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CHANGES IN THE CARDIAC MICROBIOME FOLLOWING SARS-COV-2 INFECTION AND CARDIOVASCULAR COMPLICATIONS

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Abstract

The SARS-CoV-2 pandemic has demonstrated significant and persistent effects on the cardiovascular system. While acute viral myocarditis, endothelial dysfunction, and thrombosis have been well documented, emerging evidence indicates that alterations in the gut and cardiac microbiome play a crucial role in the development of long-term cardiovascular complications associated with COVID-19.SARS-CoV-2 infection induces profound dysbiosis in the intestinal microbiota, characterized by reduced microbial diversity, depletion of short-chain fatty acid (SCFA)-producing bacteria, and enrichment of pro-inflammatory pathobionts. This dysbiosis increases intestinal permeability, facilitating the translocation of microbial metabolites such as trimethylamine N-oxide (TMAO) and lipopolysaccharide (LPS) into systemic circulation.

These changes trigger chronic low-grade inflammation, endothelial dysfunction, myocardial fibrosis, and accelerated atherosclerosis, ultimately contributing to heart failure, arrhythmias, and other cardiovascular sequelae in Long COVID patients.Although the heart was traditionally considered sterile, recent metagenomic studies suggest the existence of a low-biomass resident cardiac microbiome that may undergo significant shifts following SARS-CoV-2 infection. This review summarizes current evidence on post-COVID microbiome alterations, the mechanisms of the gut-heart axis, and their clinical implications for cardiovascular disease. Understanding the complex interplay between SARS-CoV-2 infection, microbiome dysbiosis, and cardiovascular pathology opens promising new avenues for preventive and therapeutic strategies, including microbiota-modulating interventions such as probiotics, postbiotics, dietary modifications, and fecal microbiota transplantation.

Keywords

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SARS-CoV-2, COVID-19, cardiac microbiome, gut-heart axis, dysbiosis, TMAO, Long COVID, cardiovascular complications

The SARS-CoV-2 pandemic has shaken the world not only through acute respiratory infection but also through its profound and long-lasting effects on the cardiovascular system. While early studies primarily focused on direct viral myocarditis, endothelial dysfunction, and thrombosis, recent years have highlighted the increasingly important role of the gut-heart axis and the microbiome in post-COVID cardiovascular pathology.Although the heart has traditionally been considered a sterile organ, modern metagenomic studies have demonstrated the presence of a low-biomass resident microbiota within cardiac tissues. SARS-CoV-2 infection induces significant dysbiosis in the intestinal microbiota, which leads to increased intestinal permeability, translocation of microbial products such as lipopolysaccharide (LPS) and trimethylamine N-oxide (TMAO) into the bloodstream, and the amplification of systemic inflammation. As a result, post-COVID patients exhibit an elevated incidence of heart failure, arrhythmias, accelerated atherosclerosis, and other long-term cardiovascular complications.This review examines the alterations in the cardiac and intestinal microbiome following SARS-CoV-2 infection, the underlying mechanisms linking these changes to cardiovascular complications, and the potential of microbiome-targeted therapeutic strategies in the future[1,3].

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has resulted in one of the largest global health crises in modern history. Beyond the well-known respiratory manifestations, the virus has shown a remarkable tropism toward the cardiovascular system. According to large-scale studies, approximately 20–30% of hospitalized COVID-19 patients develop cardiovascular complications during the acute phase, while Long COVID patients exhibit persistent cardiac symptoms in up to 10–25% of cases even months after recovery[1,3,4].

The main cardiovascular manifestations associated with SARS-CoV-2 include:

- Acute myocarditis and pericarditis
- Myocardial injury (elevated troponin levels)
- Arrhythmias (especially atrial fibrillation)
- Heart failure (both new-onset and decompensation of existing disease)
- Thromboembolic events (myocardial infarction, stroke, pulmonary embolism)
- Endothelial dysfunction and microvascular damage
- Accelerated atherosclerosis in the post-acute phase

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Several mechanisms have been proposed to explain these complications:

1. Direct viral invasion — SARS-CoV-2 enters cardiomyocytes and endothelial cells via ACE2 receptors.
2. Hyperinflammatory response ("cytokine storm") — excessive release of IL-6, TNF-α, and other pro-inflammatory cytokines.
3. Hypoxemia and respiratory failure leading to increased cardiac workload.
4. Endothelialitis and coagulopathy.
5. Dysregulation of the renin-angiotensin-aldosterone system (RAAS).

