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Interplay of Cardiovascular, Sleep, and Gut Microbiome Systems in Heart Failure: Implications for Disease Progression and Management.

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Abstract

Heart failure (HF) is a progressive cardiovascular syndrome associated with low efficiency of the ventricle filling or ejection, with high hospitalization rates, significant morbidity and mortality, and rising healthcare costs. However, emerging scientific evidence indicates that HF is a multisystem disorder where sleep disorders and gut dysbiosis are not just comorbidities, but a dynamic and active component in the progression of the disease via interconnected inflammatory, neurohormonal and metabolic pathways. The purpose of this review was to provide an overview of the current knowledge about the role of the heart-sleep-gut axis in the pathogenesis and progression of HF and to highlight novel therapeutic approaches. In this review we search all English language and literature reviews from past 10 years on PubMed and Google Scholar. The 19 eligible studies were screened, assessed for quality, and narratively synthesized. The evidence shows a bi-directional link between HF and sleep disorders, such as OSA, CSA, insomnia and circadian rhythm disorders. Consequences of intermittent hypoxia and sleep fragmentation are sympathetic activation, endothelial dysfunction, inflammation, oxidative stress, arrhythmogenesis and HF-induced congestion and respiratory instability further disrupt sleep. At the same time, in HF, gut barrier dysfunction, due to hypoperfusion and edema, allows the translocation of bacterial components and toxic metabolites. High levels of trimethylamine N-oxide (TMAO) have been linked with atherosclerosis, thrombosis, fibrosis and adverse cardiac remodeling, while low levels of short-chain fatty acids (SCFAs) have been related to impaired epithelial integrity and anti-inflammatory signaling. Dysregulated bile acid metabolism also plays a role in metabolic and inflammatory dysregulations. Circadian, autonomic, and immune pathways can contribute to sleep disruption and consequently, gut dysbiosis can worsen sleep disruption and influence sleep regulation via microbiota metabolites. In a therapeutic setting, continuous positive airway pressure (CPAP) may be useful in certain cases, adaptive servo-ventilation is being investigated, behavioral sleep interventions, diet changes, probiotics, and gut microbial metabolites are possibilities that need to be evaluated. Combining sleep assessment and microbiome-targeted therapies into the management of HF could impact outcomes, but large, longitudinal studies are required to demonstrate causal relationship and precision therapies.

Keywords: Heart failure, Gut Microbiome, sleep-disordered breathing, obstructive sleep apnea, insomnia, left ventricular diastolic dysfunction.

Background

Heart failure (HF) is characterized by impaired cardiac ventricular filling and/or ejection of blood to the organ systems of the body. It represents the advanced stage of structural and functional damage to the heart, causing an imbalance in compensatory and pathogenic mechanisms [1]. It is associated with a high rate of hospitalizations due to adverse outcomes and is considered a significant global healthcare challenge, which is associated with high morbidity and mortality rates. The rising prevalence of HF is remarkable and is expected to rise further in the 21st century due to an ageing population, improved

survival rates, and other factors [1]. In addition, it carries a significant economic burden as U.S healthcare spending is projected to reach $69.8 billion by 2030. Unfortunately, there is a significant challenge in reducing the occurrence of heart failure at both the individual and population levels, as many find it challenging to adhere to a healthy lifestyle, thereby reducing their quality of life. Chronic exposure to environmental stressors, such as poor diet, sleep deprivation, psychosocial stress, and gut dysbiosis, may also contribute to the development and progression of CVD, thereby increasing the risk of heart failure. It may further be exacerbated by arterial hypertension, coronary artery disease, and cardiomyopathies in their end phase [2].

Adequate sleep is of utmost importance for relieving stress and restoring mental vigor. With rapid socioeconomic development and lifestyle changes, the duration and quality of sleep among the modern generation have essentially declined. Almost 75% of heart failure (HF) patients, a population of over 26 million throughout the world, have poor sleep quality. Such patients often experience sleep-disordered breathing (SDB), insomnia, and disturbance in circadian rhythm. Sleep disordered breathing usually includes obstructive sleep apnea (OSA) and central apnea [1,2]. It is generally considered that obstructive sleep apnea is a potential cause of heart failure, while insomnia and central sleep apnea are the results of HF. However, there is an increase in the number of reports that describe the bidirectional relationship between sleep disorders and HF. Sleep disorder may contribute to left ventricular diastolic dysfunction through left atrial overload, left ventricular remodeling, pulmonary hypertension, and atrial fibrillation, which results in HF with preserved left ventricular ejection fraction and may eventually lead to the development of arrhythmia [1,2].

