Microbiota and Myopericarditis

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Contributor: Andrea Piccioni

Myopericarditis is an inflammatory heart condition involving the pericardium and myocardium. It can lead to heart failure, dilated cardiomyopathy, arrhythmia and sudden death. Its pathogenesis is mainly mediated by viral infections but also can be induced by bacterial infections, toxic substances and immune mediated disorders.

Keywords: microbiota ; myocarditis ; COVID-19 ; emergency department

1. Introduction: Microbiota and the “Heart–Gut Axis”

The growing interest in the study of the human microbiota has led to the evidence that many organs, that were once supposed to be sterile, also host their resident gut microbial communities. Interestingly, microorganisms residing in different body districts are not compartmentalized but crosstalk, through to the release of endotoxins and metabolites, that can then reach other microbial populations through the bloodstream [1]. The microbiota is the group of microbe populations living in the human body, and it includes bacteria, archaea, and viruses [1]. The gut microbiota is made up of the largest number of microbes, consisting of over one thousand resident microorganisms. Among bacteria, the main phyla are Firmicutes, Proteobacteria, and Bacteroidetes. While obtaining their habitat and nourishment from the host, these microbes protect the host from other pathogens, preventing infections. Indeed, their interaction with the intestinal surface, which constitutes the microbial niche, works as a physical barrier, increases competition for nutrients, helps produce antimicrobial peptides, and modulates immune cell function both in a pro- and anti-inflammatory fashion. All these effects have an impact on the immune system and consequently affect the susceptibility and the clinical course of many diseases.

Gut dysbiosis consists of an imbalance in the composition of the microbiota. It can lead to cardiovascular diseases [2][3]. At the same time, the presence of cardiovascular disorders can be responsible for gut dysbiosis. In fact, when cardiovascular function is impaired, the blood supply of the gut is not sufficient to maintain a health gut barrier, thus promoting a “leaky gut” situation [4].

More specifically, the “gut–heart axis” relies both on metabolism-dependent and metabolism-independent processes. In metabolism-dependent pathways, the gut microbiota acts like an endocrine organ that generates bioactive metabolites, including the trimethylamine/trimethylamine N-oxide (TMAO), short-chain fatty acids (SCFA), and primary and secondary bile acids (BA). In metabolism-independent mechanisms, impaired heart function contributes to splanchnic circulation congestion, bowel wall edema, and altered intestinal barrier, resulting in bacterial translocation, passage of bacterial products in the bloodstream, and subsequent pro-inflammatory state. Besides negatively influencing the function of many other organs, these changes may also worsen the heart function itself, in a vicious circle [2].

There is evidence of the role of the microbiota in atherosclerotic disease, coronary artery disease, and myocardial infarction pathogenesis. In particular, the atherosclerotic plaque contains DNA of the oral and the gut bacteria, and people with unstable plaques present reduced levels of anti-inflammatory peptides producing bacteria in the stool [5]. Moreover, high levels of TMAO have been associated with vulnerable coronary plaque, plaque rupture, and long-term risks of incident cardiovascular events in patients with acute coronary syndrome [6].

In the light of the described evidence, the modulation of microbial gut communities is an emergent topic to offer therapeutic strategies in heart disease. For example, some authors reported that—in animal models—the administration of antibiotics or probiotics reduces the extension of myocardial infarction size [7][8]. In an experimental study conducted on rats with coronary artery disease, the administration of the probiotic *Lactobacillus rhamnosus GR-1* for 6 weeks significantly improved the systolic and diastolic function of left ventricle, with benefits postinfarction heart remodeling and heart failure [8]. This probiotic was chosen owing to its ability to modulate the immune system via the gut, thus confirming the strict communication between gut and heart, through immune-mediated mechanisms [8]. In addition, this *Lactobacillus* was proved to contribute positively to the cardiac metabolism profile, preserving the cardiac cells taurine content [8].

Taurine is an amino acid abundantly expressed in the heart, with a role in heart failure and ventricular function. In the same way, *Lactobacillus rhamnosus GR-1* promotes gut health and reduces the concentration of some adipokines as leptin, providing protective effects on cardiac tissue [8].

