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1. Introduction

End stage renal disease (ESRD) affects over 400,000 Americans, and over 8 million have chronic renal insufficiency [1]. Chronic renal insufficiency (CRI) describes a continuum of impaired renal function based on several parameters including glomerular filtration rate and serum creatinine. As renal function deteriorates, the risk of all-cause mortality increases [1]. The most prevalent form of renal replacement therapy is hemodialysis (HD), with over 75% of ESRD patients being treated with this modality [2, 3]. Patients requiring chronic HD have been noted to experience an increase in cardiovascular morbidity and mortality [4]. In fact, between 10-20% of patients who require HD die each year and approximately 45% of these deaths are attributable to cardiovascular causes [2, 3]. Hemodialysis itself is associated with substantial morbidity, including complications related to vascular access and those inherent to the HD procedure itself.

One of the most common complications of hemodialysis is intradialytic hypotension (IDH), which occurs in approximately 25% of HD sessions [5]. There are several therapeutic options available for the treatment of IDH. However, “resistant” forms of IDH do occur and a multimodality approach is usually necessary in such cases. The aim of this chapter is to discuss IDH and outline existing clinical approaches to IDH. Specifically, we will focus on the use of methylene blue (MB) in the treatment of IDH. Methylene blue, a nitric oxide pathway mediator, has shown promise in prevention or treatment of IDH in difficult-to-treat cases [6, 7].

2. Overview of intradialytic hypotension

IDH is seen in approximately 20-30% of hemodialysis sessions and is an independent risk factor for mortality [8]. During a typical HD session, an ultrafiltrate volume of 5 liters or greater may be removed with a concomitant 10-20% reduction in plasma volume [9, 10]. Intradialytic hypotension is likely multifactorial, and the inability of the cardiovascular system to adequately respond to the reduction in circulating plasma volume is among the leading factors.

Most patients are able to compensate for the ultrafiltration fluid losses by “mobilizing” fluid from extravascular/interstitial space, and tissue hydration state has a strong influence on changes in plasma volume during fluid removal and subsequent repletion [11].
where IDH occurs, available strategies include a combination of vasopressor administration, intravascular volume expansion with intravenous colloid or crystalloid solutions, positional patient changes, and discontinuation of ultrafiltration [12]. Detailed discussion of the underlying physiology and therapies available to treat IDH will now follow.

2.1 Physiology of intradialytic hypotension

Intradialytic hypotension can have very serious sequelae, up to and including the development of life-threatening end-organ (i.e., cardiac, cerebral) hypoperfusion [12]. Factors contributory to IDH can be broadly divided into those related to the HD procedure and those related to underlying patient condition(s) [12]. Patient related factors, the focus of this chapter, can be further divided into cardiac (i.e., left ventricular hypertrophy, chronic volume overload, anemia (acute or chronic), diastolic and systolic dysfunction, cardiac arrhythmias, ischemic myocardial syndromes) and vascular (i.e., vasoplegia or impaired maintenance of appropriate vascular tone/systemic vascular resistance) [7, 12]. Hemodialysis related factors include the ultrafiltration rate, possible intra-procedural blood loss, and dialysate temperature profile [12, 13].

We will focus on the vascular-related aspects of IDH, concentrating on the vasoplegia associated with the HD procedure. The amount of fluid available in the interstitial space for “vascular refilling” is one of the primary determinants of IDH. In the presence of excess fluid in the interstitial space, the patient is theoretically more likely to tolerate higher volumes of ultrafiltrate removal [11]. Conversely, patients with relatively smaller amounts of volume in the interstitial space are more susceptible to even small amounts of volume removal. Therefore the determination of the patient’s true dry weight is important to planning the amount of ultrafiltrate removal [14, 15]. It is important to remember that fluid shifts from the interstitial space to the intravascular space constitute a dynamic process and exhibit anatomic variations. For example, intravascular refilling is more vigorous in lower extremities because of the relative excess of extracellular fluid [16].