However, in many patients with Long COVID, persistent symptoms occur even without clear evidence of direct viral damage. This has led researchers to investigate indirect mechanisms, particularly the role of the microbiome and chronic low-grade inflammation. Growing evidence suggests that disruption of the gut microbiota during and after COVID-19 plays a significant mediating role in sustaining systemic inflammation and promoting cardiovascular pathology long after viral clearance. Recent meta-analyses have shown that patients with severe COVID-19 and those with Long COVID display more pronounced gut microbiota alterations, which strongly correlate with the severity and duration of cardiovascular symptoms.This section provides the epidemiological and clinical foundation necessary to understand why the microbiome has become a critical area of investigation in post-COVID cardiovascular disease[5,6].

The SARS-CoV-2 pandemic has shaken the world not only as an acute respiratory infection but also through its profound and long-lasting impact on the cardiovascular system. Millions of people worldwide continue to suffer from Long COVID, with cardiovascular complications representing one of the most serious and frequent sequelae. While initial research primarily focused on direct viral myocarditis, endothelial dysfunction, and thrombotic events, scientific attention has recently shifted toward the critical role of the microbiome and the gut-heart axis.For decades, the heart was considered a sterile organ devoid of microorganisms. However, advances in metagenomic sequencing technologies have challenged this traditional view by revealing the existence of a low-biomass resident microbiota in cardiac tissues. SARS-CoV-2 infection causes significant disruption (dysbiosis) in the intestinal microbiota. This dysbiosis increases intestinal permeability ("leaky gut"), allowing bacterial products such as lipopolysaccharide (LPS) and pro-atherogenic metabolites like trimethylamine N-oxide (TMAO) to enter the bloodstream. The resulting chronic systemic inflammation, oxidative stress, and immune dysregulation contribute substantially

to the development and progression of post-COVID cardiovascular diseases, including heart failure, arrhythmias, accelerated atherosclerosis, and myocardial fibrosis[5,7,8]

This review aims to comprehensively analyze the changes occurring in the intestinal and cardiac microbiome following SARS-CoV-2 infection, to elucidate the pathophysiological mechanisms linking microbiome alterations to cardiovascular complications, and to explore potential microbiome-targeted therapeutic strategies for prevention and treatment of Long COVID-related heart disease.The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has resulted in one of the largest global health crises in modern history. Beyond the well-known respiratory manifestations, the virus has shown a remarkable tropism toward the cardiovascular system. Approximately 20–30% of hospitalized COVID-19 patients develop cardiovascular complications during the acute phase, while Long COVID patients exhibit persistent cardiac symptoms in up to 10–25% of cases even months after recovery. The main cardiovascular manifestations associated with SARS-CoV-2 include acute myocarditis and pericarditis, myocardial injury, arrhythmias (especially atrial fibrillation), heart failure, thromboembolic events, endothelial dysfunction, and accelerated atherosclerosis in the post-acute phase[3,6,7].

Several mechanisms have been proposed to explain these complications, such as direct viral invasion through ACE2 receptors, hyperinflammatory response (cytokine storm), hypoxemia, endothelialitis, coagulopathy, and dysregulation of the renin-angiotensin-aldosterone system. However, in many patients with Long COVID, persistent symptoms occur even without clear evidence of direct viral damage. This has led researchers to investigate indirect mechanisms, particularly the role of the microbiome and chronic low-grade inflammation. Growing evidence suggests that disruption of the gut microbiota during and after COVID-19 plays a significant mediating role in sustaining systemic inflammation and promoting cardiovascular pathology long after viral clearance.The human gastrointestinal tract harbors a vast and complex ecosystem known as the gut microbiota, consisting of trillions of microorganisms. In a healthy state, this microbial community maintains a delicate balance (eubiosis) that plays fundamental roles in digestion, immune system regulation, metabolism, and protection against pathogens. The gut microbiota ferments dietary fibers and produces short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate, synthesizes vitamins, maintains intestinal barrier integrity, and modulates both local and systemic immune responses[2,6,8].

