Dying to Feel Better: The Central Role of Dialysis–Induced Tissue Hypoxia

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“|understand why I need dialysis, but how can something that makes me feel so terrible not be hurting me?” This is posting from a patient on dialysis on why he or she failed to attend dialysis treatments. In this edition of the Clinical Journal of the American Society of Nephrology, Meyring-Wösten et al. (1) from the Renal Research Institute present the findings of a large study into hemodialysis (HD)-associated hypoxia. Although it is unclear if this is a result of an oxygen delivery-utilization mismatch or more direct respiratory effects, it is clear that this phenomenon is common and associated with highly negative consequences. These include more severe systemic inflammation, higher ESA requirements, and significantly higher risk of death. This editorial suggests that these important findings should be considered within the broader conceptual framework of HD-induced challenges to tissue oxygenation by the reduction in organ perfusion, with the full range of negative consequences that are increasingly becoming appreciated.

Patients requiring dialysis because of CKD face three central challenges: death, dependency/depression, and symptoms, a triad that has remained relatively immutable since the inception of chronic HD. These challenges can be mapped to specific organ systems. Death is predominantly a result of cardiac injury, dependency/depression is brain specific, and uremic symptoms are highly dependent on the gastrointestinal system. Although advances in treatment have been directed at the extension of this high–cost, low–volume therapy to millions of patients around the globe, there is now increasing focus on mitigating the patients’ symptomatic burden, with a view to improving both outcomes and quality of life.

All vascular beds are part of one contiguous endothelial surface. Reduced oxygen delivery is, thus, simultaneously experienced in multiple vascular beds. Recently, we have begun to appreciate that conventionally administered HD results in recurrent circulatory stress (2). The observed pattern of organ dysfunction reflects a composite loss of individual organ vasoregulatory reserve and mechanisms to promote repair (3). It is also recognized that injury to one system induces additional cycles of injury within the same organ system (4) and/or increases the vulnerability of additional systems (5).

An appreciation of HD–induced, perfusion–based injury is central to understanding the full consequences of treatment. It allows us to improve outcomes by tackling the inadequate tolerability of conventional dialysis in concert with a strong biologic plausibility relating to the reduction of mortality and quality of life. HD is usually associated with removal of significant amounts of fluid that are accumulated between treatments. The reduction in intravascular volume is often inadequately offset by plasma refill, resulting in circulatory stress and hypotension. Higher ultrafiltration rates and interdialytic weight gains have been consistently identified as associated with increased mortality. Objective measures of mismatched oxygen delivery–consumption, such as central venous oxygen saturation (ScvO₂), show the scale of HD–induced systemic circulatory stress. ScvO₂ predicts prognosis in septic shock, acute coronary syndromes, and patients at high risk in surgery. HD results in significant falls in ScvO₂ to levels of <50% (which are associated with a significant risk of death in patients in the intensive care unit), proportional to the degree of fluid removal (6). These observations are indicative of a circulation that has lost the ability to autoregulate, making perfusion excessively dependent on pressure.

A substantial body of evidence now exists to show that subclinical myocardial ischemia occurs during HD that is driven, to a large extent, by ultrafiltration volume and change in BP during therapy (7). HD–induced myocardial hypoperfusion has been directly visualized using advanced imaging techniques (8) as well as indirectly by detecting the resultant regional left ventricular dysfunction with intradialytic echocardiography (9). The repetitive nature of this injury has a cumulative effect, leading to fixed reductions in left ventricular systolic function and conferring an increased risk of both cardiac events and mortality (10). Dialysis–induced myocardial ischemia may also act as a trigger for arrhythmias (11). Reduction in hemodynamic instability with a simple dialysis–based intervention can protect against loss of systolic function, diastolic function, and left ventricular hypertrophy (12).

Abnormalities of cognitive function are characteristically found in patients on HD (13) and seem to be predominantly driven by vascular injury. Around 75% of patients exhibit mild cognitive impairment (14), and high proportions of patients have formal diagnoses of dementia (e.g., 15% of patients on dialysis in...
Ontario). Mild cognitive impairment in this setting is predominantly nonamnestic (affecting nonmemory skills, such as thinking and planning) and develops early after starting dialysis. It is associated with devastating consequences and an early functional decline (e.g., 50% reduction of activities of daily living in elderly patients on dialysis within 6 months of starting dialysis) (15).