In central apnea, we have repetitive episodes of apnea, hypopnea, and hyperpnea, which frequently occur in patients with heart failure. Such episodes are found to cause sleep disruption, arousals, intermittent hypoxemia, hypercapnia, hypocapnia, and changes in intrathoracic pressure. These pathophysiologic consequences have deleterious effects on the cardiovascular system, often most pronounced in existing heart failure and coronary artery disease. HF patients may also be present with insomnia symptoms, which can be associated with other general symptoms such as fatigue, depression, excessive daytime sleepiness, poor function, incident HF, and mortality. Previous studies revealed that the circadian system strongly influences cardiac repair post-MI [3]. Severe disruption of circadian rhythm balance triggers a series of unfavorable events such as immune dysfunction, metabolic disorders, and premature death. In addition to this, there is evidence suggesting that prolonged sleep deprivation may trigger various mechanisms associated with CVDs, including endothelial dysfunction characterized by increased vascular inflammation, production of ROS, and sympathetic upregulation, seen in healthy adults as well. The intestinal microbiome plays a crucial role in human health and disease. The human gut microbiome refers to all the microorganisms present in the gut, also known as the microbiota. Determining the composition of this natural microbiome is a complex process [3,4].

Disruption in this microbiome is known as gut dysbiosis. There is growing evidence suggesting that gut dysbiosis has been contributing to the progression of several risk factors of heart failure, such as atherosclerosis, obesity, diabetes, kidney disease, and hypertension [4].These factors, in turn, are also

known to affect gut microbiota by disrupting the integrity of the intestinal barrier, which is usually homeostatic and tightly regulated. However, when cardiac function is compromised, it leads to the development of edema in the intestinal wall, which results in structural disruption of the mucosal epithelial barrier and increased permeability. This increase in permeability releases endotoxins, microbial elements (LPS), and microbial metabolites (TMAO and SCFA) from the intestine into the systemic circulation, thereby triggering an immune response and amplifying the ongoing systemic inflammation. The bioactive compounds produced by gut dysbiosis may further worsen heart failure by directly affecting cardiac tissues, leading to decreased cardiac output. It also worsens HF outcomes by impairing normal inflammatory responses in infarcted myocardium by elevating adverse cardiac gene biomarkers [3,4].

Although many studies have discussed the role of sleep disorders and gut microbiome changes in heart failure separately, only a limited number of reviews exist explaining the interaction between the above three systems [5]. At present, the impact of sleep deficiency on gut microbiota and microbiome-associated human diseases remains inconclusive. However, disruption in multiple factors influenced by the brain-gut-microbiome axis, including the Vagus nerve, the immune system, the neuroendocrine system, and bacterial metabolites, has the potential to contribute to both sleep disorders and cardiovascular diseases. Furthermore, serotonin, a precursor of melatonin, which regulates the circadian rhythm, has been proposed to be associated with certain intestinal bacteria.Nevertheless, direct evidence proposing a relationship between inadequate sleep and gut microbiomes remains insufficient. Despite this, emerging findings suggest that metabolic disturbances associated with sleep loss may be mediated through the overgrowth of specific gut bacteria. In contrast, the products of bacterial species that thrive in response to sleep loss have the potential to induce fatigue. In general, recent studies seem to suggest a multi-directional relation among gut microbiome, sleep, and the cardiovascular system, although mechanisms aren't entirely understood. Thus, this review aims to highlight the complex interplay between the cardiovascular system, gut microbiome system, and sleep disorders in the development of heart failure and vice versa [5].

Methodology

A comprehensive literature review was carried out to explore the connection between cardiovascular factors, sleep and gut microbiome systems within the Heart Failure pathology. The aim of this paper is to identify, analyze and summarize the findings from published peer-reviewed literature. The articles were chosen from PubMed and Google Scholar from the year 2016 to 2026 on these topics. The search strategy included the use of keywords and Medical Subject Heading (MeSH) terms to find the relevant articles in the advanced search bar of PubMed. The MeSH terms used include "cardiovascular diseases", "Dysbiosis", "Gastrointestinal microbiome", "Inflammation", "Heart Failure", "Microbiota", "Sleep Apnea, Obstructive" and "Cardio-renal syndrome" which were combined using the Boolean operators (AND, OR). Keywords used include Heart failure, Cardiovascular, Remodeling, Gut microbiota, Microbiome, Sleep, Sleep disorders, Cardio-metabolic, Metabolism and Insomnia.

The inclusion criteria used to select the papers were whether they were peer-reviewed, published in English, based on human studies, systematic reviews and those clearly discussing the relationship between the gut microbiome, sleep and heart failure risk. Articles excluded were those based on animal studies, duplicate publications, those not peer-reviewed, published prior to the selected time period from 2016-2026 and articles not directly related to the research topic.

The articles were then selected, and their relevance was explored by reviewing the abstracts and the suitable articles were shortlisted. Out of the 20 articles initially selected, 19 were chosen as the final source material after excluding repeated papers. Articles then underwent a full-text review to assess the quality of the selected material. The relevant information was then extracted using standardized data extraction methods which included the authors, year of publication, study design, sample size, main outcomes, findings and mechanisms of connections. The collected data was then further analyzed, arranged narratively and grouped by breaking them down into the pathophysiology, sleep disorders in Heart Failure, Gut microbiome variations in Heart Failure, their combinations through the exploration of the Heart-Sleep-Gut Axis and their Therapeutic and Clinical importance while assessing the validity and quality of the selected studies. Gaps in the current literature were identified and used to guide the future directions segment.