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The Gut-Heart Axis refers to the bidirectional communication between the intestinal microbiota and the cardiovascular system. This axis operates through metabolic, immune, neural, and endocrine pathways. One of the most studied metabolites is trimethylamine N-oxide (TMAO), which is produced by certain gut bacteria and is strongly associated with atherosclerosis, platelet hyperreactivity, heart failure, and adverse cardiovascular events. Conversely, SCFAs exert protective effects by reducing inflammation, strengthening the intestinal barrier, improving endothelial function, and inhibiting cardiac fibrosis. Disruption of this finely tuned gut-heart communication — known as dysbiosis — has been linked to hypertension, atherosclerosis, heart failure, and arrhythmias. The SARS-CoV-2 virus appears to be a potent trigger of such dysbiosis, creating a vicious cycle of gut barrier dysfunction, systemic inflammation, and cardiovascular damage.SARS-CoV-2 infection triggers a cascade of events that significantly disrupt the gut-heart axis. The mechanisms linking post-COVID microbiome alterations to cardiovascular complications are multifactorial and interconnected[2,4].

The primary mechanisms include:First, the depletion of SCFA-producing bacteria leads to reduced production of butyrate and other short-chain fatty acids. Butyrate is essential for maintaining tight junctions in the intestinal epithelium. Its reduction causes increased intestinal permeability, allowing lipopolysaccharide (LPS) to enter the systemic circulation. This endotoxemia activates Toll-like receptor 4 (TLR4) on immune cells and endothelial cells, resulting in chronic low-grade inflammation and endothelial dysfunction[4].

Second, dysbiosis increases the population of bacteria that metabolize dietary choline and L-carnitine into trimethylamine (TMA). In the liver, TMA is converted to trimethylamine N-oxide (TMAO). Elevated TMAO levels promote foam cell formation, platelet hyperreactivity, vascular inflammation, and myocardial fibrosis. Multiple studies have reported significantly higher TMAO levels in post-COVID patients with persistent cardiac symptoms[3,4,7].

Third, the imbalance in gut microbiota alters bile acid metabolism, which affects lipid homeostasis and systemic inflammation. Reduced secondary bile acids impair anti-inflammatory signaling through FXR and TGR5 receptors in the heart and vessels.Furthermore, microbial dysbiosis influences the autonomic nervous system via the vagus nerve and alters the production of neurotransmitters and metabolites that affect cardiac rhythm and contractility. This may explain the high prevalence of arrhythmias and postural orthostatic tachycardia syndrome (POTS) observed in Long COVID patients.At the cardiac level, translocation of microbial products and inflammatory mediators can directly affect the resident cardiac

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microbiome, potentially shifting it toward a more pro-inflammatory profile. Although the biomass is low, these changes may contribute to localized myocardial inflammation and fibrosis even in the absence of direct viral presence. These interconnected mechanisms create a self-sustaining vicious cycle: gut dysbiosis → systemic inflammation → cardiovascular damage → further worsening of gut barrier function. This explains why many patients continue to experience cardiovascular symptoms long after the virus has been cleared from the body[2,5,8].

Following SARS-CoV-2 infection, several studies using metagenomic analysis of cardiac tissues and circulating microbial DNA have reported notable shifts in the cardiac microbiome composition. There is often an increase in the relative abundance of opportunistic pathogens such as Enterococcus, Streptococcus, and certain Proteobacteria species. Some researchers have also detected viral RNA fragments and changes in the bacteriophage population within the heart, suggesting possible direct or indirect viral influence on the resident microbial community[6,7,9].

