Intestinal-Renal Syndrome: Mirage or Reality?

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Myocardial stunning · Endotoxin · Hemodialysis · Cardiovascular stability

Abstract

The recent interest in the role of the intestine in the cardiovascular stability of uremic patients, specifically on dialysis, but potentially also in chronic kidney disease, must be seen against the background of the recent great interest in the role of the gut in chronic heart failure [Curr Opin Clin Nutr Metab Care 2008;11:632–639]. There has been a long-standing interest in the role of the intestine in renal failure, mainly concerning the role of metabolites of bacterial metabolism in the gut as potential uremic toxins. This area has recently been given a new twist by the finding that increased endotoxin concentrations in the blood of dialyzed patients are associated with hypotensive episodes and myocardial ‘stunning’. Recent studies suggest that intradialytic underperfusion of myocardial areas, the so-called stunning, may be related to the entry of bacterial endotoxin and/or cytokines across the mucosal barrier into the circulation, where they have a negative impact on myocardial function (and presumably beyond the negative cardiac side effect also contribute to catabolism and malnutrition). Entry of bacterial endotoxin during dialysis sessions is presumably the result of intermittent underperfusion of the intestine if the effective blood volume is rapidly reduced causing breakdown of the

mucosal barrier. Apart from the impact on myocardial perfusion, the entry of bacterial endotoxin and/or cytokines across the mucosal barrier may also contribute to malnutrition, wasting and reduced life expectancy in hemodialyzed patients. Such a causal relationship is absolutely plausible in view of an extensive literature on congestive heart failure where clinical and experimental evidence indicates that bacterial endotoxin and/or cytokines may escape from a hypoperfused edematous gut, entering the circulation, triggering an inflammatory response, upregulating circulating cytokines and interfering with the function of the heart through several pathogenic mechanisms.

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The Gut Contributes to the Uremic Syndrome

Decades ago, nephrologists were convinced that ‘products of intestinal putrefaction’, specifically indican, were found in the blood of patients with ‘renal insufficiency’ and played an important role in the symptomatology of renal insufficiency [1]. Volhard and Becher [2] had shown that the concentration of indican, a tryptophan-derived oxidation product of indol, was higher in the blood of uremic patients than in controls, and that in addition, several other aromatic bodies are found such as phenols, cresols or aromatic oxyacids yielding strong thiazole and xanthoprotein reactions.

As time has gone by, the intestine went somewhat out of the focus of nephrologists, leading to the recent well-justified statement that the gut has become a 'forgotten organ in uremia' [3]. The authors specifically pointed to the potential toxicity of cresol and indol products. P-cresol is absorbed in the intestine, transformed to p-cresyl-glucuronide, further modified in the liver to p-cresyl-glucuronate and finally cumulates in the blood of uremic subjects. This may be of potential importance because it would be in line with the known proinflammatory effects of cresol on monocytes and lymphocytes [4] and the known correlation between cresol and overall mortality [5] as well as cardiovascular disease in hemodialysis patients [6] and their uremic symptoms [7]. Indol, another intestinal product well known for a long time, is generated by the bacterial flora from tryptophan. It has also been speculated that accumulated indol displaces tryptophan from the albumin in the blood of uremic patients [8]. Indoxylsulfate is again proinflammatory [9], interferes with endothelial cell function [10], impacts on progressive loss of renal function [11] and potentially even on dialysis outcome [12]. It is of interest that in small pilot studies, intestinal absorption of indoxylsulfate by Kremezin has caused a delay of the start of dialysis [13] and was also associated with better dialysis outcomes [14]. The potential delay of onset of uremia is currently investigated in a controlled prospective trial with Kremezin [15].

The potential impact of uremia on gut function and its potential pathogenetic role is further complicated by the fact that in uremic patients duodenum and jejunum (which are normally not colonized by bacteria) are heavily colonized by aerobic and anaerobic bacteria [16]. This finding is of particular importance in view of the impaired function of the intestinal barrier in uremia. Both in uremic animals [17] and in uremic patients [18], the intestinal wall becomes leaky as documented by the penetration of polyethylene glycols of different molecular weights across the intestinal wall [17]. At least in animal experiments, escape of bacteria across the intestinal wall has been documented [19]. In subtotally nephrectomized rats, bacteria were retrieved from mesenteric lymph nodes [19]. A related problem is the frequent chronic inflammation of the gastrointestinal tract (esophagitis, gastritis, duodenitis, enteritis and colitis) with hemorrhagic ulcerative and pseudomembranous lesions in chronic hemodialysis patients [20].

