The importance of the gastrointestinal system in the pathogenesis of heart failure

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Chronic heart failure (CHF) is a multi-organ disease with increasing evidence for the involvement of the gastrointestinal (GI) system in this syndrome. In recent research, the gut has received very little attention from cardiologists as its role in the pathogenesis of cardiovascular disease is poorly understood. Intestinal ischaemia may play an important role in bacterial translocation by increasing bowel permeability. Decreased cardiac function can reduce bowel perfusion and so clearly impairs the function of the intestinal barrier. There is an increasing evidence to suggest that a ‘leaky’ bowel wall may lead to translocation of bacteria and/or endotoxin, which may be an important stimulus for inflammatory cytokine activation in CHF. Impaired functioning of the GI system may also contribute to malnutrition and cachexia in CHF. It is hoped that by improving our understanding of the role of the gut in cardiac disease will lead to the development of novel therapeutic strategies in the future.

Methods

To identify relevant publications, we searched MEDLINE from 1966 to present, combining the textual terms ‘heart’, ‘circulation’, or ‘heart failure’ with ‘gut’, ‘intestine’, or ‘endotoxin’. We also searched the reference list of identified papers. Papers were considered for inclusion in the review if they focused on interactions between the gut and the heart or on special aspects of the pathogenesis of heart failure.

The regulation of bowel perfusion

The small and large intestines are highly vascularized, the main blood supply being via the superior and the inferior mesenteric arteries, with the venous blood pooled in the portal system. The splanchnic circulation normally receives approximately one-quarter of the cardiac output, which makes the gut the most intensively perfused organ at rest. The gut mucosa has an enormous surface area for absorption (~100 m²) created by villi and microvilli. The gut mucosa is the metabolically active area in the gut and receives well over half of the total resting organ blood flow. The small intestinal villi are oxygenated via a countercurrent circulation whereby a central, small artery diffuses oxygen across to the parallel submucosal veins. At low flow rates, a substantial fraction of the O₂ may be shunted from arterioles to venules near the base of the villus. As a result of this anatomical configuration, the tips of the villi have the lowest tissue oxygen tension (pO₂), and ischaemia to this area may be induced by relatively small changes in blood flow. In situations of physical stress and hypovolaemia, the rich sympathetic nerve supply to the splanchnic bed causes

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constriction in the pre-capillary resistance vessels and post-capillary capacitance vessels resulting in prolonged reduced splanchnic perfusion. These vascular changes can occur prior to alterations in heart rate, blood pressure, and cardiac output. During sepsis, regional hypoperfusion may be present in the hepatosplanchnic region, even when global haemodynamic and oxygen-derived variables appear adequate.

**Measurement of bowel perfusion**

In humans, the methods for assessment of splanchnic blood flow and diagnosis of gut ischaemia include endoscopy, duplex ultrasound, angiography, hepatic vein catheterization, laser Doppler flow measurement, and intestinal tonometry. Of these, tonometry is the simplest and most practical for clinical use. It is a relatively non-invasive monitoring method to assess the adequacy of splanchnic perfusion and aerobic metabolism. Currently, the most viable method of reliably measuring GI luminal CO2 levels in the clinical setting is by using automated air tonometry, which is a semi-continuous method of sampling gastric balloon air with infrared measurements of pCO2. Cellular CO2 levels depend on the balance between CO2 production via both aerobic and anaerobic metabolism and CO2 removal by blood flow from the particular tissue bed and alveolar ventilation. CO2 elimination by the lungs depends upon alveolar ventilation and perfusion, which determines how much returns to the cells in arterial blood, i.e. the CO2 content in the efferent vessels of the mucosa. Tissue CO2 therefore reflects a subtle balance gut metabolism, perfusion, and lung function.

A controlled, multi-centre study indicated that critically ill patients (25% of whom had heart failure) with an initially normal gastric intramucosal pH (pHi) could benefit from therapeutic interventions guided by tonometry, as their mortality rate was lower than that in controls in which pHi was not used to guide therapy. Interventions consisted of infusions of dopamine or dobutamine, bicarbonate, saline boluses, or red blood cell transfusions. Such studies have not been reported for patients with heart failure alone, but may be worthwhile particularly in the setting of cardiogenic shock.

