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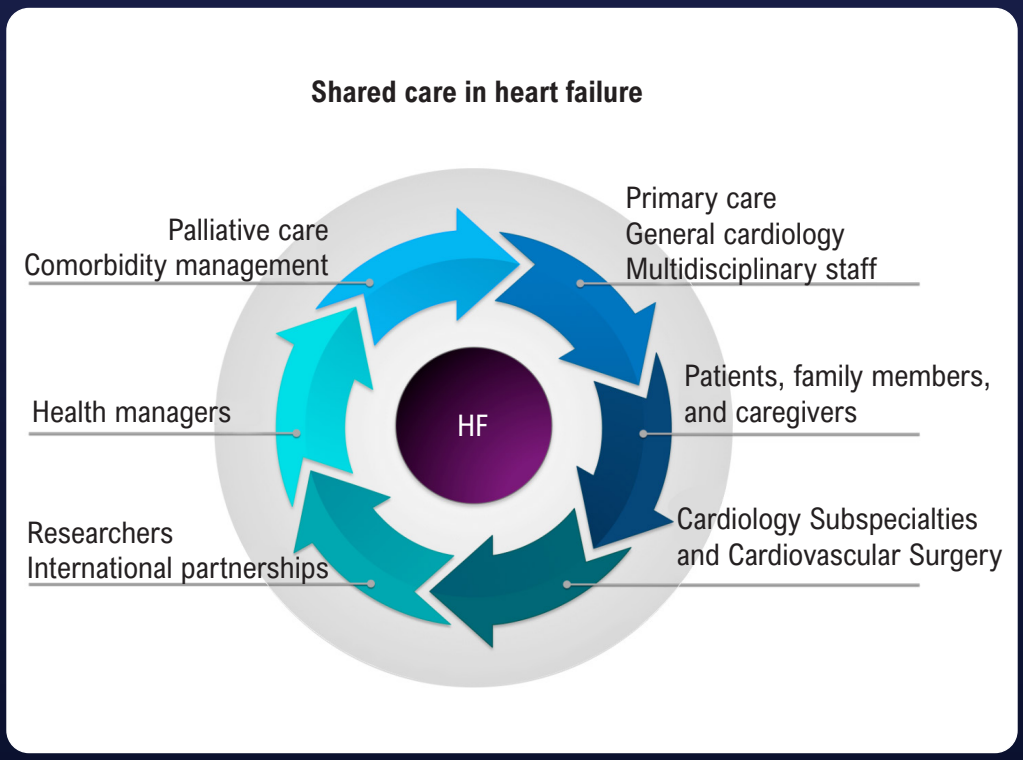

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Cardiovascular Burden of COVID-19 and the Post-Covid Era

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Coronavirus disease 2019, or COVID-19, rapidly became pandemic in 2020, causing hundreds of million cases and more than 2 million related deaths.[1] This scourge has affected a wide range of people, from children to older adults, from healthy to high-risk individuals. Since December 2019, when the first cases of a virulent pneumonia of unknown etiology emerged in Wuhan, China, COVID-19 has not only become a major global health threat but has stretched health care systems and providers to the limits worldwide.[2]

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a variable clinical presentation, encompassing a wide range of symptoms similar to those of many infectious conditions, including fever, cough, and general malaise, now well known to most physicians worldwide.[3,4] With disease progression, severe cases of COVID-19 can develop an acute lung injury with diffuse alveolar damage, producing the well-known bilateral infiltrates or ground glass opacities on chest x-ray or computed tomographic images.[5-7] Although most cases are mild, patients with severe COVID-19 are more likely to have background comorbidities such as diabetes, hypertension, older age, airways disease, and obesity, risk factors frequently shared by several cardiovascular diseases.[8]

Why COVID-19 became an issue for cardiovascular specialists? SARS-CoV-2- related myocardial injury and myocarditis

Approximately 20-30% of hospitalized patients with COVID-19 have evidence of cardiac injury, as indicated by elevated levels of high-sensitivity troponins.[9] The presence and magnitude of troponin elevation is associated with more severe disease and worse outcomes, even after adjusting for relevant risk factors. Myocardial injury portends a fatal outcome of COVID-19, while the prognosis of patients without myocardial injury, even with underlying cardiovascular disease, is more favorable.[10]

Keywords

Coronavirus-19; COVID-19; Syndrome Respiratory Acute Gravis; SARS-19; Betacoronavirus/complications; Pandemics; Cardiovascular Diseases/complications.

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The pathophysiology of SARS-CoV-2-induced myocardial injury remains a topic of active research. COVID-19 can unfavorably affect the balance between myocardial oxygen supply and demand, as with other overwhelming viral or bacterial infections (Figure 1). Fever, metabolic stress, sympathetic activation, and tachycardia increase the energy expenditure and oxygen consumption of the myocardium.[11,12] This imbalance can provoke type 2 (or "demand" type) myocardial infarction. Hypoxia from respiratory impairment can favor the production of reactive oxygen species and oxidative stress, acidosis, mitochondrial damage, and cell death.[11,13,14] Other mechanisms of myocardial injury during COVID-19 include ischemia from microvascular thrombi and toxic levels of cytokines. Cardiac damage due to direct SARS-CoV-2 infection of cardiac myocytes appears uncommon.[14-16] Indeed, the pericytes, smooth-muscle like cells that surround microvessels, express high levels of the receptor for SARS-CoV-2, angiotensin converting enzyme 2 (ACE2), while cardiac myocytes themselves have few, if any, of these portals of entry used by the virus.

Patients with COVID-19-related myocardial injury may present cardiac dysfunction and arrhythmias.[10] A single center study used advanced cardiovascular magnetic resonance (CMR) and found a high prevalence of myocardial edema and fibrosis in patients recovering from COVID-19, which was independent of preexisting conditions and of severity and overall course of the acute illness.[17] A subsequent multicenter study also used CMR to follow myocardial injury.[18] During recovery after severe COVID-19 with troponin elevation, patients still can present a myocarditis-like injury, but it is limited and without important functional consequence. Nearly half of the evaluated patients had an abnormal CMR imaging, with 3 patterns of injury: non-infarct, myocarditis-pattern injury (27%), ischemic pathology (22%), and non-ischemic non-specific scar (5%).[18]

Although viral myocarditis appears uncommon in COVID-19, clinical conditions that may injure the myocardium include microvascular dysfunction and thrombosis, stress cardiomyopathy, and type 1 myocardial infarction. Heart failure in patients with COVID-19 may be precipitated by acute illness in patients with preexisting known or undiagnosed heart disease, acute hemodynamic stress, myocardial depression due to cytokines, or incident myocardial injury produced by the above-mentioned mechanisms.[19]

In the absence of obstructive epicardial coronary disease but evidence of myocardial injury (defined as positive troponin with or without wall motion abnormalities), physicians often consider the diagnosis of myocarditis as the underlying cause, using data such as clinical and imaging markers of myocyte injury.

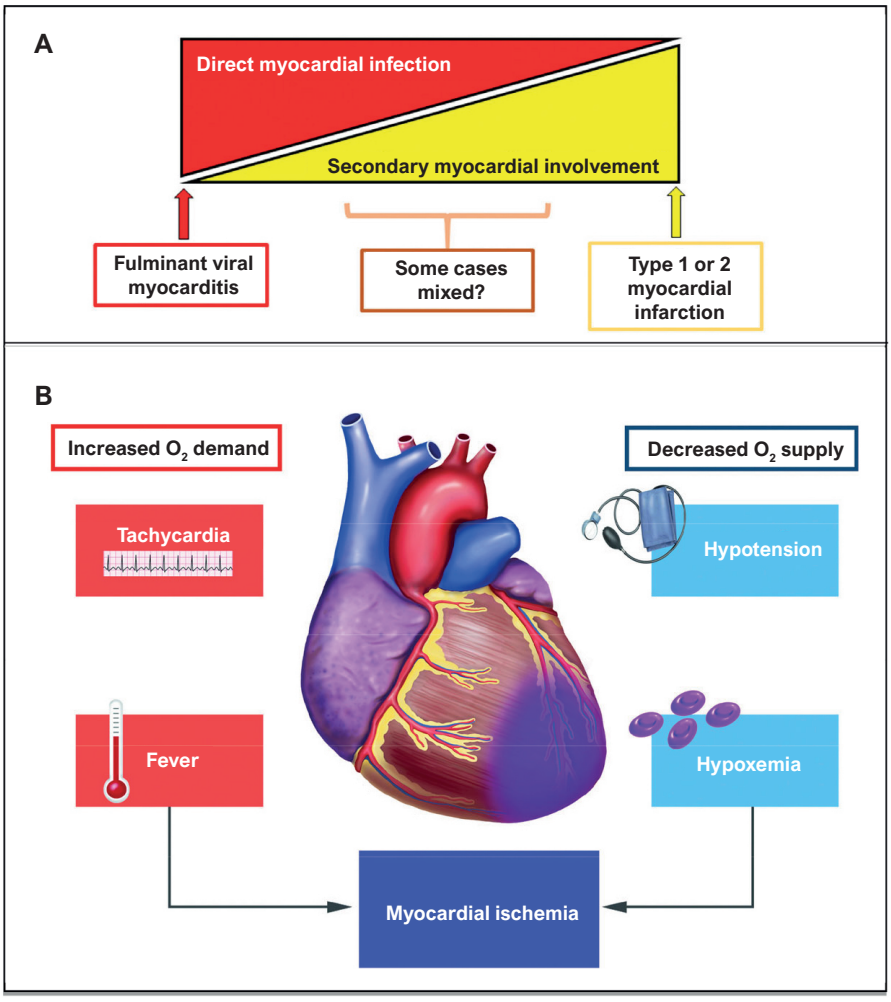

Figure 1 – *A) This hypothetical diagram represents the spectrum of myocardial involvement in coronavirus disease 2019 (COVID-19). On the left, fulminant myocarditis due to direct myocardial infection. On the right, acute coronary syndrome developed from severe pre-existing lesions triggered by systemic inflammation from an active infection. B) Physiological changes associated with infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that alter the balance between myocardial oxygen supply and demand to favor myocardial ischemia. Adapted with permission from Libby P. The Heart in COVID-19: Primary Target or Secondary Bystander? JACC Basic Transl Sci. May 2020;5(5):537-542. doi:10.1016/j.jacbts.2020.04.001.*[114]

