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Multitargeted interventions to reduce dialysis-induced systemic stress

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ABSTRACT

Hemodialysis (HD) is a life-sustaining therapy as well as an intermittent and repetitive stress condition for the patient. In ridding the blood of unwanted substances and excess fluid from the blood, the extracorporeal procedure simultaneously induces persistent physiological changes that adversely affect several organs. Dialysis patients experience this systemic stress condition usually thrice weekly and sometimes more frequently depending on the treatment schedule. Dialysis-induced systemic stress results from multifactorial components that include treatment schedule (i.e. modality, treatment time), hemodynamic management (i.e. ultrafiltration, weight loss), intensity of solute fluxes, osmotic and electrolytic shifts and interaction of blood with components of the extracorporeal circuit. Intradialytic morbidity (i.e. hypovolemia, intradialytic hypotension, hypoxia) is the clinical expression of this systemic stress that may act as a disease modifier, resulting in multiorgan injury and long-term morbidity. Thus, while lifesaving, HD exposes the patient to several systemic stressors, both hemodynamic and non-hemodynamic in origin. In addition, a combination of cardiocirculatory stress, greatly conditioned by the switch from hypervolemia to hypovolemia, hypoxemia and electrolyte changes may create pro-arrhythmogenic conditions. Moreover, contact of blood with components of the extracorporeal circuit directly activate circulating cells (i.e. macrophages–monocytes or platelets) and protein systems (i.e. coagulation, complement, contact phase kallikrein–kinin system), leading to induction of pro-inflammatory cytokines and resulting in chronic low-grade inflammation, further contributing to poor outcomes. The multifactorial, repetitive HD-induced stress that globally reduces tissue perfusion and oxygenation could have deleterious long-term consequences on the functionality of vital organs such as heart, brain, liver and kidney. In this article, we summarize the multisystemic pathophysiological consequences of the main circulatory stress factors. Strategies to mitigate their effects to provide more cardioprotective and personalized dialytic therapies are proposed to reduce the systemic burden of HD.

Keywords: biocompatibility, cardiovascular disease, coagulation, complement system, hemodialysis, inflammation, intradialytic complications, systemic stress, volume status

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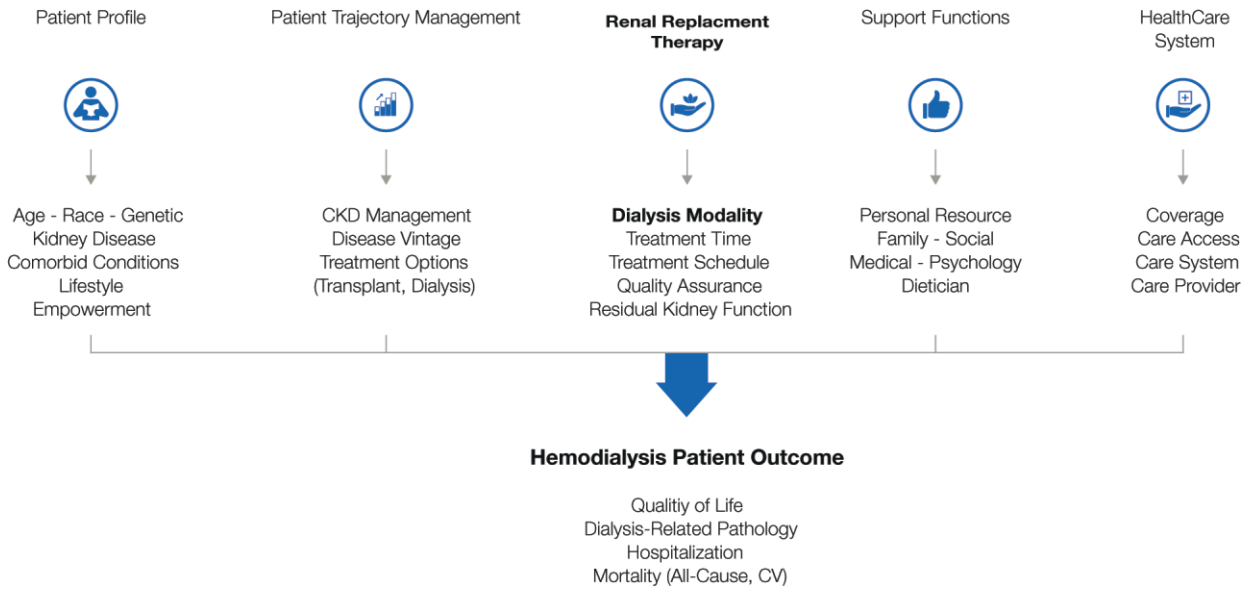

FIGURE 1: Kidney replacement therapy (e.g. HD) represents only one component of a complex array of considerations in the management of end-stage CKD. The cyclical fluctuations of various physiological processes that accompany intermittent schedules represent a repetitive, unphysiological stress condition for the patient, impacting both outcomes and quality of life.

INTRODUCTION

The success of hemodialysis (HD) as a life-sustaining therapy is undisputed: it allows most patients with end-stage kidney disease (ESKD) to lead reasonably normal and active lives for several years or even decades depending on their age and comorbid conditions. What is questioned, however, is the level of burden the disease represents to patients and to healthcare systems faced with the enormous costs of the therapy [1–3]. Patients on intermittent HD are at increased risk of cardiovascular disease (CVD), which is the leading cause of death among this population, with cardiovascular (CV) complications contributing significantly to the high incidences of hospitalization [4]. Much has been written about the poor long-term outcomes of dialysis patients compared with those with other chronic conditions and the need to develop strategies to overcome the discrepancy [5]. However, it is the intra- and interdialytic morbidity that patients encounter regularly that is debilitating [6–9]. The notion that HD *per se* contributes to this morbidity and mortality has been addressed only sporadically. HD is a systemic stress condition consisting of two main components, hemodynamic and non-hemodynamic experienced recurrently, usually thrice weekly, or more frequently depending on treatment schedules. There is growing recognition and evidence for the physiological burden and systemic cardiocirculatory stress that HD therapy represents [10] (Figure 1).