Discussion

Heart Failure as a Multisystem Disorder

Heart failure (HF) is considered as a failure of the heart to circulate enough blood for the body's needs. Now, however, it is known to be a multisystem disorder with complex interactions of cardiovascular, neurohormonal, immune, respiratory, and gastrointestinal systems. These interactions lead to gradual dysfunction and to a poor clinical outcome. One of the major mechanisms in HF is neurohormonal activation. This initially compensates for reduced cardiac output, causing activation of two systems: the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS). Chronic activation is a harmful process over time, that causes vasoconstriction, sodium and water retention, ventricular remodeling, fibrosis, and impaired cardiac function. A chronic state of inflammation and oxidation is also a characteristic of HF [1,2]. Myocardial dysfunction is related to elevation of cytokines (TNF-α, IL-1 and IL-6) and oxidative stress leads to damage of the cardiomyocytes and vascular endothelium, speeding up the progression of the disease. Clinically, these mechanisms are not only present in the heart but also play a role in other systems of the body giving rise to other clinical symptoms, including exercise intolerance, gastrointestinal dysfunction, sleep disturbance, and fatigue, and underscoring the systemic nature of HF as a whole-body disease, rather than a heart-only disease [2].

Sleep Disorders in Heart Failure

Sleep-disordered breathing (SDB) is quite common in HF and consists of obstructive sleep apnea (OSA), central sleep apnea (CSA), and Cheyne-Stokes respiration (CSR). While OSA is caused by repetitive collapse of the upper airways, CSA is due to instability in central respiratory control. With HF, circulation time is prolonged and the chemoreceptors are more sensitive to hypoxia, which makes the patient more susceptible to developing CSA and CSR. Clinically, these disorders greatly adversely affect the outcomes of HF. Recurrent hypoxia and sleep fragmentation lead to higher sympathetic activity, higher blood pressure and impaired myocardial recovery [2]. The most common complaints are fatigue in the daytime, difficulty concentrating and limited exercise tolerance. Importantly, SDB has a strong association with AF, VA, hospitalization and mortality. Even when symptoms are not controlled by treatment, sudden death while sleeping can be a real problem. There is a bidirectional relationship: pulmonary congestion and respiratory instability, both associated with HF, contribute to sleep apnea; and chronic cardiovascular stress and neurohormonal activation due to sleep apnea, in turn, worsen HF [2].

Gut Microbiome and the Gut–Heart Axis

The gut–heart axis is now recognized as a potentially important driver of the progression of HF. Gut barrier function is compromised by reduced intestinal circulation and venous congestion and LPS and metabolites such as trimethylamine N-oxide (TMAO) can enter the circulation. These substances cause systemic inflammation, dysfunction of the endothelium, and myocardial remodeling [3]. High TMAO values are linked to poor prognosis, fibrosis, increased thrombotic tendency, and mortality in heart failure patients. Increased TMAO level is correlated with poor prognosis, higher fibrosis, risk of thrombosis and mortality in HF patients. HF is also linked with gut dysbiosis, which involves decreased diversity of microbes, loss of beneficial bacteria and production of less short-chain fatty acid (SCFA). In normal circumstances, SCFAs help to maintain gut barrier integrity and regulate immune responses, but a decrease in these leads to inflammation and vascular dysfunction. On a clinical level, gut dysbiosis is associated with the severity of HF, inflammation, and the number of hospital admissions, which means it can serve as a clinical biomarker and therapeutic target. The methods of treatment include changes in diet and manipulation of microbiomes [3].

Clinical Relevance

Heart failure must be considered a systemic disease with interrelated cardiac, respiratory, and gastrointestinal problems. Hypersomnolence and gut microbiome changes are not only a result of HF, but a contributing factor to the disease process. Identification of sleep disorders early and modulation of gut dysbiosis could help in better controlling the symptoms, decrease hospitalizations and improve quality of life for the HF patients. These new routes can also be used as a basis for innovative targeted drugs in the future [2,3].

TMAO

The gut microbiome is responsible for the metabolism of substances such as choline and L-carnitine, which are derived from the diet. The main product of this process is TMA, which undergoes oxidation in the liver by an enzyme called flavin monooxygenase and produces TMAO, which is an important metabolite that connects gut dysbiosis with CVD and progression of heart failure [6]. Increased levels of TMAO in circulation have been shown to have negative effects, such as an increase in risk of occurrence of cardiovascular events, an increase in cardiac remodeling and undesirable results in patients diagnosed with heart failure. There are many pathways that seem to contribute to the toxic effects of TMAO in the case of CVD. One of the pathways by which this happens is through increased NF-κB and MAPK signaling mechanisms, which cause endothelial dysfunction and inflammation of the vasculature. Increasing TMAO reduces reverse cholesterol transport, resulting in increased foam cell formation, thereby accelerating atherosclerotic plaque formation. It also increases the formation of vulnerable coronary plaque and increases the risk of rupture of plaque, which again increases the occurrence of cardiovascular events [6].

Besides causing damage to the blood vessels, TMAO also plays a role in dysfunction and remodeling of the heart by increasing the levels of inflammasomes like ROS/TXNIP/NLRP3 and by increasing TGF-β1/Smad3 signaling pathways, which increase fibrosis of myocardium and lead to dysfunctional remodeling of the ventricles [7]. TMAO also disrupts the function of mitochondria in cardiomyocytes, reduces the contracting ability of myocardium and causes disturbances in metabolism by initiating intracellular stress pathways led by PERK. In addition, TMAO causes some changes in intracellular calcium signaling, which results in hyperresponsiveness of platelets and a pro-thrombotic state, which can worsen cardiovascular outcomes further [6,7].

