Gastroenterocardiology–or what do the gut and the heart have in common?

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Summary: The gut microbiota of our organism is a community of bacteria, archaea, fungi, viruses and parasites that make up a unique ecosystem in the digestive tract, which consists of about 1014 microorganisms. The diversity of this community between individuals occurs because of the differences in the host genome and the impact of environmental factors, including hygiene, diet, lifestyle and the use of different drugs. Significant evidence suggests that changes in the microbiota could play a role in cardiovascular diseases. The results of research papers for the last two decades have confirmed that altered gut microbiota composition (dysbiosis) contributes to the development of various diseases, including cardiovascular diseases, type 2 diabetes, chronic kidney disease, nonalcoholic fatty liver disease, chronic inflammatory bowel disease and even certain types of cancer. There is growing evidence that in the future, apart from current predisposing factors for cardiovascular and metabolic diseases, including genetic, environmental and lifestyle factors, one should count on new risk factors such as nutritional disproportion and gut dysbiosis. Thus, we look upon the relationship between the gastrointestinal tract and cardiovascular system, i.e. the "gut-heart axis" in a new way.
Key words:intestinal microbiota, nutritional disproportion, dysbiosis, cardiovascular diseases, metabolic disorders

Introduction

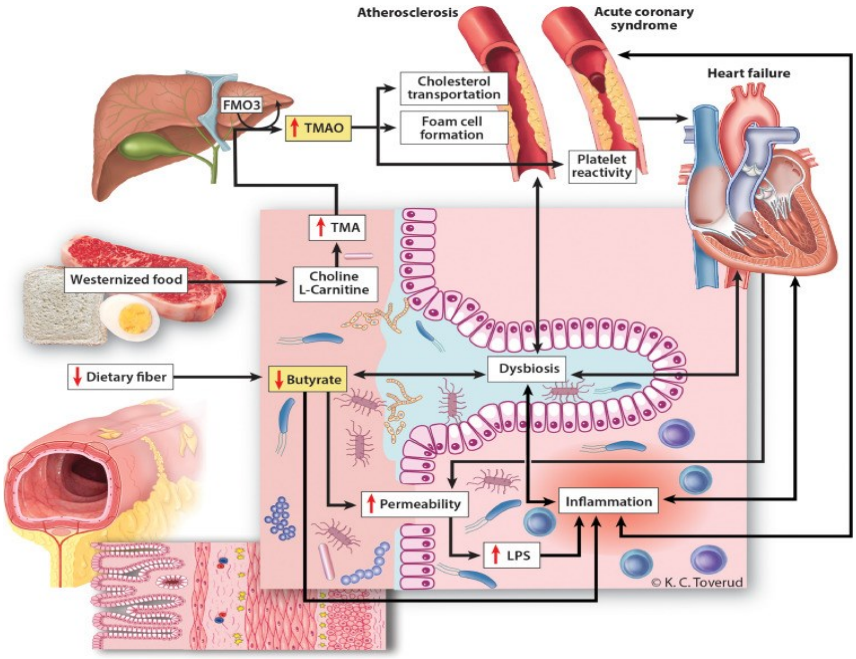
The study of the human gut microbiota and its role in various diseases has advanced significantly in the last decade. The human microbiota consists of all microorganisms that live in a symbiosis with the human body, while the microbiome represents the sum of all genes of the microbiota.