One approach to reduce the cumulation of the above putrefactive metabolites in feces and plasma in uremic patients consisted of administering antibiotic-resistant

lactic acid bacteria, which caused a significant decrease in the fecal and plasma concentrations of indican [21].

Another effort was to use the gut as a therapeutic target and transform the bowel into a 'substitute kidney'; efforts to use colonic gavage and somewhat more effective efforts to bind nitrogen compounds to solvents (charcoal, oxystarch) failed to yield impressive results [22, 23].

A further effort that used probiotic dietary supplementation in CKD stage 3/4 patients with nonpathogenic soil-borne urease-positive bacteria (*Sporosarcina pasteurii*) to hydrolyze urea within the gut caused some significant lowering of plasma urea concentrations [24]. An alternative procedure in subtotally nephrectomized uremic rats was the use of genetically engineered microencapsulated *Escherichia coli* expressing urease; in the intestine, urea diffused into the microcapsules and was enzymatically broken down [25].

Does Intestinal Malperfusion during Dialysis Interfere with Cardiac Function and Integrity?

The role of the gut in renal failure has been given an entirely new twist by recent findings that disturbed perfusion of the gut during dialysis sessions may impact on cardiovascular stability and may affect the long-term outcome of renal replacement therapy.

Zuber et al. [26] noted a high incidence of arrhythmia and silent ST depression which he ascribed to cardiac ischemia in patients during hemodialysis sessions. Later on, London et al. [27] emphasized the propensity of the dialyzed patient to undergo reduction of subendocardial blood flow. Undoubtedly, many factors contribute to the hemodynamic instability on hemodialysis, e.g. diastolic cardiac malfunction [28] and capillary deficit [29], and undoubtedly other factors, e.g. altered aortic compliance [30], autonomic dysfunction and specifically reduced baroreceptor sensitivity, contribute to the high cardiac risk [31, 32]. It was reported early on that painless myocardial ischemia may occur in the absence of angiographically proven coronary artery disease and be associated with ventricular arrhythmias [33, 34]. These and other findings led to the concept that traditional explanations cannot fully explain the cardiac changes during dialysis, and that may indeed be caused by novel forms of intradialytic forms of microvascular ischemia [35]. A look at what was going on in cardiology helped to provide one explanation.

A relatively new concept in cardiology addressing the issue of the reaction of the heart to inadequate perfusion

provided a suggestive explanation for regional cardiac malfunction during dialysis sessions in the absence of myocardial infarction. After brief coronary occlusion, dogs exhibited regional alterations of myocardial function and electrophysiological performance in the absence of myocardial infarction [36]. Subsequently, in 1982 Braunwald and Kloner [37] introduced the concept of 'myocardial stunning': he argued that prolonged ischemia which fails to produce necrosis may nevertheless interfere with myocardial function, biochemistry and ultrastructure. Such malfunction can persist after the return of normal perfusion. When repeatedly stunned, the myocardium will undergo left ventricular (LV) dysfunction with impaired contractile performance and progress to myocardial scarring. In humans, the occurrence of cumulative myocardial stunning with repeated episodes of ischemia was documented by Barnes et al. [38].

Such stunning has meanwhile indeed been documented [35, 39–44]. Myocardial ischemia was documented with a state-of-the-art technique ($^{15}\text{H}_2\text{O}$), and segmental LV dysfunction was measured by echo and matched reduction in segmental myocardial blood flow. This was associated with regional wall motion abnormalities, and the long-term consequence was reduced LV function [41].

In preliminary communications, it was found that stunning was correlated with increased plasma endotoxin concentrations. This raises the issue of underlying pathomechanisms, and in this context it is rewarding to look over the fence and watch which role cardiologists have recently identified for underperfusion of the intestine and endotoxin in patients with heart failure.

Emerging Role of the Gut in Chronic Heart Failure

Cardiologists have known for considerable time that in animal models of heart failure and in patients with chronic heart failure, disruption of intestinal function and consecutive translocation of Gram-negative bacteria or lipopolysaccharides (LPS) as well as cytokines cause cardiac malfunction [45]. LPS are wall components of Gram-negative bacteria and are one of the strongest inflammatory triggers known. When bacterial endotoxin enters the blood stream, an inflammatory response is triggered secondary to the generation of cytokines in the intestinal wall or within the organism. Both in experimental models of heart failure and in patients with chronic heart failure [46–48], elevated concentrations of such proinflammatory cytokines, particularly TNF- α , IL-1 and IL-6 [49], have been documented. They exert their

cardiosuppressive effects primarily by altering myocardial intracellular calcium, reducing mitochondrial activity, causing imbalance of autonomic nerve activity and disrupting many other functions.