During ultrafiltration, the body’s initial response to volume reduction involves sympathetic mediated vasoconstriction [17]. This vasoconstriction shifts blood flow away from dermal circulation and reduces heat loss. However, this response may not always be sufficient, either due to impaired sympathetic response itself or excessive production of endogenous vasodilators [18]. Chromogranin A levels, which are co-released with catecholamines, are decreased significantly in the post-HD plasma of patients with IDH compared to patients with stable blood pressures [19]. In addition, it has been suggested that patients with significant uremia have autonomic dysfunction that may be due to chronic hyperkalemic depolarization [20].

Endothelial cells and vascular myocytes release adenosine, which also has been implicated in the development of IDH [21]. It is hypothesized that during dialysis there are local areas of tissue ischemia that release adenosine in response. Antagonism of the A1 and A2 adenosine receptors in patients with frequent IDH has been shown to reduce the incidence modestly [21]. Also, peripheral blood mononuclear cells show greater expression of A2A receptors in IDH-prone patients [22].

Patients undergoing HD tend to experience a net increase in body temperature [23, 24]. Core temperature continues to increase throughout the dialysis procedure and may be associated with impaired sympathetic response before the development of IDH [25]. Isothermic HD may improve patient hemodynamics and may help prevent IDH [24]. It is important to note
that the protective hemodynamic effects of cool dialysate may be most pronounced among patients with lower baseline (i.e., pre-HD) body temperatures [26]. Additional aspects of vasoplegia associated with HD in the context of nitric oxide (NO) pathways will be discussed in subsequent sections, along with the role of methylene blue (MB) as a potential therapeutic agent in this setting.

2.2 Determination of dry weight and intravascular volume
The dry weight of a given patient can be difficult to determine and can fluctuate depending on any concurrent acute and chronic illnesses [14]. Several methods of estimating dry weight exist and will be discussed in this section. Commonly used techniques are based on intravascular pressure measurements, bioimpedance determination, arterial waveform analysis, and various sonographic techniques [27-29]. Specific methods include blood volume monitoring with ultrafiltration pulses, central venous and other invasive vascular pressure measurements, ultrasound measurements of the inferior vena cava (diameter and/or collapsibility) or direct bioimpedance measurements (whole-body, segmental, calf) [27-29]. Of note, the use of invasive blood volume monitoring devices has been associated with greater nonvascular and vascular access related complications and mortality [30]. Recent developments in the area of intravascular monitoring and estimation of dry weight and intravascular volume favor the use of minimally invasive or non-invasive modalities such as ultrasonography [31]. Techniques such as the pulmonary artery catheter are becoming less popular.

2.3 The role of nitric oxide in intradialytic hypotension
Analyses of plasma from patients identified to be at high risk of IDH suggest that this group may have chronic elevations in plasma nitrites as well as significantly elevated nitrite production [32]. Hemodialysis itself is associated with increased nitric oxide (NO) production [33]. When blood is exposed to hemodialysis membranes, endothelial cells show enhanced expression of inducible nitric oxide synthase (iNOS) mRNA in murine models [34]. In addition, uremic platelets produce increased amounts of NO [35]. It is speculated that cytokines, including IL-1β and TNFα, released during HD by activated mononuclear cells cause activation of NOS. Interestingly, significant increases in NO production are noted in patients who experienced a hypotensive episode during HD when compared to those that did not experience hypotension, suggesting a causal relationship [6]. However, the exact nature of this relationship remains to be elucidated.

NO is produced by two types of NO synthase (NOS) [7]. One exists in the endothelium and is constitutively active (eNOS). The other type is the inducible (iNOS) and exists in various tissues and cell types. Upregulation of iNOS results in increased NO production and generation of cGMP [7]. This can have profound effects on both the vasculature and myocardium.