Strong clinical findings show that an increase in the concentration of TMAO levels increases the severity of disease in patients with HF. Increased TMAO levels in circulation show links between acute decompensated and chronic heart failure, and high mortality and severe clinical outcomes. Altogether, these findings suggest the role of TMAO extends beyond being a biomarker of gut microbial imbalance but plays an active role in inflammation, atherosclerosis, thrombosis, and remodeling of the heart in heart failure [7].

SCFA

Another responsibility of gut microbiomes, such as Faecalibacterium, Ruminococcin, Clostridium, is fermentation of dietary fiber, resistant starch and other non-digestible carbohydrates; the result of this process is the production of short-chain fatty acids (SCFA) [8]. SCFA is mainly responsible for maintaining the integrity of the epithelium of the intestine and controls immune responses. Butyrate is an SCFA which is used by colonocytes to strengthen the integrity of tight junctions of epithelium via hypoxia inducible factor signaling, hence maintaining the gut barrier function. SCFA also initiates differentiation of T cells, reduces cellular responses of Th17 and decreases the activity of histone deacetylase enzyme; overall, these mechanisms form its anti-inflammatory properties. Low level of

SCFA is connected to an increase in permeability of the intestine, translocation of endotoxin, systemic inflammation related to CVD and progression of HF [8].

SCFA has a role in the regulation of cardiovascular function by many receptors led by mechanisms such as G protein-coupled receptors and olfactory receptors. These pathways regulate overall blood pressure by affecting vascular tone, secretion of renin and sympathetic nervous system activity. SCFAs increase the activity of endothelial nitric oxide, which increases the bioavailability of nitric oxide and causes dilation of vessels. Clinical findings show that reduction of SCFA levels relates to hypertension, dysfunction of epithelium and an increase in risk of CVD. SCFA protects the heart by decreasing inflammation, increasing the efficiency of mitochondria and limiting fibrosis of myocardium in patients with HF. SCFA plays a part in cardiac remodeling pathways such as TGF-β signaling and regulation of extracellular matrix, while at the same time improving energy metabolism of myocardium. Preclinical and clinical findings show that SCFA supplementation and a high fiber diet decrease blood pressure, reduce injury to the myocardium and improve heart function [8].

Bile Acids

The cholesterol, when it is metabolized in the liver, produces cholic acid and chenodeoxycholic acid, which are primary fatty acids which undergo the process of deconjugation, dihydroxylation and oxidation led by gut microbiome such as Bifidobacterium, Lactobacillus and Clostridium, resulting in the formation of secondary Bile acids like lithocholic acid, deoxycholic acid and ursodeoxycholic acid [9]. Bile acids are mainly involved in the digestion and absorption of fat, but recent studies show that it has another role as a signaling molecule in the axis of gut and heart. This shows that the gut microbiome that is involved in the transformation of bile acids can affect the composition of the bile acids in circulation and signaling pathways in metabolism [10].

Bile acid controls many metabolic and inflammatory processes. Farnesoid X receptor (FXR) and Takeda G- protein coupled receptor 5 (TGR5) are bile receptors present in cardiovascular tissues such as cardiomyocytes, endothelial cells, smooth vascular muscle cells and cardiac fibroblasts. The FXR signaling mainly controls metabolism of lipids and glucose, immune responses and synthesis of bile acids, whereas TGR5 plays a role in reducing inflammation of blood vessels and protects the heart. Gut microbiome via modulation of bile acid composition and receptor activation contributes significantly to the regulation of these pathways [10].

Increasing evidence indicates that dysregulated metabolism of bile is linked to the development and progression of CVD and heart failure. Heart failure patients had altered bile acid profiles, with a high secondary to primary bile acids ratio, which is linked with worse prognosis and reduced rate of survival. When bile acids get accumulated in large amounts, it can cause cardiac hypertrophy, metabolic disturbances, fibrosis, and mitochondrial injury by many mechanisms, such as inhibition of PGC-1α and reduction in oxidation of fatty acids, also activation of inflammatory pathways, such as AIM2 inflammasomes and signaling of type 1 interferon, which contributes to chronic myocardial

inflammation and adverse cardiac remodeling. Overall, studies suggest that gut microbiome-mediated bile acid metabolism shows a significant contribution to heart failure progression and cardiovascular homeostasis. Through interactions with FXR, TGR5 and other signaling pathways [9,10].

Immune and inflammatory pathways

There are two pathways that connect gut dysbiosis with the progression of heart failure: dysfunction of the immune system and long-term low-grade inflammation. The increased permeability of the intestine and gut dysbiosis increases the movement of lipopolysaccharide, which is a microbial product, into the blood circulation. This movement activates toll-like receptors and increases the inflammatory signaling pathways [11]. This leads to immune activation, the increase in tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), which are pro-inflammatory cytokines related to clinical heart failure. The gut microbiome has a powerful impact on systemic immune modulation. Decrease in beneficial bacteria such as Faecalibacterium prausnitzii and Akkermansia muciniphilia and increase in pro-inflammatory factors are main characteristics of dysbiosis; these changes lead to activation of the immune system and decrease in tolerance. These changes also lead to an increase in Th17 cell activation, reduction in the production of anti-inflammatory cytokines like IL-10, and a decrease in activity of regulatory T cells, all of which add to the inflammation of blood vessels and progression of atherosclerotic atherosclerosis [11,12].