The human microbiome contains up to 100 times more genes than the human genome.Microorganisms can be found in various parts of the human body,but the most numerous is the microbiota of the digestive organs. The microbiota is variable among healthy people but it is also unique for an individual – no two microbiomes are the same in humans, just as there are no the same fingerprints. Although there are no two people with the same composition of the microbiota, however, there are larger similarities in the composition of microbiota among the members of the same races, ethnic groups and blood relatives.Gut microbiota is a collection of approximately 1014microorganisms. The number of bacteria in every human being is larger than the number of people who have ever lived on earth.It is a community ten times more numerous than all the cells of our organism. It consists of bacteria (about 1000 different species), archaea, fungi, viruses and parasites that make up a unique ecosystem. The microbiota plays a very important role in human health. It is of utmost importance for maintaining the homeostatic functions of the gastrointestinal tract, as it participates in digestion processes of the host, metabolism and regulation of the gut immune system. (1,2). After birth, the digestive tract of the newborn is not inhabited by microorganisms. In the first hours of life, it is colonized by maternal microorganisms, initially coliform bacteria and streptococci, later lactobacilli and enterococci, and the number of microorganisms in the gut tract begins to increase, gradually forming a dynamic balance of the gut microbiota.Of course, the growth of these bacteria also depends on the method of birth - natural or by caesarean section (3). In adulthood, most of the gut microbiota consists of five groups of microbes, namely: Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, and Verrucomicrobia. The number of Gram-positiveFirmicutesand Gram-negative Bacteroidetesthat make up the most species in a healthy adult gut> 90% (4-5) is approximately proportional.The ratio between Firmicutes and Bacteroidetes remains relatively constant in a healthy individual although it is not the same in all individuals. The differences occur because of the difference in

the host genomes, environmental factors as hygiene, diet, lifestyle and use of antibiotics (4). Due to the acidic environment and intense peristalsis, fewer microorganisms (10–1000 / ml),most of which are Gram-positive bacteria, are present in the stomach and duodenum. Enterococci and Lactobacilli are present in the duodenum, and the number of bacteria in this area is usually 104 / ml. The colon, which is predominantly inhabited by gram-negative and anaerobic bacteria, is the richest in the number and variety of species (1012/ ml) (5).

It hasn't been fully clarified what a healthy microbiota actually is, but it has been shown that in the case of disturbed balance - dysbiosis, a disease can develop. When eating habits, environmental factors, gut infection, some drugs or other factors lead to changes in the type and amount of gut microorganisms, there occursgut dysbiosis, which causes inflammatory and metabolic disorders. Homeostasis of the gut microbiota is crucial for maintaining health in human beings, while dysbiosis contributes to the development of various diseases, including cardiovascular, chronic kidney disease, type 2 diabetes, nonalcoholic fatty liver, and even some types of cancer (1,6,7). Gut dysbiosis may explain why some individuals are more prone to developing certain diseases. Changes in the composition of the microbiota have recently been identified as an important factor in the dysfunction of the "gut-heart axis", which contributes to the development of atherosclerosis and hypertension - two main risk factors for the development of cardiovascular diseases (1,7,8).

Picture 1. Influence of Intestinal Dysbiosis on Cardiovascular Diseases(taken from https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30024-4/fulltext for scientific purposes and not used for commercial purposes)



The gut microbiota can be considered an endocrine organ, and each microbe has the ability to produce hundreds of different known and unknown metabolites that act beyond the gut itself. As most of the bacteria that inhabit the digestive organs cannot be colonized in the laboratory at the moment, for the purpose of determining the composition of the microbiotanext-generation sequencing method and bioinformatics analysis of extracted microbial deoxyribonucleic acid (DNA) are used.In recent years, the impact of the composition of microbiota on various chronic and autoimmune diseases has been studied, especially in animal trials (3,8). These trials demonstrate the importance of the microbiota in relation to health and immunity and offer new, as yet undiscovered possibilities for the use of this knowledge in the treatment of some other diseases, such as metabolic syndrome, insulin resistance, chronic inflammatory bowel disease, cancer (1,6,9).