We examine the case for our assertion that intradialytic morbidity is the clinical expression of systemic stress associated with each HD session and, if unchecked, may act over the years of treatment as a disease modifier, aggravating cardio- and multi organ injury, in conjunction with pre-existent comorbidities, especially in elderly patients [11]. We propose strategies that could mitigate dialysis-induced systemic stress (DISS) as well as CV risks to improve patient well-being, particularly their quality of life.

The 'unphysiology of hemodialysis' (extreme physiology of hemodialysis treatment)

As early as the mid-1970s when dialysis had already established itself as a routine therapy (greatly facilitated by the development of the shunt some 15 years earlier), Kjellstrand *et al.* [12] first raised the specter of intermittent HD inducing debilitating side effects such as nephropathy. This 'unphysiology' of HD, which is the major determinant of the side effects of HD, was attributed, among various factors, to extremes in the cycling of water and electrolytes that occur in intermittent dialysis, particularly of uncooperative patients, and may be more dangerous than high levels of uremic 'toxins'. At that time, resolution of technological restraints that had for so long impeded progress created enthusiasm to further increase the detoxification efficiency of the therapy—and profits—and any winds of caution were unwelcome [13]. Since then the cyclical fluctuations of various physiological processes that intermittent HD schedules (usually 4 h, 3/week) generate have been analyzed and debated. The unphysiology and limitations of intermittent HD schedules used today have also been expressed in mathematical terms [14–16]. The historical and scientific background of 'dialysis unphysiology' has been elegantly summarized by Kim [17]. Together with the 'trade-off' hypothesis of Bricker [18] that Depner [19] expounded upon to propose the 'residual syndrome' hypothesis, dialysis is now recognized as an imperfect therapy and a compromise, with benefits seemingly outweighing the perturbations HD creates.

Techniques to assess the impact of DISS on organ damage

The well-documented uremic and dialytic morbidity associated with the correction of uremia [removal of organic uremic retention solutes (URS) as well as inorganic compounds like water, sodium and phosphate] has repercussions beyond the

observed intra- and interdialytic adverse symptoms [20, 21]. The cumulative effects of these aberrations that result from being on HD therapy for long periods of time are observed in several body organs, impairing their normal functioning and leading to a specific dialysis-related pathology (i.e. accelerated atherosclerosis, β_2-microglobulin amyloidosis, vascular and valvular calcification, protein energy wasting, accelerated aging). In fact, the systemic circulatory stress exacerbated by the dialysis procedure starts very early into an HD session (usually the first 60 min) and increases over the course of the treatment, meaning that hypovolemia resulting from ultrafiltration may not be the only cause of this phenomenon [22–24].

The strides made in the refinement in recent years of non-invasive organ imaging techniques based on magnetic resonance imaging (MRI), computed tomography, echocardiography, angiography and ultrasound and their variants are today important tools to help better understand physiological as well as pathological processes [25, 26]. Together with sophisticated computer-aided software algorithms, astonishing functional details and mapping of organ or tissue damage can be studied with three-dimensional visualization and image acquisition and is being applied to nephrology and related fields [26, 27]. In conjunction with high-sensitivity laboratory cardiac biomarkers, the progressive effects of DISS can be monitored and studied in considerable detail [28]. A general measure of DISS that is relatively easy to assess is central venous oxygen saturation ($ScvO_2$), which was shown to correlate with cardiac output in the chronic HD patient population studied [29, 30]. In most patients, $ScvO_2$ declines during HD due to factors such as reduced preload, myocardial stunning and intermittent arrhythmias, and a high $ScvO_2$ variability is associated with all-cause mortality in dialysis patients [31]. As well as the findings of organ-specific imaging techniques, the decline in $ScvO_2$ during dialysis was found to be related to ultrafiltration volume and could evolve into a novel marker to monitor hemodynamic response to HD [31].

The multisystemic effects of hemodialysis-induced systemic stress: examples of organ damage

Cardiac stunning. Myocardial stunning is a transient post-ischemic cardiac dysfunction characterized by a temporary reduction in myocardial perfusion and contractility in various segmented areas; transient myocardial ischemia (MI) may lead to left ventricular (LV) dysfunction that can persist after the return of normal perfusion [32]. Three possible outcomes of MI are death of myocardial cells resulting in infarction and tissue scarring (i.e. myocardium fibrosis) with no recovery of cardiac functionality either contracting (systolic dysfunction) or relaxing (diastolic dysfunction) [33]; duration and severity of MI are not long or severe enough to kill cells and by reperfusion myocardium is viable but stunned, exhibiting contractile and biochemical dysfunction with potential sequelae; and chronic low blood flow that causes hibernating myocardium contractile abnormalities, viability and dedifferentiated cells [34].

The procedure of HD exerts acute stress upon the CV system that begins early (especially during the first 30–60 min) in a session and increases during the course of the treatment [10, 22, 35]. Conventional HD itself has been shown to be a sufficient CV functional stressor to precipitate such recurrent ischemic insults, leading to myocardial functional and structural changes [36]. Several factors contribute to cardiac stress in HD, including dialysis modality, treatment time, ultrafiltration volume and rate and electrolyte management (discussed below). In chronic HD, recurrent stunning contributes to heart failure and cardiac death, with ultrafiltration and intradialytic hypotension (IDH) being the principal determinants of this injury; even in critically ill acute kidney injury patients, initiation of continuous kidney replacement therapy was shown to be associated with cardiac stunning despite stable hemodynamics [37]. Importantly, the same process of dysregulated blood flow under the stress of HD that affects the myocardium also affects perfusion of a variety of vascular beds and may be an important element in the development of the poor outcomes in HD patients, manifested by dysfunction of key organ systems.

