

# Effects of hemodialysis on cardiac function

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Hemodialysis (HD) patients are subject to an enormous excess of cardiovascular morbidity and mortality. This appears to be largely driven by factors that are different from those at play in the general population. Chronic HD patients are already primed by a large number of structural and functional peripheral vascular and cardiac abnormalities to experience demand myocardial ischemia. Conventional HD is capable of inducing myocardial ischemia. Recurrent ischemic insults lead to myocardial functional and structural changes, eventually resulting in fixed systolic dysfunction and heart failure (conferring a dismal prognosis for patients undergoing dialysis). Modifications of the HD process to improve the hemodynamic tolerability of the treatment have been shown to reduce the perturbation of myocardial blood flow and functional evidence of dialysis-induced ischemia. Although it is uncomfortable to consider that much of the observed disease burden in HD patients may be an artifact of current dialysis treatment regimes, understanding the role that conventional dialysis plays in the pathophysiology of cardiac injury in HD patients has the potential to provide us with additional dialysis, and non-dialysis, based novel therapeutic targets to reduce currently excessive rates of cardiovascular morbidity and mortality.

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It is well recognized that dialysis patients display hugely elevated rates of cardiac mortality.<sup>1</sup> It is also becoming appreciated that this rate of cardiovascular attrition is not driven by the same variety of risk factors, or pathophysiological processes that are important in the general population.<sup>2</sup> Classical complicated atherosclerotic disease appears not to be the predominant mode of death in hemodialysis (HD) patients. Records from the US Renal Data System have shown that HD is an independent risk factor for the development of both *de novo* and recurrent heart failure with a 2-year mortality after a diagnosis of congestive heart failure as high as 51%,<sup>3</sup> making it the one of the most common causes of cardiovascular mortality in this patient group. In addition, a significant percentage of cardiac mortality is due to sudden death, and sudden death appears to be temporally related to the dialysis procedure.<sup>4</sup> Abnormal ventricular morphology and function appear to be major determinants of cardiac arrhythmias in this patient group.

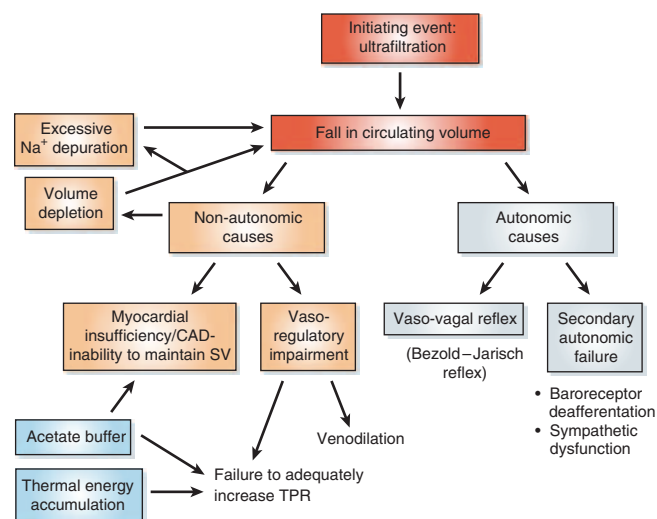
It has long been suspected that myocardial ischemia may be precipitated by HD. Short intermittent HD treatments exert significant hemodynamic effects, and 20–30% of treatments are additionally complicated by episodes of significant intradialytic hypotension (IDH).<sup>5</sup> In conjunction with this, HD patients are particularly susceptible to myocardial ischemia. In addition to the high prevalence of coronary artery atheroma, diabetic dialysis patients have been shown to have a reduced coronary flow reserve in the absence of coronary vessel lesions.<sup>6</sup> HD patients characteristically also exhibit left ventricular hypertrophy, reduced peripheral arterial compliance, impaired microcirculation,<sup>7</sup> and ineffective vasoregulation (in the face of HD coupled with ultrafiltration). All of these factors also predispose to demand cardiac ischemia. This article aims to review the evolving concepts surrounding HD-induced acute, recurrent myocardial ischemia and its contribution to the genesis of the observed constellation of cardiac abnormalities in patients undergoing maintenance HD and longer-term adverse cardiac outcomes.