In HF, signaling of inflammation is reinforced because of the activation of nuclear factor kappa B (NF-κB) and the NLRP3 inflammasomes, which are part of intracellular pathways. Other factors, like TMAO, play a role in the dysfunction of the endothelium and remodeling of the heart by activating ROS/TXNIP/NLRP3 inflammasome signaling [12]. Oxidative stress acts as an upstream signal and a downstream amplifier of inflammation, and the increase in ROS causes damage to the endothelium, increases blood vessel permeability and launches inflammatory cascades like NF- κB. sleep disorders and psychological stress also influence systemic inflammation in patients heart failure, other than intestinal mechanisms. Sleep apnea and sleep fragmentation are associated with elevated levels of inflammatory cytokines like TNF-α and IL-6 in the blood, and gut dysbiosis (disruption of the gut flora) further drives immune system activation. To conclude, current findings clearly show a link between gut dysbiosis, sleep disorders and progression of heart failure [12].

The Heart-Sleep-Gut axis

Sleep-Gut interaction

Through circadian and neuroendocrine regulation, disturbance in sleep had a direct and reciprocal impact on the integrity of the intestinal barrier and composition of gut bacteria. A decrease in the diversity of microbes and loss of beneficial anaerobic and SCFA-producing species like Lachnospira, Roseburia and Prevotella is associated with shorter sleep duration and impaired circadian rhythm. This

change in gut microbes indicates a decrease in metabolic resilience and a rise in the inflammatory potential of gut ecosystem [13]. Amongst the major consequences of sleep disruption, there is an increase in intestinal permeability, which allows translocation of lipopolysaccharide and triggers immune response. Low levels of SCFA disrupt the epithelial barrier and trigger the production of pro-inflammatory cytokines, while inhibiting anti-inflammatory cytokines.

Sleep disorders trigger metabolic abnormalities (hyperglycemia, hyperinsulinemia, and increased caloric consumption) that, in turn, affect the composition of gut bacteria even further. These effects along with autonomic imbalance (decreased vagal tone and sympathetic dominance) result in decreased perfusion of mucosa and gastrointestinal motility. Such disruption of circadian rhythm further alters these pathways by inhibiting pathways in microbial metabolism including tyrosine, phenylalanine and tryptophan, and enhancing sulfur pathways. The changes in composition can activate additional inflammation and neuropsychological disorders [13]. Furthermore, metabolic abnormalities associated with vitamins (e.g. enhanced B6 breakdown) may cause fatigue and neurocognitive deficits. All the above processes are interconnected and contribute to sleep disruption, which in turn is linked to gut dysbiosis.

Gut-Sleep interaction

Gut microbiota affects the physiology of sleep through neurochemical, immune, and autonomic systems, being an essential element of the brain-gut microbiome axis (BIGMA). The tryptophan produced due to microbiome regulation serves as the basis for serotonin synthesis; it transforms into melatonin, which controls circadian rhythms and sleep-wake cycles. The function of sleep is governed by afferent vagal signaling from the gut microbiome [13]. Sleep is stabilized by microbial metabolites through vagal pathways regulating neuroimmune signaling and anti-inflammatory reflexes. The disturbance in the autonomic balance and sleep is caused by gut dysbiosis, and at the same time, the microbial composition regulates the balance of the sympathetic and parasympathetic nervous systems. In both cases, there is negative influence on the quality of sleep. It is important to note that the studies demonstrated the causal effect of the gut microbiota on the inflammation during sleep, since the inflammatory responses after sleep deprivation are reduced without microbes and can be transferred through microbiome transplantation. This proves the idea that gut microbiota is an active mediator of sleep-induced physiological changes [13].

HF-gut-sleep interaction

Heart failure affects and is affected by gut dysbiosis and sleep disorders, demonstrating a complex two-way network within the heart–sleep–gut axis. The main mechanism which links HF to gut dysbiosis is impairment of intestinal perfusion. Intestinal hypoperfusion, bowel wall edema, and disruption in the integrity of the epithelial barrier are the result of decreased cardiac output and systemic venous

congestion in HF [14]. These changes create a positive environment for the development of gut dysbiosis in which there is a reduction in the diversity of the microbiome and changes in the abundance of beneficial bacteria. Dysbiosis, which is related to heart failure, adds to the progression of disease by disturbing the production of beneficial metabolites of microbes such as SCFA and by increasing the levels of pro-inflammatory metabolites like TMAO. Considering that low concentration of SCF adversely affects the structure of intestinal barrier and increased concentration of TMAO results in the development of oxidative stress, impaired anti-inflammatory signaling, dysfunction of endothelium, inflammasome activation, fibrosis and maladaptive cardiac remodeling. In general, these processes form a vicious cycle through which HF stimulates dysbiosis, which, in its turn, increases systemic inflammation and damage of cardiovascular system [14].

