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REVIEW

The heart and other organs

The heart and the gut

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The heart and the gut seem to be two organs that do not have much in common. However, there is an obvious and clinically relevant impact of gut functions on the absorption of drugs and oral therapies on the one hand. On the other hand, the gut determines the quantity of nutrient uptake and plays a central role in metabolic diseases. Patients with inflammatory bowel diseases appear to have a higher risk for coronary heart disease despite a lower prevalence of 'classical' risk factors, indicating additional links between the gut and the heart. However, they certainly have a 'leaky' intestinal barrier associated with increased permeability for bacterial wall products. An impaired intestinal barrier function will be followed by bacterial translocation and presence of bacterial products in the circulation, which can contribute to atherosclerosis and chronic heart failure (CHF) as recent data indicate. Impaired cardiac function in CHF vice versa impacts intestinal microcirculation leading to a barrier defect of the intestinal mucosa and increased bacterial translocation. These pathways and the most recent insights into the impact of the gut on acute and chronic heart disease will be discussed in this review.

Keywords Intestinal microbiome • Intestinal barrier • Bacterial translocation • Atherosclerosis • Chronic heart failure

The gut and its impact on heart diseases

The gut certainly is not the first organ we would think about when we consider the pathophysiology of heart diseases. However, its basic functions, digestion, and absorption are obviously clinically relevant for almost all oral drug treatments of diseases.

The absorption of drugs from the small intestine is altered in its kinetics in patients with Crohn's disease or celiac disease.[1] Patients with undetected celiac disease or with inconsequent diet have a decreased expression of some cytochrome P450 (CYP) isoenzymes such as CYP3A.[2] CYP3A is constitutively expressed in small intestinal villi and contributes to an important pre-hepatic metabolism of a number of drugs. Already in the intestine, CYP3A mediates the oxidative biotransformation of various clinically important drugs.[3] Macrolide antibiotics (which will be discussed in another role further below) are important inhibitors of CYP3A.[3] Statins have been reported to increase CYP3A isoenzymes expression[4] and, on the other hand, are metabolized by them.[4] CYP3A4 and CYP3A5 metabolize statins and thus have been demonstrated to influence the pharmacokinetics, efficacy, and safety of statins,[4] indicating that small intestinal disease such as Crohn's disease and celiac disease may well have a profound impact on the medical therapy of heart diseases.

It is not surprising that diarrhoea, associated with the mentioned diseases but also with other gut pathologies such as infectious enteritis, ulcerative colitis, radiation colitis, alters the absorption of drugs,[5,6] which has to be kept in mind when treating patients with heart diseases.

Gut and heart disease: is there a link?

Several intestinal diseases have been reported to be associated with an increased risk for coronary heart disease (CHD). In a recent study from Finland, it was found that CHD occurred significantly more frequently in inflammatory bowel disease (IBD) patients compared with an age- and sex-matched control group ($P = 0.004$).[7] Patients with IBD, however, usually do not have the 'classical' risk factors. In a respective analysis, only hypertension was confirmed as risk factor.[8] In addition, Crohn's disease patients seem to have lower levels of high-density lipoprotein (HDL).[9] This could be due to the

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chronic inflammation, as it was mainly associated with flares of the disease.[9] As most patients with IBD are in remission, the question arises whether there could be additional clinically relevant connections between the gut and the heart. A lower absorption of drugs during active flares of the disease as indicated above might certainly be relevant; however, the increased risk for CHD was also observed in IBD patients without cardiological medication.

The gut, the intestinal bacteria, and general health/metabolic syndrome

Recent years have brought interesting insights into the interaction of the gut microbes (the so-called microbiome) with the intestinal mucosa. Those interactions may impact the function of other organs such as the lung, the heart, or the lymphatic system. It is obvious that learning more about these interactions will become clinically relevant in the near future. Signals sent out from the intestinal microbiome, factors released by microbes and then absorbed, components of microbes (such as endotoxin or DNA) or factors induced in and secreted by intestinal epithelial cells or intestinal dendritic cells appear to have important physiological and pathophysiological functions.

