The vicious cycle of intradialytic hypotension, inflammation and myocardial stunning: overview of pathophysiological aspects

Intradialytic hypotension (IDH) represents a well-known and intractable complication in hemodialysis patients. Despite the innovations in hemodialysis techniques, its tenacious presence indicates the complexity of underlying pathophysiological mechanisms. The need of an integrated approach in understanding its pathogenesis is thought to be imperative as it may prevent devastating consequences through the implementation of more successful avoidance tactics. It is well established that IDH has been associated with impaired myocardial function and peripheral vascular resistance, attributed to either the hemodialysis procedure per se or patients’ unique features.

This review aims to describe traditional risk factors of IDH and focus on non-traditional but crucial factors of hemodynamic instability related to endothelial dysfunction. In particular, chronic subclinical inflammation may be considered the missing link in the vicious cycle of IDH, ischemia and myocardial stunning. Repeated episodes of enteric ischemia during hemodialysis represent an additional source of chronic systemic inflammation that induces the phenomenon of bacterial or endotoxin translocation through the impaired enteric epithelial cell barrier. Thus, increased endothelial dysfunction and oxidative stress result in decreased left ventricular pumping function and finally permanent systolic dysfunction through genetic adaptations. In total, these pathophysiological mechanisms preserve the vicious cycle of IDH.

KEYWORDS: Hemodialysis, intradialytic hypotension, myocardial stunning, chronic subclinical inflammation, bacterial translocation

Introduction

Intradialytic hypotension (IDH) represents a common complication of hemodialysis and is considered an important and independent predictor of morbidity and mortality in hemodialysis patients [1,2]. IDH incidence ranges in different cohorts between 17.2 and 33% of hemodialysis sessions and is characterized by extremely variable symptomatology with different severity and course, even within the same patient (National Kidney Foundation) [3]. Patients with predisposing factors present repeated episodes of symptomatic or asymptomatic IDH which in rare cases of severe and prolonged tissue ischemia may lead to coronary, cerebral or mesenteric ischemia [4,5]. Tisler et al have reported that older age, hyper-phosphatemia and diabetes mellitus represent independent predictors of repeated IDH episodes [6]. In addition, it is known that low predialysis blood pressure levels, evident in approximately 10% of hemodialysis patients, increase the risk of IDH and mortality [7].

Progressive hypovolemia due to ultrafiltration and parallel removal of osmotically active substances during a relatively short time period play a central role in hemodynamic instability, taken into account that compensatory mechanisms of cardiovascular homeostasis are either exhausted or insufficient [8]. Everyday clinical practice has shown that recent innovations in technical hemodialysis parameters aiming to address these issues, do prevent neither hemodynamic disequilibrium nor IDH [9].

Thus, beyond traditional risk factors, additional mechanisms are implicated in patient susceptibility to IDH [10]. Chronic systemic subclinical inflammation, oxidative stress and endothelial dysfunction have emerged as significant factors of hemodynamic instability [11].

In addition, repeated episodes of subclinical myocardial ischemia have been associated with post-ischemic ventricular dysfunction that seems to preserve the vicious cycle of IDH and reduced cardiac output [12]. The latter leads to mesenteric ischemia, which in turn...

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Impaired ventricular repolarization and possibly arrhythmogenesis or sudden death. Furthermore, it should be noted that low calcium bath ([Ca$$^+$$]: 1.25 mmol/L), though beneficial for patients with bone metabolism disorders, has been also associated with increased IDH incidence. On the contrary, the bath with [Ca$$^+$$]: 1.75 mmol/L improves hemodynamic stability affecting mainly peripheral vascular resistance and possibly systolic cardiac function through increased sensitivity to endogenous catecholamines. Of note, significant reduction of plasma [Mg$$^+$$] during hemodialysis has been also linked with IDH. Regarding bath Na$$^+$$ concentration, optimal values are still controversial. Currently it is known that a mild individualized reduction improves not only ultrafiltration needs but also the number of symptomatic IDH episodes per week. Similarly, more frequent hemodialysis schedules or longer duration sessions have been associated with reduced IDH incidence and morbidity due to reduced ultrafiltration rates.

Regarding the changes in the cardiac pumping function the underlying pathophysiological mechanisms involve the down-regulation of b-adrenergic receptors and desensitization of the adrenergic path through chronically increased sympathetic activity. As a result, myocardial systolic function is impaired and exacerbated by increased nitric oxide (NO) levels. NO represents an important mediator.
in hemodynamic instability observed in IDH and has been also associated with reductions in peripheral vascular resistance and systolic cardiac function. These reductions occur either directly or indirectly, mediated by the aberrant sensitivity to noradrenergic stimuli [26].