## MYOCARDIAL ISCHEMIC POTENTIAL IN HD PATIENTS

The first report of silent ST-segment depression during dialysis dates back to 1989.<sup>8</sup> However, this concept of subclinical ischemia (occurring without acute atherosclerotic plaque rupture) has received remarkably little attention, despite its theoretical plausibility. Short intermittent HD treatments exert significant hemodynamic effects (Figure 1),

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**Figure 1 | Physiological responses to hemodialysis that might be involved in the pathogenesis of IDH.** IDH, intradialytic hypotension.

and 20–30% of treatments are complicated by IDH. In conjunction with this, HD patients are particularly susceptible to myocardial ischemia. This is as a result of large vessel and microcirculatory changes resulting in a reduced coronary flow reserve. This determines the ability to increase blood flow to the myocardium during increased demand. In part, this may be due to left ventricular hypertrophy, present in up to around 75% of patients on dialysis, which reduces coronary flow reserve and is associated with a myocyte-capillary mismatch. Increased peripheral artery stiffness is also recognized to have an adverse effect on myocardial perfusion and reduces the ischemic threshold.<sup>9</sup> Therefore, left ventricular hypertrophy in tandem with increased vascular stiffness may lead to a propensity to reduced myocardial blood flow (MBF), and particularly subendocardial MBF.

In non-uremic patients, blood pressure (BP) is largely independent of cardiac output, due to the full gamut of functional vasoregulatory mechanisms. HD patients characteristically exhibit defective BP control in the face of ultrafiltration requirements (due to impaired baroreflex sensitivity, etc.). This leaves patients at the end of HD with BP, which becomes increasingly dependant on a maintained cardiac output,<sup>10</sup> further increasing the risk of myocardial hypo perfusion as a result of hypotension.

All of these factors coexist with the well-recognized high prevalence of ‘conventional’ large vessel epicardial coronary artery disease (CAD). The relative contributions of the macro and micro cardiac circulations to the genesis of dialysis-induced ischemia do however remain unclear. Indeed, several studies have reported no correlation between the development of intradialytic ST depression and angiographically proven CAD.<sup>11,12</sup>

### MYOCARDIAL STUNNING AND HIBERNATION

In patients with CAD, but without chronic kidney disease, transient myocardial ischemia may lead to left ventricular

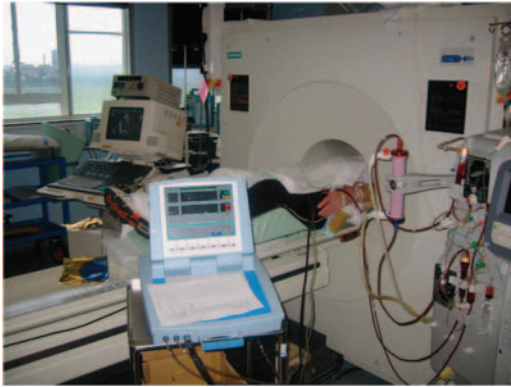
(LV) dysfunction that can persist after the return of normal perfusion. This prolonged dysfunction is known as myocardial stunning.<sup>13</sup> Repetitive episodes of ischemia can be cumulative and have been shown to lead to prolonged LV dysfunction. Myocardial stunning has been well described, in the non-dialysis patient population, as a causative mechanism for heart failure.<sup>14</sup>

Repeated episodes of myocardial ischemia lead to a spectrum of disease encompassing myocardial stunning through to myocardial hibernation and ending in myocardial remodeling and scarring, with irreversible loss of contractile function. Standard conventional thrice weekly HD as a cause of repetitive myocardial stunning might lead to such a process, resulting in chronic LV dysfunction. Myocardial hibernation may represent a functional adaptation to chronic hypoperfusion that can be reversed with restoration of regional MBF (the ‘smart heart’ hypothesis).<sup>15</sup> There is evidence to suggest that hibernating myocardium is still highly vulnerable to increases in demand or reductions in oxygen supply, such as further hemodynamic stress during HD. Therefore, ongoing recurrent episodes of ischemia precipitated by HD may have negative consequences on this adaptive balance leading to further myocardial injury and eventual non-viable myocardium with irreversible reduction in LV function.