It is estimated that there are 1000–1500 bacterial species that colonize the human gut, and that the gene content of microbes in the human gut may exceed that of the host by a factor of 100 or more.[10,11] Recent analyses of the human microbiome have revealed that even healthy individuals differ remarkably in their gut microbes.[12] It is clear that diet, bacterial composition of the environment, and host genetics play an important role for the individual composition of the microbiome.[12]

Many acute and chronic disorders affecting the heart, such as obesity[13–18] or metabolic syndrome,[19] have been linked to inadequate or disturbed post-natal microbiome acquisition or environmental micro-organism exposure during early childhood.[20] Obese patients seem to harbour different bacterial species compared with the lean population, especially *Firmicutes*.[13–18] Further, chronic inflammatory diseases such as atopic dermatitis,[21] asthma,[22] allergy,[23] and IBD[24–27] also have been linked with disturbances of the intestinal microbiome.

The commensals are important components of the digestive system and provide a number of micronutrients and small molecules further shaping the metabolome of the gut[28] and the overall metabolism of the organism. The commensal flora takes part in orchestrating immune responses in physiological and pathophysiological situations.[29]

As mentioned, obesity and metabolic syndrome, well-known risk factors for hypertension or heart disease, have been linked to the presence of specific bacteria or families of bacteria in the intestinal microbiome.[13–18,30,31] Especially, the landmark studies by Turnbaugh and Gordon have raised important insights into the role of gut bacteria for the metabolic syndrome.[14,17,18,32,33] Lean mice transplanted with the microbiome of obese mice showed a significant weight gain despite no change in food intake. Similar microbiome patterns as in obese mice were observed in obese patients or individuals with a metabolic syndrome. Unfortunately, the transplantation of the microbiome of lean mice into obese mice did not induce a weight loss in the latter. Therefore, these findings have no impact on clinical practice so far. However, the findings indicate that there are indeed patients who may have more weight gain and higher blood glucose levels with the same amount of daily caloric intake depending on the type of bacteria they host in their gut. This may at least change our attitude to patients with metabolic syndrome to some extent.

The gut and atherosclerosis

A recent study by Wang *et al.*[34] using a metabolomics approach identified a novel pathway linking dietary lipid intake, gut microflora, and atherosclerosis. The investigators identified the metabolism of phosphatidylcholine by the gut flora to be important for the development of cardiovascular disease.[34] Three metabolites of phosphatidylcholine (choline, trimethylamine *N*-oxide and betaine) were shown to predict risk for cardiovascular disease in a large clinical cohort. This was not observed in germ-free animals, confirming a crucial role for the gut flora in phosphatidylcholine metabolism. Additional prospective studies will be needed to evaluate whether these parameters are useful in clinical practice.

The above results have raised a number of speculations that probiotic interventions may be beneficial and prevent the development of atherosclerosis and heart disease. Such conclusions should be handled with care. Health claims for food products are now more restricted and supervised by the European Food Safety Authority.

Several studies have shown an association between both viral and bacterial infections and degree of atherosclerosis. The mechanisms through which viral infections may favour the development of atherosclerosis are not obvious, although there is plausibility for the influence of intestinal bacterial infections and atherosclerosis.[35] Bacterial lipopolysaccharides (LPS) may interact with low-density lipoprotein (LDL) and influence lipoprotein metabolism, thereby contributing to the development of atherosclerosis.[36–40] Furthermore, LPS induces endothelial cell damage[41–43] and stimulates the production and release of superoxide anions (O_2^-)[44,45] and the oxidation of LDL.[46] Oxidized LDL in turn favours the development of atherosclerosis and the release of cytokines, such as interleukin-1 and tumour necrosis factor alpha (TNFα), from macrophages, stimulating their transformation into foam cells (*Figure 1*).[47,48]

Whether the progression of atherosclerosis is supported or accelerated by bacterial infection or by LPS is still a matter of speculation. Although the results of antibiotic intervention studies have been somewhat discouraging, mechanistic evidence suggests a shift of focus from bacteria to endotoxins. Patients with highest serum LPS levels have an increased incidence of carotid atherosclerosis.[49] This might be clinically relevant in patients with an impairment of the intestinal barrier function, such as IBD patients or patients with liver cirrhosis. Those patients frequently have largely increased serum LPS levels. Since the ability of endotoxin to promote atherosclerosis may depend on its ability to initiate an inflammatory response, additional regulatory factors have been investigated. Polymorphisms of the Toll receptor 4, which is the receptor for endotoxin of Gram-negative bacteria, have been implicated in the development of coronary artery disease.[50] The Toll receptor 4 is expressed among other tissues on cardiomyocytes and foam cells.[47,51–54] Kiechl *et al.*[50] have shown that the presence of a