Gut dysbiosis andatherosclerosis

Atherosclerosis is the main risk factor for cardiovascular diseases. This process is characterized by the accumulation of cholesterol and macrophages (inflammatory cells) in the vascular walls, which contributes to the formation of atherosclerotic plaques.Recent studies have shown that gut dysbiosis can contribute to the development of atherosclerosis by modulating inflammatory processes and by forming certain microbial metabolites (10-15).Integrity of the gut mucosa is the first barrier that protects the host from the intrusion of pathogens, the passage of intestinal contents and bacterial components into the blood vessels. Reduced concentrations of proteins that ensure close cell contacts and their impermeability, including zonula occludens-1 (ZO-1) also known as Tight junction protein-1 (TJP1), claudin 1, and occludin, allow increased permeability of the gut wall by disrupting the balance between mucosal cell death and regeneration of the mucosal cells (1,13,14). If the mucous barrier is damaged, the penetration of microbes and their products into the blood vessels triggers an immune response, tissue and systemic inflammation. Impairment of the gut barrier integrity caused by gut dysbiosis, therefore, acts as a risk factor that triggers a chronic inflammation that underlies various diseases, including atherosclerosis. The main molecules-products of bacteria that are the drivers of the immune and inflammatory response are ''Pathogen-associated molecular pattern''- PAMP. PAMPs activate the innate immune response, protecting the host from infection. A wide range of different types of molecules can serve as PAMP, including glycans and glycoconjugates. Bacterial lipopolysaccharides (LPS), endotoxins found on cell membranes of Gram-negative bacteria, are considered a prototype class of PAMP.The relationship between plasma LPS levels and cardiovascular risk was first studied in 1999 by Niebauer et al. (15). The results of the study confirmed that the level of endotoxemia was the highest in patients with the most severe cardiovascular disease. Cani et al. confirmed in their study that gut dysbiosis prevented the formation of "close contact proteins", which resulted in increased permeability of gut mucosa, and thus the passage of LPS into the blood (16). LPS, which are produced in increased amounts in intestinal dysbiosis, can play an important role in modulating "toll-like receptors (TLRs)" which recognize bacterial products and regulate the host's immune system. TLRs are a class of proteins that play a key role in the innate immune system. They are single-pass transmembrane receptors commonly found on sentinel cells (first-line defense cells) such as macrophages and dendritic cells, which recognize structurally conserved molecules derived from microbes. Once microbes break through physical barriers such as the skin or lining of the gut tract, they are recognized by TLRs that activate immune cell responses.Clinical studies have shown that an increase in TLR is associated with anti-inflammatory activity and promotes the development of atherosclerosis in humans. The results of these studies in recent years thus confirm the role and importance of gut microbiota and dysbiosis as risk factors in the development of atherosclerosis (8,9,10,17).

In the metabolism of gut bacteria, various metabolites that participate in the development of atherosclerosis are formed. Among the most important are various amines, methylamines, polyamines, short-chain fatty acids, trimethylamine and secondary bile acids. In particular, short-chain fatty acids (SCFA) are a group of intestinal microbial metabolites that are important for metabolic diseases. Studies have shown that the intestinal microbiota is involved in the formation of trimethylamine N-oxide (TMAO) (8,14). Trimethylamine (TMA) is a by-product of bacterial metabolism that is absorbed into the bloodstream and converted to TMAO in the liver by specific liver enzymes, flavin-containing monooxygenases. Different bacterial compositions naturally have different abilities to form TMAO. Studies in mice have confirmed that TMAO accelerates the development of atherosclerosis by stimulating cholesterol influx, inhibiting cholesterol excretion, inhibiting secondary bile acid metabolism, and / or by excessive platelet activation (3,8,10). According to researchers, apart from the role of a biological marker for atherosclerosis and cardiovascular diseases, TMAO could also represent a possible therapeutic goal in the future. Interestingly, inhibitors of TMAO production have been developed that target various microbial TMA lyases. These drugs reduce TMAO levels and reverse atherosclerosis in animal models. TMA lyase has become the current potential therapeutic target of TMAO modulation (18).

Gut microbiota and hypertension

Apart from dyslipidemia and atherosclerosis, hypertension is another major risk factor for CVD that is genetically sensitive and influenced by environmental factors (19). As early as 1982, it was shown that antibiotic treatment could cause higher blood pressure (15). On the other hand, a number of studies showed that antibiotic use had a beneficial effect on blood pressure.These data, as well as the observed

relationship between dysbiosis and cerebrovascular events, indirectly suggested a relationship between the gut microbiota and hypertension as assessed in recent studies. (20,21).Furthermore, in spontaneously hypertensive rats, a significant decrease in the number and diversity of microbes in the gut and a decrease in the number of cecal "good bacteria" from the species Bacteroidetes was documented, which was accompanied by a proportional increase in the number of "bad bacteria" from the species Firmicutes.The studies have also shown that transplantation of cecal microbiological content from hypertensive animal donors can reproduce hypertension in previously normotensive animals (22). In a study on mice, it was shown that dysbiosis of the gut microbiota can cause angiotensin-II-induced vascular dysfunction and hypertension. As another study found, the absence of gut microbiota protects mice from angiotensin II-induced arterial hypertension, vascular dysfunction, and end-organ damage caused by hypertension (23,24).