Brain. Kidney impairment and elements of the HD procedure itself may increase the risk of stroke; dialysis patients experience a 10-fold higher incidence, with case fatality rates reaching 90% [38]. High hemodynamic fluctuations, high variability of blood pressure, dialysate and anticoagulants, vascular access, dialysis amyloidosis, vascular calcification (VC) and years on dialysis may trigger both ischemic and hemorrhagic strokes [39]. Dialysis initiation constitutes the highest stroke risk period; in a 22-year, single-center study, among 151 HD patients with acute stroke, almost half of brain infarcts and more than one-third of brain hemorrhages occurred during or <30 min after the start of a dialysis session [40]. Patients undergoing long-term maintenance dialysis are at increased risk of stroke, with HD patients more likely to develop hemorrhagic stroke than those undergoing peritoneal dialysis [41]. A US analysis of ∼21 000 older dialysis patients found that stroke rates reached a peak during the first 30 days after dialysis initiation [42]. However, it is now well established that arrhythmias (i.e. atrial fibrillation) frequently unrecognized in HD patients may be the cause of ischemic stroke while the preventive use of anticoagulant (warfarin) in chronic atrial fibrillation may be associated with severe hemorrhagic stroke [43–48].

The high burden of cognitive impairment in HD patients is also well established by several studies [49–51]. Up to 70% of elderly HD patients have moderate–severe chronic cognitive impairment depending on the tool used. A recent study exploring HD-associated brain injury by means of a sophisticated diffusion tensor MRI showed that conventional hyperthermic HD resulted in significant brain injury leading to brain white matter damage, which was prevented by hypothermic dialysis [52]. As this study suggests, recurrent and cumulative brain ischemic insults may contribute to acute decline in cognitive function during dialysis and may be prevented by hypothermic dialysis [53].

Gut. The acute circulatory stress effects of dialysis itself may contribute significantly to the development of gastrointestinal dysfunction to induce 'gut stunning' [10]. Ultrafiltration-induced gut ischemia may lead to bacterial endotoxin translocation from the gut to the bloodstream [54]. The link between endotoxins and systemic inflammatory reactions in dialysis is well established [55]. Increased gut permeability (also causing increased release of gut-derived uremic toxins such as indoxyl sulfate into the systemic circulation) and blood endotoxin has also been associated with cardiac stunning, with more frequent HD regimens being associated with lower endotoxin levels [56, 57]. HD-induced endotoxemia represents a plausible link between intradialytic hemodynamics and chronic inflammation.

Liver. The hepatic circulation is involved in adaptive systemic responses to circulatory stress and hepato-splanchnic circulatory stress has been proposed as an important effect of HD [58]. The liver receives a high proportion of cardiac output and holds

a significant volume of blood (10–15% of total blood volume) and has a role in the maintenance of hemodynamic stability during circulatory stress and is also vulnerable to chronic hypervolemia and hypovolemia, which are common in HD patients [59, 60]. An observational study suggested that the complex hepatic response to ultrafiltration changes may play an important role in IDH and fluid shifts [61]. In contrast to the reduced total body water content, liver water content did not decrease post-HD, consistent with a diversion of blood to the hepatic circulation, in those patients with signs of greater circulatory stress.

Vasculature. Arterial stiffening is highly pronounced in patients with chronic kidney disease (CKD). Carotid artery stiffening is not only a powerful predictor of CV mortality and morbidity but correlates better with LV mass in dialysis patients than brachial artery blood pressure [62]. Arterial stiffening involves various mechanisms that include long-term ones such as atherosclerosis and VC in relation with the uremic milieu and the endothelial dysfunction, but also short-term ones such as those due to vascular sodium content increase or physical deconditioning [63–68]. VC is believed to be a major cause, but the phenomenon is complex, involving the interplay of promoters and inhibitors of calcification in a uremic milieu, dietary phosphate, use of vitamin D and calcimimetics, phosphate removal by binders and dialysis [69]. Dialysis vintage is a major risk factor for VC in CKD [70, 71]. Dialysis procedure and delivery impact vessel stiffening as changes in dialysate calcium levels result in changes in pulse wave velocity, an indicator of target organ damage [72]. Although calcium accumulation begins predialysis, dialysis accelerates VC through the induction of vascular smooth muscle cell (VSMC) apoptosis during HD, disabling VSMC defense mechanisms and leading to overt calcification [73].

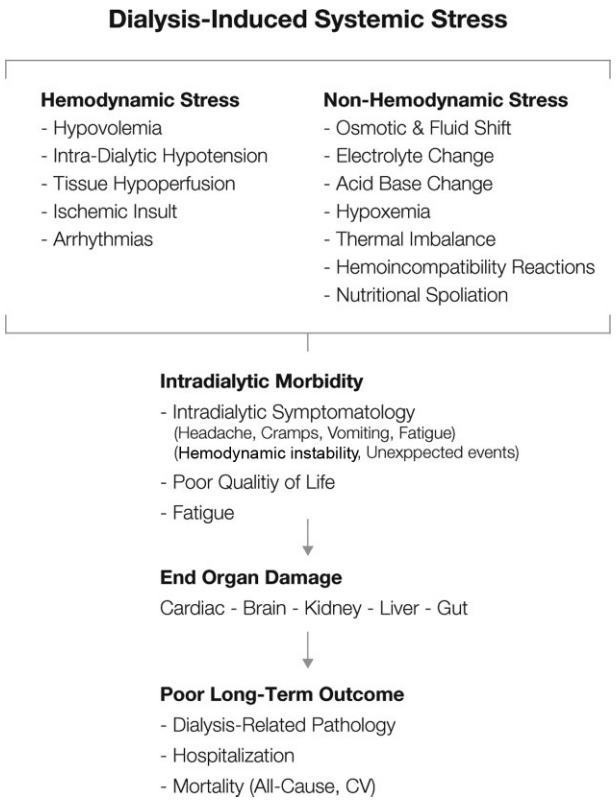

FIGURE 2: The various origins of multisystemic stress induced by HD therapies can be divided into two main categories, hemodynamic and non hemodynamic. DISS acts as a negative disease modifier to worsen long-term outcomes and contributes significantly to end damage of vital organs and the symptom burden of HD patients.