Because the clinical presentation of myocarditis may vary, including vague or nonspecific symptoms such as fatigue, dyspnea, palpitations, and chest discomfort, the diagnosis of myocarditis in this setting is not straightforward. Indeed, most published cases of presumed myocarditis induced by COVID-19 infection were based on blood troponin levels or CMR, without biopsy confirmation.[20,21] However, there have been few reported cases of histologically confirmed myocarditis, and viral myocarditis caused by SARS-CoV-2 has generally not been definitively demonstrated by histologic and viral genome analysis.[19]

From a pulmonary perspective to vascular and thromboembolic consequences

Initially conceived as a respiratory viral disease, the understanding of COVID-19 has broadened to encompass a heterogeneous and complex multi-organ condition.[22,23] Emerging data indicates that COVID-19 patients have increased risk of broad systemic effects, including thrombosis,[24-26] kidney failure,[27,28] neurological events,[29,30] and cardiovascular complications, such as heart failure[31,32] and cardiogenic shock.[33]

A retrospective study comparing COVID-19 survivors and non-survivors showed that non-survivors had significantly higher levels of D-dimer and fibrin degradation products, as well as longer prothrombin time and activated partial thromboplastin time at clinical presentation.[34] These differences increased during serial measurements, with 71.4% of non-survivors meeting the International Society on Thrombosis and Hemostasis (ISTH) diagnostic criteria for overt disseminated intravascular coagulation. The coexistence of coagulation abnormalities, hyperfibrinolysis, and large-vessel thrombosis in patients with severe COVID-19 has been linked to multiple organ dysfunction syndromes.[35-37]

COVID-19-related endothelial activation, dubbed endothelitis by some, explains systemic microcirculatory impairment in different vascular beds and its clinical sequelae in patients with SARS-CoV-2 infection (Figure 2).[38-40] In addition to pericytes, arteriolar smooth muscle cells can express ACE2, and might act as target cardiac cells of SARS-CoV-2.[41,42] SARS-CoV-2 and SARS-CoV-1 share almost identical receptor-binding domains. Some clinical features of COVID-19 resemble those of other coronavirus infections, including SARS-CoV-1, which emerged in 2002, and MERS-CoV, which threatened a pandemic in 2012.[43] However, the SARS-CoV-2 binding site has a more compact and stable conformation, with structural features that enhance affinity for ACE2 and a furin cleavage site that increases the ability to infect target cells.[43,44] The expression of ACE2 receptors on pericytes and microvascular smooth muscle cells, as well as findings of acute endothelitis in patients with COVID-19, provides a potential mechanism of direct viral injury through an infection-mediated vasculitis.[38,41,45] Moreover, the presence of a furin cleavage site, which can be processed by near-ubiquitous furin-like proteases, sets SARS-CoV-2 apart from SARS-CoV-1 and other SARS-related coronaviridae that possess a monobasic cleavage site processed upon entry of target cells.[46-48] Understanding the mechanisms and pathophysiology of SARS-CoV-2 infection and how it affects endothelial cells may provide useful insight on therapeutic and preventive strategies to avoid disease complications.

Recruitment of immune cells can cause widespread endothelial dysfunction associated with apoptosis.[49,50] Pathologic data from patients with SARS-CoV-1 shows evidence of vasculitis with monocyte and lymphocyte infiltration, vascular endothelial cell injury, and stromal edema in the heart.[51] Likewise, biopsies and post-mortem histological examination in patients with COVID-19 revealed lymphocytic endothelitis with apoptotic bodies and viral inclusion structures in multiple organs, including heart, lungs, kidneys, and intestine.[7,38,52] The presence of viral elements within endothelial cells and accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death, suggests that SARS-CoV-2 infection yields endothelial activation in several organs, in addition to host's inflammatory response.[53] Marked inflammation and endothelitis can also augment tissue factor expression, leading to a prothrombotic state.[54-59] Analysis of pulmonary vessels in patients who died from COVID-19-related respiratory failure showed extensive thrombotic microangiopathy.[52] Similar pathophysiology can apply to other organs affected by advanced COVID-19 as well.

Endothelial dysfunction resulting from infection and inflammation may lead to decreased coronary flow and destabilization of pre-existing atherosclerotic plaque, triggering a type 1 acute coronary event.[60] Higher incidences of acute coronary syndromes, arrhythmias, heart failure-related events, and cardiovascular mortality observed during seasonal influenza outbreaks suggest a combination of systemic inflammation, vascular injury, and hypercoagulability.[61,62] Additional reports of severe Kawasaki-like disease in children support the hypothesis of systemic hyperinflammation and widespread endothelial dysfunction in the pathogenesis of the most severe forms of COVID-19.[63-65] The Kawasaki-like disease, also termed multisystem inflammatory syndrome in children, is characterized by persistent fever, gastrointestinal symptoms, rash, and conjunctivitis.[63,64,66] Those children will typically present with 3-5 days of fever, followed by vasodilatory shock that is often refractory to volume resuscitation, requiring vasopressors and, occasionally, mechanical circulatory support.

Conceiving COVID-19 as a vascular disorder provides a rationale for endothelium-stabilizing therapies that can also impact viral replication, such as renin-angiotensin-aldosterone system inhibitors,[38,67-70] statins,[71-73] and anti-cytokine agents.[74-76] These strategies could be particularly helpful in high-risk patients with preexisting endothelial dysfunction, such as those with hypertension, diabetes, obesity, and overt cardiovascular disease, all of which are associated with worse outcomes in COVID-19. Data available so far support the continuation of ACE inihibitor/angiotensin receptor blocker (ARB) and statins in patients taking them for pre-existing cardiovascular conditions.[77] The blockade of interleukin (IL)-6, a cytokine produced by macrophages that induces a proinflammatory response and is often elevated in patients with COVID-19, has been recently studied, with contradictory results.[78-83] We must await additional rigorously performed, properly powered, well-controlled, randomized trials before adopting or rejecting such therapies.

The clinical clouds gather: the heart may not resist a cytokine storm.

Massive cytokine release contributes to the most severe complications in COVID-19.[53] Such an aggressive host inflammatory response commonly precipitates hemodynamic instability affecting all vessels, from veins to arteries of all calibers, and the microcirculation of many organs, as well as embolic phenomena, renal failure and shock. Acute heart failure with decrements of myocardial contractility can accompany this profound septic state.[3,4,84]

Intense inflammatory responses will involve overactivation of innate immunity, led by infections, or other stimuli, and will follow an uncontrolled rise in cytokines concentrations, causing collateral damage in tissues and multiple organs.[85,86] The term "cytokine storm" first appeared in an article published in 1993 that describes the effects of graft-versus-host disease.[87] It gained notoriety after being used to describe the effects of the avian H5N1 virus infection in 2005.[88] Cytokine storm can complicate many infectious diseases, including SARS-CoV-1 and SARS-CoV-2,[86,89] influenza virus,[90] variola virus,[91] cytomegalovirus,[92] and group A streptococcus.[93]