Thus, it is obvious that the gut microbiota is involved in the development or worsening of hypertension. Although the exact underlying mechanisms and the relationship between the gut microbiota and hypertension have not been established, existing evidence from animal trials and clinical studies highlights the role of short-chain fatty acids -SCFA and oxidized low-density lipoprotein (ox-LDL) in the development of hypertension. Short-chain fatty acids, such as acetate, proprionate, and butyrate, are formed mainly from soluble dietary fiber polysaccharides (23). The groups of microbes in the gut that metabolize polysaccharides to different types of SCFA are specific. The main acetate-producing bacteria are Streptococcus, Prevotella, Bifidobacterium, Clostridiums, and A. Muciniphila (25). Propionates are produced by Bacteroides, Salmonella, Dialister, Veillonella, Roseburia, Coprococcus, Blautia, and others. (26). Butyrates areproduced by Lachnospiraceae, Ruminococcaci Acid amino coccaceae (27). Fiber and acetate supplementation led to an increase in the number of Bacteroides acidifaciens and was associated with improved gut dysbiosis, hypertension, and heart failure in hypertensive mice (28). Too many butyrate-producing bacteria have been associated with elevated systolic and diastolic blood pressure in pregnant women (29).G protein-coupled receptors (GPCRs) are receptors on the cell surface that detect SCFA molecules outside the cell and activate cellular responses. The three GPCRs regulated by SCFA are: GPR41, GPR43, and GPR109A (30). SCFAs stimulate GPCR-regulated pathways to affect the renin-angiotensin system to modulate blood pressure. Olfactory receptor 78 (Olfr78) is another type of GPCR expressed in the kidney that detects SCFA (31). Both Olfr78 and GPR41 are expressed in smooth muscle cells ofsmall-diameter blood vessels. In another study, stimulation of GPR41 resulted in a reduction in the hypotensive response (32). SCFA, propionate induces vasodilation and produces an acute hypotensive response in mice by modulating the activity of Olfr78 and GPR41 (33). All these findings reveal that the gut microbiota plays an important role in modulating blood pressure via SCFA and suggests that hypertension is associated with dysbiosis.

Apart from altered regulation of various receptors via SCFA, gut dysbiosis also contributes to hypertension by Oxidized LDL-mediated vasoconstriction(34). Microbial dysbiosis promotes the expression of pro-inflammatory cytokines and induces oxidative stress that stimulates LDL oxidation (35). Higher levels of oxidized LDL (Ox-LDL) reduce NO production, reduce the degree of vasodilation and stimulate the production of vasoconstrictor substances, including endothelin-1, which plays a crucial role in maintaining vascular tone and cardiovascular homeostasis. Disturbed balance leads to hypertension. However, the causal relationship between gut dysbiosis and hypertension is complex and has not been fully assessed. The exact role of the gut microbiota in mediating hypertension, the pathways and mechanisms involved require further detailed research.

Gut microbiota and heart failure

There is growing evidence of a connection between the gut microbiota and the pathogenesis of heart failure. In the English literature, the term "gut hypothesis of heart failure" (36-39) is used to define this connection. This hypothesis explains that decreased cardiac output (DCO) and increased systemic arrest can cause gut ischemia and / or edema of the gut wall, leading to increased bacterial penetration into blood vessels, thus increasing the concentration of endotoxins in the circulation. This can trigger inflammation in patients with heart failure. Exogenous factors such as diet, exposure to bacterial infections, or medication may reduce the diversity of the gut flora. Endogenous factors such as acute humoral imbalance, chronic gut congestion or ischemia-hypoxia, acid-base imbalance, impaired gastrointestinal motility, and nutritional deficiency can potentially alter the gut flora (40).With the