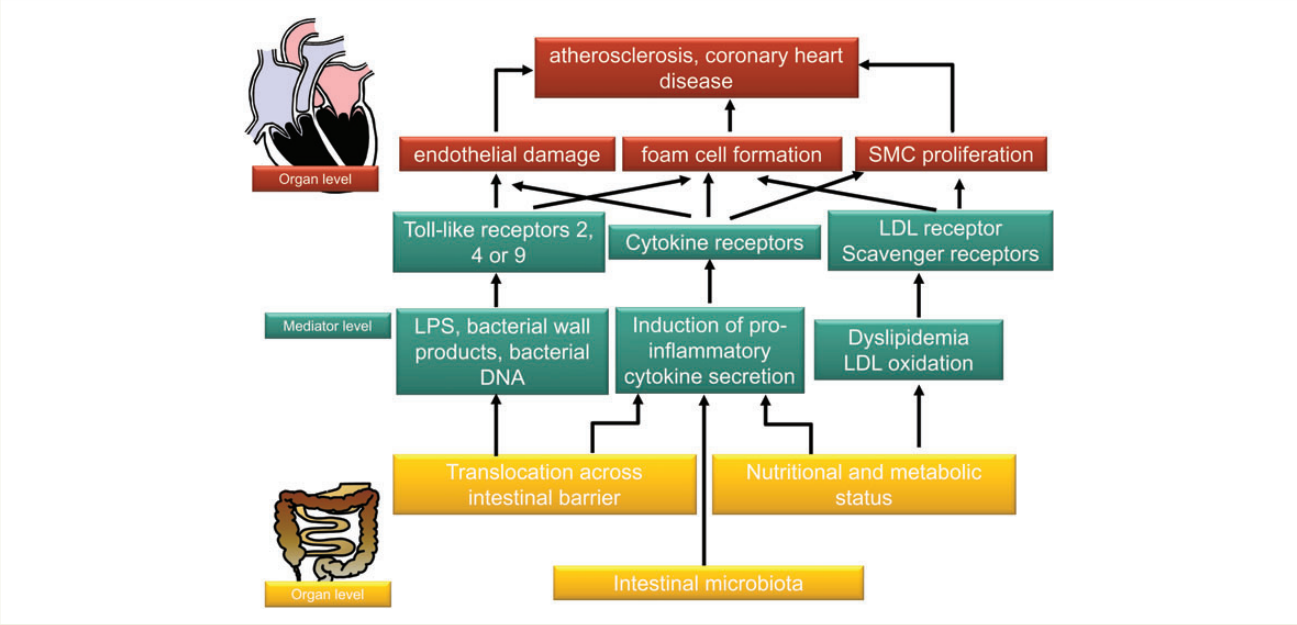

Figure 1 Potential pathways of gut involvement in the pathogenesis of atherosclerosis and coronary heart disease. The intestinal microbiota has a profound influence on mucosa barrier functions and on the nutritional/metabolic status of its 'host'. Certain bacterial families such as *Firmicutes* contribute to a higher uptake, for example, of short-chain fatty acids. In addition, a leaky barrier or impaired intestinal epithelial barrier function allows bacterial products such as lipopolysaccharide, bacterial DNA (CpG motifs), or peptidoglycans to enter the circulation. Furthermore, the microbiota can directly influence the cytokine production of epithelial cells and innate immune cells. Those mediators also enter the circulation. Lipopolysaccharide itself but also the metabolic situation can induce the production of oxidized low-density lipoprotein. These mediators are recognized by specific receptors (such as Toll-like receptors for bacterial wall products, cytokines receptors, or scavenger receptors) on (or in) endothelial cells, macrophages, or smooth muscle cells (SMCs) of the arterial wall. They are able to induce endothelial damage, foam cell formation, and SMC proliferations, which are features of atherosclerosis and coronary heart disease.

common polymorphism of TLR4 predicted low levels of circulating inflammatory molecules and conferred a reduced risk of atherosclerosis. Thus, some evidence supports a link between gut-originated endotoxins and progression of atherosclerosis; however, further studies are needed to confirm this link, to understand better the mechanisms and develop clinical consequences.