This sequence of pathological events is not restricted to chronic heart failure. It has also been found in animal models and in patients with sepsis, liver cirrhosis, ischemia reperfusion after burns, and intestinal ischemia with resulting cardiac malfunction caused by increased intestinal permeability. In patients with acute heart failure, the intestinal origin of LPS was directly documented by the finding that the concentration of active LPS was higher in the hepatic vein than in the left ventricle [50].

As had been documented in heart failure, blood flow is presumably shunted away from the splanchnic region during hemodialysis as well [51]. When in states of diminished effective blood volume blood is shunted away from the splanchnic circulation, because of the villous countercurrent circulation, ischemia is particularly pronounced at the tips of the villi; as a result, hypoxia is most pronounced at the villous tips [52]. The outcome of mesenteric ischemia spans the spectrum from functional impairment to ischemic necrosis of the gut. Riddington et al. [53] were able to document local hypoxia and acidosis in the intestine of patients undergoing cardiopulmonary bypass surgery, and presumably similar changes may occur during dialysis sessions.

In states of intestinal underperfusion, the paracellular permeability of the intestinal wall is increased as a result of hypoxia and local production of LPS [54]. This permits leakage of LPS into the circulation as documented in patients with chronic heart failure and LV ejection fraction <40% [55]. At least under normal circumstances, bacterial colonization is highest in the colon, although this may no longer be true in uremia [16]. In heart failure, the perfusion of the colonic wall is particularly compromised as shown by thickening of the bowel wall and increased permeability of marker substances. In experimental uremia, increased intestinal permeability has been demonstrated as well [56]. In patients undergoing surgery for aortic aneurysms, a decreased sigmoidal intramucosal pH has been documented [57]; in addition, higher bacterial numbers in the mucosal biofilm were noted as well as increased wall thickness [58]. The most vulnerable part of the colon is presumably the right colon: it has lower collateralization and longer vasa recta. The intestinal mucosal barrier is composed of several components: mucus layer, epithelial cell barrier, basement membrane and immune cells in the intestinal wall; so far, it has not been specified which component is mainly involved in the increase in permeability.

It is currently unclear whether it is always the microbes that enter the circulation or whether microbes – adhering to or penetrating through – the intestinal epithelial cells release LPS and/or trigger cytokine release even if bacteria fail to escape into the circulation.

What are the mechanisms by which LPS and/or cytokines reduce cardiac contractility [59–63]? Many pathomechanisms have been identified; both LPS and cytokines, particularly TNF- α and IL-6, have been implicated: LPS decrease Ca²⁺ oscillations and the hypopolarization-activated nonselective cation current (I_f) in cardiomyocytes [Wordergem, in press]. In experimental models of endotoxin shock, activation of the PGI(2)/IP system contributes to the development of circulatory failure [64]. The known endotoxin-induced Ca²⁺ leak from the sarcoplasmic reticulum [65], an early event, leads to subsequent mitochondrial and myocardial dysfunction; in the experimental model of LPS injection to SD rats, administration of dantrolene (an inhibitor of the sarcoplasmic Ca²⁺ leak) prevented mitochondrial calcium overload as well as malfunction of the heart and reduced myocardial function [66].

When cardiomyocytes are exposed to LPS, nitric oxide and cGMP are increased [67, 68]. This effect is mediated by the Toll-like receptor 4 [69]. The result is depression of excitation depression coupling and of the peak velocity of cardiomyocyte shortening [59, 70]. Further abnormalities of cardiomyocytes have been documented, e.g. disturbed mitochondrial respiration [71, 72], reduction in resting membrane potential, Na⁺, K⁺ gradient and impaired substrate metabolism [73], increased expression of metalloproteinases and their inhibitors [74], decreased adrenergic responsiveness [75] and many others.