Low gastric intramucosal pHi has been reported as being a predictor of major complications after cardiac surgery and aortic surgery. Gastric mucosal tonometry is able to detect hypovolaemia during cardiopulmonary bypass and can be used as an indirect marker of cardiac output.

**Cardiac causes of impaired bowel perfusion**

In intensive care patients, inadequate splanchnic perfusion is associated with increased morbidity and mortality. A low cardiac output syndrome with tissue hypoperfusion is an infrequent but serious complication of coronary artery bypass surgery. Regional tissue hypoxia may develop despite apparently stable haemodynamics, as suggested by episodes of gastric mucosal acidosis, in up to 50% of patients after cardiac surgery. The gastric mucosal pH continues to decrease, reaching its minimum 5 h post-operatively. This suggests that a regional mismatch between oxygen delivery and demand may persist after the stabilization of systemic haemodynamics.

**Therapeutic improvement of bowel perfusion**

It has been suggested that angiotensin-converting enzyme (ACE) inhibitors can improve gut perfusion (as measured by gastric tonometry) in critically ill patients and that this effect appears to be independent of changes in systemic cardiac function. In one open study, 18 patients received 0.625 mg enalaprilat as a single dose intravenously. The intramucosal–arterial pCO2 difference was improved after enalaprilat administration.

**Mucosal ischaemia and ischaemia–reperfusion injury**

Ischaemia–reperfusion injury is of paramount importance in situations where there is an interruption in blood supply, as occurs in the vascular surgery of the abdominal aorta or of vessels which supply the gut. Incomplete splanchnic cellular resuscitation has been associated with the development of multiple organ failure and increased mortality in critically ill patients. Ischaemia–reperfusion injury can diminish the barrier function of the gut and can promote an increase in the leakage of molecules (intestinal permeability) or the passage of microbes across the wall of the bowel (bacterial translocation). Ischaemia–reperfusion injury to the gut can also result in the generation of molecules that may harm systemic tissues. Yassin et al. investigated the effect of limb ischaemia–reperfusion injury to the lower limb on the bowel in Wistar rats. Their data suggest that reperfusion of acutely ischaemic extremities produces structural and functional changes in the small intestine (i.e. decreased mucosal thickness, villus height, and crypt depth). This has not yet been studied in humans with peripheral vascular disease.

**Intestinal permeability**

The intestinal epithelium functions as a selective barrier that permits the absorption of nutrients, electrolytes, and water, but prevents the entry of toxins, antigens, and micro-organisms from the lumen into the systemic circulation. In 1972, the terms 'tight' and 'leaky' were introduced for epithelia demonstrating different permeabilities, as indicated by the electrical resistance of the paracellular pathway. In the intestine, it is the epithelial cell layer that constitutes the principal barrier to permeability through which molecules pass either by paracellular (via tight junctions) or by transcellular route (Figure 1). Inflammatory cytokines, physical factors (such as osmotic stress), drug therapy (such as non-steroidal anti-inflammatory agents), and malnutrition can increasingly alter gut permeability through their action on tight junctions. Furthermore, bacterial colonization of the gut has effects on bowel permeability. Colonization with *Escherichia coli*, * Klebsiella pneumonia*, and *Streptococcus viridans* significantly increases bowel permeability, whereas colonization with *Lactobacillus brevis* has been shown to have the opposite effect.

**Bacterial translocation and endotoxaemia**

Gut barrier function is maintained by a well-balanced intestinal flora, an intact mucosa, and a normal functioning immune system. If one or more of these three protective mechanisms are disrupted, viable bacteria (or bacterial products like endotoxin (i.e. lipopolysaccharide, LPS)) may cross the gut mucosa and spread to the mesenteric lymph nodes or more distant organs, such as the liver and the spleen, a process termed bacterial translocation. Three mechanisms have been suggested to explain the phenomenon of bacterial translocation: altered intestinal barrier function, bacterial overgrowth, and impaired host defence. Although bacterial translocation is widely considered a pathological and potentially harmful phenomenon, translocation of gut bacteria appears to be common early in life and may be important for mucosal antigen sampling in the gut.

