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Changes in Cardiac Output and Perfusion during Hemodialysis and Hemodiafiltration Treatments Determined by Cardiac Magnetic Resonance Imaging

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Buchanan *et al.* should be congratulated on performing magnetic resonance imaging (MRI) studies during a dialysis treatment, and transforming hospital domestic water to ultrapure water for dialysis with water treatment, including reverse osmosis.[1] They compared various aspects of cardiac function during a single session of high flux hemodialysis (HD) and hemodiafiltration (HDF). Before dialysis, left ventricular cavity dimensions appeared relatively small, in keeping with the remodeling associated with preexisting hypertensive cardiac disease. Although not significant, the cardiac T1 signal increased with the first MRI scan at around 60 minutes into dialysis. This increase in cardiac tissue water could reflect an inflammatory response to the extracorporeal circuit, or changes in cellular osmolytes and water content, and warrants further investigation. During dialysis, left ventricular cavity dimensions decreased further, associated with ultrafiltration, and as there was no significant increase in heart rate, estimated cardiac output fell and systemic vascular resistance increased. In addition, dialysis treatment was associated with reductions in coronary artery blood flow and myocardial perfusion, affecting

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both global and regional contractile function. How could these treatment-related effects influence long term outcome? It seems likely that repeated hypoperfusion increases the risk for myocardial ischemia, infarctions, cardiac fibrosis, and arrhythmias. Indeed, there is increasing evidence that HD is associated with bradyarrhythmia and tachyarrhythmia, typically occurring during and shortly after the dialysis session, coinciding with the greatest risk of cardiac and other tissue hypoperfusion.[2]

This study also addresses the question of whether there is a difference in the hemodynamic effects between HD and HDF. A recent meta-analysis of all individual data from the available randomized trials comparing HD and HDF on clinical outcome, suggests an overall survival benefit for HDF and a reduction in cardiovascular mortality, especially when high convection volumes were delivered.[3,4] In all studies online HDF was applied. Online means that substitution fluid is "online" produced by the dialysis machine. This methodology is approved by the European regulatory authorities. In a subsequent analysis of the individual patients enrolled into these trials, cardiac mortality was decreased with HDF treatment, whereas there was no difference for noncardiac cardiovascular mortality.[5] It is tempting to speculate that a difference in hemodynamic stability with HDF, as reported in some studies, could help explain this survival advantage. During the 2016 European Renal Association–European Dialysis and Transplant Association meeting (Vienna, May of 2016), Japanese researchers reported data comparing the outcome of approximately 5000 patients on HD with 2500 who switched from HD to high volume HDF (predilution mode) and 2500 who switched from HD to low volume HDF.[6] The survival curves separated shortly after the modality switch and were in favor of high volume HDF. Although this was not a randomized trial but a prospective observational registry study, the data suggests that any difference between high volume HDF and standard HD or low volume HDF is detectable shortly after a switch to high volume HDF. In view of the short timescale to demonstrate improved survival, it is tempting to speculate a hemodynamic benefit rather than changes in cardiac structure, as this would require greater time before such changes would become detectable. Indeed, in an accompanying editorial[7] to the recent HDF versus HD meta-analysis, it was argued that the cooling of the patient, which occurs because of the large volumes of fluid that are infused during HDF, may be the key feature in understanding the possible advantage of HDF. The effect of heat transfer in the extracorporeal circuit on maintaining intradialytic hemodynamic stability was pioneered by Maggiore *et al.* more than three decades ago[8]: greater thermal cooling results in increased compensatory sympathetic nervous system activity and norepinephrine secretion, reducing the incidence of intradialytic hypotension.[7]