In end stage renal disease, not only is there in increase in baseline NO production, there is also an increase in inhibitors of NO, namely asymmetric dimethylarginine (ADMA) [36]. It turns out these inhibitors are dialyzable, which suggests that disturbances within the baseline interplay between specific activators and inhibitors during HD may contribute to hemodynamic instability [36, 37]. Direct serum measurements during HD confirm higher nitrate generation, which combined with a decrease in inhibitory factors may lead to IDH.
In addition to the vasodilatory effects of NO, hypotension may also result from NO’s negative inotropic properties [38]. Cholinergic agonists are known to elevate cGMP levels in cardiac myocytes and cGMP analogs may also produce profound negative chronotropic effects [39]. Exposure of cardiac myocytes to carbachol, a cholinergic agonist, results in suppressed contractility and chronotropy as well as profoundly increased levels of cGMP. This effect can be ameliorated by co-administration with methylene blue (MB) which suggests that NO dependent pathways may be involved [39]. Schematic representation of MB mechanism of action as well as pertinent metabolic pathways can be seen in Figure 1.

Fig. 1. Schematic representation of NO/cGMP-dependent pathways. Note the endothelial (eNOS) and inducible (iNOS) isoforms of the nitric oxide synthase (NOS) and their associated functional steps. Methylene blue inhibits (white arrow on right) the action of soluble guanylyl cyclase (sGC) and thus prevents vasodilation. Adapted from Bosoy et al [65].

2.4 Treatment for intradialytic hypotension
Evidence shows that episodes of intra- and post-dialytic hypotension are associated with increased morbidity and mortality [8]. This makes treatment and prevention of IDH an important part of both short- and long-term HD strategy. Several approaches to this problem exist and will be discussed in this section.
At the core of IDH is uncompensated response to reduction in circulating blood volume [40]. The patient may exhibit a blunted response to this reduction or the reduction may be too large to mount an effective response. Active monitoring of the dialysis patient’s blood volume can provide real-time data to the clinician concerning the patient’s volume status. Monitoring usually includes hematocrit, total protein and hemoglobin measurements, which cumulatively provide an estimate of total blood volume [41]. While the physiologic response to blood volume reduction varies considerably between patients, blood volume monitoring allows the clinician to tailor the treatment so the maximal tolerated blood volume changes are not exceeded. Clinical evidence shows that based on blood volume monitoring physicians are able to identify this maximum tolerated blood volume change in approximately 70% of patients, and the majority of hypotensive episodes occurred when this value is exceeded [42]. However, in almost 30% of patients such value could not be determined, suggesting that blood volume monitoring alone may not be sufficient for predicting risk of IDH in all patients. Ultrafiltration rate is also a very important determinant in the incidence of IDH. Altering the ultrafiltration rate to achieve a predetermined blood volume profile can reduce the incidence of IDH [43].

It has also been shown that limiting the reduction in plasma osmolarity during hemodialysis by altering the dialysate sodium concentration can enhance hemodynamic stability. In this paradigm, maintaining higher dialysate sodium concentration facilitates the maintenance of adequate intravascular blood volume [44]. The disadvantage to this method is that the higher sodium concentrations increase the amount of sodium available for exchange and may actually increase weight gain and precipitate hypertensive episodes. As discussed earlier, HD is associated with an increase in core body temperature and concomitant propensity for IDH. Preventing increases in core body temperature allows for a more stable blood pressure throughout the dialysis process [23]. Low temperature dialysate settings (approximately 37-38°C) significantly decrease the severity and frequency of symptomatic IDH [13]. In addition, the low temperature improves capacitance and resistance of peripheral blood vessels and may result in improved cardiac contractility [45]. The use of thermal neutral dialysis reduces the frequency of IDH events by approximately one-fourth.

Several pharmacologic interventions also exist for the treatment of IDH. Midodrine is a prodrug that when metabolized acts as an alpha-1-receptor agonist. It can provide modest increases in both peripheral vascular resistance and cardiac output [46]. It is a well-tolerated medication with the most common side effects being piloerrection, scalp itching/burning and nausea. Caution should be taken when administering midodrine concurrently with negative chronotropic agents including β-blockers, digoxin and calcium channel blockers. Treatment regimens incorporating midodrine on the days of HD result in significant reductions in both intra- and post-dialytic hypotension [47].