The major stressors of systemic stress in hemodialysis

The multisystemic stress induced by HD has various origins (Figure 2). The mode of delivery of HD, components of the extracorporeal circuit (ECC) as well as patient-related factors collectively contribute to the stress load. Pathophysiological drivers of the phenomenon can be divided into two distinct categories, those of hemodynamic (i.e. cardiocirculatory) origin and non-hemodynamic drivers pertaining to the HD session (i.e. hypoxemia, osmotic and electrolytic changes, bioincompatibility). Significantly, these stress factors contribute to the symptom burden patients with kidney failure carry, negatively impacting their perception of the therapy and quality of life and impairing their cognitive functions, but they also contribute to the end damage of vital organs.

Hemodynamic systemic stress factors

The current standard mode of delivery of HD (4 h sessions, thrice weekly) exposes patients to wide fluid volume fluctuations in the short intradialytic (~4 h) and the extended interdialytic phases (~44–68 h), a highly unphysiological profile. Mechanistically, these are two separate hemodynamic stress states, an acute intradialytic hemodynamic stress phase reflecting intravascular fluid depletion induced during the HD session (ultrafiltration and sodium removal) followed by the prolonged chronic interdialytic hemodynamic period of extracellular fluid accumulation and overload.

Intradialytic hypotension and hypovolemia. Acute hemodynamic stress is induced by ultrafiltration, sodium and fluid removal, which are fundamental to all HD sessions to meet the clinical need of removing excess water (equating to typically 1–4 kg weight gain, most of it water) that accumulates during the interdialytic period. Cyclical volemic changes (hypovolemia alternating with hypervolemia) result in chronic cardiac loading and acute unloading, causing repetitive stretching and shortening of the myocardium to promote cardiac fibrosis. Although less severe hypovolemia may go unnoticed by the physician, it may still have important consequences such as IDH or subclinical organ damage that can accumulate over the years of treatment [35]. Ultrafiltration and/or the HD procedure itself contributes to a decline in circulating blood volume that is partly compensated by blood redistribution and vascular refilling from the interstitial space. As during most HD sessions, the vascular refilling rate (driven, for example, by an increase in plasma protein concentration and oncotic pressure) does not fully compensate for the ultrafiltration rate and there is a decline of effective blood volume. The result is IDH and reduced tissue perfusion, potentially having a long-term structural and functional impact on all vital organs. The main causes of dialysis-induced hypotension are age hypovolemia (rapid ultrafiltration) and coexisting diseases (e.g. autonomic neuropathy, CVDs, diabetes) [74]. Cardiac stunning, a temporary reduction in myocardial perfusion and contractility, can occur in the absence of ultrafiltration (besides hypovolemia, dialysis-associated factors may be involved in the pathogenesis of HD-induced regional LV dysfunction) [23]. However, the dialysis treatment itself or rapid fluid removal by ultrafiltration—expressed in volume per time scaled to body weight—and hypovolemia contribute to cardiac stunning due

to a decline in myocardial tissue perfusion [35, 75–78]. The systemic response to the patient–HD interaction and fluid removal is even more complex since it involves other factors such as thermal balance, reflecting dialysate-patient temperature gradient, electrolyte fluxes that depend on dialysate-patient gradients and also the individual patient's baseline cardiac and hemodynamic reserve and the neurohumoral stress response.

Furthermore, detailed intradialytic imaging studies have shown that it is causally related to the ultrafiltration rate and occurs even in the absence of coronary artery disease. In the face of ongoing ultrafiltration, dialysis-induced intravascular volemia and decreased stroke volume, arterial blood pressure and tissue perfusion are maintained by an increase in vascular tone, mainly in vasoconstriction in alpha-adrenoceptors, and venous return, although this response can be mitigated by a dialysis-induced increase in core temperature. A number of associations between mortality and ultrafiltration, change in blood pressure and end-organ ischemic injury have been reported [79]. Potential mechanistic pathways include ultrafiltration-related ischemia to the heart, brain and gut and volume overload–precipitated cardiac stress from reactive measures to ultrafiltration-induced hemodynamic instability [80].

Interdialytic fluid overload and hypertension. Sodium and fluid accumulation that occur in dialysis patients over time due to repetitive positive fluid imbalance is responsible for chronic extracellular fluid overload and its adverse effects, mainly hypertension and CV consequences leading to poor outcomes including frequent hospitalization for pulmonary edema [81]. Hypertension as part of this constellation of disorders is widely recognized as a leading cause for LV cardiomyopathy and accelerated atherosclerosis, including coronary artery disease, peripheral artery disease and cerebrovascular disease [82–84]. Interestingly, as shown in recent studies, the presence of fluid overload acts either as an independent risk factor or as an additive risk factor of hypertension to worsening outcomes [85]. In addition, apart from cardiac consequences, chronic fluid overload is associated with other derangements that include inflammation (fluid overload–inflammation axis) and related metabolic disorders (i.e. protein energy wasting, aging, insulin resistance) [86].

Management of sodium and fluid excess to restore fluid status homeostasis is frequently summarized by the 'dry weight' probing approach [87]. Although this clinical approach has been associated with benefits in CV outcomes, it is now challenged by studies showing that the intensity or aggressiveness to remove sodium and fluid excess (i.e. ultrafiltration volume, dialysate sodium concentration) in conventional thrice-weekly HD might induce excessive hemodynamic stress and potential organ damage, with potentially deleterious consequences on long-term outcomes. Interestingly, it is widely recognized that a long interdialytic gap in a thrice-weekly treatment schedule is associated with a significant increase in hospitalization and mortality from CV origins [88–90]. From a clinical perspective, it is well perceived that assessment and management of the fluid status of HD patients is not an easy task. Whatever the complexity, that should remain the basic fundamental and permanent aim in HD patient management, to control blood pressure and to restore hemodynamic equilibrium. In that context, it is clear that precise sodium, fluid and pressure management will rely in the future on a stepwise approach including clinical assessment and management (i.e. patient probing), instrumental tools support (i.e. inferior vena cava diameter, relative blood volume change, bioimpedance, lung ultrasound), cardiac and volemic biomarkers (i.e. B-type natriuretic peptide, copeptin, troponins) and advanced analytic tools (i.e. artificial intelligence, deep learning) [91, 92]. Furthermore, management of HD patients will also require new treatment perspectives, including a more personalized approach (i.e. treatment option, time, frequency) and new tools (i.e. dialysate sodium management, blood volume monitoring) [93].