### DIALYSIS-INDUCED ISCHEMIA

Initial evidence of HD-induced myocardial ischemia has previously come from electrocardiogram-based studies, augmented by some limited isotopic perfusion imaging work and observations relating to humoral biomarkers of cardiac injury. Around 10 studies, after the initial report by Zuber *et al.*,<sup>8</sup> have demonstrated silent ST-segment depression occurring during dialysis. These studies report occurrence of dialysis-induced ST depression at rates that vary between 15 and 40%. Singh *et al.*<sup>16</sup> assessed dialysis-induced ischemia using sestamibi single-photon emission computed tomography. In an unselected group of 10 dialysis patients who were not known to have CAD, seven developed perfusion defects during dialysis.

It is well recognized that cardiac troponins are often elevated in dialysis patients, and that elevated levels predict mortality. Although there was initial debate about the origin of elevated troponins in renal disease, it is now clear that the troponins are cardiac in origin, and it is the intact molecule (as opposed to smaller fragments) that are detected by the current assays. Some evidence exists that HD itself is related to an increase in troponin levels.<sup>17</sup> Several authors have reported significant rises in cardiac troponin T (cTnT) post-dialysis, whereas others have found no difference in pre- and post-dialysis cTnT or cardiac troponin I (cTnI) levels, or found that any difference that is observed disappears after correction for hemoconcentration resulting from ultrafiltration. However, measuring post-dialysis troponin levels to look for dialysis-induced ischemia may be flawed; it is well recognized that plasma troponin levels may only become



**Figure 2 | Patient undergoing assessment of intradialytic segmental myocardial perfusion using cardiac positron emission tomography.**

elevated after 6 to 12 h following an episode of ischemia. This is beyond the window of blood sampling utilized in most of the currently available studies. We have previously reported higher pre-HD serum cTnT levels in patients prone to IDH as compared with patients without significant hypotensive response to HD. However, this does not necessarily reflect dialysis-induced cTnT release and alternatively could be explained by a greater cardiac disease burden in those unstable patients.<sup>18</sup> Hung *et al.*<sup>19</sup> demonstrated that cTnI rose significantly when measured 44 h after dialysis sessions complicated by IDH (that is, measured at the subsequent dialysis session) as compared with sessions in which patients were stable.

### DIALYSIS-INDUCED MYOCARDIAL STUNNING

Hemodialysis-induced ischemia, and myocardial stunning, can be studied by echocardiographic means, looking for the development of LV regional wall motion abnormalities (RWMA), with resolution after the cessation of the hemodynamic stress of HD being characteristic of stunning. The development of new LV RWMA during physiological or pharmacological stress occurs in response to ischemia, and its onset precedes that of symptoms and electrocardiographic changes. This principle underlies dobutamine stress echocardiography. A recent study using  $H_2^{15}O$  positron emission tomography to measure MBF during dialysis demonstrated that HD precipitates reductions in MBF to the levels at peak dialytic stress consistent with the development of myocardial ischemia (Figure 2). This was true even in the absence of angiographically significant coronary disease (all patients having undergone coronary angiography to exclude CAD). The same study also confirmed that HD-induced segmental LV dysfunction (measured echocardiographically) correlates with matched reduction in segmental MBF.<sup>20</sup>