3. Overview of methylene blue characteristics

Despite different therapeutic approaches to IDH, a significant proportion of patients undergoing dialysis continue to experience HD-related hypotension. In a quest for effective therapy for IDH, methylene blue (MB) has been evaluated as a potential adjunct in the setting of refractory hypotension. Methylene blue, a “natural pressor”, is an
aromatic chemical compound used in analytical chemistry, biology and medicine. It is a soluble compound that can be administered intravenously or orally/enterally. It functions by inhibiting guanylyl cyclase in vascular smooth muscle, and decreases the levels of cGMP [7, 48-51]. Methylene blue also scavenges nitric oxide and inhibits nitric oxide synthesis [7, 50].

3.1 Pharmacology of methylene blue
Methylene blue is available in both an intravenous and oral form. Both forms undergo primarily urinary excretion with a half-life of approximately 4-5 hours [52]. Small amounts of MB are excreted in bile and feces as well [53]. Distribution appears to differ substantially between the two enteral and intravenous forms. Intravenous administration results in significantly higher concentrations within the blood and brain 1 hour after infusion when compared to the oral route. Bioavailability from oral administration ranges from 53-97% [54]. Oral administration results in much higher concentrations within the bowel wall and liver, with <3% of the administered MB remaining within the intestinal lumen after ingestion. Once in the blood, MB readily enters erythrocytes where it is reduced to leucemethylene blue at low concentrations. In high concentrations it can act as an oxidizing agent, potentially leading to hemolysis, methemoglobinemia and hyperbilirubinemia [53].

Most side effects of MB appear to be dose-dependent and do not occur with doses below 2 mg/kg [55]. Methylene blue can turn urine greenish-blue, and while this may be alarming to patients, it usually resolves within a few days of discontinuing MB. In addition, mild skin discoloration is common, but is self-limiting and treatable with administration of dilute hypochlorite solution [56]. Other side effects may include abdominal pain, nausea, vomiting, headaches, fever, confusion and diaphoresis [54]. Subcutaneous and intradermal injections should be avoided because they have been associated with necrosis and abscess formation [57]. Encephalopathy has been noted in one series that included five patients that received preoperative intravenous MB (3-5 mg/kg in 500 mL saline) for parathyroid adenoma localization. All five cases of encephalopathy occurred in female patients taking serotonin-metabolism modifying agents [58].

In the neonatal and pediatric populations, enteral MB administration of >2 mg/kg has been associated with severe methemoglobinemia, hemolytic anemia, Heinz body anemia, and hyperbilirubinemia [53]. Anemia following MB administration typically manifests within 24 hours, peaks at 4-5 days and can persist for up to 12 days [59]. Furthermore, photosensitive epithelial desquamation after MB administration has been reported among infants undergoing phototherapy. This may be due to lysosomal membrane breakdown after interacting with light in the presence of photosensitizing MB [60]. Practitioners caring for patients receiving MB infusions have to be aware of falsely depressed oxygen saturation readings due to methylene blue interfering with the pulse oximeter’s light emission [61].

3.2 The use of methylene blue in hypotensive patients
Because of its ability to lower plasma levels of the endogenous vasodilator NO, methylene blue has been investigated in the clinical setting of difficult-to-treat hypotension. Investigational studies of MB in various hypotensive settings have been carried out, with some of the most compelling evidence coming from the areas of cardiac surgery, trauma, renal failure, and other forms of distributive shock.
Animal models of acute shock have been developed that facilitate objective testing of the role of MB in various forms of shock. Refractory hemorrhagic shock is seen most commonly in trauma patients and carries a high morbidity and mortality. In canine models, untreated animals usually die within 30 minutes of onset of refractory hemorrhagic shock. When treated with an initial bolus of MB and volume resuscitation the mortality was 0% at 120 minutes, compared to 75% for animals treated with volume resuscitation alone [62]. Animals treated with MB and volume resuscitation maintained significantly higher mean arterial pressures, increased cardiac output, better tissue perfusion, and increased oxygen delivery. Furthermore, MB administration has been associated with significant neurologic and myocardial protective effects during cardiopulmonary resuscitation. This is thought to be due to the effect of MB contributing to improved coronary perfusion pressure and cardiac index, as well as reduced cerebral peroxidation and inflammation [63].