The gut and coronary artery disease

The link between enteric bacterial translocation and coronary artery disease is more elusive. Lam *et al.*[55] treated rats orally with the broad-spectrum antibiotic vancomycin to reduce total microbiota numbers and change the composition of the gut microbiome in an ischaemia/reperfusion model of myocardial infarction. Orally administrated vancomycin is absorbed only to a very low amount, thus excluding a direct effect on the myocardium. The addition of the antibiotic to the drinking water was associated with a reduction of infarction size, and cardioprotection already was achieved after 2 days of antibiotic treatment.[55] The protection, however, was lost again after vancomycin supplementation was stopped for >3 days. It remains unclear whether the association between CHD and bacterial pathogens, such as *Helicobacter pylori* and *Chlamydia pneumonia*, may play a role here.[56–62] It is generally believed that a chronic infection with these bacteria and the subsequent immune responses are a pre-requisite for a slow development of atherosclerosis.[63–65] Subsequently, those mechanisms are not likely to play a role in an ischaemia/reperfusion model of myocardial infarction. Nevertheless, a direct anti-inflammatory effect of the drug in this artificial setting cannot be excluded.

As a clinical attempt to improve the outcome of acute myocardial ischaemia in patients, the administration of various antibiotics was studied in well-designed randomized trials. In the STAMINA trial, 325 patients with acute myocardial infarction or unstable angina (acute coronary syndromes) were randomized to receive either a 1-week course of placebo or two different classical *Helicobacter* eradication antibiotic therapies [either amoxicillin (500 mg twice daily), metronidazole (400 mg twice daily), and omeprazole (20 mg twice daily) or azithromycin (500 mg once daily), metronidazole (400 mg twice daily), and omeprazole (20 mg twice daily)].[66] Patients were followed for 1 year; the endpoint was cardiac death or re-admission with acute coronary syndrome. The authors report 17 cardiac deaths and 71 re-admissions with acute coronary syndrome in their study group. No difference was observed between the two antibiotic treatments; however, at 12 weeks and during the 1-year follow-up, there was a 36% reduction in all endpoints in patients receiving antibiotics compared with placebo ($P = 0.02$).[66]

In the ROXIS study, the effect of roxithromycin on the outcome of 202 patients with unstable angina or non-Q-wave myocardial

infarction was assessed in a double-blind, randomized, prospective, multicentre, parallel-group, placebo-controlled study.[67] Patients either received the macrolide roxithromycin 150 mg orally twice a day or placebo orally twice a day for 30 days.[67] The primary clinical endpoints (cardiac ischaemic death, myocardial infarction, and severe recurrent ischaemia) were assessed at day 31 in 202 patients on an intention-to-treat basis, and a statistically significant reduction in the primary composite triple endpoint rates was observed in the roxithromycin group.[67] As reported in the publication, the rates of severe recurrent ischaemia, myocardial infarction, and ischaemic death were 5.4, 2.2, and 2.2% in the placebo group and 1.1, 0, and 0%, in the roxithromycin group.[67]

In contrast to the two described studies in the WIZARD trial, no positive effect was reported—7747 adults with previous myocardial infarction that had occurred at least 6 weeks previously were randomized to placebo treatment or azithromycin (600 mg/day for 3 days during week 1, then 600 mg/week during weeks 2–12; $n = 3879$).[68] After a median of 14 months of follow-up, no significant risk reduction in the likelihood of occurrence of death, nonfatal re-infarction, coronary revascularization, or hospitalization for angina was found comparing azithromycin with placebo [RRR: 7% (95% confidence interval: −5 to 17%), $P = 0.23$].[68]

For the interpretation of the results, it appears to be important that in the large WIZARD study, patients were included with an AMI at least 6 months previously (median 2.6 years), thus lacking those cases with early cardiac events after AMI. This is in contrast with STAMINA and ROXIS studies, which evaluated patients with ACS treated with antibiotics shortly after the initial event.

It has been discussed that the positive effects of the clinical interventions may be attributed to the anti-*Chlamydia* activity of the antibiotics. However, as the impact of *Chlamydia* on atherosclerosis has been suggested to be mediated by a chronic inflammatory response, the positive effect to the antibiotic treatment in acute myocardial infarction especially with respect to short-term (and not long-term) outcome is surprising. A direct anti-inflammatory effect of the antibiotics also might be relevant. Further studies are needed to finally answer these questions as an RRR between 37 and 80% would be clinically very important.

The gut and heart failure

An involvement of the gut in the progression and clinical evolution of heart failure has been discussed for years. Although the pathogenetic role of the gut microbiome and function have only recently started to be investigated in more detail in patients with chronic heart failure (CHF), data are accumulating to suggest that the gut plays an important pathophysiological role in both chronic inflammation and malnutrition in CHF.