Furthermore, sympathetic nervous system (SNS) impairment in patients with increased IDH risk has been established as a significant pathophysiological mechanism of cardiovascular imbalance [27]. This mechanism is based on the SNS vasoconstrictor, chronotrophic and inotropic actions leading to increased peripheral vascular resistance and cardiac function, under steady hemodynamic conditions [28].

Left ventricular diastolic dysfunction and arterial stiffness represent long-established cardiovascular risk factors in hemodialysis patients [29] that both induce myocardial stunning and IDH [30]. Moreover, Barberato et al. have suggested left atrial enlargement (LAVI > 35 ml/m²) as an independent predictor of IDH [31]. In experimental IDH models, left ventricular diastolic dysfunction represents a subtype of myocardiopathy, called uremic myocardiopathy, related to changes in Na⁺/Ca²⁺exchanger [32] or Na⁺/H⁺ antiporter [33].

Nette et al. have associated IDH with inadequate increase in arterial tone and cardiac output during the episode in patients predisposed or not to IDH with similar reductions in relative blood volume [34]. Nevertheless, we should bear in mind that excessive interdialytic increase of body weight increases the incidence of IDH, since the ultrafiltration rate exceeds the compensatory mechanisms of plasma refilling and venous return. Thus, higher interdialytic body weight increase and subsequent high ultrafiltration rate (UFR> 13 ml/h/ Kg) may lead to abnormal hemodynamic changes that exacerbate left ventricular cardiac reserve [35].

As mentioned before, patients predisposed to IDH present with dysfunction in baroreceptors and cardiac output in the setting of repeated episodes of myocardial ischemia [36]. Owen et al. have identified the inadequate increase in cardiac output and less the disturbed adaptation of peripheral vascular resistance as the most significant pathogenetic factor in the group of patients with recurrent IDH episodes [37]. Subclinical myocardial ischemia presenting with ST depression and impaired left ventricular systolic function seems to precede the hypotensive episode and contribute to its occurrence [38]. Repeated episodes of myocardial ischemia during conventional hemodialysis sessions have been also associated with the meta-ischemic myocardial stunning that preserves the vicious cycle of IDH and reduced cardiac output [12, 39].

Pathophysiologica mechanisms involved in myocardial stunning are complex and include changes in metabolic pathways, microcirculation, electrophysiology and neuronal function (Table 1). Major metabolic pathways involved are free oxygen radical production and calcium overload while, in the next step of genetic adaptations, contractile protein expression is down-regulated to prevent permanent cellular damage (hibernating myocardium) [40]. Finally, chronic functional adaptation to repeated ischemia causes remodelling, scarring and permanent loss of systolic and electrical stability causing increased incidence of sudden death in these patients [41]. Risk factors of myocardial stunning include chronic systemic inflammation, left ventricular hypertrophy and diastolic dysfunction, vascular calcifications, the malnutrition – inflammation – atherosclerosis (MIA) syndrome and uremic myocardiopathy.

Persistent systemic subclinical inflammation characterizing end-stage chronic kidney disease (ESRD) [42] and cytokine imbalance are implicated by the accelerated atherosclerotic process through interrelated increased oxidative stress, endothelial dysfunction and vascular calcification [43]. Patients predisposed to IDH are exposed to endotoxemia due to repeated enteric ischemia that causes bacterial translocation from the gastrointestinal tract into the systemic circulation. The induced systemic inflammation could possibly be the missing link

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in our understanding of the vicious cycle of IDH-inflammation-myocardial stunning (Figure 2) [13]. Kubota et al. have hypothesized that the favorable effect of sevelamer on the nutritional status of patients with increased endotoxin burden may be attributed to endotoxin binding of negatively charged components in a dose-dependent manner [44], as previously reported by Marangon et al. [45].

**Peripheral vascular resistance disorders**

Peripheral vascular resistance disorders represent the second parameter relating to IDH incidence and are mainly correlated to SNS and vasoactive substances.

- **SNS disorders:** SNS failure is considered a significant factor of hemodynamic instability during hemodialysis. SNS activation during progressively established hypovolemia contributes to maintain normal blood pressure levels through increased heart rate and systolic function and concomitantly, recruits the main veins that represent blood storages of alterable capacity [26].

  Inadequate increase of peripheral vascular resistance during ultrafiltration causes additional reduction of venous return and end-diastolic volume filling (phenomenon Dejager - Krogh) leading to impaired cardiac output (Frank-Starling’s law) [8].