development of heart failure, the characteristics of the bacterial community change. Studies have shown that the number of gut flora in patients with chronic heart failure decreased, and the number of pathogenic bacteria increased significantly with the progression of the disease, including Campilobacter, Shigella, Salmonella, Yersinia enterocolitica and Candida species (41,42,43). 16SrRNA analysis in patients with heart failure has reported a reduction in SCFA-producing bacteria, such as Eubacterium rectale and Dorea longicatena (43). Another study showed that the composition of the gut microbiota in chronic heart failure is characterized by a decrease in the number of bacteria with the potential to produce butyrate (44). Butyrate exerts local anti-inflammatory effects in the gut mucosa and stimulates regulatory T cells (45). It has been observed that the number of microbiological genes for LPS biosynthesis and TMAO production is increased, while the abundance of genes for butacetate acetoacetate coenzyme A transferase (key enzyme for butyrate production) is reduced in chronic heart failure (41).It was also observed that patients with heart failure and peripheral edema had higher plasma endotoxin and inflammatory cytokine levels compared with patients without edema. After short-term diuretic therapy, serum endotoxin but not cytokine concentrations (46) decreased. In another study, the researchers confirmed that patients with heart failure and reduced gut blood flow had higher serum concentrations of immunoglobulin A - anti-lipopolysaccharide. Compared with the control group, patients had a different composition of the microbiota, the number of beneficial bacteria decreased, and the number of pathogens increased (24). The onset and development of heart failure may be associated with a decrease in SCFA-producing bacteria and an increase in TMAO-producing bacteria, which may become a new target for the treatment of heart failure. Recently, in studies in mice,the effects of trimethylamine-lyaseenzyme inhibitors have been shown to have an effect similar to that of anti-atherothrombotic agents. (47.48).

Gut microbiota and myocardial infarction

Atherosclerotic plaques contain bacterial DNA. However, the types of bacteria found in atherosclerotic plaques are also present in the gut of the same individuals (18,19,36). A study from South Korea shows that the presence of bacteria (microbial rRNA) was detected in the coronary thrombus during the acute phase of STEMI. The microbiological signature in the coronary thrombus showed a correlation with oral and intestinal microbiome (20). From this it can be concluded that gut microbial communities can be a source of bacteria in plaque, which can affect plaque stability and the development of cardiovascular diseases. A recent study in rats reported a connection between the gut microbiota and the extent of myocardial infarction (38,39).

The study looked into Dahl Salt-Sensitive Rats-rats fed with foods high in salt - 8% NaCl) that drank drinking water with antibiotic vancomycin, which reduced the level ofcirculating leptin by 38%, causing a smaller myocardial infarction (area reduction of 27%) and improved restoration of postischemic myocardial contractility compared to control animals that did not receive the antibiotic. Vancomycin changed the abundance of gut bacteria and fungi measured by the amount of 16S and 18S rRNA (39).

In rodent-based studies the use of Lactobacillus plantarumas a probiotic resulted in the reduction of circulating leptinby 41%, myocardial infraction by 29% and better recovery of myocardial contractile function by 23%.However, if rodents received leptin at a dose of 0.12 μg / kg i.v. the protective effect of probiotics on the heart was reversed. This study is the first to confirm a direct link between changes in the gut microbiota and myocardial infarction. This shows that the addition of probiotics can reduce the degree of myocardial infarction (46). Another animal study using Lactobacillus rhamnosus showed a beneficial effect on cardiac function after an artificially induced myocardial infarction (49).