In patients with CHF, disturbed intestinal microcirculation and barrier function may trigger cytokine production that in turn contributes to impaired cardiac function.[69] On the other hand, the circulatory adaptations that occur in patients with CHF as consequence of myocardial dysfunction may favour microcirculatory injuries leading to a disruption in the intestinal barrier, thereby amplifying inflammation.[69–71]

Patients with CHF have morphological and functional alterations of the gut.[69–71] In these patients, all parts of the large bowel display a thickened wall compared with control subjects of similar age.[70] This is associated with a functionally altered gut mucosa with increased permeability for lactulose/mannitol and sucralose in both the small and large intestine as well as with a reduced passive carrier-mediated transport for D-xylose. Furthermore, in patients with CHF, the concentration of bacteria in the sigmoidal mucosal biofilm and the extent of their adherence are higher than those in control subjects.[72]

The translocation of bacteria across the intestinal barrier and the systemic presence of endotoxin such as LPS or other bacterial wall compounds such as peptidoglycans (e.g. muramyl dipeptide) may also play a pathophysiological role in CHF.[73] The hypothesis is supported by increased levels of soluble CD14 in patients with CHF.[74] CD14 is a part of the LPS receptor, and soluble CD14 (a form of CD14 that is shed from the cell membrane) is believed to have important regulatory functions in the sensing of LPS. As mentioned above, another component of the LPS receptor, the Toll-like receptor 4 (TLR-4), is expressed on cardiomyocytes.[75] Binding of endotoxin to TLR-4 on cardiomyocytes is associated with impaired function,[76] decreased contractility,[52–54] induction of an inflammatory response,[52,54] and structural tissue damage.

It is well known that CHF is a state of chronic inflammation with elevated circulating levels of pro-inflammatory cytokines, such as TNFα. In patients with CHF, increased circulating levels of pro-inflammatory cytokines have been shown to be closely related to predict poor short- and long-term survival.[77,78] Circulating cytokines have cardiosuppressor effects via different pathways that include alterations in myocardial intracellular calcium homeostasis, reduction in mitochondrial activity, alterations in matrix metalloproteinase expression, cardiomyocyte hypertrophy, and apoptosis.[79–83]

Although the origin of inflammation in patients with CHF with elevated concentrations of pro-inflammatory cytokines is still a matter of debate, it has been shown that very small, but pathophysiologically relevant amounts of LPS may induce TNFα release.[84,85] Furthermore, growing evidence suggests that increased amounts of LPS enter the systemic circulation because of an altered intestinal microcirculation in CHF, with LPS levels being 35% higher in the hepatic venous blood than in the left ventricle.[86] An important point in gut-derived inflammation in patients with CHF is the altered gut circulation as a consequence of reduced cardiac output and venous congestion (*Figure 2*).

In patients with CHF, increased sympathetic tone and peripheral vasoconstriction contribute to a redistribution of blood flow away from the splanchnic circulation. The reduced intestinal perfusion may lead to an increase in intramucosal carbon dioxide pressure. Intramucosal acidosis may occur in nearly 50% of patients with circulatory failure, suggesting the presence of inadequate oxygen supply and intestinal ischaemia.[87,88] The altered mucosal perfusion increases intestinal mucosal permeability with the disruption of the epithelial barrier function that favours the bacterial colonization and the penetration of LPS. Besides its effect on the release of cytokines that further aggravates CHF, LPS is able to trigger catecholamine release by granulocytes and phagocytes.[89] This increased release of catecholamines exerts additional unfavourable effects on gut perfusion and further increases the already hyperactive sympathetic tone.

Another mechanism through which CHF may favour bacterial translocation is related to intestinal mucosa congestion as a consequence of raised right atrial pressure. As CHF is associated with