Similar results were obtained with the use of a probiotic juice composed *Lactobacilli* (i.e., *Lactobacillus Plantarum*) and *Bifidobacterium* (i.e., *Bifidobacterium Lactis*) that also decreased the levels of leptin achieving the same benefits in terms of myocardial protection [7].

The administration of antibiotics in a study conducted on rats with coronary artery disease was demonstrated to have a protective effect on cardiac cells, too [7]. In fact, the treatment with vancomycin reduced the levels of the cytokine leptin with favorable effects on cardiac cells. Moreover, the antibiotic vancomycin given orally with water in these animals was tested to be effective in achieving cardio-protection. The same antibiotic introduced directly into the coronary circulation did not achieve the same result. Authors hypothesize that the intravenous administration did not modulate the gut microbiota, differently from the orally administration that reached the intestine [7][8]. This underlines that there is a link between gut microbiota and cardiovascular disease with the possibility of gut microbiota to have an effect on cardiac protection. Moreover, the protective cardiac effect obtained after two days of oral therapy ended three days after stopping the treatment and more studies are needed to explore this issue [7].

2. Microbiota and COVID-19

In the process of viral invasion, the intestinal microbiota plays a key role, acting as a barrier, interacting directly or indirectly with the virus, and stimulating the innate and adaptive immune responses. Viral infections also have the potential of changing the composition of the gut microbiota [9]. Indeed, during COVID-19, modifications in microbiota composition have been reported [10][11][12][13]. Patients with COVID-19 had a higher number of opportunistic pathogens and depletion of beneficial commensals. On the one hand, the baseline abundance of some pro-inflammatory bacteria such as *coprobacilli* and *Clostridiodes* was higher and correlated with a more severe disease course. On the other hand, anti-inflammatory bacteria like *Faecalibacterium prausnitzii*, *Eubacterium rectale* and bifidobacteria were underrepresented. Interestingly, some bacteroides (*B. dorei*, *B. thetaiotaomicron*, *B. massiliensis*, and *B. ovatus*) downregulate the expression of angiotensin-converting enzyme 2 (ACE2), reducing the possibility of virus-entry thus causing a lower SARS-CoV-2 viral load in fecal samples of patients [11][12][13].

Liu et al. studied the effect of fecal microbiota transplantation in 11 patients who recovered from COVID-19 and who had suffered with gastrointestinal symptoms, gut dysbiosis and alteration of their immune status. Fecal microbiota transplantation restored gut microbiota and alleviated gastrointestinal disorders, but also had an impact on the immune system as demonstrated by changes in the peripheral lymphocyte subset [14]. In addition, there was also an increase in *Bifidobacterium* and *Faecalibacterium* and restored Actinobacteria and Proteobacteria. The modulation of gut microbiota was also proven to reduce COVID-19 disease severity, with beneficial effects on gastrointestinal symptoms, too [14]. Additionally, other study groups are investigating the effects of gut microbiota modulation during COVID-19 infection. In particular, studies are focusing on the effects of microbiota in modulating the immune system of the host, particularly in terms of progression of cytokine storm. It is well known that gut microbiota strictly interacts with host immune system. Their relationship is complex and dynamic. Factors such as viral infections can modify this balance, triggering inflammatory and immune diseases [12]. However, many studies focusing on the interaction between immunity and microbiota have tried to sequence and characterize the microbiome's profile and to investigate on gut–microbiota modulators [11][12][13][14]. Another aspect that has been investigated is the role of KB109, a synthetic peptide, that can act as a microbiota modulator. In two trials it is currently being investigated whether or not it could significantly and positively impact microbiota composition, as a positive effect of COVID-19 disease [15][16][17].

3. Inflammatory Cardiomyopathies and COVID-19

The first reports in scientific literature regarding cardiac involvement during SARS-CoV-2 infection go back to the first months of the pandemic outbreak.

Many authors have described cases of patients with COVID-19 and inflammatory cardiomyopathies, mostly myocarditis [18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35] but also pericarditis [36][37][38][39][40][41]. In some cases, the cardiac disease was the first manifestation of the viral infection [19][27][37]. In other patients it was a life-threatening early complication, [22][23][29][36][42], or a fatal one [18]. Moreover, it could clinically display after infection recovery [28][30][33][35][43], or some-times remain subclinical, being detected only after cardiac imaging taking place for other reasons [44]. Manifestation could be cardiac tamponade or constrictive pericarditis, overall varying widely.