Hemodialysis is capable of inducing subclinical myocardial ischemia, and this phenomenon is related to ultrafiltration and hemodynamic instability. We have recently concluded a study of 70 prevalent HD patients. HD-induced myocardial stunning was assessed utilizing serial intradialytic

echocardiography and RWMA measurement to evaluate the extent and severity of HD-induced cardiac injury.<sup>21,22</sup> This study identified around 60% of patients as developing HD-induced myocardial stunning. In multivariate analysis intradialytic reduction in BP and ultrafiltration volume both independently determined the propensity to suffer HD-induced cardiac injury. Fluid removal of 1 over a standard 4 h HD session conferred a five times greater risk of developing HD-induced myocardial stunning, this risk rose to 26 times greater for a 2 ultrafiltration volume, with consequently higher ultrafiltration rate. Presumably this additional effect of ultrafiltration volumes, over and above effects on BP, relates to potential hemoconcentration with increasing microcirculatory shear stress and reduced microperfusion leading to myocardial ischemia. Currently it is not clear how the risk of a high ultrafiltration volume can be ameliorated by the modification of the dialysis session to reduce ultrafiltration rate. The only other associated factors of significance from this model were patient age and cTnT level (pre-dialysis levels almost three times higher in affected patients). These four factors displaced all other standard biochemical/hematological, historical and dialysis treatment-based variables.

The importance of hemodynamic stability in the pathogenesis of HD-induced ischemic injury is illustrated in two studies of modification of dialysis technique to assist in the maintenance of BP without the alteration of ultrafiltration volume removal. In the first of these studies we compared standard bicarbonate HD with a biofeedback technique (Hemocontrol, Gambro-Hospal, Mirandola, Italy) that responded to significant declines in relative blood volume by temporarily reducing ultrafiltration rate and increasing dialysate conductivity.<sup>23</sup> This was performed within defined limits to ensure total fluid, and sodium depuration was unaffected. Biofeedback dialysis (BFD) has been shown to reduce IDH in several studies. In the second study in a different group of stable chronic HD patients, we compared standard dialysis with dialysate temperatures of 37°C and cooled dialysate at 35°C.<sup>24</sup> This latter intervention, well recognized to reduce IDH, has the advantages that it is extremely simple to perform, is available on all dialysis monitors and does not incur additional treatment costs, although the long-term tolerability of such a significant reduction in dialysate temperature may represent a problem. Both studies contained small numbers of patients, which were relatively short-term focusing on the acute effects of the interventions and were prospective and crossover in design.

In both studies, a significant number of new RWMA occurred during standard dialysis. By improving mean BP and reducing IDH episodes with either BFD or reduced temperature dialysis, a significant reduction in the number of new RWMA was observed. Although most RWMA improved after the cessation of HD, approximately 30% of affected regions still displayed abnormal motion at the relatively short 30 min post-dialysis recovery period. Effect of a longer recovery period is currently unknown. In addition to

segmental changes we also observed a higher overall LVEF, with both BFD and cool dialysis. It may be that either the higher mean BP or the reduction in IDH was responsible for the reduction in the incidence of RWMA, although it is also conceivable that the effects of both of these factors were synergistic, with IDH that occurs at a lower mean BP potentially having a greater detrimental effect on myocardial perfusion. In positron emission tomography-based study of intradialytic MBF, the use of BFD resulted in reduced instability only in the later part of HD and this was associated with a significantly better recovery of MBF post-HD,<sup>20</sup> supporting the contention that at least with BFD the beneficial changes with respect to MBF are linked to maintenance of intradialytic BP.

The potential role for a combination of microcirculatory dysfunction, ischemic potential of reduced peripheral arterial compliance, in addition to the other non-atheromatous consequences of the uremic milieu, is further suggested by recent study of pediatric HD patients. We studied 12 children established on maintenance HD. This represented a good model of uremic cardiovascular disturbances, in the absence of conventional cardiovascular risk factors. The dialysis treatments were characterized by particularly large ultrafiltration requirements and relative dialysis-induced hypotension. A high proportion of the children (11/12 patients) exhibited evidence of acute dialysis-induced myocardial stunning (utilizing similar methodologies to the above studies), with some biochemical evidence of cardiac injury.<sup>25</sup>