One of the most common reasons for sleep disturbances is HF, especially sleep fragmentation, insomnia, and sleep-disordered breathing such as obstructive apnea and central sleep apnea. Intermittent hypoxia and recurrent arousals linked with sleep apnea initiate activation of the sympathetic nervous system, oxidative stress, dysfunction of the endothelium and systemic inflammation. All these changes worsen cardiovascular stress and ventricular remodeling and add to gut microbial imbalance by affecting the perfusion of the intestine, autonomic regulation, and mucosal immune function. The role of autonomic dysfunction is a key point in the formation of this axis. The HF is known for chronic sympathetic activation and vagal suppression which adversely affects cardiac activity, intestinal motility, mucosal perfusion and regulation of sleep. Dysbiosis can additionally affect autonomic dysfunction through vagal impairment and neuroinflammation due to endotoxin [14].

Shared Mechanisms

The common mechanisms that affect the heart- gut-sleep axis are inflammation, oxidative stress, autonomic dysfunction and HPA axis activation. Dysbiosis, sleep deprivation and heart failure are all linked to an increase in levels of inflammatory mediators, activation of the immune system and increased production of pro-inflammatory cytokines due to sleep disorders. This prolonged immune activation contributed to endothelial dysfunction, cardiac remodeling and sleep disruption. Oxidative stress creates an excess of Reactive Oxygen Species (ROS) which further enhances this axis [15].

Autonomic dysfunction refers to chronic hyperactivity in the SNS and hypofunction of the VNS. Sleep apnea-induced sleep deprivation and intermittent hypoxia associated with sleep apnea, which is associated with vascular dysfunction and chronic cardiovascular stress. Overactivity causes dysbiosis, and consequently impairment of the epithelial barrier which further contributes to autonomic dysfunction and cardiovascular injury.

Sleep dysregulation, gut dysbiosis, and systemic inflammation and cardiovascular dysfunction are part of an important neuroendocrine axis known as the hypothalamic–pituitary–adrenal (HPA) axis, which links these various pathophysiological conditions within the heart–sleep–gut axis. Corticotropin-releasing hormone (CRH) from the hypothalamus is stimulated by chronic sleep disruption and physiological stress and triggers the release of adrenocorticotropic hormone (ACTH) and cortisol [15].

Chronic activation of the HPA axis results in chronic low-grade inflammation and immune dysregulation and metabolic imbalance, all of which play a role in the progression of heart failure.

Therapeutic and Clinical Implications

Sleep-focused interventions

Interventions aimed at improving sleep are a promising and important adjunct for treatment in HF, likely related to the complex interaction between sleep-disordered breathing, autonomic dysfunction and disease progression. The phenomenon of sleep apnea is common in HF and leads to intermittent hypoxia, sympathetic activation, and endothelium dysfunction, which together lead to impairment of cardiac performance. Positive airway pressure–based therapies remain an important management technique in this setting [13,14].

The most employed non-invasive treatment option in the case of HF patients with obstructive sleep apnea is continuous positive airway pressure (CPAP). CPAP results in improved airway opening, fewer episodes of apnea and hypopnea, less frequent interruptions in sleep patterns, and hypoxemia during sleep. Such physiological improvements can be explained by decreased activation of the sympathetic nervous system in these patients. The adaptive servo-ventilation (ASV) approach has been recommended as a new strategy to improve ventilation in HF patients suffering from central sleep apnea (CSA) and Cheyne-Stokes respiration (CSR). The mechanism underlying adaptive servo-ventilation consists of applying dynamic pressure support to regulate breathing and minimize respiratory oscillations typical for CSA. Despite the promising concept of ASV, the application of this therapeutic method in the treatment of HF has become subject to controversy. Studies performed on patients with HF and low EF demonstrated efficacy of ASV on the reduction of the incidence of breathing disorders, but this did not always result in an improvement of the cardiovascular prognosis, therefore the efficacy of ASV is controversial [13,14].

In addition to device-based approaches to HF control, the effects of sleep hygiene and circadian regulation are now increasingly recognized. Sleep hygiene includes consistent sleep-wake cycles, reduced nocturnal stimulus and creating a perfect environment for sleeping, all of which led to better-quality sleep and lower sleep fragmentation. In addition, behavioral sleep therapy has been shown to benefit HF patients by reducing symptoms of insomnia, fatigue, and impairment of functional ability [14].

It is also becoming evident that circadian dysregulation plays an active role in the pathogenesis of HF. The autonomic tone, inflammatory processes, and cardiometabolic factors are affected by changes in circadian rhythm, hence further worsening the disease. Optimal circadian rhythms involve proper timing regarding sleep and waking time, which ensures that all activities are coordinated with the body's natural rhythm while ensuring sufficient environmental light. This may increase the efficiency

of the autonomic function and reduce physiological stress in HF patients; however, further research needs to be conducted on this aspect [14].