Patients on HD have specific patterns of progressive brain injury. Leukoaraiosis describes changes in the white matter caused by loss of axons and myelin and results in the characteristic MR appearances seen in vascular cognitive impairment. Leukoaraiosis has been described as a risk factor for developing dementia, mobility problems, and strokes (16) and is universally present in patients on HD, even after correcting for age, diabetes, and BP (17,18). Severity of reduction in cognitive function is proportional to the degree of white matter injury, with predominant loss of subcortical functions (executive functioning) (19). Of even more potential effect is the recent realization that subcortical subclinical ischemic white matter changes are associated with the interruption of intracerebral circuits, loss of thymic balance, and development of clinical depression (20).

Brain injury is also associated with the circulatory stress of dialysis (18,21), and it is the principal independent determinant of accelerated brain ageing in this population. We showed in both a cohort study and a prospective randomized, controlled trial (18) that functionally significant brain injury is determined by instability of BP during HD and that a dialysis-based intervention to maintain BP (and perfusion) during dialysis is capable of protecting the brain from this otherwise inevitable progressive injury.

Patients requiring HD characteristically suffer from high levels of mortality and poor health–related quality of life. Although generalized uremic symptoms (such as nausea, fatigue, and pain) are common, uremic itch is particularly painful, and pruritus (22) is associated with increased mortality, worsened physical/mental wellbeing, and poor sleeping patterns. The pathogenesis of uremic pruritus remains obscure and poorly explained by currently acknowledged associations with serum calcium and phosphate levels (23). Multiple treatments are traditionally used and often fail to effectively alleviate patient symptoms.

Uremic toxins are derived from the gut and processed by the liver. They are largely derived from intestinal putrefaction and gastrointestinal dysbiosis (24). The gastrointestinal system is affected by dialytic hemodynamic stress, resulting in translocation of intestinal contents, such as endotoxin (5). The liver receives all products of intestinal absorption via the portal circulation and is the final barrier before the systemic circulation. Damage to the liver has been shown to lead to an impaired functional barrier, leading to a greater exposure to these substances systemically (25).

The liver is vulnerable to circulatory dysfunction, receiving 20%–25% of cardiac output through a dual blood supply (70% from the portal vein and 30% from the hepatic artery). Maintenance of global hepatic perfusion by increasing portal contribution results in potentially greater delivery of gut-derived toxins (and proinflammatory factors) under stress. Subsequent falling perfusion limits the ability of the liver to process this load (26). Transient reduction in excretory function can occur without sufficient hepatocellular injury to raise levels of commonly measured liver function tests. Hepatic dysfunction is potentiated by heart failure, hypoxic injury, venous congestion, increased myocardial demand, endotoxemia, and microcirculatory dysfunction—all present during HD. We recently performed an initial assessment of hepatic perfusion and excretory function during HD. Dialysis was performed with a 256 ultraslice computed tomography instrument, allowing serial measurement of perfusion. This study has confirmed HD-induced reductions in hepatic perfusion, increased relative contribution by the portal circulation, and reduction in function (C. McIntyre and L. Crowley, unpublished observations).

These insights create a novel paradigm to approach the challenges that patients on dialysis face. However, we also need to develop a new approach to the testing of therapies in this field. Use of advanced imaging techniques (e.g., ultraslice computed tomography, ultrasound, magnetic resonance imaging, and PET) allows for new therapeutic target discovery, intervention development, and testing of safety and efficacy. This will allow the use of clinically relevant surrogate imaging end points for rapid evaluation and refinement of interventions in early–phase clinical study before large-scale testing to facilitate rapid take up by general clinical practice. Phase 3 equivalent studies will use end points relating to mortality, hospitalization, and dependency. We have created the prototype, methodology, and investigator network for a dialysis–based intervention study within Ontario, Canada. MY-TEMP is a cluster-randomized, waived consent study of individualized dialysate cooling using administrative data sources to provide outcomes data (trials registration no. NCT02628366). This design allows for cost-effectiveness and includes patients who are ordinarily excluded by traditional randomized, controlled trial design. Individualized dialysate cooling is one of a pipeline of dialysis-based interventions directed at reducing tissue hypoxia or increasing organ–based ischemic tolerance. The study by Kotanko et al. (1) suggests that direct consideration of oxygenation may be worthy of similar attention.

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