Acute myocardial dysfunction during the early course of COVID-19 has been retrospectively reported in 16–36% of patients [45][46]. While the etiology is unclear, it has been suggested that cardiac damage in COVID-19 could be attributed to stress-induced cardiomyopathy and immunological and microvascular damage [47].

The virus can indeed directly infect cardiac cells, entering in the endothelial blood vessels and activating immune response with endothelitis. Moreover, it can dysregulate hormonal pathways and activate proinflammatory responses with the release of many cytokines and the involvement of neutrophils, macrophages, platelets, and lymphocytes, thus provoking a prothrombotic state and a predisposition for clotting. This can happen both in the cardiac micro- and macro-vessels, with potentially many complications [47].

Moreover, it can dysregulate hormonal pathways and activate proinflammatory responses, with the release of many cytokines and the involvement of neutrophils, macrophages, platelets, and lymphocytes, thus provoking a prothrombotic state and a predisposition for clotting. This can happen in the cardiac micro and macrovessels. There are many different possible consequences, which range from the above discussed myocarditis and pericarditis, but also sudden arrythmias, heart failure and cor pulmonaris, plaque rupture. Another manifestation, closely associated with stress-induced mechanisms, is Takotsubo syndrome [47].

Post-mortem examination of hearts revealed potentially COVID-19-related cardio-vascular histopathologic findings, such as macro or microvascular thrombi, inflammation, and presence of intraluminal megakaryocytes. Even if these manifestations have been reported in almost half of autopsies (47.8%), functionally significant myocarditis was identified in only 2% of all cases [48]. Interestingly, when analyzing myocardial biopsies of patients with myocarditis/myopericarditis, no evidence of intracellular virus was reported [49]. Yet, some authors reported the presence of SARS-CoV-2 mRNA in the endomyocardial biopsies of patients with clinically suspected myocarditis, both testing positive [50] or negative for COVID-19 by nasopharyngeal swab [51]. SARS-CoV-2 particles were found in the cardiac macrophages or in the endothelial cells [52] but not directly in cardiomyocytes; some authors have thus suggested that the cardiovascular damage was caused by overall immune activation, rather than by direct viral induced damage [53].

The above discussed evidence has contributed to identifying and describing the “acute COVID-19 cardiovascular syndrome” (ACoVCS) in adults [54]. Yet, even though it has been identified as a clinical entity, its pathogenesis still remains largely unknown. Molecular mimicry and endothelial dysfunction have been hypothesized, but more studies are needed to confirm these results [49].

Even if our review focuses on adult patients, it is interesting to note that the ACoVCS presents some similarities with the “multisystem inflammatory syndrome in children” (MIS-C) described by Most, that has been reported in children with SARS-CoV-2 infection [54]. At a cardiac level, the MIS-C can present itself with coronary dilatation, which resembles Kawasaki disease [53][54]. Other manifestations can be elevated troponin, cardiogenic shock, and reduced biventricular function. In this study, all children tested negative for SARS-CoV-2 by polymerase chain reaction (PCR) test, but they also had specific IgG antibodies. The authors thus concluded that MIS-C could depend on a post-infectious inflammatory state that occurs several weeks after a primary infection [54].

There is much more evidence on the association between COVID-19 and cardiovascular complications, such as myocarditis, pericarditis, fulminant myocarditis with arrhythmias, as described above, but there is a gap of knowledge in understanding the different pathogenic mechanisms [55]. Fox et al. analyzed myocardial biopsies of COVID-19 patients with myocarditis and found an increased number of CD68 + cells (that indicate monocyte/macrophage lineage), compared to myocarditis which are not associated to COVID-19 infection [56]. Similar observations have been reported by other authors as well [50]. The significance of these data has not been clarified yet and the possible association with prognosis and mortality is unclear. Lethal complications of myocarditis (such as end stage heart failure, cardiogenic shock, etc.) have also been observed in patients with COVID-19 infection [49]. Sawalha et al. noticed that cardiac tamponade was present in 20% of echocardiograms in patients with COVID-19 infection. Moreover, patients who died usually also had a serious acute respiratory distress syndrome as well [57].

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