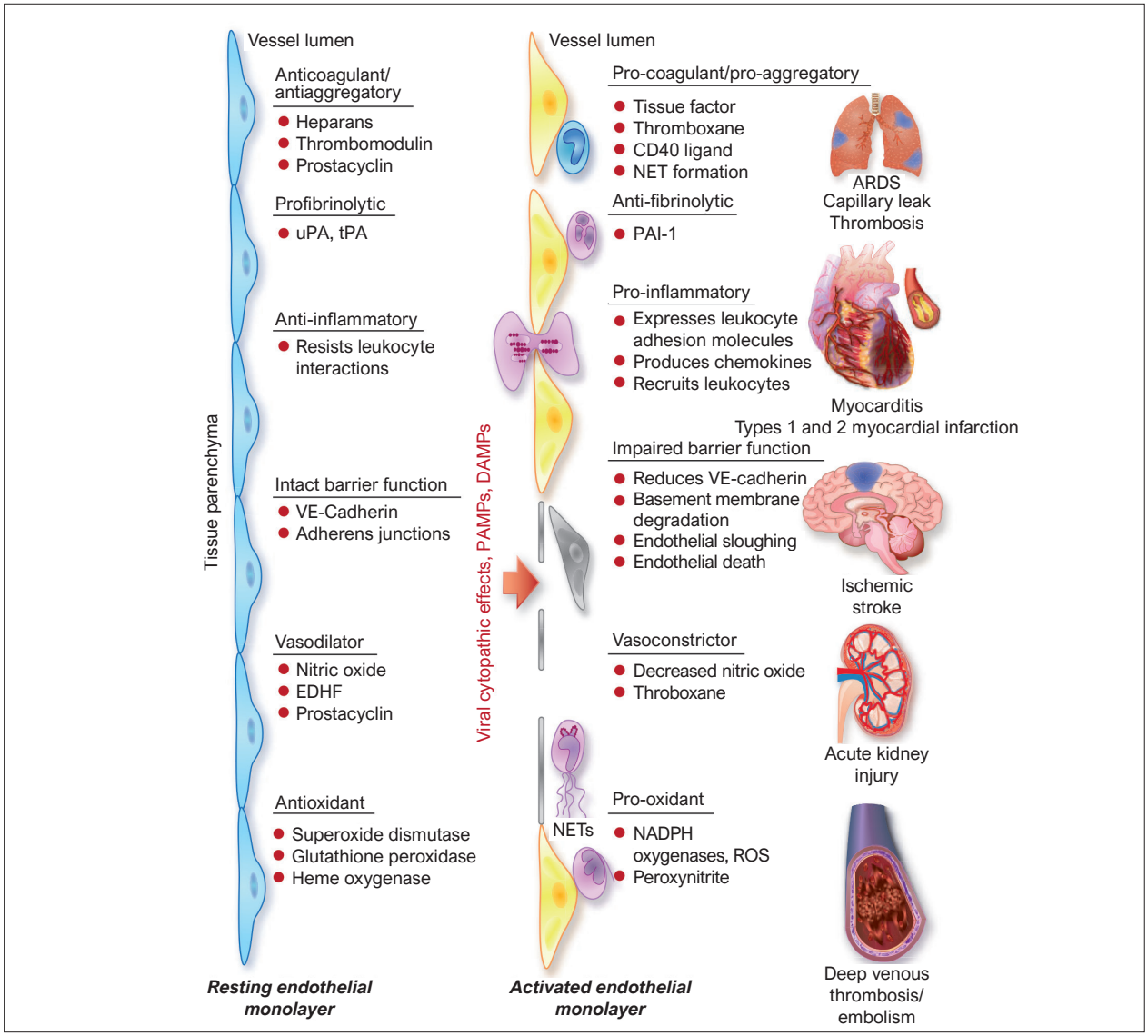

Figure 2 – *The left side of the diagram depicts a resting endothelial monolayer with the endothelial cells of squamous morphology resting on an intact basement membrane. When the endothelial cells undergo the cytopathic effect of a viral infection such as that caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or encounter pathogen-associated molecular patterns (PAMPs) derived from viruses or bacteria, such as lipopolysaccharide, proinflammatory cytokines such as interleukin (IL)-1 or tumor necrosis factor (TNF), or damage-associated molecular patterns (DAMPs) derived from dead or dying cells, the endothelial cells become activated. The endothelial cells display more columnar morphology. They can express adhesion molecules that attract leucocytes and chemokines that direct their migration into the subendothelial space. Sloughing of endothelial cells uncovers the thrombogenic basement membrane. Adherent neutrophils can undergo formation of neutrophil extracellular traps (NETs) that provide an amplifier for endothelial damage mediated in part by IL-1a. Inflammatory activation of endothelial cells can disrupt VE-cadherin largely responsible for the integrity of the endothelial barrier function. Activated endothelial cells can also express matrix metalloproteinases that can degrade the basement membrane and further interrupt endothelial barrier function. In small vessels, such as those that embrace alveoli in the lung, this impaired barrier function can lead to capillary leak. These various disturbances in endothelial function, depicted in the middle part of the diagram, lead to end organ damage, including adult respiratory distress syndrome (ARDS) and thrombosis in the lungs, predispose to plaque rupture and thrombosis in coronary arteries, and affect the microvasculature leading to myocardial ischemia and damage. The thrombotic diathesis provoked by endothelial dysfunction can also predispose towards strokes. Microvascular and macrovascular injuries can potentiate acute renal failure. Hepatic dysfunction can also result from microvascular thrombosis among other mechanisms. Deep venous thrombosis can occur as endothelial dysfunction represents an important part of Virchow's triad, and sets the stage for pulmonary embolism. Thus, loss of the endothelial protective function and unleashing of the mechanisms depicted can lead to multiorgan system failure that characterizes the advanced stages of coronavirus disease 2019 (COVID-19). Adapted with permission from Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. Eur Heart J. 09 2020;41(32):3038-3044. doi:10.1093/eurheartj/ehaa623.[39] uPA: urokinase-type plasminogen activator; tPA: tissue-type plasminogen activator; EDHF: endothelium-derived hyperpolarizing factor; PAI-1: plasminogen activator inhibitor 1; NADPH: nicotinamide adenine dinucleotide phosphate; ROS: reactive oxygen species; MI: myocardial infarction.*

Editorial

In the case of COVID-19, from the entrance of SARS-CoV-2 into a host cell, an active innate immune system responds with a cascade of processes, leading to the release of cytokines, such as interferons type I/III, tumor necrosis factor alpha (TNF-α), IL-1β, IL-18, and IL-6. Conversely, proinflammatory cytokines will alter endothelial cell homeostatic functions in a manner that can lead to thrombosis and local tissue injury. Within this inflammatory microenvironment, endothelial cells and invading leukocytes will produce IL-1, which can elicit the production of chemoattractant molecules, stimulating migration and penetration of more inflammatory cells into local tissues.[94] IL-1 can induce its own gene expression, triggering an amplification loop that can fuel a cytokine storm (Figure 3).[95-97] IL-1 can also enhance the gene expression of other proinflammatory cytokines, including TNF-α.[98] IL-1 potently sparks the production of another proinflammatory cytokine, IL-6.[99,100] This induction of IL-6 production by IL-1 provides another strong contributor for the amplification loop that will maintain the overwhelming cytokines production that characterizes a cytokine storm. IL-6 will act by boosting, in the liver, the synthesis of fibrinogen (precursor of clots), of plasminogen activator inhibitor 1 (PAI-1) (major inhibitor of fibrinolysis), and of C-reactive protein, a biomarker that is consistently elevated in COVID-19.[101] IL-6 plays a major role in acute lung injury and serves as a biomarker to predict the severity of COVID-19.[102-105] Consistently, high levels of other inflammatory biomarkers, as C-reactive protein, IL-2, TNF-α, interferon-g, D-dimer, and ferritin, also correlate with severe manifestations and worse outcomes of patients with COVID-19. Lymphopenia and thrombocytopenia are frequent in this late phase of COVID-19.[3,4,75,84,106,107] As components of the cellular immune response, natural killer (NK) cells and macrophages will undergo local activation, releasing cytokines to coordinate with activated T cells and other humoral responses in an attempt to resolve the infection rapidly.[86] Severe COVID-19 can entail functional exhaustion of NK cells and CD8+ T lymphocytes, an evolution that favors virus persistence, macrophage activation, and further cytokine release.[108,109] Antibody and cytotoxic T cell responses towards SARS-CoV can persist long after full recovery, with a moderate decline after one year from the onset of symptoms.[110]

Regarding cardiac dynamics, transient left ventricular dysfunction may occur during the acute phase of cytokine storm. A comparative echocardiographic study with SARS patients at the acute stage of infection and 30 days later showed a significantly higher left ventricular index of myocardial performance and a lower left ventricular ejection fraction, which characterized a subclinical diastolic impairment without systolic involvement at the acute phase. Furthermore, after 30 days, this impairment improved with clinical recovery.[111] Patients who have recovered from cytokine storm syndrome may still bear long-lasting scars, such as pulmonary fibrosis, functional disability, and reduced quality of life.[112] The long-term effect of myocardial injury sustained during acute COVID-19 will require careful attention in the coming years. Even in those who appear to recover fully from acute COVID-19, myocardial scarring could impair reserves required to withstand future insults. Fibrotic foci in the healed myocardium could nonetheless become substrates for reentrant arrhythmias as well as a long-term consequence of the acute SARS-CoV-2 infection.

At the level of the coronary arteries, the elevation of systemic cytokines can activate inflammatory cells resident in pre-existing atheroma and trigger a type 1 acute coronary syndrome due to plaque rupture.[113] Cardiac ischemia can also arise from an imbalance between oxygen supply and demand. Even in the absence of epicardial atherosclerosis, the release of cytokines from a systemic or neighboring infection, such as pneumonitis, can activate the coronary microvascular endothelium and predispose to vasomotor abnormalities, augmented thrombosis, reduced fibrinolysis, increased leukocyte adhesion, and other aspects of dysfunction of heart microvessels.[40,114]

Perspectives

Is this pandemic ending or just beginning?

We are still learning about COVID-19 and new variants of SARS-CoV-2. Current evidence supports the use of remdesivir, glucocorticoids, prophylactic doses of anticoagulants, and anti-SARS-CoV-2 antibodies in certain hospitalized patients with COVID-19. We still need more evidence-based therapies for shortening the course of COVID-19 or reducing the need of mechanical ventilation or intensive care. The use of anticytokine agents might help to improve in more severe scenarios, in which there is dysfunction of biological systems and higher risk of fatalities. It is crucial to block an overwhelming wave of elevated cytokines, although we await the results of rigorous trials in this regard.[74-76] There are few reports of reinfections following 50 days from recovery,[115] and breakthrough infections can occur, albeit uncommonly, in those already vaccinated. Recovery from some symptoms, such as anosmia[116] or fatigue,[117] can also be incomplete.