The question arises, given the evidence suggesting favorable effects on cardiac outcomes for high volume HDF, why did Buchanan *et al.* not find any difference in their study? Firstly, this was a small study of 12 patients, who were described as "relatively healthy" patients, and were on average >10 years younger than those patients enrolled into the recent HD versus HDF trials. Secondly, as high volume HDF was delivered, one might have expected a fall in core temperature with HDF and a rise with HD when using dialysate fluid at the same temperature, whereas the authors report that both modalities resulted in a similar reduction in core temperature. Cooling may have occurred because of the lower room temperature of the MRI scanner, patients only wearing a thin gown, and the additional length of the blood lines. Ultrafiltration rates were low, around 4 ml/h per kilogram body wt, compared with around 7–9 ml/h per kilogram body wt in patients enrolled into the recent HDF versus HD trials.[3,4] In the Hemodialysis Study, only ultrafiltration rates exceeding 10 ml/h per kilogram body wt were associated with worse outcomes.[9] Very few intradialytic hypotensive episodes were reported, in keeping with the lower ultrafiltration rates. Despite this, Buchanan *et al.* reported changes in cardiac perfusion. It is not clear how dry weight was assessed, and the lower ultrafiltration rates suggest that, on average, patients were potentially close to normovolemia. The ultrafiltration volume was an average of 1.1–1.3 L per session, whereas cardiac output fell by 1.5–2.0 L. This fall could be caused by a specific depressant effect of dialysis on cardiac output, pooling in venous capacitance vessels, or indicate reduced or absent circulatory refill. As such, the authors correctly concluded that the absence of a difference in their study does not allow us to conclude that the two modalities have identical effects on the heart. It is important to realize that although short term hemodynamic effects may be important, longer term effects on cardiac structure and function may be equally or more important. Longitudinal studies have suggested that there is some evidence that left ventricular hypertrophy may reduce (or not increase), and patients have lower levels of chronic inflammatory variables, such as IL-6 and C-reactive protein, when switched to HDF as compared to continuation of treatment with standard HD.[10,11] Reduction in cardiac mortality reported with high volume HDF may potentially be associated with increased erythropoiesis sensitivity, or reduction in phosphate and other azotemic toxins.[12]

Although there was only one patient reported to have suffered symptomatic intradialytic hypotension, this study observed generalized hemodynamic stress to the circulation, with reductions in coronary artery flow and myocardial perfusion affecting global and regional contractile function. It is therefore likely that dialysis sessions that induce greater hemodynamic stress will result in more severe adverse effects. Given the advanced arterial disease in many patients on dialysis, it would not be surprising that if coronary blood supply falls to critically low levels, resulting in critical ischemia which will induce arrhythmias and infarction, especially when coupled with rapid electrolyte and acid-base shifts.

How should we proceed? From a scientific point of view, it remains highly challenging to further unravel possible mechanism(s) for the difference in clinical outcomes between standard HD and high volume HDF, as suggested by recent meta-analysis. Apart from mechanistic studies, real life

experience of everyday practice is also important.[13] Two recent large observational cohorts confirm the reduced mortality with HDF.[14,15] The recent initiative of large dialysis providers to join forces may be additionally helpful in this respect.[16]

What about the United States? In 2013, an editorial was published in the *Journal of the American Society of Nephrology* accompanying the publication of the Catalonian HDF trial, entitled "Has the time now come to more widely accept hemodiafiltration in the United States?"[17] Has there been any change since then? It is for our American colleagues and the United States regulatory authorities to review the evidence on HDF. However, we would emphasize again that HD using high flux membranes, which is seen by most guidelines as the preferred treatment, is a form of low dose HDF, as the actual ultrafiltration volume is larger than the net fluid removal but is automatically compensated for by backfiltration, with dialysate fluid passing into patient's blood stream. This automatically means, or should mean, that the same dialysis water quality standards apply for HD using high flux membranes and HDF. So, if one accepts that the infrastructure of the dialysis center needs to be such that dialysis water of adequate quality is produced, then one might as well choose the treatment for which currently available evidence suggests a benefit for patients, *i.e.*, online HDF, albeit without fully understanding the underlying mechanism(s).

So, the most important message from this study is that MRI is possible during a dialysis session, allowing a detailed study of myocardial function, and so opens a new approach to better understand the consequences of the multitude of changes that occur during an average dialysis session of 4 hours. However, the challenges in understanding potential mechanism(s) underlying the differences reported between HD and high volume HDF on clinical outcome remain.

DISCLOSURES

None.

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