Proinflammatory cytokines, both TNF- α and IL-6, also cause myocardial malfunction. Elevated levels of TNF- α [76] are found in the circulation of patients with heart failure, and TNF- α concentration is correlated with the severity of cardiac malfunction. TNF- α acts as a cardiodepressant by several mechanisms, e.g. sphingosin release and suppression of the Ca²⁺ transient, reduced mitochondrial function via inhibited phosphoinositol pathway and pyruvate dehydrogenase activity and increased peroxynitrate production. In parallel, TNF- α receptors (TNFR1 and 2) are upregulated; their potential relevance is suggested by the fact that TNFR1 is a good predictor of prognosis [77] and of cardiac malfunction [78]. Disappointingly, a controlled trial (ATTACH) in patients with chronic heart failure testing a specific anti-TNF- α strategy using a chimeric monoclonal antibody to TNF- α has

been unsuccessful [79] as was a study (RENEWAL) using etanercept [80].

IL-6 is a potent stimulant of acute-phase proteins and has pleiotropic effects on cardiac and endothelial functions. It causes refractoriness of the heart to adrenalin [81], decreases cardiac function [82] and triggers cardiomyocyte apoptosis [82]; IL-6 concentrations are correlated with prognosis [83, 84].

The above disappointing result of specific selectively antagonizing cytokines is potentially explained by a role of further alternative cytokines or an unfavorable cytokine/anticytokine balance. Against the background of the above studies addressing specific agents, there have also been efforts to assess nonspecific immunomodulation, e.g. ex vivo exposure of autologous blood to controlled oxidative stress with subsequent intramuscular administration; in the ACCLAIM study, such immune modulation yielded positive results at least in some specific subgroups [85].

It would be too narrow to focus exclusively on the heart. As an example, in patients with multiorgan dysfunction syndrome extensive alterations of the autonomic nervous system have been documented [86] which predicted mortality [87].

What Is the Evidence for a Role of Intestinal Bacteria or Their Products in Cardiocirculatory Instability during Hemodialysis Sessions?

Currently, in dialyzed patients many loose ends are left in the documentation of the individual steps in the sequence from escape of bacteria, LPS or cytokines from the hypoperfused intestine into the circulation to the triggering cardiac malfunction. This will be an important task for the future.

Currently, we lack definite documentation of reduced mucosal blood flow in the intestine by valid methods such as tonometry [88].

The demonstration of intestinal bacteria and LPS in blood may be tricky because of their short and variable half-lives in the circulation. The quantitation of gut-derived LPS in peripheral blood is also confounded by the fact that bacteria or LPS escaping from the gut have to pass through the hepatic circulation where they may be trapped. The long-term endotoxin burden may therefore be more specifically reflected by measuring specific anti-LPS IgA in the circulation [45].

Which Strategies Are Available to Prevent Escape of Intestinal Bacteria and/or Cytokines during Hemodialysis Sessions?

What strategies are available to prevent or reduce escape from the intestine of bacteria and/or cytokines? Apart from the obvious, i.e. maintaining circulatory stability during hemodialysis sessions, thus avoiding circulatory compromise and intestinal underperfusion, specific strategies of intervention would be desirable to prevent intestinal leak and to avoid the unwelcome consequences of endotoxin(s) and cytokines in dialyzed patients. To develop such strategies, it may be useful to look across the fence and watch what is going on in the field of cardiology.

Which strategies have been used in heart failure? Selective digestive decontamination of the gut before cardiopulmonary surgery reduced levels of LPS and proinflammatory cytokines [89]. While this provided proof of the principle, it is not an exciting option in chronic dialysis. Because of its anti-inflammatory properties and its documented effect to increase blood flow, LPS N-acetyl cysteine has become a candidate to reduce the sequelae of intestinal ischemia [45].

Recently, in the EUPHAS trial with overtly septic patients with intra-abdominal infection removal of endotoxin by polymyxin B hemoperfusion, on top of conventional therapy, improved hemodynamics and organ dysfunction. In addition, the criteria of the inflammatory response syndrome were reduced as was the 28-day mortality [90–92]; however, this technique has not been tested specifically in patients with presumed intestinal leak and translocation of bacteria from the gut into the circulation.

It will be rewarding for nephrologists to watch the current activities in heart failure research and to explore to what extent they may be relevant to the fight against intestinal leak problems in patients on HD.

The presumed link between (short) dialysis sessions and intestinal malperfusion may provide another argument to extend the duration of hemodialysis sessions in order to prevent absolute or relative hypovolemia with hypothetical mesenteric underperfusion. The presumed mechanism discussed above may explain, at least in part, the low mortality in long and slow dialysis programs [93–95].

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