Our current best approach to eradicate or, at least, control the SARS-CoV-2 threat is vaccination. There are many vaccines, based on different approaches, with results varying from reducing new cases to muting the advanced manifestations of COVID-19. The development of a variety of vaccines in rapid succession to confront the COVID-19 crisis represents a victory of medical science. We have reaped the benefits of decades of investment in basic research and in pharmaceutical development faced with this murderous pandemic. Since its recognition in December 2019, this pandemic has spurred many developments, strikingly altered most lives, disrupted daily routines, work, social gathering, exercising, with consequent challenges to both mental and physical health.

With the economic burden, strain on health systems, and urgent demand for vaccine, governments have struggled to accomplish the full vaccination of populations in a timely manner. We need to learn the durability of immunity conferred by the vaccines, and develop booster vaccinations that will prolong protection and broaden the spectrum of variants covered.

As a society, we must learn from this crisis to prepare ourselves to face future global health challenges in a more coherent and organized fashion. As professionals devoted to health care, we need to allow science rather than political considerations to lead our responses to public health disasters such as we have faced with COVID-19. To prepare for future outbreaks, investigators need to organize a priori to cooperate

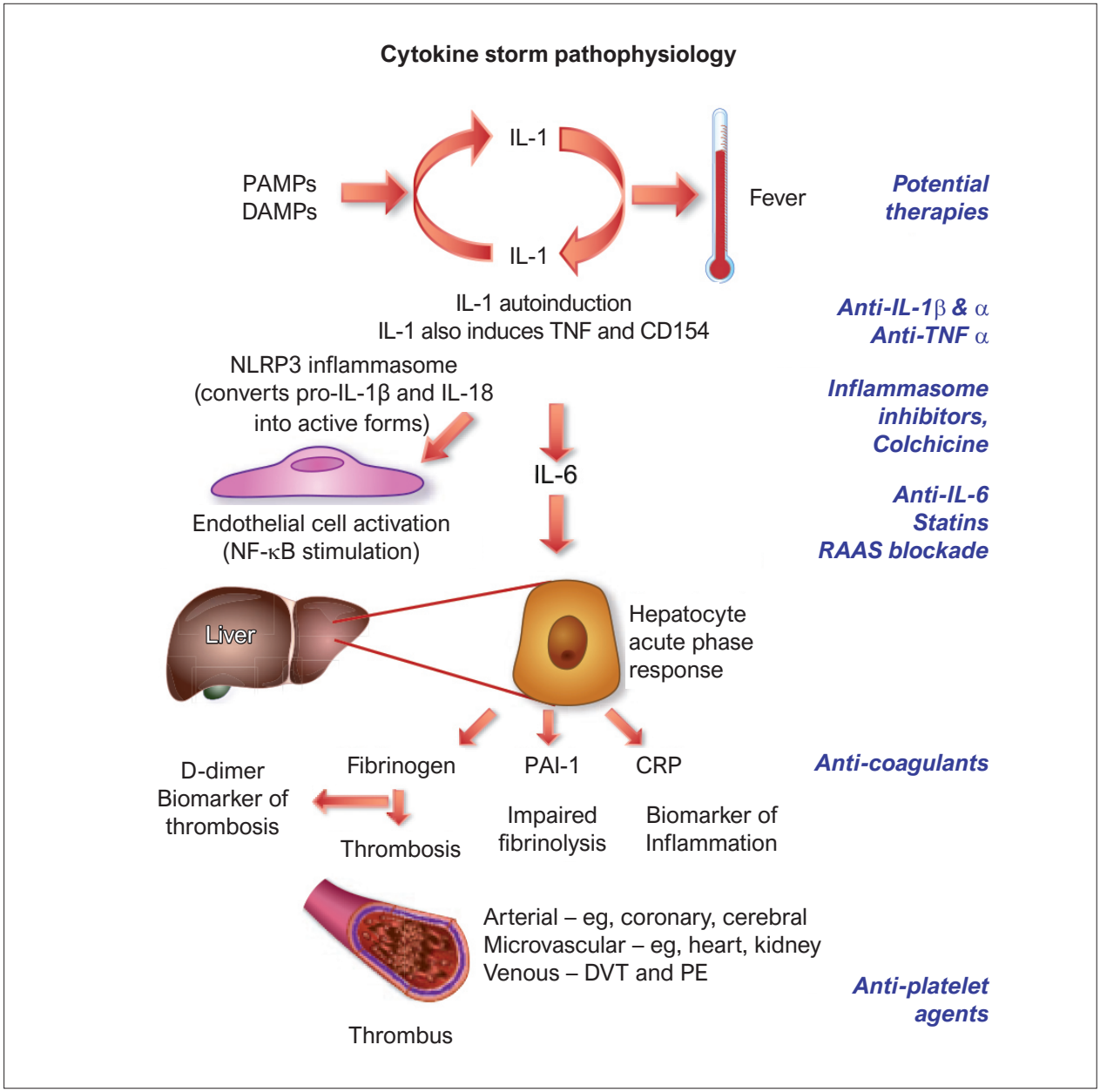

Figure 3 – *Cytokine storm. Proinflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor alpha (TNF-α) induce each other's gene expression, unleashing an amplification loop that sustains the cytokine storm. The endothelial cell is a key target of cytokines, as they induce action of a central proinflammatory transcriptional hub, nuclear factor kappa beta (NF-kB). IL-1 also causes substantial increases in production by endothelial and other cells of IL-6, the instigator of the hepatocyte acute phase response. The acute phase reactants include fibrinogen, the precursor of clot, and plasminogen activator inhibitor 1 (PAI-1), the major inhibitor of our endogenous fibrinolytic system. C-reactive protein (CRP), commonly elevated in coronavirus disease 2019 (COVID-19), provides a readily measured biomarker of inflammatory status. The alterations in the thrombotic/fibrinolytic balance due to the acute phase response promotes thrombosis in arteries, in the microvasculature, including that of organs such as the myocardium and kidney, and in veins, causing deep vein thrombosis (DVT) and predisposing towards pulmonary embolism (PE). Thus, the very same cytokines that elicit abnormal endothelial functions can unleash acute phase response, which, together with local endothelial dysfunction, can conspire to cause the clinical complications of COVID-19. The right side of this diagram aligns therapeutic agents that attack these mechanisms of the cytokine storm and may thus limit its devastating consequences. Adapted with permission from Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. Eur Heart J. 09 2020;41(32):3038-3044. doi:10.1093/eurheartj/ehaa623.[39] PAMPs: pathogen-associated molecular patterns; DAMPs: damage-associated molecular patterns; RAAS: renin–angiotensin–aldosterone system.*

internationally to perform randomized, blinded, controlled, and adequately powered trials, rather than a scattershot of smaller observational or poorly controlled studies. Scientific rigor is the only proper way forward. Interventions based on anecdote and unproven plausibility delay progress and thus represent a threat to public health. We must confront the glaring inequities this pandemic has aggravated among less privileged segments of society. We have a chance to learn lessons from this grave situation. It is our duty to do so, to prevent the inevitable future pandemics from taking such a deadly toll on our society in upending so many lives.

Declaration of Competing Interest

Dr. Peter Libby: Dr. Libby is an unpaid consultant to, or involved in clinical trials for Amgen, AstraZeneca, Baim Institute, Beren Therapeutics, Esperion Therapeutics, Genentech, Kancera, Kowa Pharmaceuticals, Medimmune, Merck, Norvo Nordisk, Merck, Novartis, Pfizer, Sanofi-Regeneron. Dr. Libby is a member of scientific advisory board for Amgen, Corvidia Therapeutics, DalCor Pharmaceuticals, Kowa Pharmaceuticals, Olatec Therapeutics, Medimmune, Novartis, and XBiotech, Inc. Dr. Libby's laboratory has received research funding in the last 2 years from Novartis. Dr. Libby is on the Board of Directors of XBiotech, Inc. Dr. Libby has a financial interest in Xbiotech, a company developing therapeutic human antibodies. Dr. Libby's interests were reviewed and are managed by Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict of interest policies. Dr. Libby receives funding support from the National Heart, Lung, and Blood Institute (1R01HL134892), the American Heart Association (18CSA34080399), the RRM Charitable Fund, and the Simard Fund.

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Editorial

The Role of the Heart Failure Specialist: Benefits for Both the Patient and the Cardiology Community

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In recent decades, the advancement of knowledge of cardiovascular diseases has been remarkable. Heart failure (HF) has a prominent role among the conditions of greatest epidemiological relevance for the population, given its high prevalence and incidence worldwide, including Brazil.[1-4] Thus, mastery of this condition is key to cardiologist training. However, the understanding of the complexity of the different diseases and pathophysiological mechanisms potentially involved in the development, progression, and prognosis of HF has advanced, and a broad and intricate spectrum of therapeutic options has emerged, especially in the past two decades. These advances allowed a significant improvement in the clinical outcomes of HF patients; however, as knowledge and consequent therapeutic challenges became more complex, it was clear that a new type of training and expertise in the field of Cardiology was needed.