Gut microbiota and metabolic diseases

Many studies show a link between the composition of the gut microbiota and metabolic disorders in the body (50,51,52). The role of the gut microbiota in the development of obesity has been proven by studies conducted on dehydrated mice (germfree-GF-mice) compared with conventionally bred mice (CONV-R). Sterile, germ-free mice are bred in isolators that completely block exposure to microorganisms, with the intention of protecting them from detected bacteria, viruses, and eukaryotic microbes.CONV-R mice have a 40% higher body fat content than GF-mice, which is a phenomenon independent of food intake. However, after colonization of GF-mice by gut flora coming from CONV-R mice, a significant increase in body weight and ~ 60% increase in body fat was observed, together with increased synthesis of liver triglycerides in faecal transplant recipients (GF mice), independent of food intake and total energy

consumption (53). It appears to be the mechanism by which gut microbes contribute to increased energy absorption by the formation of short-chain fatty acids (SCFA), which is the result of hydrolysis and fermentation of dietary polysaccharides. SCFAs, such as propionate, butyrate, and acetate, perform complex metabolic actions that affect host appetite, gut transittime, and fat absorption and deposition (52).SCFAs also increase the internal absorption of monosaccharides by stimulating the expression of the sodium-glucose transporter 1. SCFAs also contribute to the modulation of host appetite and food intake in interaction with G-linked proteins expressed by enteroendocrine cells and promote the release of glucagon-like peptide-1 that affects satiety. Apart from that, SCFAs affect lipid metabolism by increasing lipogenesis and inhibiting fatty acid oxidation (53).Studies have shown specific changes in the composition of the gut microbiota in genetically obese mice compared to genetically lean mice, showing a 50% decrease in abundance of Bacteroidetes and a proportional increase in Firmicutes. These specific changes appear to contribute to increased SCFA production and fat accumulation in obese mice and in GF mice colonized by obese microbiota (54). There are other possible mechanisms. A high-fat diet has been shown to increase the proportion of Gram-negative species in the gut microbiota, which contributes to the increased absorption of gut fragments of bacteria, such as lipopolysaccharides (LPS) in the gut. Increased circulating LPS levels lead to "metabolic endotoxemia" which manifests as weight gain, fasting hyperglycemia, and hyperinsulinemia (55). There is growing evidence to suggest that a high-fat diet promotes changes in the composition of the gut microbiota, but the later development of the obesity phenotype is associated with metabolic endotoxemia (56).In recent years, researchers have also studied the links between dysbiosis and obesity, type 2 diabetes, dyslipidemia, and nonalcoholic fatty liver disease (NASH) (50,51). Initial studies in animals and humans supported a correlation between obesity and the abundance of the Firmicutes group of bacteria compared to the Bacteroidetes group; type 2 diabetes, however, is associated with a reduced abundance of butyrate-forming bacteria and an increased abundance of Lactobacillus spp (1,3,8,10). The gut microbiota is involved in the development of dyslipidemias via secondary bile acids (52,53). In the research of NASH, it was determined that some bacteria (Clostridium coccoides, Lactobacillus reuteri, Parabacteroides) affect fat metabolism, integrity of the gut wall and the process of fibrosis, thus affecting dyslipidemia (52).

Application in practice

Examples of clinical benefit of long-term microbiota change are: dietary measures, pre and probiotic therapy, antibiotic therapy, intake of targeted enzyme inhibitors, fecal microbial transplantation, etc. (57,58). Studies have shown that even a five-day change in diet leads to a short-term rearrangement of the number and types of gut microbes (4). An example of this is the dietary approach aimed at stopping hypertension (DASH diet - Dietary Approaches to Stop Hypertension), which consists of meals with fruits, vegetables, whole grains, etc. (59).Patients in the study who were on this diet showed an improvement in quality of life and better elasticity of arterial blood vessels after three months of adherence to the measures (60). Besides, it has been described that individuals who do not follow a prescribed diet and have a “Western diet” high in fat and red meat have elevated levels of TMAO in their urine compared to patients who follow a prescribed DASH regimen (61,62).Reduced dietary fiber intake is associated with reduced bacterial production of short-chain fatty acid butyrate, which has immuno-modulatory effects in the gut mucosa and also serves as a major energy substrate for colonocytes.Decreased levels of butyrate in the gut could induce local inflammation, worsen dysbiosis and contribute to impaired gut barrier function, resulting in "leakage" of bacterial toxins such as LPS, which further induces local and systemic inflammation. A high-fiber diet can improve the growth of acetate-producing bacteria, reduce high blood pressure, and prevent heart fibrosis and hypertrophy (63).