Mechanistically, in bacterial translocation, bacteria initially attach themselves to intestinal enterocytes, the cell membranes of the latter then rupture, and this allows bacteria to penetrate and reach the basal membrane. Once this has taken place, intestinal lymphatic drainage carries bacteria to the mesenteric lymph nodes from where they can spread to other organs and tissues. Bacterial translocation has been reported in a variety of conditions including total parenteral nutrition, haemorrhagic shock, pyrexia, coronary artery revascularization, and aortic clamping in patients undergoing abdominal aortic surgery. All these conditions can occur in patients under the care of cardiologists.
**Therapeutic reduction of bacterial translocation**

The two methods for attenuating the process of bacterial translocation are by stimulating intestinal motility (e.g. with propranolol)\(^3^6\) or by the treatment of bacterial overgrowth (e.g. with antibiotics or lactobacilli). Furthermore, allopurinol has been shown to reduce bacterial translocation following haemorrhagic shock in rats, which is thought to be due to an inhibition of the reperfusion injury mediated by xanthine oxidase-derived oxidants.\(^3^7\)

Sorkine et al.\(^3^8\) examined whether gut decontamination, which reduces the amount of bacteria in the bowel lumen, can modulate or prevent acute lung injury which often follows intestinal ischaemia. They found lower serum levels of endotoxin (0.09 ± 0.005 vs. 0.33 ± 0.005 EU/mL; \(P < 0.01\)) and TNF (56.2 ± 6 vs. 173 ± 56 pg/mL; \(P < 0.01\)) in the decontamination group.

**Endotoxin**

The lipid A domain of LPS is a unique, glucosamine-based phospholipid that constitutes the outer monolayer of the cell membrane of most gram-negative bacteria (Figure 2). Lipid A is also known as endotoxin. One single bacterium contains ~2 × 10^6 lipid A molecules and 2 × 10^7 glycerophospholipids.\(^4^0\) Many of the effects of endotoxin are secondary to the production of cytokines, such as TNF\(_{\alpha}\) and IL1\(_{\beta}\), by macrophages. Endotoxaemia frequently occurs in the absence of gram-negative bacteria. This indicates that it cannot be assumed that circulating endotoxin is always derived from gram-negative bacteria in the circulation, and therefore, that the types of endotoxin causing inflammation or sepsis may not reflect the species of gram-negative bacteria isolating during bacteraemia. In addition, endotoxin can persist in the circulation.
after host defences and/or antibiotics have rendered blood cultures negative. In a study by Brunkhorst et al.,13 38 patients with cardiogenic shock showed evidence of endotoxaemia, but none had positive bacterial cultures.

Endotoxin in cardiac patients

With respect to cardiac diseases, the role of endotoxin has been examined primarily in the context of studies on the aetiology of coronary artery disease and on cardiopulmonary bypass surgery (CPB). The association between bacteria and presence of arteriosclerosis has been hypothesized more than a decade ago.42 This leads to several studies using antibiotics to prevent coronary artery disease and its complications. The results of recent large-scale studies are discouraging.43 More mechanistic studies have lead to a shift of focus from bacteria to endotoxin as an important factor in the development of arteriosclerosis. Wiedermann et al.44 reported that patients with the highest decile of LPS levels showed a increased risk of developing carotid arteriosclerosis. It was also found that a polymorphism of the Toll receptor 4, which is the receptor for endotoxin of gram-negative bacteria, related to a lower frequency of coronary artery disease.45 This polymorphism causes a functionally inefficient subtype of the endotoxin receptor, suggesting that protection against mediated effects also protects against development of coronary artery disease.