The American Heart Association (AHA) and the European Society of Cardiology (ESC) were the first to encourage the growth and strengthening of the HF specialty, with the creation of study groups, departments, and journals focused on this condition.[5-7] Several specific HF congresses have been organized and brought together a growing number of participants for about 20 years. Concomitantly, several cardiology centers of worldwide relevance have developed fellowship programs in HF and heart transplantation, many of which more recently also cover mechanical circulatory support. Finally, certification examinations for HF specialist by the American Board of Internal Medicine (ABIM) and the ESC Heart Failure Association were created in 2013 and 2014, respectively.[5,8] In 2020, an expert consensus of the American College of Cardiology (ACC) together with the Heart Failure Society of America (HFSA) and the International Society for Heart and Lung Transplantation (ISHLT) introduced a list of requirements for HF specialist training, based on the core competencies of the Accreditation Council for Graduate Medical Education (ACGME).[9] This document outlines, in particular, the expectations for physicians who treat advanced HF patients or heart transplant recipients, and recommends specific skills in mechanical circulatory support, cardiac resynchronization therapy, heart transplantation, and pulmonary hypertension. The authors also recommend that there be a maintenance of certification process based on participation in continuing medical education programs and collaboration with national databases and registries.[10] Table 1 exemplifies and adapts the HF training model used at Brigham and Women's Hospital, Harvard University, Boston, United States.

In Brazil, although the Department of Heart Failure (DEIC) at Brazilian Society of Cardiology (SBC) completed 20 years in 2020 and ran its 19th annual congress in 2021, the HF specialty still lacks recognition among cardiologists, noncardiologists, multidisciplinary staff, health administrators, and patients and their caregivers.[11] Also, there is a limited number of specific training options, although some Brazilian centers grant HF specialization degrees with an additional year of training, following completion of cardiology residency. Some institutions have also designed specific medical residency programs accredited by the Brazilian Ministry of Education or Ministry of Health in the field of heart transplantation, which have included comprehensive content on HF and its different dimensions.[12] HF training programs currently available in Brazil are shown in Table 2.

These training programs aim to qualify the cardiologist to care for patients in all stages of HF, especially those with advanced disease who often require hospitalization, vasoactive drugs, invasive hemodynamic monitoring, mechanical circulatory assist devices, or heart transplantation. Technical skills and specific procedures may vary in the different HF training programs depending on the characteristics of the settings where graduates will work. Furthermore, these programs aim to prepare HF professionals to work in clinical settings collaboratively, seeking to integrate the different cardiology specialties that are important in the evaluation and care of HF patients. The advancement in the field of HF has expanded the scope of action of HF specialists, which is not restricted to the management of patients requiring advanced therapies and may currently involve evaluation and treatment of diseases of complex etiology, comorbidities, or pulmonary hypertension; cardio-oncology; multimodality imaging in cardiology; electrophysiology; cardiac rehabilitation; genetics; cardiac intensive care; and palliative care. It is worth noting that these physicians should be prepared to play a care coordinator role for HF patients in situations that very often include professionals from different disciplines, such as making prompt and critical decisions involved in the management of cardiogenic shock or chronic illnesses. Additionally, HF specialists play a growing role for improving research in this field.

Keywords

Heart failure/prevalence; Specialization; Learning; Continuity of Patient Care; Epidemiology; Cross-Sectional Studies.

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Table 1 – Adapted list of specific competencies and skills that are included in the Advanced Heart Failure, Heart Transplantation, and Ventricular Assist Device fellowship program at Brigham and Women's Hospital, Harvard University (Boston, United States)

General competencies
Patient care
Medical knowledge
Practice-based learning and lifelong education
Interpersonal and communication skills
Professionalism and ethics in professional conduct
Systems-based practice
Technical skills/procedures
Monitor and interpret cardiopulmonary stress testing
Monitor right heart catheterization and interpret a pulmonary vasodilator challenge
Monitor interrogation of ICD and CRT devices
Observe implantation and monitor interrogation of VAD
Monitor outpatient care for patients with VAD
Monitor organ harvesting, heart transplant surgery, and outpatient care for transplant patients
Monitor and discuss endomyocardial biopsy
Participate in end-of-life discussions and/or palliative care

CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; VAD, ventricular assist device.

Table 2 – Medical residency programs and specialization degrees in advanced heart failure and heart transplantation available in Brazil

1. Instituto Dante Pazzanese de Cardiologia
Continuing Education on Heart Transplant in Adults
2. Sociedade Beneficente Israelita Brasileira Hospital Alberto Einstein
Continuing Education on Transplant and Heart Failure
3. Instituto do Coração (Incor) – HC-FMUSP
Specialized Complementation Program: Congestive Heart Failure and Ventricular Assist Devices Heart Transplant Residency
4. Universidade Federal de São Paulo – UNIFESP
Medical Residency at Escola Paulista de Medicina Optional year: Heart Transplant
5. Hospital de Clínicas de Porto Alegre
Medical Residency – Additional year: Heart Transplant
6. Instituto de Cardiologia do Rio Grande do Sul/Fundação Universitária de Cardiologia
Medical Residency – Additional year: Heart Transplant Education
7. Instituto de Medicina Integral Professor Fernando Figueira – IMIP
Specialized Complementation Program – COMESP in Heart Transplant and Advanced Heart Failure

Source: Mesquita ET, Mendes AP, Moura L, Figueiredo Neto JA, Marcondes-Braga FG, Bacal F, Moreira MDCV, Clausell NO. The Challenges of Heart Failure Yesterday, Today and Tomorrow and the 20 Years of DEIC. Arq Bras Cardiol. 2021 Feb;116(2):359-362.[12]

In several countries and, most likely, in Brazil, family physicians, geriatricians, and general practitioners provide care to a large number of HF patients, in addition to general cardiologists.[13] In countries where the HF specialty is developed and recognized, this care pathway is based on an adequate flow of referral and counter-referral between nonspecialists and specialists, with significant interactions in the shared care model.[10,14] Nonetheless, several studies suggest that care provided by HF specialists improves clinical outcomes, including reduced hospitalizations and increased survival.[15,16]

Preliminary data from a research project conducted by our group, with support from SBC, indicate that HF patients may account for 25 to 50% of all patients treated by many general cardiologists; however, referral to HF specialists still seems to be infrequent. Limited recognition by both peers and patients was one of the main aspects considered by HF specialists to be barriers to the development of the specialty in Brazil (unpublished data). Our data suggest that, despite the efforts made in recent years to highlight the importance of the HF specialty in the cardiac care scenario in Brazil, there is still a long way to go so that this specialist is properly recognized and can positively impact the outcomes of HF patients.

In conclusion, given the increasing prevalence of HF and limited access to specialized care, more institutions should encourage physicians to train and become HF specialists. Additionally, it seems a good time to work on the idea that the presence and action of the HF specialist in a cardiology group or center will contribute to the growth of the field, leading to strengthened shared management practices with general cardiologists and potentially expanding the validation and the call for other cardiac specialties and multidisciplinary staff. With the inclusion of HF specialists, health managers and researchers will find a wide scope of practices to improve care and innovation processes, respectively. Finally, recruiting HF specialists to work on institutions will not only benefit the patients in terms of clinical outcomes but also add quality and progress through interdisciplinarity, which is a strong characteristic of contemporary care for these patients (Figure 1).

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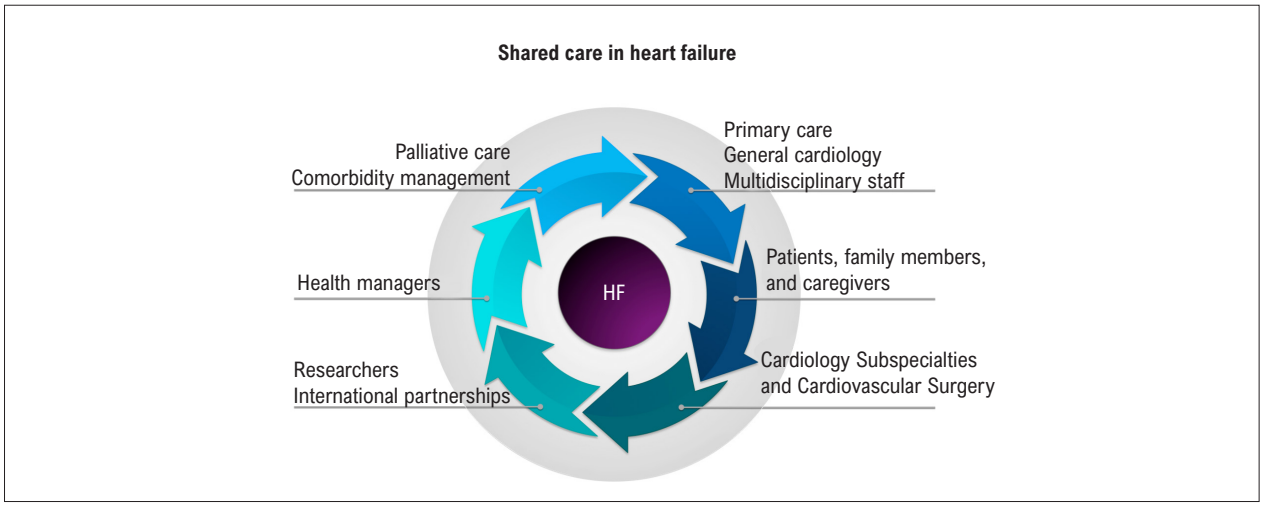

Figure 1 – *Graphical representation of interdisciplinarity in contemporary care of patients with heart failure. HF: heart failure.*

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Beyond the Disease – History of the House for Patients with Chagas Disease and Heart Failure of Pernambuco (Casa do Portador de Doença de Chagas e Insuficiência Cardíaca de Pernambuco)/PROCAPE-UPE/Brazil

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"Utopia is on the horizon. I move two steps closer; it moves two steps further away. I walk ten steps and the horizon runs ten steps further away. As much as I may walk, I will never reach it. So what is the point of utopia? The point is this: to keep walking".