Probiotics and prebiotics

Probiotics are living microorganisms which, when given in appropriate amounts, bring health benefits to the host (64). Probiotics in clinical use contain bacterial and fungal microorganisms, including the genera Lactobacillus and Bifidobacterium and the fungus Saccharomyces boulardii (65). The results of animal models suggest that certain strains of lactobacilli could have cardioprotective effects. Rats treated with a supplement containing Lactobacillus plantarum 299v prior to coronary artery ligation reduced infarct size and improved left ventricular function (66).Another study showed similar cardioprotective results in a rat model of myocardial ischemia after supplementation with Lactobacillus rhamnosus GR-1 (67). A pilot study in humans reported not only reduced systemic inflammation, but also improved

ejection fraction after intervention with probiotic yeast Saccharomyces Boulardii in patients with chronic heart failure (68). Given the potential clinical impact of microbiota modulation, as well as high morbidity and mortality from heart failure, microbiota modulation is not completely risk-free (69). Careful clinical monitoring and pre-defined safety measures which should follow the same standards as in other clinical trials are recommended, (70) because recent genomic and epidemiological evidence of probiotic-related bacteremia or transfer of bacteria from probiotic capsules into the blood of patients in intensive care units has been reported (71).Prebiotics are substrates that microorganisms of the host selectively use and provide potential health benefits. Dietary fiber and oligosaccharides are most commonly used as prebiotics (72). Most modern studies that deal with microbiota processing in patients with cardiovascular disease report NAPOMENA – NEJASNO microbial depletion with SCFA-forming capacity such as butyrate. Prebiotics that promote microbiological fermentation of dietary fiber in SCFA may, therefore, be of potential benefit in improving metabolic regulation (73). Some prebiotics, such as inulin, have the potential to counteract the harmful effects of antibiotics by promoting the diversity and functional capacity of the gut microbiota (74).A randomized study with inulin food supplement or inulin-proprionate ester showed a decrease in markers of systemic inflammation with increased generation of SCFA proprionate in the colon (75). Therefore, targeting the production of microbial SCFAs with inulin supplements or other prebiotics is an attractive strategy for future cardiovascular disease testing, although current scientific evidence does not provide validated recommendations for the use of probiotics or prebiotics as adjunctive therapy in patients with heart failure or coronary heart disease.

Antibiotics

The use of antibiotics affects the composition, diversity and function of the normal flora (76). Antibiotics have been used successfully in animal models to reduce the degree of damage to heart cells after myocardial infarction (77,78). Previous studies in patients with heart failure focused on gut decontamination with broad-spectrum antibiotics to reduce biotome translocation and bacterial inflammation. Although this approach succeeded in reducing markers of systemic inflammation, a clinical effect was not demonstrated (79,80).

A recent study showed that a broad-spectrum oral antibiotic cocktail significantly increased postinfarction rupture and death in a mouse model of coronary artery ligation (81), which could suggest that an intact microbial community is needed for proper myocardial recovery at the time of myocardial injury. This study is in contrast to a previous animal experimental model that showed that oral vancomycin reduced infarct size and improved postinfarction cardiac function in rats (82), and to a study reporting that a combination of streptomycin, neomycin, polymyxin B, and bacitracin reduced infarct size along with changes in metabolites associated with the microbiota (83).

Regardless of the differences, these animal studies strongly indicate the role of gut microbiota composition in acute myocardial infarction, but the direction of microbiota changes and potential metabolic or inflammatory pathways are not yet well known. Modifying cardiovascular diseases with antibiotic therapy is not a new idea.