In CPB surgery, endotoxin may be present in the extracorporeal circuit or may be translocated across the intestine secondary to non-pulsatile, low-flow perfusion.46 Splanchnic vasoconstriction during cardiopulmonary bypass can result in gut mucosal ischaemia, which could lead to changes in intestinal permeability and endotoxin release into the circulation.47,48 These studies have generally demonstrated only transient low-level endotoxaemia during CPB, with rapid resolution following completion of CPB in the majority of patients.49

Lequier et al.50 examined the potential role of endotoxin in the pathogenesis of cardiac dysfunction in children with severe congenital heart failure, both prior to and following CPB. It was found that higher LPS levels related to worse survival after corrective surgery. We have recently been able to show raised LPS levels in patients with grown-up congenital heart disease, which related to clinical severity and raised inflammatory cytokine in serum.51 In addition, Lequier et al. also measured the plasma levels of lipopolysaccharide-binding protein (LBP), which increases in response to endotoxin.52 In contrast to LPS, LBP is a plasma protein with a relatively long half-life and can be reliably assayed by enzyme-linked immunosorbent assay. In a study by Niebauer et al.4 LBP levels did not differ between healthy volunteers and oedematous and non-oedematous CHF patients, respectively. Niebauer showed that endotoxin concentrations and pro-inflammatory cytokines are raised in patients with CHF who have peripheral oedema. The raised endotoxin concentrations were normalized by intensified diuretic treatment. The increase of LPS in CHF patients in NYHA class IV patients was recently confirmed in a second study.53 This study demonstrated that LPS levels as found in CHF patients, ex vivo, can stimulate a strong inflammatory response in whole blood. Von Haehling et al.54 recently have shown that the cellular responsiveness to LPS in CHF patients and controls is to some degree age dependent.

Exercise and the gut

It has been reported that at maximal exercise intensity, the flow may be reduced to 20% of the resting value in both trained and untrained people.55 Sympathetic output plays an important role in redistributing blood flow during exercise. Splanchnic blood flow may be decreased to critical levels during maximal stimulation. As a result, GI motility, intestinal absorption, and mucosal integrity can be disturbed.56 This may be a cause for exercise-induced abdominal symptoms and bacterial translocation.

Influence of heart failure to the GI system

GI protein loss is common in patients with right heart failure, especially in congenital heart disease. In some cases, these patients show the syndrome of protein-losing enteropathy, characterized by clinical symptoms of hypoproteinaemia, like oedema, effusions, and so on, as well as raised levels of faecal alpha-1-antitrypsin.57 Protein loss from the gut might contribute to the syndrome of cardiac cachexia. Further causes for wasting in CHF patients may be anorexia, malabsorption, and mental depression.60 However, neurohormonal activation with chronic inflammation may play the biggest role in cardiac cachexia. Recent studies have shown that the degree of body wasting is strongly correlated with neurohormonal and immune abnormalities, and weight loss is independently linked to impaired survival of patients with CHF.51

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Future directions and therapeutic options

We have hypothesized that bacterial endotoxin is of pathophysiological relevance in patients with heart failure.1 Table 1 summarizes possible directions for future research. Several potential mechanisms through which therapeutic agents may be directly or indirectly effective against endotoxin have already been studied.

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<th>Table 1</th>
<th>Topics for future research in heart failure and immune activation</th>
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<td>Topic</td>
<td>Rationale, possible agents</td>
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<tr>
<td>Reducing oedema and bacterial translocation</td>
<td>ACE-inhibitors, ARB</td>
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<td>Reducing intestinal bacterial load</td>
<td>Selective decontamination of the gut using antibiotics; application of Lactobacilli</td>
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<td>Reducing circulating endotoxin</td>
<td>Binding endotoxin by micelle forming substances, e.g. Lipoproteins, BPI</td>
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<td>Inhibition of TNF-alpha</td>
<td>Pentoxifylline, thalidomide, anti-TLR4 antibodies</td>
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<td>Anticytokine therapy</td>
<td>Identifying subgroups of patients who will benefit from anti-TNF antibody therapy, e.g. those with proven high TNF levels (like patients with cardiac cachexia)</td>
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<tr>
<td>Anti-inflammatory therapy</td>
<td>Statins (especially those not lowering plasma lipoprotein levels); allopurinol</td>
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ARL, angiotensin receptor blockers; TNF-alpha, tumor necrosis factor-alpha; BPI, bactericidal/permeability-increasing protein; statins, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors.
Improving splanchnic blood flow
In healthy volunteers, one study has shown increased intestinal blood flow after ingestion of 50 mg captopril when compared with vitamin C in 12 subjects. In critically ill patients, we have previously described the reports of Kincaid et al. (using enalapril applied intravenously) and Gutierrez et al. (using tonometry to guide intensive care). Maynard et al. found an increase in splanchnic blood flow after dopexamine infusion. The effectiveness of positive inotropic drugs or those improving endothelial function (like statins) is not known and could be assessed using parameters of regional perfusion, e.g. lactate levels, diuresis, and regional pCO₂.

