae JM: Randomized crossover trial of blood volume monitoring guided ultrafiltration biofeedback to reduce intradialytic hypotensive episodes with hemodialysis. *Clin J Am Soc Nephrol* 12: 1831–1840, 2017
2. Sinha AD, Light RP, Agarwal R: Relative plasma volume monitoring during hemodialysis AIDS the assessment of dry weight. *Hypertension* 55: 305–311, 2010

3. Leung KC, Quinn RR, Ravani P, MacRae JM: Ultrafiltration biofeedback guided by blood volume monitoring to reduce intradialytic hypotensive episodes in hemodialysis: Study protocol for a randomized controlled trial. *Trials* 15: 483, 2014
4. Reddan DN, Szczech LA, Hasselblad V, Lowrie EG, Lindsay RM, Himmelfarb J, Toto RD, Stivelman J, Winchester JF, Zillman LA, Califf RM, Owen WF Jr.: Intradialytic blood volume monitoring in ambulatory hemodialysis patients: A randomized trial. *J Am Soc Nephrol* 16: 2162–2169, 2005
5. Schneditz D, Schilcher G, Ribitsch W, Krisper P, Haditsch B, Kron J: On-line dialysate infusion to estimate absolute blood volume in dialysis patients. *ASAIO J* 60: 436–442, 2014
6. Kron S, Schneditz D, Czerny J, Leimbach T, Budde K, Kron J: Adjustment of target weight based on absolute blood volume reduces the frequency of intradialytic morbid events [published online ahead of print August 1, 2017]. *Hemodial Int* doi: 10.1111/hdi.12582
7. Secher NH, Van Lieshout JJ: Normovolaemia defined by central blood volume and venous oxygen saturation. *Clin Exp Pharmacol Physiol* 32: 901–910, 2005
8. Torino C, Gargani L, Sicari R, Letachowicz K, Ekart R, Fliser D, Covic A, Siamopoulos K, Stavroulopoulos A, Massy ZA, Fiaccadori E, Caiazza A, Bachelet T, Slotki I, Martinez-Castelao A, Coudert-Krier M-J, Rossignol P, Gueler F, Hannedouche T, Panichi V, Wiecek A, Pontoriero G, Sarafidis P, Klinger M, Hojs R, Seiler-Mussler S, Lizzi F, Siriopol D, Balafa O, Shavit L, Tripepi R, Mallamaci F, Tripepi G, Picano E, London GM, Zoccali C: The agreement between auscultation and lung ultrasound in hemodialysis patients: The LUST Study. *Clin J Am Soc Nephrol* 11: 2005–2011, 2016
9. Cai Y, Zimmerman A, Ladefoged S, Secher NH: Can haemodialysis-induced hypotension be predicted? *Nephron* 92: 582–588, 2002
10. Hecking M, Rayner H, Port FK: More evidence needed before lower dialysate sodium concentrations can be recommended. *Am J Kidney Dis* 65: 519–520, 2015
11. Mann H, Stiller S, Schallenberg U, Thömmes A: Optimizing dialysis by variation of ultrafiltration rate and sodium concentration controlled by continuous measurement of circulating blood volume. *Contrib Nephrol* 74: 182–190, 1989
12. Ettema EM, Kuipers J, Groen H, Kema IP, Westerhuis R, de Jong PE, Franssen CFM: Vasopressin release is enhanced by the Hemocontrol biofeedback system and could contribute to better haemodynamic stability during haemodialysis. *Nephrol Dial Transplant* 27: 3263–3270, 2012
13. Shimizu K, Kurosawa T, Ishikawa R, Sanjo T: Vasopressin secretion by hypertonic saline infusion during hemodialysis: Effect of cardiopulmonary recirculation. *Nephrol Dial Transplant* 27: 796–803, 2012
14. Kooman JP, van der Sande F, Leunissen K, Shaldon S: From isolated ultrafiltration to blood-temperature-controlled feedback: An odyssey started by Jonas Bergström. *Blood Purif* 24: 218–221, 2006
15. Antlanger M, Josten P, Kammer M, Exner I, Lorenz-Turnheim K, Eigner M, Paul G, Klauser-Braun R, Sunder-Plassmann G, Säemann MD, Hecking M: Blood volume-monitored regulation of ultrafiltration to decrease the dry weight in fluid-overloaded hemodialysis patients: A randomized controlled trial. *BMC Nephrol* 18: 238, 2017

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