Hepatic failure may also be complicated by vasoplegia and hypotension. Hepatic failure is commonly associated with increased plasma concentrations of endotoxin in addition to other endogenous vasodilators. Moreover, up to 40% of patients with cirrhosis develop hepatorenal syndrome within 5 years of initial diagnosis [64]. Published case reports describe the use of MB in refractory hypotension associated with hepatorenal syndrome, where vasoplegic patients with refractory hypotension were able to become vasopressor free within 5 days of initiation of MB therapy, suggesting a role of increased NO activity in the pathogenesis of hepatorenal syndrome-associated vasopragia [65]. See Figure 2 for a clinical vignette demonstrating MB use in the setting of difficult-to-treat vasoplegia. For additional information regarding clinical uses of MB for hypotension in various clinical settings the reader is referred to Table 1.

Fig. 2. Hemodynamic profile and vasopressor requirements of a middle-aged vasoplegic male patient after methylene blue (MB) administration. The patient experienced profound hypotension refractory to conventional management on day #2 following repair of type A aortic dissection. After the patient became essentially unresponsive to escalating vasopressor support, he received an intravenous injection of 2 mg/kg MB over 30 minutes (A and B, MB administration timing shaded in blue). A) Blood pressure response to MB injection showing increase in both systolic and diastolic blood pressures. B) Vasopressor doses immediately prior, during, and after MB infusion. All vasopressors were weaned completely within 9 hours of MB administration. Legend: MB – methylene blue; Infusion rates – Vasopressin units/min; Epinephrine – mcg/kg/minute; Norepinephrine – mcg/kg/minute; Blood pressure listed in mmHg.
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<th>Author (ref., year)</th>
<th>Clinical Setting</th>
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<td>Peer (67, 1995)</td>
<td>Prospective medical-surgical ICU study involving patients with hypotension refractory to vasopressor therapy (n = 14). MB was given as a bolus (2 mg/kg) over 15 minutes. Additional dose was needed in 6 patients due to transient response to the initial bolus. MB administration was associated with increased mean arterial pressure and systemic vascular resistance. A decrease in serum lactate following MB administration was noted. On non-dialysis days, the bolus dose was given.</td>
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<td>Daemen-Gubbels (68, 1995)</td>
<td>Non-randomized clinical trial involving MB administration in the setting of sepsis. The trial involved consecutive patients with a pulmonary catheter in place (n = 9). MB was administered as an intravenous bolus (2 mg/kg). MB administration resulted in increased mean arterial pressure and increased myocardial function and oxygen delivery. MB use was also associated with increased myocardial function and oxygen delivery.</td>
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<td>Peer (6, 2001)</td>
<td>Investigational study of MB administration in HD patients. (n=41, 18 HD patients with hypotension, 18 HD patients without hypotension, and 5 healthy controls). MB was given as a bolus (1 mg/kg) followed by an infusion (0.1 mg/kg) for 210 minutes until the end of HD session. On non-dialysis days, only the bolus dose was given. In hypotension-prone patients, MB prevented the hypotension during dialysis and increased both systolic and diastolic blood pressure on non-dialysis days. In normotensive patients, MB increased blood pressure during the first 90 minutes of dialysis and during the first hour of non-dialysis and on non-dialysis days. The blood pressure in healthy controls remained unchanged.</td>
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Table 1. Clinical studies and reports describing the use of methylene blue for hypotension in various clinical settings. HD = hemodialysis; MB = methylene blue; NO = nitric oxide.
Table 1. Clinical studies and reports describing the use of methylene blue for hypotension in various clinical settings. Legend: HD – hemodialysis; MB – methylene blue; NO – nitric oxide. (Continuation)