  Barnas et al. [46] have described the following two types of IDH: i) asymptomatic progressive intradialytic fall of systolic blood pressure accompanied by increased heart rate and ii) acute, sudden symptomatic IDH with bradycardia. Acute IDH has been associated with Bezold-Jarisch (B-J) reflex that is characterized by a preceding short period of sympathetic overactivity and is followed by inhibited SNS function, sinus bradycardia and peripheral vasodilation [47]. The reflex is activated because of the severe contraction after the progressive reduction of left ventricular filling and causes activation of cardiac mechanoreceptors. Then, afferent vagal stimuli cause cardiovascular inhibition and deactivation of baroreceptors. In addition, central nervous system ischemia and NO involvement in inhibition of the SNS activity are considered crucial steps in B-J reflex. In terms of pathophysiology, the paradox in B-J reflex hides a cardioprotective mechanism that negates myocardial ischemia due to hypovolemia through reduction of cardiac output. SNS inhibition that is determined by myocardial $^{[123]}$I-MIBG scintigraphy and spectroscopic analysis of heart rate variability seems to be largely impaired in diabetic patients with IDH [48]. According to Chang YK et al, heart rate variability can also be a useful tool in the struggle of recognition IDH-predisposed hemodialysis patients [49]. On the contrary, uremic polyneuropathy is not strongly associated with IDH [50], although induced muscular atrophy, through reduced vein return, could affect the end-diastolic volume filling and thus, cardiac output [14].

  The association between IDH and SNS failure has not been clearly determined and remains debatable. Pelosi et al. [51] and Barnas et al. [44] speculate that SNS failure represents a major pathogenetic mechanism in IDH; whereas Rubinger et al. [52] emphasize on left ventricular diastolic dysfunction as the major cause of hemodynamic instability. In total, dysautonomy plays a crucial role in IDH presence in patients with concomitant failure of other compensatory mechanisms [53,54]. Cavalcanti et al. implicate both dysautonomy and left ventricular diastolic dysfunction into IDH pathogenesis and also suggest SNS assessment as a prevention measure for IDH and cardiovascular dysfunction [27].

  Impaired SNS activity has been further studied in the effect of dialysis bath...
temperature on adequate compensatory vasoconstriction. Body temperature is increased during hemodialysis sessions because of heat transferring from the bath to patients with low predialysis temperature, skin vasoconstriction and inflammatory mediated thermogenesis [55]. Therefore, lower bath temperature has emerged as a compensatory measure of hemodynamic stability [56]. This favorable effect is mediated by increased peripheral vascular resistance and venous return [57]; while baroreflex sensitivity increases [58,24]. Lastly, Yamamoto et al. have shown that acute symptomatic hypotension reflects both dysautonomy and vascular wall dysfunction, as shown in the imbalance of vasoactive substances [59].

- **Vasoactive substances imbalance:** Progressive hypovolemia is normally characterized by changes in important vasoactive substances. Hemodynamically stable patients present with a compensatory increase of catecholamines and antidiuretic hormone (ADH) and a decrease in atrial natriuretic peptide (ANP) and cyclic guanosine monophosphate (cGMP) [60]. On the contrary, patients predisposed to IDH present not only with a lack of increased noradrenaline and ADH [61] but also with significant imbalance of the system NO – endothelin 1 (ET1) [26].

The role of NO in cardiovascular homeostasis consists of both direct effects on vascular tone through cGMP and indirect inhibitory effect on SNS activity. From the hemodynamic point of view, IDH may be an epiphenomenon of the complex interaction between the NO-ET1 system, cardiac dysfunction and intravascular volume. Of note, intravascular vasoconstriction regards primarily hemodialysis and secondarily isolated ultrafiltration. This fact supports the hypothesis of either removal of vasoconstrictive substances or production of vasodilating substances in IDH. Beasley et al. [62] as well as Noris et al. [63] have linked increased NO concentration with levels of proinflammatory cytokines and activated platelets, respectively. Nitric anions [NO₃⁻] are considered stable metabolites of NO and possibly prognostic risk factors of IDH [64], since they have been significantly associated both with acute symptomatic IDH and chronic hypotension of hemodialysis patients [65]. Similarly, Matsumoto et al. have documented increased excretion of NO in exhaled air of patients with increased levels of interleukin-1β (IL-1β) and interferon-γ (IFN-γ), possibly attributed to increased endogenous production [66].