These alterations in the cardiac microbiome may contribute to localized chronic inflammation, myocardial fibrosis, and impaired contractility. Translocation of microbial products from the gut (LPS and other endotoxins) can further activate resident immune cells in the heart, such as macrophages and mast cells, leading to persistent low-grade myocarditis even after viral clearance, the interaction between the altered gut microbiome and the cardiac microbiome appears to amplify pathological processes. Elevated TMAO and other pro-inflammatory metabolites can reach the heart tissue via systemic circulation and modulate the activity of cardiac resident bacteria and immune responses. This bidirectional communication between the gut and heart microbiomes is believed to play an important role in the development of post-COVID heart failure, arrhythmias, and pericardial inflammation[1,4,7].

The alterations in the gut and cardiac microbiome following SARS-CoV-2 infection are strongly associated with a wide range of clinical cardiovascular complications in both the acute and post-acute phases of COVID-19.In the acute phase, patients with severe gut dysbiosis show higher rates of myocardial injury, as evidenced by elevated troponin levels. Persistent endotoxemia and high TMAO concentrations correlate with increased risk of arrhythmias, particularly atrial fibrillation and ventricular tachycardia. Several cohort studies have demonstrated that COVID-19 patients with marked reduction in SCFA-producing bacteria are more likely to develop acute heart failure and cardiogenic shock. In Long COVID,

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the connection becomes even more evident. Many patients experience persistent symptoms such as palpitations, chest pain, exertional dyspnea, and postural orthostatic tachycardia syndrome (POTS). These symptoms frequently correlate with ongoing microbiome dysbiosis. Patients with prolonged reduction in microbial diversity and elevated TMAO levels show higher rates of subclinical myocardial fibrosis detected by cardiac MRI, diastolic dysfunction, and reduced ejection fraction[7,9,10].

Microbiome dysbiosis appears to accelerate atherosclerosis. Post-COVID patients with persistent gut barrier dysfunction exhibit faster progression of coronary artery disease and increased carotid intima-media thickness. Chronic low-grade inflammation driven by microbial products also contributes to pericarditis and myocarditis that can last for months after the initial infection.This clinical evidence highlights that the microbiome is not merely a bystander but an active participant in the pathogenesis of post-COVID cardiovascular disease. Understanding these associations opens important opportunities for risk stratification and early intervention in affected patients[4,7].

Conclusion: the SARS-CoV-2 pandemic has not only caused acute respiratory illness but has also unveiled the critical importance of the microbiome in cardiovascular health. This review demonstrates that SARS-CoV-2 infection induces significant and often persistent dysbiosis in both the intestinal and cardiac microbiomes, which plays a substantial role in the development of acute and long-term cardiovascular complications.The disruption of the gut-heart axis through multiple mechanisms — including reduced production of protective short-chain fatty acids, increased TMAO levels, endotoxemia, and chronic low-grade inflammation — creates a vicious cycle that can continue long after viral clearance. These microbiome alterations are strongly associated with myocardial injury, heart failure, arrhythmias, accelerated atherosclerosis, and various manifestations of Long COVID.

The traditional view of the heart as a sterile organ has been challenged, with emerging evidence supporting the existence and clinical relevance of a low-biomass cardiac microbiome. Although research in this field is still evolving, current data clearly indicate that microbiome dysbiosis is an important contributor to post-COVID cardiovascular disease.New understanding opens promising therapeutic horizons. Microbiome-targeted interventions — such as carefully selected probiotics, postbiotics, dietary modifications rich in fiber, and potentially fecal microbiota transplantation — may become valuable tools in preventing and treating Long COVID-related heart disease.Future research should focus on large-

scale, longitudinal multi-omics studies to establish causal relationships and develop personalized microbiome-based strategies. Early restoration of a healthy microbiome after COVID-19 may prove to be one of the most effective approaches to reducing the global burden of post-pandemic cardiovascular complications. SARS-CoV-2, the microbiome, and the heart reminds us once again that human health is deeply interconnected across different systems. A holistic approach that considers the microbiome as a vital organ will be essential in the post-COVID era of cardiovascular medicine.

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