Microbiome-targeted therapies

There are many findings that show a connection between gut dysbiosis and microbiome-derived metabolites to heart failure, which has led to increased research on therapeutic strategies focused on modifying the ecosystem of the gut microbiome. These therapeutic techniques rely on restoring microbial diversity, increasing the integrity of the intestinal barrier, reducing systemic inflammation and regulating the formation of toxic metabolites such as trimethylamine N oxide (TMAO). Current microbiome-focused approaches include changes in diet, consuming probiotics and prebiotics, fecal microbiota transplantation (FMT), postbiotic supplementation and inhibition of microbial metabolic pathways [15]. This approach targets the restoration of microbial diversity, increasing the integrity of the intestinal barrier, reduces inflammation, and controls the secretion of toxic compounds, including trimethylamine N oxide (TMAO). The composition of microbiome and production of metabolites such as short-chain fatty acids (SCFA), which are the main anti-inflammatory and cardioprotective mediators, is very much affected by diet, hence dietary changes are an important therapeutic technique. Diets that are rich in Fiber, resistant starch, fruits, vegetables, legumes and whole grains increase the number of SCFA-producing bacteria, whereas a diet high in fat and refined carbohydrates increases dysbiosis, reduces microbial diversity and increases permeability of the intestine [15].

The Mediterranean diet plays an important role in cardiovascular prevention, as it is linked with better diversity in microbiome, an increase in production of SCCFA, a decrease in inflammatory signaling, and better vascular function, which collectively decreases the progression of Heart failure.

Probiotics and prebiotics also have a therapeutic scope in the modulation of the composition of the gut microbiome. Probiotics are living in beneficial microorganisms, whereas prebiotics act as substrates that particularly enhance the growth of favorable bacteria. Both approaches are combined to enhance the restoration of diversity in microbial species. Research shows limited but positive results in HF patients [15]. Use of supplements containing Saccharomyces boulardii over the period of three months in HF patients was linked with reduced high-sensitivity C-reactive protein (hsCRP) and mild improvement in left ventricular ejection fraction (LVEF) without any significant improvement in function. In post-myocardial infarction population supplement containing Lactobacillus rhamnoses GG showed reduced circulating TMAO and transforming growth factor-β (TGF-β), which shows potential on inflammatory and fibrotic mechanisms, although there was no noticeable effect on cardiac function. Likewise, the HFrEF patients who were taking probiotic yogurts containing the strains of Lactobacillus acidophilus La5 and Bifidobacterium lactis Bb12 had lower levels of oxidized LDL and NT-proBNP, indicating the improvement in inflammatory and neurohormonal markers. However, the results were obtained from small study groups, with variability in probiotic strains and without long term follow-up information [15].

Fecal microbiota transplantation is an effective way of restoring microorganisms through transferring them directly into the recipient's body using stool samples from healthy people. It is one of the treatment options for patients who suffer from recurrent and/or resistant infections caused by C. difficile. In other diseases, including HF, where the condition is associated with dysbiosis, the role of this procedure is still under investigation. However, according to clinical data, FMT may influence the microbiome structure and host metabolism. The variations in the effect of the microbiome transfer depending on the donor have been noted; TMAO changes after the procedure were not always consistent. It was not used in the treatment of cardiovascular diseases due to the lack of safety and reproducibility of the procedure as well as the risk of pathogen transmission. Thus, FMT is not applied in HF [16].

Focusing therapeutic strategies on metabolites produced by the microbiome, such as TMAO, shows great promise in delaying the progression of heart failure. TMAO demonstrates a strong link with atherosclerosis, thrombosis and adverse cardiac remodeling. Reducing choline and carnitine-rich foods can reduce substrate availability to produce TMA by microbes. Drug-focused strategies have shown potential in altering this pathway. Use of low-dose aspirin has been shown to decrease the production of TMAO by choline-induced pathway, possibly via inhibiting microbial trimethylamine lyase activity, while statins have shown TMAO-lowering effects in post hoc analyses, although their direct role in microbial manipulation remains to be explored. Preclinical evidence shows that inhibition of TMA production by microbes can reduce atherosclerosis progression, thrombosis and adverse cardiac remodeling [16].

Standard HF therapies and microbiome

Standard drug therapies used for the management of heart failure (HF) are becoming more widely accepted as active components in the modulation of gut microbiome aside from their normal therapeutic role. In fact, exposure to therapeutic drugs is one of the main factors that determines the composition of the gut microbiome more than dietary and demographic factors [14,16].

Among drug therapies prescribed for HF, sodium–glucose cotransporter- 2 (SGLT2) inhibitors show beneficial properties in relation to modulation of microbiomes. These drugs increase the number of bacteria such as Faecalibacterium prausnitzii, Coprococcus and Eubacterium, which are responsible for the formation of SCFA and at the same time reduce the amount of toxic microbial metabolites such as p-cresol sulphate in blood circulation. The increase in the number of microbial species like Roseburia, which protects the heart by its anti-inflammatory properties, has been connected to the use of ACE inhibitors and β-blockers. But these drugs can only affect certain microbial species, for example, Coprococcus is a gut microbiome that can metabolize Ramipril, which is an ACE inhibitor, hence affecting its anti-hypertensive effects in some people. β-blockers and ACE inhibitors can affect cardiometabolic pathways that depend on the microbiome indirectly by hemodynamic and neurohormonal pathways [14,16].