#### LONG-TERM CONSEQUENCES OF RECURRENT HD-INDUCED ISCHEMIC INJURY

Twelve month follow-up of HD patients, initially studied with dialysis-based echocardiography to identify those suffering from HD-induced cardiac injury, revealed significant effects on cardiac structure, function and patient survival. Those patients who did not develop HD-induced myocardial stunning (27/70) by 1 year of follow-up had experienced only one significant cardiac event, no change in segmental shortening fraction, no reduction in overall LVEF, and 100% survival. This was in stark contrast to the group characterized by the development of dialysis-induced myocardial stunning (43/70), where 28% of the patients (12/43) had died. In those patients who survived to 1 year follow-up, there had been a rough halving of shortening fraction of those ventricular segments identified as suffering dialysis-based RWMA and a reduced overall LVEF (at rest and at peak during HD) by around 10% (absolute) in conjunction with an attendant significant increase in cTnT levels.<sup>22</sup>

Intadialytic BP was significantly lower in patients who stunned c.f. baseline, whereas in patients who did not, their hemodynamic tolerability of HD was unchanged. However, the only patients that had a significant deterioration in their BP (systolic and diastolic) during HD after 12 months were in the group that developed regional fixed systolic reductions of > 60%. This is not attributable simply to volume overload. A small subset of patients with below average ultrafiltration

volumes had significant reductions in SBP. In addition, SBP at the end of HD is primarily determined by cardiac output<sup>10</sup> and therefore it is likely that the absolute reduction in SBP seen is at least in part secondary to the reduction in LVEF. IDH is known to be associated with increased mortality.<sup>26</sup> Given the underlying vulnerability of hibernating myocardium to increases in demand, coupled with decreased coronary flow reserve in HD patients, it may be that this adaptive process actually leads to further segmental injury by exacerbating intradialytic instability. This may be one of the reasons that prevalence of heart failure is so high, and survival so poor in HD patients that start to develop myocardial contractile dysfunction.

Survival may also be determined by the incidence of intradialytic and post-dialytic ventricular arrhythmias. In 40 patients, serial echocardiography was augmented with 12 lead Holter recording to capture pre-, intra-, and post-dialytic electrocardiogram changes over a 48 h period. Dialysis-induced myocardial stunning was associated with an increased rate of intradialytic and post-dialytic ventricular arrhythmias,<sup>21</sup> suggesting that this phenomenon may be important in both of interlinked major identifiable causes of CV mortality in HD patients (sudden cardiac death and heart failure).

#### CONCLUSIONS

The procedure of HD exerts significant acute stress upon the cardiovascular system. There is an increasing body of evidence to suggest that subclinical ischemia is precipitated by dialysis, and that this is a common phenomenon. Episodes of ischemia may potentially have a role in the development of cardiac failure, and as a trigger for arrhythmias. Therefore, reducing the acute impact of dialysis on the cardiovascular system would seem to be a desirable therapeutic target.

A variety of interventions, both dialysis based (hemodiafiltration, refinements of dialysate cooling, dialysate magnesium concentration manipulation, hypoxia avoidance, isothermic HD, and quotidian HD) and non-dialysis based, predominantly focused on reduction in required ultrafiltration volume (intensive insulin therapy in diabetics to reduce hyperglycemia with subsequent free water ingestion and improved sodium management) are currently under active investigation. These studies are designed to both further elucidate the pathophysiology involved and identify and select optimal therapies for future large scale RCT study of 'hard' end points. This is of particular importance given the almost universal lack of effectiveness of other cardiovascular interventions developed within the non-dialysis-based population. It appears reasonable that in selecting a therapeutic change, synthesized within an enhanced understanding of the pathophysiological processes involved in the major cause of death of our HD patients, we may have a realistic chance of making an impact on the current appalling survival figures. Clearly, though, this requires focused large-scale collaborative study of interventions with significant potential to be both high impact and cost effective.

**DISCLOSURE**

The author declared no competing interests.

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