Cardiac arrhythmias. Sudden cardiac death (SCD) and cardiac arrhythmias (CA) are frequent in HD patients [94]. According to US Renal Data System data [95], SCD and CA are the leading causes of death in HD patients, accounting for 26.9% of all-cause mortality in prevalent HD patients. The prevalence of symptomatic atrial and ventricular arrhythmias has been reported to range from 20 to 70%, with an average of 26%, in HD patients depending on the markers or tools used [96]. Most of studies exploring CA in HD patients have involved short-term Holter monitoring and reported that atrial arrhythmias are most prevalent, not necessarily requiring treatment [97, 98]. However, the prevalence of arrhythmias in intermittent HD patients is likely to be underestimated when it is based on symptomatic arrhythmias. When continuous cardiac rhythm monitoring over a prolonged period of time is performed using implantable loop recorders, the prevalence of significant asymptomatic arrhythmias is much more frequent than expected [94, 99]. In a recent prospective study involving 66 HD patients using such recorders to detect asymptomatic arrhythmias, 1678 CA events were recorded in 44 patients. The majority were bradycardias ($n = 1461$), with 14 episodes of asystole and only 1 of sustained ventricular tachycardia. The CA rate was highest during the first dialysis of thrice-weekly HD sessions and increased during the last 12 h of each interdialytic interval, particularly the long interval. Atrial fibrillation, although not defined as clinically significant arrhythmias, was detected in 41% of patients and was highest during the HD session. HD conditions and efficiency contributed to favor arrhythmia occurrence, including warm dialysate ≥37°C (hyperthermic dialysis), low dialysate calcium (<1.25 mmol/L), low dialysate potassium (<2 mmol/L) and sodium modeling [100, 101]. Although the CKD5 dialysis patients are known to be at increased risk for arrhythmias, the underlying mechanisms of CA and its association with SCD have not been completely delineated. Various pathogenetic factors, including hypertension, pre-existing cardiomyopathy or coronary artery disease, and HD conditions have been implicated in triggering CAs. Indeed, among them, cyclical cardiac structural changes (stretching and shortening) due to volemic fluctuations induced by intermittent ultrafiltration, pulmonary arterial hypertension, electrolyte and acid-base disorders as well as acute changes are believed to be important contributing factors [102]. Furthermore, dialysate calcium and magnesium concentration changes, interacting with other ion changes (i.e. potassium, acid–base), as well as hemodynamic insults linked to HD sessions are recognized as pro-arrhythmogenic conditions [103, 104].

Non-hemodynamic systemic stress factors

Hypoxemia (impaired respiratory function). Other than reduced tissue perfusion, hypoxemia observed in patients is believed to contribute to increased mortality, CA and CV events [105]. The phenomenon of hypoxemia has been known for some time in relation to sequestration of neutrophils in the pulmonary vasculature due to bioincompatibility and is usually apparent within the first hour of initiation of dialysis, suggesting the occurrence of respiratory stress resulting from impaired pulmonary gas

exchange or an impaired ventilator drive. With the advent of more biocompatible dialysis, reduced ventilatory drive due to a rapid increase in plasma bicarbonate likely plays a larger role. The causes of hypoxemia are thus multifactorial, with the interplay of both direct HD-related factors as well as pathologies related to kidney failure and underlying lung disease [106]. Pulmonary lung hypertension due to chronic fluid overload may also be considered as a potential cause of impaired gas exchange [102]. Hypoxia has also been implicated in an increase in sympathetic tone, oxidative stress and inflammation [107]. Recently hypoxemia has been associated with intradialytic and peridialytic paradoxical hypertension with increased mortality [108], possibly mediated by sympathetic activation and endothelin-1 secretion [109, 110]. Extended intradialytic hypoxemia is likely to aggravate end-organ damage by reducing further tissue oxygen delivery, although it is difficult to distinguish the effects of intradialytic hypoxemia from those of pre-existing respiratory pathologies, sleep apnea and fluid overload in relation to outcome. In addition to these factors, capillary rarefaction and reduced mitochondrial efficacy can further affect the balance between cellular oxygen supply and demand contributing to aggravate cell damage [111].

Thermal (hyper- or hypothermic dialysis). The reduction in frequency of symptomatic hypotension and slowing of the rate of decrease in blood pressure by cool dialysate has been known for some time [112]. Regional systolic LV function was significantly less impaired at low dialysate temperatures, with fewer episodes of hypotension as a result of higher peripheral resistance and no difference in stroke volume [113]. Adjusting HD thermal balance by reducing dialysate temperature is thus a simple, low-cost strategy to improve hemodynamic tolerance with a low degree of patient discomfort [113, 114]. The potential mechanisms and determinants of extracorporeal energy balance and the hemodynamic consequence of HD-induced thermal stress have been described by Kooman *et al.* [35].