Reducing bacterial translocation and endotoxaemia
Gennari et al. have shown a reduction of bacterial translocation in endotoxaemic rats after the application of enalapril. Selective decontamination of the gut could prevent ICU-acquired infections in humans. Allopurinol has been shown to reduce bacterial translocation in rats, probably by reducing the oxidative damage caused by the activity of local xanthine oxidase.

Interestingly, treatment with growth hormone (GH) and IGF-I in rats with experimental obstructive jaundice reduces bacterial translocation and improves liver histology. This lead to a reduction of endotoxaemia. The application of GH has not yet been proved successful in CHF patients. The application of IGF-I has not been tested yet. Particularly, in patients with cachexia, treatment with GH and/or IGF-I may have importance, causing an anabolic stimulus and possibly also beneficial immunological effects.

Binding endotoxin
Antibodies targeted directly against endotoxin have been investigated in sepsis in major trials with disappointing results. The other approaches to bind endotoxin with high-density lipoproteins or bactericidal/permeability-increasing protein may be more promising.

Focus on CHF
There is increasing evidence that endotoxin may be an important stimulus for the production of TNF in the context of CHF. Endotoxin is known to induce the liberation of TNF from isolated peripheral monocytes, cardiomyocytes, and myocardial fibroblasts in vitro. Increased circulating levels of soluble CD14 receptors (which reflect previous monocyte/macrophage endotoxin interaction) have been demonstrated in patients with CHF. More evidence for the role of LPS as a mediator of immune activation in CHF comes from a prospective study by Niebauer et al. on the effects of diuretic therapy on LPS and cytokine levels in CHF patients with an acute oedematous exacerbation. Prior to diuretic treatment, levels of endotoxin and inflammatory cytokines were significantly higher than in healthy control subjects, with endotoxin levels falling to within the normal range after intensified diuresis, which is thought to be due to decreased intestinal wall oedema. In addition, it was found that CHF patients with acute decompensation showed higher levels of endotoxin in the hepatic vein when compared with the left ventricle. This suggests that the increased endotoxin levels in CHF patients indeed have their origin in the gut. A further study looked at possible splanchnic hypoperfusion in CHF patients using gastric tonometry. When compared with age-matched controls, CHF patients showed a significant increase in gastric pCO₂ during exercise stress testing, suggesting presence of intestinal mucosal ischaemia.

Conclusion
CHF is a multi-system disorder with abnormalities in the cardiovascular, renal, musculoskeletal, neuroendocrine, and immune systems. To date, there has been relatively little research into the role of the gut in the pathogenesis of this syndrome. There is increasing evidence to suggest that a ‘leaky’ bowel wall may lead to translocation of bacteria and/or endotoxin, which may be an important stimulus for inflammatory cytokine activation in CHF. Furthermore, decreased cardiac function can contribute to reduce bowel perfusion and thereby impair the function of the intestinal barrier, leading to a vicious circle. Recent studies have shown that intestinal ischaemia may play an important role in bacterial translocation by increasing bowel permeability. It is hoped that by improving our understanding of the role of the gut in cardiac disease will lead to the development of novel therapeutic strategies in the future.

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