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<th>Author (ref, year)</th>
<th>Clinical Setting</th>
<th>Major results/findings</th>
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<td>Bosoy (65, 2008)</td>
<td>Report describing MB use in vasoplegic patients with simultaneous hepatic and renal failure. One patient received MB bolus (1 mg/kg) followed by another dose of 0.5 mg/kg at 12 hours. Another patient received MB infusion of 1 mg/kg, followed by an enteral-based MB regimen (1 mg/kg every 12 hours).</td>
<td>Both patients experienced significant hemodynamic improvement following MB administration. The first patient was successfully weaned off dual vasopressin-norepinephrine regimen. The second patient was able to leave the hospital and receive palliative care at home due to his ability to be vasopressor-free utilizing enteral (oral) methylene blue regimen.</td>
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<td>Jaskille (69, 2008)</td>
<td>Case series of patients with severe burns (80-95% TBSA, n=2) and persistent hypotension despite simultaneous vasopressin and norepinephrine. Patient received single intravenous infusion (2mg/kg) of MB.</td>
<td>Response to MB noted within 30 minutes. Significant reductions in pressor requirements including complete resolution of vasoplegia within 2 hours in 1 patient.</td>
</tr>
<tr>
<td>Del Duca (70, 2009)</td>
<td>Case series of patients with intraoperative anaphylaxis during cardiac surgery. One case was a reaction to protamine, the other was a reaction to aprotinin. The patients were treated with intravenous MB (2mg/kg).</td>
<td>Both patients had prompt resolution of hypotension and did not require additional doses. There were no adverse effects.</td>
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3.3 The use of methylene blue in hemodialysis and intradialytic hypotension
The use of MB may reduce the incidence of IDH in patients who are prone to this hemodynamic disorder [6]. Initial studies utilized a pre-HD bolus of MB and noticed lower incidence of intra- and post-dialytic hypotensive episodes. When given continuously to hypotension prone patients during HD, episodes of IDH were significantly reduced. Of interest, MB administration to normal controls did not cause appreciable changes in blood pressure, which corroborates the role of nitrate generation during HD as contributory to IDH.

As discussed earlier, there is usually a reduction in circulating plasma nitrates during HD procedure [66]. However, following the procedure certain patients appear more prone to the development of circulating nitrate increases. Among patients who are more prone to develop IDH, a significant increase in nitrate production was noted on post-dialysis day 1 compared to dialysis patients who are not prone to hypotension (1.21 +/- 0.13 µmol/min versus 0.61 +/- 0.11 µmol/min) [6]. In addition, when patients with propensity for IDH were treated with MB during the procedure, their 24-hour plasma nitrate production decreased significantly compared to untreated individuals, further supporting the role of NO production and cGMP mediated pathways for the development of IDH.

4. Conclusions
Intradialytic hypotension continues to be a significant challenge. Despite multiple therapies, no single agent or modality has been proven universally effective in the management of IDH. For patients who are refractory to traditional therapies (fluid infusions, vasopressor administration, modification of ultrafiltration rates) adjunctive treatments may hold promise. One of those approaches is the use of methylene blue, an inhibitor of guanylyl cyclase in vascular smooth muscle, as well as nitric oxide synthesis inhibitor and scavenger. Although early research in this promising area is encouraging, further investigation is needed before more widespread implementation of this therapy is undertaken.

5. References


The book provides practical and accessible information on all aspects of hemodialysis, with emphasis on day-to-day management of patients. It is quite comprehensive as it covers almost all the aspects of hemodialysis. In short it is a valuable book and an essential aid in the dialysis room.

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