Biochemical stressors: solute, electrolyte and osmotic imbalances. The success of HD as a therapy depends on the bidirectional transport processes occurring across the semipermeable membrane. Facilitating the movement of substances in both directions, i.e. from blood to the dialysate compartment and *vice versa*, is fundamental to HD: in removing uremic toxins and water from the blood in one direction, blood has to be simultaneously replenished with electrolytes and buffers in the opposite direction. These transport processes, either passive (diffusion) or forced (convection), are highly unphysiological and the biological fluctuations carried out intensely and intermittently during each session alter body composition, inducing large osmotic and biochemical composition changes, but also removing useful substances such as glucose, amino acids and nutrients (i.e. vitamin E as a natural antioxidant), to aggravate other stressors of circulatory stress through their deleterious action on endothelial cells. The intradialytic biochemical changes, large osmotic pressure fluctuations (e.g. due to urea), acid–base imbalance and electrolyte and water shifts are described as 'dialysis disequilibrium syndrome' [19, 115]. Clinical manifestations of these shifts range from minor (fatigue, headache) to severe (impaired cognition, arrhythmias), including neurologic manifestations that progress sequentially as cerebral edema worsens and intracranial pressure rises, and if not promptly recognized and managed, can lead to coma and even death [116].

Blood-incompatibility reactions including inflammation and complement. In leaving the protective environment of the endothelium that lines all vessels of the circulation, blood contacts air and interacts with different artificial surfaces of the ECC, triggering a series of reactions. While the dialysis membrane is the focus of the separation processes of HD and of blood–material interactions, the ECC comprises several polymeric materials, each of which represents a different stimulus for the activation of blood cells and diverse biochemical pathways. Activation of the coagulation, complement, immune and inflammation pathways has been the most widely studied of reactions during HD. The resultant blood incompatibility that occurs has been documented to have severe effects on patients and the functioning (solute removal) of the therapy.

Dialysis necessitates the use of anticoagulants, which themselves trigger unwanted reactions. Heparins, the most widely used anticoagulants worldwide, trigger heparin-induced thrombocytopenia in certain patients; although the incidence of these reactions is very low, the consequences can be severe. Long-term use of heparins has been associated with some metabolic side effects (i.e. hypoaldosteronism, osteoporosis and bone fracture) and other potential safety issues [117–120]. Heparin is also problematic for patients on other medications such as antithrombotic agents (e.g. warfarin and aspirin) or at high-bleeding risk and needs to be administered and monitored with care due to the potential hemorrhagic risk [121, 122]. Contact of blood with the ECC induces complement activation and generation of pro-inflammatory cytokines that are also produced by endotoxins entering the bloodstream by the mechanism of backtransport from dialysis fluids with bacterial contamination. Components of the polymers of the ECC may leach into the blood and cause cytotoxic reactions. Direct physical trauma to red cells (hemolysis) by pumps releases substances that cause platelet aggregation, and denaturation of plasma proteins occurs at the blood–air interface, especially in the bubble trap chamber.

Approaches to mitigate hemodialysis-induced circulatory stress: cardioprotective strategies

The multifactorial and multisystemic effects of circulatory stress that creates an unphysiological environment are believed to be largely responsible for the array of symptoms in HD patients [123]. The result is both direct, short-term physical discomfort (headaches, nausea, itching, fatigue) that patients regularly must endure, as well as sustained multiorgan damage that impairs normal functioning of various organs to impact patient survival and general quality of life. Both can be alleviated by a combination of judicious selection of patient- and treatment-specific conditions to prevent dialysis-induced cardio- and multiorgan damage [93] (Figure 3).

Better patient management: targeting fluid volume control and restoring sodium, volume and pressure homeostasis. Reducing and preventing dialysis-induced hemodynamic stress is crucial toward more multiorgan-protective therapy approaches and improving patient experiences. The quest for optimal fluid volume of HD patients related to hemodynamic management—intradialytic as well as interdialytic—is a cornerstone of dialysis adequacy and prescription. The highly contentious topic remains a matter of concern as opinions vary regarding how best to restore homeostasis of extracellular volume, achieving adequate blood pressure control and preserving hemodynamic equilibrium [105, 124, 125]. Achieving patient-specific fluid balance is challenging in dialysis patients, as chronic fluid overload

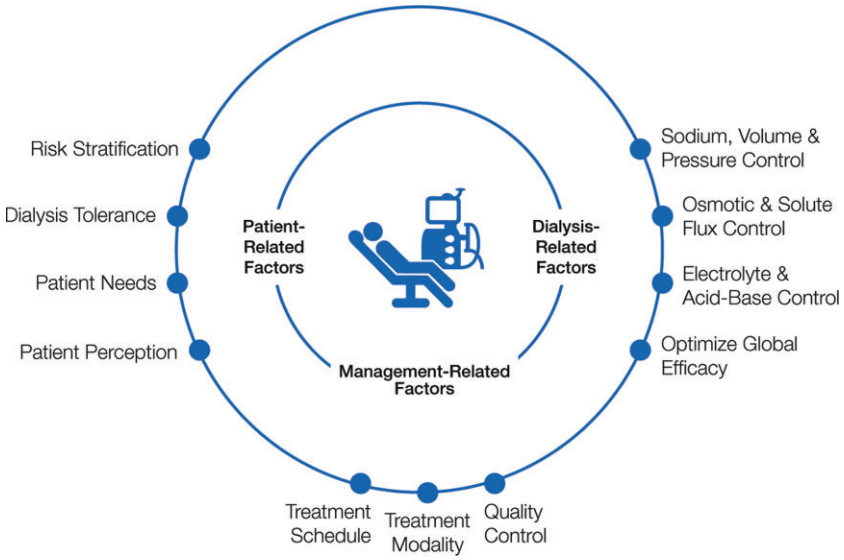

FIGURE 3: Potential approaches to mitigate the effects of DISS. HD treatment factors [reduced blood flow, treatment schedule (i.e. increased time or frequency of treatment)] can reduce DISS. In addition, a more personalized approach, coupled with 'smart machine' options to adjust therapy conditions according to patient characteristics, would help alleviate multisystemic stress for the patient.

is commonly associated with increased CVD mortality and morbidity, whereas excessive or too fast fluid removal can lead to multiorgan damage (e.g. myocardial, gut, brain 'stunning') [126–128]. Extracellular fluid status should be a component of sufficient dialysis, such that approaching normalization of extracellular fluid volume is a primary goal of dialysis care.