Fernando Birri.

Where it all began

The history of the Chagas Disease and Heart Failure Outpatient Clinic of the Prof. Luiz Tavares Cardiology Emergency Unit of Pernambuco, at Universidade de Pernambuco (UPE), began in August 1987 at Hospital Universitário Oswaldo Cruz (HUOC). When it was created, in 1884, this hospital worked mainly providing care for patients with infectious and parasitic diseases. Since that time, the hospital worked with diseases that later became known as unassisted (nowadays named and classified as neglected diseases by the World Health Organization, WHO) and became a breeding ground for the inauguration of the Chagas Disease Outpatient Clinic.

In 1964, HUOC became a teaching hospital and started receiving medical students from Faculdade de Ciências Médicas de Pernambuco. At this moment, the hospital became the first referral center for clinical and surgical cardiology in the state, being the main and only public emergency unit exclusively dedicated to this specialty. The emergency demand was massive and various sectored wards were established for treating and caring for patients with heart disease. Among them, the myocardiopathies and heart failure ward, in the late 1970s, was coordinated by Professor Wilson de Oliveira Jr. In general, patients arrived at the cardiology emergency unit with decompensated heart failure, being cared for and referred to the myocardiopathy ward (Figure 1). Once compensated, these patients were discharged without systematic outpatient care, which resulted in various new hospitalizations. Many of these patients had chagasic heart failure.

Keywords

Chagas Disease; Heart Failure; Outpatient.

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This finding led physicians Wilson Oliveira Jr. and Cassandra Barros Correia to propose to the hospital board of directors the creation of an outpatient clinic specifically for patients with Chagas disease who left the myocardiopathy ward, whose social implications were and continue to be very specific. The idea was embraced with enthusiasm by the HUOC director at the time, who was also a cardiologist, Ricardo Paiva (Figure 2). The proposal aimed to positively impact the hospital's emergency and hospitalization demands. Patients with controlled disease would not need to seek this more complex care. At that moment, the ideal that would guide the organization of the Unified Health System (SUS), which was created in 1988, was already taking shape at HUOC, with the hierarchization of health services.

Therefore, with a small room, two physicians and one nurse (Valdinete Paiva), the HUOC's Chagas Disease Outpatient Clinic began operating, defending the motto "Humanizing for caring." Due to the restricted space and reduced staff, the assistance provided by the clinic was limited to the biomedical sphere. In face of the complexity of Chagas disease, with its social, economic, and psychological implications, the team felt the need to transcend the strictly biomedical approach into a more complete care, meaning a whole health care performed by a multidisciplinary team, which to the current day has been scientifically proven as the best option when caring for chronic patients.[1] In this perspective, the need to evaluate the patient as a whole was already clear, with the challenge of adopting the biopsychosocial model of care: It proposes a view of much more than a sick organ but also the person, his or her history, family, and socioeconomic context. For this, a group of professionals that helped increase the perception of various aspects of the reality of an individual was needed.[2]

At the same time, the clinic team had always sought to empower patients, providing them with more conscience of the social issues involving the disease and of the need to articulate and associate for together having more strength and amplifying their voices for fighting for their causes and for supporting each other, especially considering the neglected characteristic of this disease. The understanding was that the patient had to play an active role and not only be on the receiving end of the information flow. This is how the Pernambuco Association of Chagas Disease Patients was born, with the motto "A commitment with life"; it was the world's first association of people with Chagas disease.

Figure 1 – *Operating outpatient clinic at HUOC.*

Figure 2 – *First years of the outpatient clinic. On photo No. 4, from left to right: physicians Enio Cantarelli, Wilson de Oliveira Jr., Cassandra Barros, and Ricardo Paiva.*

As years went by, the outpatient clinic gained capillarity and included the pharmacological and non-pharmacological treatment of Chagas disease, chagasic and non-chagasic heart failure, and the evaluation and follow-up of patients with pacemakers (PMs) and implantable cardioverter-defibrillators (ICDs). As the work expanded and became known beyond the walls of HUOC, the Chagas Disease Outpatient Clinic was sought by the board of directors of the Pernambuco Hematology and Hemotherapy Center (Hemope), who aimed to refer blood donors with positive Chagas disease serology tests for diagnostic characterization and the follow-up of confirmed patients.

At the beginning of the 21st century, the activities performed by the clinic and the association had spread far beyond the state of Pernambuco. The result obtained through the adoption of the whole health model of care,

which also involved the association of patients and family members, surpassed territorial boundaries. In 2007, the physician Wilson de Oliveira Jr. answered an invitation by the WHO and represented the service, which he coordinated, in presenting the successful experience performed in the state of Pernambuco; it later became a model and inspiration for other organizations and associations worldwide.

In 2006, with the inauguration of the Prof. Luiz Tavares Cardiology Emergency Unit of Pernambuco, at Universidade de Pernambuco – Procape, envisioned and founded by Professor Enio Lustosa Cantarelli, (Figure 3) in addition to an increase in the number of patients (especially those with PMs and ICDs), a physical space was needed to accommodate the activities of the Chagas Disease and Heart Failure Outpatient Clinic, as well as the Pernambuco Association of Chagas Disease Patients' headquarters.

By the end of 2009, owing to the Chagas Disease Outpatient Clinic coordinator and his team, the Procape director, and association volunteers, a fundraising campaign was launched, receiving donations both from individuals and private institutions, with the aim of instituting House for Patients with Chagas Disease and Heart Failure of Pernambuco (Casa do Portador de Doença de Chagas e Insuficiência Cardíaca de Pernambuco)/Procape-UPE. The project was supported by Professor João Regis and the university dean Carlos Calado. A building that could accommodate the clinic and the association headquarters was purchased, and it was inaugurated in December 2010.

Figure 3 – *Visit of Professor Enio Cantarelli. Carolina Medeiros, Wilson Oliveira Jr, Maria das Neves Dantas, and Silvia Marinho Martins.*

Over time, the "Casa de Chagas" (Figure 4) house allowed a better welcome and care of these patients. The service has four specialized consultation rooms, is suited to patients with special needs, completely computerized, and connected to Procape via electronic medical records; it also offers a space for welcoming and socializing, equipped with audio and video resources, where special projects are conducted (Figure 5).

A neglected disease

Chagas disease is among the 21 diseases considered as neglected by WHO/2021. These are diseases that could be treated and cured in most cases, but that unfortunately affect entirely neglected populations. As opposed to global diseases such as arterial hypertension and diabetes, despite the progress of science, neglected diseases do not raise interest by the pharmaceutical industry and continue being diagnosed and treated as they were years ago, without significant advancements due to the lack of research funding. In addition to Chagas disease, the neglected diseases list includes schistosomiasis, malaria, Hansen's disease, and other conditions. These diseases end up resulting in significant stigma for the patient. Therefore, it is fundamental to understand that the patient with Chagas disease, just as the condition, is also neglected. His or her life conditions determine the onset of the disease.

The WHO estimates that between 6 and 7 million people are contaminated by Chagas disease worldwide, living precariously in endemic and non-endemic countries and with limited power for revindication. Nowadays, Chagas disease is predominantly urban, since more than two-thirds of the infected individuals live in cities, and the high proportion of undiagnosed cases represents a great challenge. It is estimated that less than 10% of people with Chagas disease worldwide are adequately diagnosed and treated.[3]

Even 112 years after the discovery of the now considered "the most Brazilian of diseases" by Carlos Chagas, this condition continues to represent a severe global public health problem. At the moment of the discovery, with its acute social conscience, the physician described its clinical manifestations and natural reservoirs, in addition to the profile of affected persons, thus establishing a cause-effect relationship between low socioeconomic classes and the presence of the disease.

The infection was originally restricted to rural areas. With the human presence in this environment, Chagas disease began affecting man and became a zoonosis. With the strong rural exodus occurred in the 20th century, patients with Chagas disease brought the disease to the city. It is estimated that currently, in Brazil, 70% of the patients with Chagas disease live in the outskirts of large cities in endemic Latin American countries, shaping a true urban endemic.[4] In the 1990s/2000s, due to the increase in migration between continents, Chagas disease was considered globalized, with affected persons throughout the globe.

These social aspects were fundamental for guiding the clinic's actions. Biopsychosocial demands transcended the uniquely biomedical health care. At first, most patients who arrived at the HUOC ward came from the countryside and were young adults with severe visceral impairment, mainly

Figure 4 – *Casa de Chagas house front.*

Figure 5 – *Part of the team in one of the consultation rooms of the house.*

of cardiac nature. A family history of sudden death was frequently reported, with prematurely lost lives, having a strong psychological impact with the fear of the imminent possibility of death. After improvements in the clinic's infrastructure with a space dedicated to these patients, the team began an active search between family members aiming to perform the early diagnosis of new cases, especially among asymptomatic patients exposed to the same contamination risk.