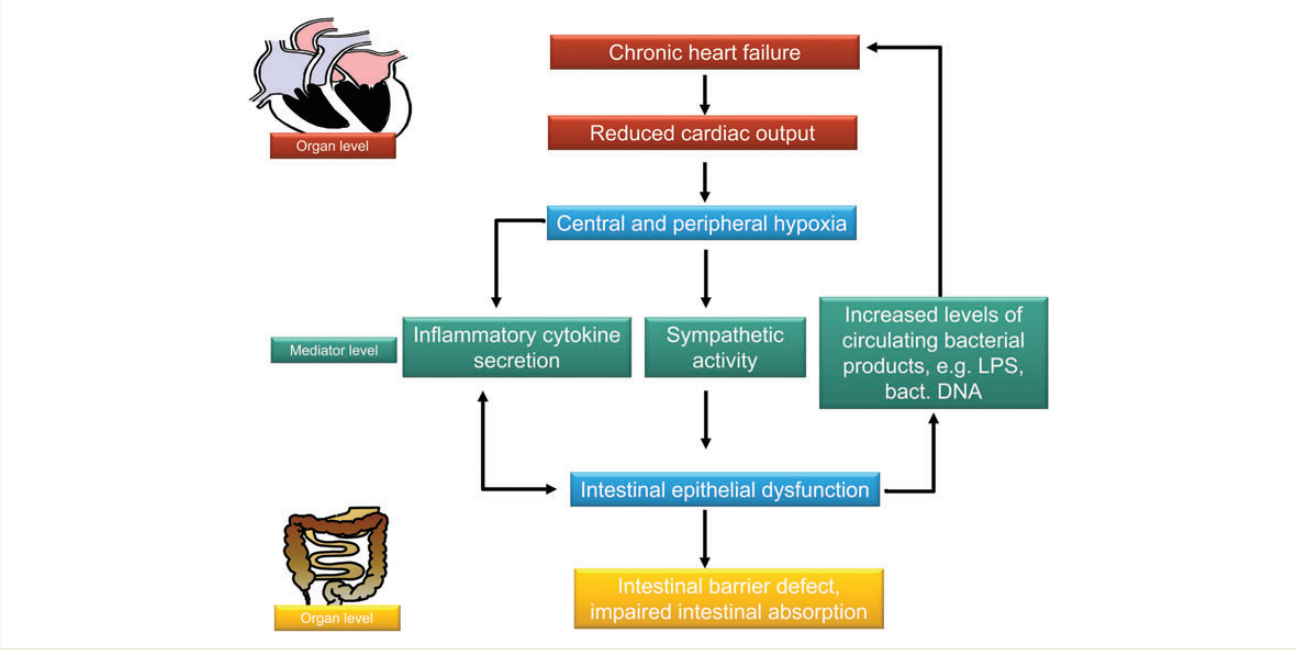

Figure 2 The heart and the gut in the pathophysiology of chronic heart failure. Chronic heart failure will cause a reduction in cardiac output which in turn will cause central and peripheral hypoxia. Among the organs that are affected by peripheral hypoxia is the small and large intestine. Hypoxia will cause an increase in inflammatory cytokine production, sympathetic activity, and production of other mediators (such as leucotrienes, prostaglandins, and others that are not depicted in this graph). These mediators and the sympathetic activity may cause a malfunction of the gut. A further contributor will be a venous stasis increasing mucosal hypoxia. The mentioned factors have been shown to impair epithelial barrier function leading to a penetration of bacterial products across the intestinal barrier. Preliminary data indicate that the presence of those products in the circulation further aggravate chronic heart failure. Further studies with modern technologies such as mass spectroscopy and pyro sequencing of bacterial DNA will be necessary to confirm this. On the other hand, a dysfunction of the intestinal barrier will also cause impaired absorption negatively influencing the nutritional status of patients with end-stage heart disease.

Table 1 Alterations of gastrointestinal function in patients with chronic heart failure (according to Sandek *et al.*[70])

Increased small intestinal and large intestinal paracellular permeability in stable compensated chronic heart failure patients
Diminished carrier-mediated transport for D-xylose
Excessive enteric protein loss in infants with severe congenital heart disease
Decreased absorption of fat and protein
Thickened bowel wall of the terminal ileum and the colon
Elevated collagen content in small intestinal biopsies
Increased distance between the capillary wall and the basal membrane of the enterocyte
Increased bacterial biofilm on sigmoid biopsies

mucosal oedema in the intestine, which will impair the intestinal barrier function, this again may be followed by increased bacterial translocation (across the impaired barrier), increased amounts of endotoxin in the circulation,[90] and aggravated heart disease—a typical vicious circle. Niebauer *et al.*[90] found that intensified diuretic treatment normalized circulating endotoxin concentrations in patients with acute exacerbation of chronic heart disease.

A number of alterations in gastrointestinal function have been described in patients with CHF (*Table 1*). It remains a matter of discussion whether these alterations are primary to the heart disease or caused by it.

In summary, recent data on potential interaction between the gut and the heart are intriguing. However, the evidence we have so far is preliminary. In large cohort studies, it needs to be evaluated whether, indeed, increased levels of bacterial products can be found in patients with atherosclerosis or CHF. The interesting and innovative field of heart–gut interaction still waits for more cardiologists and gastroenterologists to collaborate on these important topics.

Authors' contribution

Both authors wrote the manuscript together.

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