Between 1995 and 2005,> 19,000 patients were included in a study to treat pneumonia in patients with coronary heart disease. The study in these patients showed no clinical benefit from antibiotic therapy in relation to coronary ischemia (84). Apart from the apparent risk of antimicrobial resistance, other safety concerns have recently emerged with potential significance for future testing. A recent ten-year follow-up showed increased cardiovascular death in patients with stable coronary heart disease treated with clarithromycin (85), leading to a 2018 FDA warning on the use of clarithromycin in patients with coronary heart disease. The FDA advises caution before prescribing clarithromycin antibiotic to patients with heart disease because of a potential increased risk of heart problems or death that may occur years later.(https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-review-finds-additional-data-supports-potential-increased-long). In December 2018, the FDA issued a warning on the use of fluoroquinolones indicating the possibility of aortic rupture and aortic dissection in high-risk patients, such as elderly patients with hypertension or peripheral atherosclerotic vascular disease(https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-review-finds-additional-data-supports-potential-increased-long).Another study reported increased risk of cardiovascular events in older women with increased cumulative antibiotic exposure in adulthood (86). The explanation for this increased risk is not fully known in all patients, but it could include QT prolongation, arrhythmias or pro-inflammatory activities mediated by gut microbiota translocation, or other effects mediated by the gut

microbiota. Considering these safety concerns and the lack of a completely clear clinical effect antibiotics have on the microbiota, caution should be exercised in future studies targeting the use of antibiotics in cardiovascular patients.

Targeted enzyme inhibitors

Apart from the above-mentioned use of TMA lyase (18), mention should be made of the results of a study in which mice used choline analogs that inhibit the action of enzymes in TMA metabolism, thereby reducing plasma TMAO concentrations. The use of choline analogues could, therefore, provide a new approach to reducing the risk of thrombosis (69). Another interesting active ingredient that acts as a protective factor for the gut mucosa is Urolitin A (UroA) and its synthetic analogue UAS03, which improve close cell contact and gastrointestinal barrier function (87).

In recent years, fecal microbial transplantation (FMT) has been among the most mentioned interventions used to treat intestinal dysbiosis. The introduction of "good bacteria" taken from healthy subjects into the gastrointestinal tract of patients suffering from gut dysbiosis and its consequences is a new and effective therapeutic strategy. In a clinical study examining people with metabolic syndrome, there was a significantly improved insulin sensitivity after 6 weeks of FMT in which the donors were healthy people of normal weight. At the same time, FMT increased the amount of butyrate-producingbacteria (88). Although the acceptance of the therapeutic use of FMT is increasingly present, due to the perception of this method as a "natural" treatment and relatively cheap application, the risk-benefit ratio particularly in CVS diseases remains insufficiently clearly defined because the published experience with FMT is limited and the legal norm of this therapy has not yet been precisely regulated. Furthermore, there is a fear of the infectious potential of the therapy, which led researchers to investigate the use of "synthetic stool" products with a defined population of bacteria to alleviate such problems, and the use of "frozen donor material" such as the concept of a stem cell bank is being considered (89).

Concluding remarks

New knowledge and technologies are significantly changing medical doctrine, enabling a new, different view of the body, organs and health, as well as the causal factors of diseases. Research in the recent past, and sometimes surprising findings, have confirmed that the gut microbiota can affect the health of the host and trigger the disease by means of various pathophysiological mechanisms. Gut microbiota and dysbiosis are areas of research which,in the future,willlikely change the established methods of prevention and treatmentof diseases.

Although we can change the composition of the microbiota with prebiotics, probiotics, antibiotics, diet and "targeted enzyme inhibitors", for the time being we cannot predict and provide a detailed assessment of all the effectsof these interventions in the prevention of various diseases. With all the data obtained in biomedicine in recent decades, it seems unusual that it took so long before scientists and cardiologists began to systematically deal with the impact of 2 kg of microorganisms that colonize us and live with us "for better or worse". Although only some of the mechanisms that link the gut microbiota and certain cardiovascular diseases are presented, we must be aware of the possibilities of this research area in the development of potential drugs in the future. The newly clarified connections between dysbiosis and the pathogenesis of cardiovascular diseases offer new possibilities for early and targeted action.

P.S.Perhaps the new research will lead to a new subspecialization in internal medicine, which, as prof. Miodrag Krstićanecdotallymentionedin his lecture at the Congress of Internal Medicine in 2019, will be calledgastroenterocardiology.

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