As years went by, this patient profile gained new nuances. In the early 1990s, with the appearance and spread of HIV, blood centers were required to perform a series of tests for releasing blood donations. The serology test for Chagas disease was among the tests that were previously only recommended and became mandatory. Therefore, these ex-blood donors, now patients of the clinic, shaped a new profile of people affected by Chagas disease. These "new" patients were young, predominantly male, asymptomatic, and born and living in urban areas. Many of them did not know the forms of transmission of Chagas disease and had epidemiological clinical data that differed from those of the group of patients previously treated by the ward. These young patients were frequently anxious when arriving at the clinic, with many doubts and taboos regarding the disease.

The successful partnership between the clinic and blood centers guaranteed adequate care to many patients and enabled the registration and comprehension of the size of the disease presence in the state of Pernambuco. It also promoted improvements in the physical structure of the clinic and the incorporation of new professionals for acting on health care, research, and education regarding the disease.

In this scenario, in May 2011 the Health Secretary of Pernambuco (SES) created the Program to Combat Neglected Diseases/Sanar, aiming to "reduce or eliminate transmissible neglected diseases".[5] The creation of the Sanar program was recognized as a successful action in Brazil and was an important turning point in the planning and actions for addressing Chagas disease in Pernambuco. This initiative positively impacted the actions of the Chagas Disease and Heart Failure Outpatient Clinic/Procape-UPE, establishing it as a State Referral Outpatient Clinic for Chagas Disease and Heart Failure; this way, partnerships for decentralization, training, professional allocation, education, and associative actions were developed. The partnership between the Referral Clinic and Sanar joined forces for creating strategies that would help fighting this disease.

Perhaps the action deserving the most attention is the decentralization program for the care of patients with Chagas disease, which is still active. Since 2012, a group formed by members of the clinic and Sanar teams have visited health care management units (GERES–Gerências regionais de Saúde) throughout the state in order to prepare health teams of these regions to receive and care for patients with Chagas disease. Formative work was performed with these professionals so that the patient could receive care at his or her region without having to be transferred to Recife. Moreover, an interconnected human serological diagnostic network was created, and the state pharmacy network was trained for the regional distribution of continuous-use medications and Benznidazole for the etiological treatment of Chagas disease, when recommended.

This action aims to provide care for patients with a positive serological test but no clinical manifestations and those with mild symptoms who can be treated at primary health care services, performing health care exactly as done by the SUS. This way, the clinic would receive a profile of patients with more severe heart failure or those in need of a PM and/or ICD. The proposal also includes telemedicine and a communication channel between the end point physician and specialists at Casa de Chagas (Figure 6).

Profile of patients cared for by the State Referral Outpatient Clinic for Chagas Disease and Heart Failure

Unfortunately, many years after the discovery of this disease, the sociodemographic profile of patients cared for by the clinic remains very similar to that described by Carlos Chagas, except for the older age. In the last statistical analysis performed by the clinic team, out of 880 patients, 69% were women, the mean age was 62 years, 38% were born at the Pernambuco Zona da Mata region, while 17% were born in the Sertão region, 24% were from the Agreste region, 5% were

Figure 6 – *Meeting with the inland management teams, in partnership with Sanar and the Telessaúde Center (Nutes).*

from the outskirts of Recife, and 16% were born in other states. Regarding their place of residence, 45% lived in the outskirts of Recife, although most of them were from endemic areas in the countryside. More than half of the patients were of mixed race and 69% of them did not finish primary school; 82% had an income of a minimum wage or less and 35% were rural workers. In this demographic, the clinical classification of the disease was presented as follows: 21% as A, 46% as B1, 7% as B2, and 26% as C (various degrees of heart failure), classified according to the I Latin American Guideline for Chagas Disease, 2011.[6] Among the most frequent comorbidities in this group, we cite systemic arterial hypertension (73%), Diabetes Mellitus (17%), and coronary artery disease (8.5%). This profile is similar to that described by other Brazilian studies when considering the mean age and socioeconomic and cultural characteristics of patients.[6]

Currently, services that care for patients with Chagas disease, considering the ageing of this population, should be alert for the appearance of comorbidities that are more prevalent in this age group, as demonstrated by the presented data. The presence of a cardioembolic ischemic stroke in patients with Chagas disease negatively impacts their progression. The development of brain ischemia is one of the most severe complications. Many causes have been related to the development of strokes in patients with Chagas disease with cardiac involvement.[7] A recently studied sample of patients with chronic Chagas cardiomyopathy, followed-up on an outpatient basis, presented ischemic stroke in 10% of the cases, probably due to a cardioembolic mechanism.

The profile of patients with heart failure of all etiologies has some peculiarities. Most of them are from the outskirts of Recife (69%), male (61%), and have a higher schooling level (48.7% with primary education) and income (35% earn more than a minimum wage). This goes to show that, although patients with heart failure have an overt clinical syndrome, they live in a socioeconomic situation (schooling, income…) that is far from ideal, but still better than that of patients with Chagas disease.

A different experience was reported in May 2019, with the first combat of acute Chagas disease cases in the state of Pernambuco. The outbreak probably happened due to oral contamination (clinical and epidemiological data), affecting 77 people with 27 laboratory-confirmed cases within a religious mission in the city of Ibimirim, in the Sertão region of the state. All patients with laboratory confirmation were treated with Benznidazole for 60 days. There were no deaths, although 6 patients had more severe manifestations of the acute disease and required hospitalization.

The need for whole health care

Considering the complexity of Chagas disease, from the beginning the clinic proposed to offer a whole health care that would consider its previously mentioned peculiarities. Nowadays, it is known that a multi-professional team is the best alternative for providing health care to patients with chronic diseases.[8] The multidisciplinary team of the Chagas Disease Outpatient Clinic includes physicians, nurses, nursing technicians, an occupational therapist, and a psychologist. Each of these members has a defined role and is aware of his or her limitations, possibilities, and responsibilities, in a process of continuous exchange and dialogue.

The family is fundamental as a part of the treatment (Figure 7). It is the third vertex of the so-called therapeutic triangle (physician, patient, and family) and has an active role in the whole process. It is essential for the patient's adhesion to medication-based (or not) treatment. Therefore, the whole health approach promotes close contact with the family, which receives the same guidance as patients, in addition to psychological support. The presence of a family member during consultations and meetings helps professionals comprehend the patient's life context and thus better direct their care. The education offered to the patient and family members begins with the assessment of their knowledge on the disease and its treatment. Through periodic educational actions, the

Figure 7 – *Activities promoted by occupational therapy.*

multi-professional team may clarify aspects of the disease progression and treatment.

In addition to the clinic's multi-disciplinary team, focused on the patients and their families' health care and education, it is important to highlight the role of teaching and research, since this is a part of a university hospital training health professionals. The clinic thus receives medical students and residents who have the opportunity to experience and learn with the implemented practices. The outpatient clinic has, each year, expanded its academic profile, considering that multi-professional work is the ideal scenario for exchanging knowledge and practicing teamwork (Figure 8).

Throughout the years, the service has raised interest in the development of research by undergraduate (scientific initiation) and graduate (masters and PhD) students, in various areas of knowledge. In addition to biomedical research, other areas connected to the humanities such as philosophy have been the object of research. Partnerships with universities and research institutes (such as FIOCRUZ) have progressively contributed to scientific production.

A group of academics participates in various activities at the clinic — the Science for Life Project (Projeto Ciência para a Vida) —, being involved in care and research activities. They feel motivated, thus collaborating with the multi-disciplinary team in periodic scientific initiation meetings (education and self-care) and performing musical presentations (Figure 9). They also participate in continued (Figure 10) education programs and conferences in the area, being more and more involved in the best possible care of patients with Chagas disease and heart failure (Figure 11).

Last but not least, volunteers have performed excellent work along with the multi-professional team and patients for the last 24 years. Most of them are also patients who, through associative actions, are empowered and become knowledgeable in the intricacies of the disease and are available for helping new patients. In reality, the attention of volunteers is aimed at the subjective and affective characteristics of patients. They welcome patients, help with educational actions on Chagas disease and general health promotion, and organize workshops and events that may help fund the association's activities (Figure 12).

Figure 8 – *Educational meetings for patients and family members with multidisciplinary team.*

Figure 9 – *The Science for Life Project (Projeto Ciência para a Vida).*

Figure 10 – *Students during teaching activities.*

The strength of associativism

As already mentioned, Chagas disease is neglected and strongly marked by a social bias. This characteristic renders the union and associativism of patients a natural path for them to collectively make sure they are heard. Patient associations are bio-social groups of volunteers based on common biological issues with several goals, from the guidance of patients and family members regarding treatment and quality of life to an active participation in the elaboration and implementation of public healthpolicies.[9]

In the case of neglected diseases, these groups are even more important. In Brazil, we highlight the Movement for the Reintegration of Persons Affected by Hansen's disease (Movimento de Reintegração das Pessoas com Hanseníase,

Figure 11 *Participation of the outpatient clinic team and students at DEIC 2019, Fortaleza.*

Figure 12 – *On holidays, volunteers and the team promoted actions for the patients.pacientes.*

Morhan), founded in 1940. Regarding Chagas disease, the worldwide pioneer was the group created in the state of Pernambuco, in 1987, along with the team of the Chagas Disease Outpatient Clinic at HUOC. The aim of this initiative was to mainly tend to the psychosocial demands of patients affected by this disease, which transcended purely biomedical aspects. The Pernambuco association is a nonprofit organization with no political affiliation, whose board of directors is formed by patients who are elected by general assembly, respecting determinations by the Brazilian Civil Code. The association currently has 740 active members living in the outskirts of Recife and inland regions. This collective action overcame challenges, conquered spaces, empowered patients, and helped them emerge from invisibility.