D-precision medicine

The microbiota and the metabolites derived from the bacteria found in the gut have recently emerged as the key targets for drug treatment in HF and their role in precision medicine has started attracting more attention. TMAO, which is one of the metabolites produced by microbiota, is the most studied one in the context of the pathogenesis of HF. Increased concentration of TMAO is involved in the development of atherosclerosis, thrombosis, and maladaptive remodeling of the heart. Formation of TMAO requires substrate, such as choline, metabolism by gut microflora, which can be used as a molecular basis for future therapy development [17].

Another approach directed at the microbiome and applicable to HF includes fecal microbiota transplantation (FMT). Even though it has been proven to be an effective treatment for recurring C. diff infections, its role in heart failure remains undefined. Based on the present response, the efficacy of FMT is highly dependent on the microbial makeup of the donors, which may differ in their results. Moreover, its implementation now is not possible due to various safety issues, a lack of standardization, and the potential transmission of pathogenic organisms. Consequently, the personalization of medicine based on specific microbiome makeup and metabolic products, especially those associated with TMAO production, becomes a widely discussed topic. Nevertheless, its importance in heart failure remains hypothetical due to a lack of practical application [17].

Future directions

There is a vast scope yet to be explored when it comes to finding how gut microbiota can transform dietary and endogenous molecules into metabolites such as TMAO, SCFAs and LPS which act on and influence the peripheral organs and tissues of a host [18,19]. We can use advanced molecular and systems biology tools while integrating a multiomics approach when investigating these connections. Furthermore, it is essential to explore how the individual variations of gut microbiota composition interact with the host genetics in the occurrence of Heart failure. Once we manage to unravel the specific pathways, we can create tailored therapeutic approaches to modify these metabolites when treating the patients [18,19]

We could explore the ability of natural compounds such as flavonoids, omega-3 fatty acids and resveratrol in dysbiosis reversal which will in turn provide a cardio protective effect. We could also carry out longitudinal studies with human subjects and larger sample sizes to find the effect of sleep disorders or circadian rhythm interruption on the gut microbiota via circadian microbial mapping. This can help us identify how we can modify sleep and the gut microbiome as a non- pharmacological target in treating Heart Failure and other cardiovascular disorders [18,19]

Limitations

The small sample sizes analyzed during the publishing of the selected articles remain a limitation. The complexity of individualized host responses to microbial interaction as well as methodological challenges in targeting specific microbial processes remain the biggest hurdle that needs to be overcome when creating a gut microbiome forward pharmacotherapy in treating HF [20]. It is also necessary to carry out large and longitudinal studies to investigate the influence of individual host factors such as genetics, habitual diet, sex, age and lifestyle modulation which might cause epigenetic changes in the gut- heart axis because their exact relationship is yet to be fully unexplored. Furthermore, the relationship between microbe- microbe interactions and microbe-host interactions in disease susceptibility is still not properly understood. Even though there is proof currently that there is an effect of circadian influence on gut physiology benefiting cardiac repair, this information is not yet conclusive for human models. Another limitation is the lack of comprehensive analysis on the specific effects of partial versus prolonged sleep deprivation in the gut microbial composition [20].

Conclusion

Gut microbiome and its effects on the cardiovascular system is an upcoming topic of research with a multitude of applications in diagnostics, therapy and prevention. Gut- heart axis describes the interaction between gut microbiome and its metabolites as a risk in CVD genesis and its progression. By identifying these metabolites, we can alter the host's physiological processes and utilize these pathways as a potential therapeutic target for treating cardiovascular diseases. can also modulate the gut microbiota through diet, physical activity, pre- and probiotics, and targeted non-lethal antimicrobial enzyme inhibitors which will help the host prevent CVDs. This modulation along with the better understanding of gut bacteria helps us to modify the effectiveness of current HF medicine. Elevated levels of certain microbial metabolites could be either protective or a risk factor in the pathology of heart failure. Dysbiosis can also contribute to systemic inflammation, vascular dysfunction and disease progression through its metabolites.

Gut microbiotas are vulnerable to changes in sleeping patterns and sleep disturbances lead to changes in microbiota titers and vice versa. Also sleep deprivation leads to changes in functional pathways, where those with reduced sleep duration have a potential increased risk of incidence of cardio metabolic diseases. It has also been found that sleep disorders often accompany CVDs like Heart Failure. Obstructive Sleep Apnea has a very close association with the different phenotypes of HFpEF and treatment of it with CPAP and ASV may help to improve HFpEF or prevent its onset. It has also been found that Cognitive Behavioral Therapy for insomnia (CBT-I) may be a valuable addition to Heart Failure Management in addition to standard pharmacotherapy.

Studies show that Oxidative Balance Score (OBS) plays a role in the mortality risk of Cardiovascular-Kidney- Metabolic (CKM) score, with an increase in OBS leading to lower CKM severity and decreased mortality due to greater antioxidant exposure. In conclusion, the interplay of sleep, gut microbiota and

other systemic factors play an important role in the etiology and management of Heart Failure. Despite the vast potential of this association, its translation into practice remains constrained.

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