The conventional approach to optimal management of fluid and sodium imbalance in dialysis patients is achieved by adjusting salt and fluid removal through dialysis and salt intake restriction, and fluid gain between HD sessions. This 'dry weight adjustment approach' may provide benefits in CV outcomes but is not conducive because of the discontinuous nature of the HD treatment and/or patient intolerance to fluid and sodium removal. Recent studies have shown that the intensity or aggressiveness of removing fluid during conventional thrice-weekly dialysis might induce excessive hemodynamic stress and potential organ damage, with potentially deleterious consequences in the long term [10, 126]. Longer session treatment times and/or increased frequency of therapy sessions are the obvious answer and evidence suggests reduced levels of dialysis-induced cardiac injury [129]. As circulatory stress is mainly time-dependent, prolonged or more dialysis treatment may reduce the homeostatic burden on the patient. In this regard, compressing the 3-day interdialytic interval by moving to every other day dialysis treatment would have the potential to mitigate this additional CV risk [130]. The benefits of increased HD time and frequency, particularly for better removal of uremic toxins, are undisputed [131–133]; however, the increased costs related to nursing time, consumables and logistics is an impediment to the approach [92, 134]. Thus fluid removal should be gradual and routine HD treatment duration should not be <4 h without justification based on individual patient factors [124].

Ultrafiltration is the denominator that is common to most of the circulatory stressors that are believed to contribute to multiorgan damage [135]. Considering the complexity of the hemodynamic response to ultrafiltration, it has been suggested that the time of dialysis should be adjusted in such a way that patients would not suffer from symptoms related to rapid ultrafiltration, which is associated with higher mortality risk [76, 80, 133, 136, 137]. Barbieri *et al.* [138] have reviewed different approaches based on the absolute or relative blood volume (automated or closed-loop feedback control) of ultrafiltration to prevent critical reductions in circulating blood volume and improve hemodynamic stability and reduce the incidence of hypotension. Adapting the ultrafiltration rate, dialysate sodium and treatment time (i.e. dialysis prescription) in a more precise and personalized way with the application of modern technology and analytical tools to ensure optimal fluid status control would help minimize the risks associated with hemodynamic stress [139].

An increase in core temperature could induce an undesired hemodynamic response (vasodilation, tachycardia or drop in ejection fraction). An effective strategy to improve hemodynamic tolerance is adjusting thermal balance by delivering iso- or hypothermic HD (both effectively reduce hypotension rates) to prevent the patient from warming during the HD session and is most easily achieved by setting the dialysate temperature 0.5–1°C below the patient's core temperature. Isothermic dialysis requires the use of a blood temperature monitor device embedded on the HD machine that can precisely control the patient's thermal balance by adjusting the dialysate temperature in response to the blood temperature in the ECC [140].

Strategies to reduce blood incompatibility reactions of the extracorporeal circuit. Interaction of plasma proteins and blood cells with artificial surfaces of the ECC is an inevitable 'unphysiological' reality of all extracorporeal blood purification treatment modalities [141]. Biomaterials science has advanced considerably to provide materials that are more compatible with biological substances, but constraints related to the special demands of each therapy application mean that blood components are altered and undesirable biochemical reactions are triggered. The consequences are both short term (relevant for the duration of the therapy) and longer term (persistent insult over several years). Dialysis-induced blood incompatibility can add to the high hemodynamic stress burden dialysis patients already carry, i.e. traditional (hypertension, diabetes, age, obesity,

hyperlipidemia, smoking, etc.) and uremia-related risk factors (inflammation, oxidative stress, salt water overload, anemia, malnutrition dyslipidemia) [142, 143]. Mitigation of the intensity of dialysis-related CV burden is clearly crucial to patient well-being.

An effective conceptual approach to diminish the effects of the blood–ECC circuit interaction is the engineering and design philosophy. First, improvement of the ECC involves using the minimal possible amount of polymer material(s) for the tubing system taking blood to and from the dialyser. By using compact, specially designed blood cassettes incorporating a minimal blood trauma-causing pumping system, blood is exposed to markedly less tubing material. Circuitry geometry is an important consideration in the overall blood incompatibility equation, as blood rheology in the ECC impacts the intensity of the blood–material interaction. Short tubing systems are also designed to minimize the blood–air interface (especially in the venous bubble trap chamber). which is known to denature proteins and create air microemboli and result in serious sequelae.

Anticoagulation. Prevention of activation of coagulation is mandatory to prevent the risk of thrombosis complications within the body and clot formation within the ECC that could, together with increased protein adsorption, impair the functioning of the dialyser [120]. Constriction of the lumen of the hollow fibers, particularly in the header region of the filters (where blood flow stagnation regions promote clotting), and plugging of the pores by fibrin clots reduces the effectiveness of the device in clearing uremic toxins from the blood. It should be noted that well before clotting is visible in the ECC, soluble fibrin formation occurs through a combination of inadequate anticoagulation and factor XII activation–initiated coagulation [144]. Heparin, either unfractionated or low molecular weight fractions, is used universally except in rare cases where patients need alternative anticoagulants. The heparin dosage should be titrated to each patient's individual needs; however, there is a general tendency to give suboptimal doses to patients to prevent post-dialysis bleeding events. Heparin-induced thrombocytopaenia, although relatively infrequent, can have severe consequences [120].

Two possible approaches to mitigate the effects of ECC-induced coagulation that have been attempted since the early days of HD are surface modification of polymers used for the manufacture of the membranes and tubing materials. Attachment of either chemical groups or heparin onto surfaces to reduce their thrombogenicity have met with limited success so far [145]. In many instances, significant amounts of heparin have been shown in the laboratory to be attached to surfaces either passively or via covalent attachment [146, 147]. However, heparin (or its derivatives or heparin-like compounds) attached to surfaces is biologically inactive and unable to freely bind antithrombin III to achieve effective and consistent anticoagulation. Recently a novel non thrombogenic material system has been developed that shows promising results toward the goal of having 'heparin-poor dialysis' [148].