Increased cytokine production in the setting of chronic subclinical inflammation that characterizes End Stage Renal Disease (ESRD) has been profoundly associated with hemodialysis per se. Bioincompatibility of hemodialysis membranes, endotoxemia due to back filtration and endotoxin diffusion from hemodialysis bath induce monocyte activation. Therefore, biosynthesis of proinflammatory cytokines and NO production are triggered [67]. Recently, intestinal micro-flora of uremic patients and circulating microbial DNA fragments has been identified as contributors to chronic inflammation [68]. Disturbances in intestinal micro-flora are considered fundamental mediators of the uremic syndrome (p-cresol and indoxyl sulfate) and endotoxemia due to translocation has been associated with microbial overgrow, impaired immunological mechanisms and epithelial cell barrier [69,70]. Regarding to fragments of bacterial DNA, Bossola et al have shown that DNA fragments pass through the hemodialysis bath and significantly contribute to proinflammatory cytokines production from activated monocytes, since they originate from bacteria in water or hemodialysis bath [71].

The role of heparin in increasing NO concentration has been investigated both in experimental [72] and clinical studies. The latter have shown that heparin administration is associated with increased expression of the human hepatocellular growth factor (hHGF) and nitric anions. Increased hHGF expression induces NO production and NO-mediated IDH [73]. In addition, it should be also noted that hematocrit increase up to the target levels, causes IDH incidence reduction because of the inhibitory effect of hemoglobin on NO expression [8].

Regarding the accumulation of dimethyl-arginines in patients with chronic kidney disease, asymmetric dimethyl-arginines (ADMA) is nowadays considered a novel uremic toxin and a strong mediator of endothelial dysfunction [74]. ADMA represents the major endogenous inhibitor of NO synthetase and has emerged as an independent cardiovascular and total morbidity and mortality predictor [75]. ADMA accumulation is implicated in the pathophysiology of uremic syndrome and atherosclerosis observed in patients with ESRD [76]. Its pathophysiologic role is emphasized by the presence of the enzyme DDAH (dimethyl-arginine dimethylaminohydrolase) that
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selectively catalyzes ADMA [77].

ADMA reduction during hemodialysis [78] is expressed by increase nitric anions plasma levels and has been associated with IDH. In post dialysis period, a rapid increase of plasma dimethy-arginines is observed due to a novel balance between plasma and other compartments. In conclusion, ADMA represents a significant mediator between ESRD-endothelial dysfunction-accelerated atherosclerosis, through reduced NO bioavailability [79] and consequently an optimal marker of cardiovascular risk in patients with ESRD [80].

Blood pressure fall induced by hypovolemia leads to reduced blood flow in tissues and organs of high metabolic activity that in turn, excrete adenosine. Adenosine is another strong endogenous mediator with vasodilating and cardio suppressive effects [81]. Following its release, adenosine induces peripheral vasodilatation through a2 receptors and exerts its cardio protective actions through a1 receptors, detaining ischemia-induced cellular death [82]. Adenosine plays an important role in acute symptomatic hypotension [83] since peripheral vasodilatation and negative inotropic and chronotropic myocardial effects [84] exacerbate blood pressure fall and maintain tissue ischemia causing more adenosine excretion (adenosine hypothesis). In a regional level, adenosine inhibits noradrenaline excretion and maintains blood flow in the splanchnic circulation (Dejager-Krogh phenomenon) while it is also implicated in B-J reflex stimulation [8]. These actions lead to severe ischemic events including mesenteric ischemia that has been also linked with bacterial translocation and episodic endotoxemia.

**Conclusion**

IDH remains the most common complication of hemodialysis with potentially devastating consequences despite the technological advances regarding the hemodialysis techniques of the last decades. The increasing number of advanced age patients, diabetics and patients with cardiovascular comorbidities undergoing hemodialysis emphasizes the need on implementation of new IDH avoidance tactics.

IDH origin is multifactorial and linked to interrelated disorders in peripheral vascular resistance and cardiac pumping activity that are both attributed in hemodialysis procedure and patients’ characteristics. Pinpointing the causes of IDH remains a complicated task and justifies the extraordinary explosion of interest on this field while the role of chronic subclinical inflammation and myocardial stunning seems to be still in their infancy.

Meanwhile, it is of great importance to take into account the role of time and frequency in preventing IDH incidence. The implementation of an individualized program for each patient and possibly alteration of conventional hemodialysis establishments could be the optimal approach in order to solve the riddle of IDH-inflammation-myocardial stunning, even if it has to break the rules.
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