Complement and immune response. Complement proteins are perceived as sensors and transmitters of 'danger signals' that trigger and modulate immune responses to pathological conditions [149]. The proteolytic cascade of events and cell activation with the release of various pro-inflammatory mediators represents a 'biologic or cytokine storm' or circulatory stress situation. The complement activation pathway has an historical association with HD and together with thrombogenicity is the stimulus for the blood incompatibility and hypersensitivity phenomena associated with HD membranes [150–152]. Although the clinical significance of HD membrane-initiated complement activation and associated leukopenia remains to be fully elucidated, it is widely seen as an undesirable stress factor in HD and needs to be kept to a minimum [153].

Inflammation. CKD, like most chronic diseases, is essentially an inflammatory condition; any additional pro-inflammatory reactions during the delivery of HD or by the ECC increases the CV load for the patient [154]. Other than membrane or material-related stimuli, a well-recognized and potent source of inflammation in HD is the presence in dialysis fluids of endotoxins that arise from bacterial contamination of the water treatment systems of dialysis units [55, 155, 156]. During growth and lysis, the outer leaflet of Gram-negative bacteria releases lipopolysaccharide (LPS, chemical designation of endotoxins) fragments and other compounds of various sizes into the water. As transport processes in HD membranes are bidirectional, LPS may diffuse into or be forced into the bloodstream by the process of back-transport to trigger systemic inflammation [54, 157, 158]. Other than ensuring that microbiological water quality standards are met from 'tap to machine', the CV risk presented endotoxins entering the blood can be reduced by using special endotoxin-retention filters that are today an essential part of modern HD machines [159]. However, the final line of defense is offered by certain types of dialysers that contain membranes that are capable of retaining endotoxins should the ultrafilters be used in ways not recommended by the manufacturers [160].

Mitigating the effects of systemic stress effects of solute fluxes

The 'biochemical stress' that reflects rapid biochemical changes occurs because of solute, water and osmotic fluxes (e.g. disequilibrium syndrome). The intensity of such alterations is directly related to the plasma–dialysate gradient and operating conditions (e.g. blood and dialysate flow) during the HD treatment. The systemic stress induced by fluctuations in solute gradients and fluxes (e.g. of dialysate electrolyte levels of sodium, calcium, magnesium, potassium, bicarbonate) depends on their intensity and magnitude and are potentially modifiable factors of HD prescription [17, 161–163] (Figure 3). Approaches to mitigate their effects include reducing blood flow or increasing treatment time or frequency of treatment, which are generally better tolerated and result in less circulatory stress compared with short HD schedules. More personalized approaches based on the use of smart HD machines to adjust solute fluxes according to patient characteristics are currently under clinical evaluation. Today, the most advanced option relies on automated sodium and water management (i.e. isonatremic or zero diffusive sodium dialysis) using dialysate conductivity sensors coupled to specific algorithms embedded in the HD machine [164–166].

Patient-related factors (risk stratification, personalized treatment)

It is important to consider that the response to systemic stress factors detailed in this article may be modulated according to various patient-related considerations, e.g. age, gender, comorbidity, medication. These may explain individual or temporal variations in hemodynamic adaptation. Whatever the reason, the hemodynamic stress of dialysis must be considered as a potent disease modifier, especially in an already highly

vulnerable population, e.g. decreased body cell mass associated with aging and muscle attenuation. Patient involvement is crucial to the alleviation of adverse effects of stress factors. The benefits of dietary counseling through patient education programs to advise patients with consistently high interdialytic weight gain to practice salt restriction can help toward achievement of optimal fluid volume status [124, 167]. Personalized dialysis treatment will take advantage in the future of new technologies relying on pervasive smart sensor monitoring devices (i.e. connected watches) and/or point-of-care testing and/or online monitoring devices integrated in dialysis machines [168–170].

CONCLUSIONS

The cost-conscious rather than physiology- and/or personalized-based delivery of modern HD therapies is characterized by poor treatment tolerability and suboptimal long-term outcome [10, 12, 13]. This observation reflects the dual intrinsic limitation of current short HD treatment schedules due to their intermittent character and their limited global efficiency when compared with native kidney functions. In this report we addressed specifically the role of conventional thrice-weekly HD treatment as a potential negative disease modifier, the so called dialysis adequacy criteria, and voluntarily excluded the impact of global treatment efficiency that has been addressed in other reports.

DISS leads to both a significant reduction in overall quality of life and direct physical impacts with potential end-organ damaging effects abstracted in intradialytic morbidity complex syndrome. Conventional HD treatment is a sufficient CV functional stressor to provoke significant systemic circulatory stress [36]. This appears to affect most HD patients and cuts across age and comorbidity-defined groupings. Although significant progress has been achieved over the last few years in improving hemodynamic stability and reducing CV mortality, a more balanced and precise approach is required to reduce DISS in this high-risk population [171–173].

To satisfy this unmet need, it is time to move to a broader approach embracing the entire management of HD patients in a more physiologically based and holistically oriented way rather than focusing only on one component, such as hemodynamic management or HD efficiency. DISS results from multifactorial components that may act as a disease modifier, resulting in multiorgan injury superimposed on pre-existent comorbidities [91]. Intradialytic morbidity is the clinical expression of a composite phenomenon that includes hemodynamic stress (i.e. hypovolemia, IDH, arrhythmias) and non-hemodynamic factors (i.e. osmotic changes, electrolytes changes, hypoxia, inflammation).

Recognition that intradialytic morbidity has variable causes may allow tailoring of personalized treatments and multitargeted interventions in the future to improve outcomes. In this context, three main streams are envisaged: first, establishing initial RRT schedules and various options, based on the patient's risk stratification profile and choice would probably improve short- and mid-term patient perceptions and outcomes; second, positioning kidney replacement treatment in a patient's management integrated trajectory (i.e. incremental HD, home therapy, kidney transplantation) would definitively improve long-term outcomes; third, using innovative technologies based either on smart HD machines and on support of artificial intelligence and i-health-connected tools.

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CONFLICT OF INTEREST STATEMENT

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