In 2005, the WHO Program for the Control of Neglected Tropical Diseases classified Chagas as an extremely neglected disease, corroborating the need for the affected population to form associative groups. In this context, APDCIM (Associação dos portadores de Doença de Chagas, Insufiência Cardíaca e Miocardiopatia de Pernambuco)

became an important reference worldwide due to its effectivity and pioneer nature, influencing the creation of other groups in Brazil and other countries.

Currently and with equal importance, 20 associations of persons affected by Chagas disease are distributed throughout various countries (Argentina, Australia, Bolivia, Brazil, Colombia, Spain, USA, Italy, Mexico, Switzerland, Venezuela, and Japan) and have been working in a collective biocitizenship project. This group of associations has fought for the construction of a collective identity and for the mobilization and production of knowledge, culminating in public policies .

The associations of people affected by Chagas disease thus have a fundamental role in the world to help identifying similarities, clarifying and guiding people through the disease and its development process, as well as through the need for diagnosis and treatment regardless of the person's location. In spite of their regional differences, associative movements aimed at Chagas disease, in Brazil and worldwide, have one fight and mission in common: the wellbeing of the affected person. Whether they are in endemic or non-endemic countries, these associations seek to contribute to the construction of a solid identity and to strengthen citizenship.

In April 2009, during the II Catalan Journey of International Health – Tropical Medicine and the inauguration of the Barcelona patient association, the dream of creating a global federation that could unite all groups was born, as a historical milestone for the 100th anniversary of the discovery of the disease. In October of the same year, the dream began to take shape during the 25th Annual Meeting on Applied Research in Chagas Disease, in Uberaba (MG), presided by Professors José Rodrigues Coura and João Carlos Pinto Dias, where the first Meeting of Associations of Patients with Chagas Disease of the Americas, Europe, and Western Pacific took place. This meeting approached the creation of a World Federation that would be capable of welcoming and strengthening current associations and stimulating the creation of new social movements, especially in regions where the person affected by Chagas disease was in a situation of increased vulnerability. Finally, the seed of the future federation was planted, being properly founded in Pernambuco in 2010 and named International Federation of Associations of People Affected by Chagas Disease/FINDECHAGAS (Figure 13).

Many meetings and assemblies followed, uniting patients from throughout the world. The exchange of information and experiences is extremely fruitful, has brought concrete impacts to the quality of life of patients with Chagas disease, and has propagated their voice more strongly. Among the many achievements of FINDECHAGAS, we highlight the recognition of April 14 as the World Chagas Disease Day by WHO. This date was chosen because on this day, in 1909, the researcher Carlos Chagas presented his discovery to the scientific community (Figure 14).

Undoubtedly, considering all difficulties and barriers faced by patient associations, they have gained increasing importance by organizing collectively and by federation in the last decades. This joint action promotes a change in paradigm

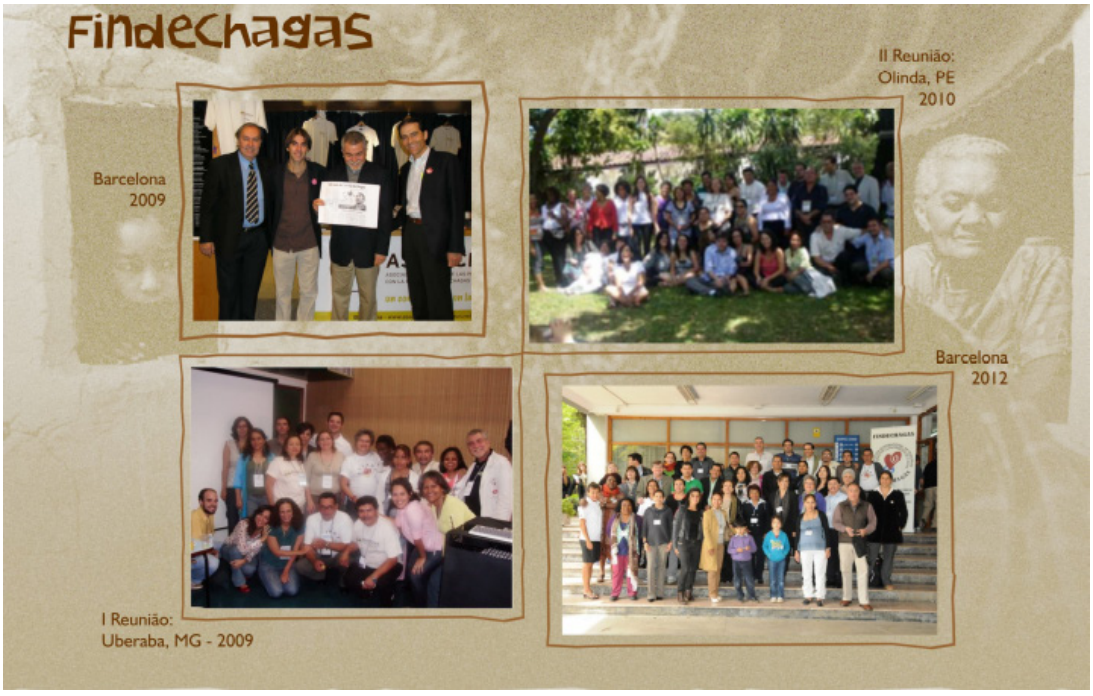

Figure 13 – *(1) ASAPECHA Inauguration, Barcelona (2) First international reunion of Associations of Patients with Chagas Disease/Uberaba-MG (3) Creation of FINDECHAGAS/Olinda-PE (4) II FINDECHAGAS Assembly/Barcelona.*

Figure 14 – *Activities promoted on April 14.*

where the patient moves from a passive role in his or her therapeutic process to an active position, performing patient advocacy. This proactive posture, with critical conscience of their rights and needs, favors decision making towards the best options for their health and that of the group. These groups work as a link between the State and society, thus exerting social control.

Final considerations

Today, in 2021, the history of the Chagas Disease and Heart Failure Outpatient Clinic and the Association of Chagas Disease and Heart Failure Patients follows its path and faces new challenges. As of last year, the new coronavirus pandemic directly impacted the manner of organizing and acting. The clinic had to adapt to sanitary measures so that it could continue providing care, teaching, and research, remaining alert to patients that were strongly impacted by new dynamics imposed by the pandemic. APDCIM has worked to secure funding for food items, personal and home hygiene kits, masks, medications, etc. destined to patients in need, in addition to fighting for COVID-19 vaccination priority for this group.

Throughout more than 30 years of activities, the clinic and the association have made a difference in the treatment and welcoming of patients with Chagas disease and heart failure. Their successful activity became an inspiration for many other services that today, together, can echo the voice of these patients. The perspective remains the same: to look beyond the disease and see the person in his or her whole context, welcoming, listening, and caring. The motto remains the same, today and always, "A commitment with life." All of this was only possible thanks to the cohesion of the team that faced and still faces barriers and difficulties for implementing their mission: "Humanizing for Caring."

Author Contributions

Conception and design of the research: Martins SM, Carrazzone CFV, Oliveira Junior W; Acquisition of data: Martins SM, Carrazzone CFV, Medeiros CA, Oliveira Junior W; Analysis and interpretation of the data: Martins SM, Moura CBC, Cavalcanti MGAM, Carrazzone CFV, Medeiros CA, Oliveira Junior W; Writing of the manuscript: Martins SM, Carrazzone CFV, Medeiros CA, Oliveira Junior W; Critical revision of the manuscript for intellectual content: Martins SM, Moura CBC, Cavalcanti MGAM, Carrazzone CFV, Oliveira Junior W.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Potential Conflict of Interest

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Original Article

Acute Inspiratory Muscle Training Modifies Hemodynamic Indices in Patients with Heart Failure with Preserved Ejection Fraction

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Abstract

Background: Heart failure with preserved ejection fraction (HFpEF), a syndrome associated to decrease functional capacity, is quite difficult to manage. Inspiratory muscle training (IMT) has been used to treat symptoms and to improve functional capacity of patients with HFpEF. Thus, we aimed to evaluate the immediate effects and after 1 h of IMT on arterial pulsatile hemodynamics and on hemodynamic indices of left ventricular filling derived from Doppler echocardiography in patients with HFpEF.

Methods: Eighteen patients with HFpEF who underwent IMT at an intensity of 80% of maximum inspiratory pressure were evaluated by Doppler echocardiogram in the pre, post-immediate and post-late periods; furthermore, pulsatile hemodynamic variables were collected. Functional capacity was assessed using the 6-minute walk test.

Results: The population was composed predominantly of women (66.7%), mean age of 61.3 (7.2) years. Modifications were observed in the non-invasive LV filling pressure index (E/e') (pre: 10.33 (SD, 3.15) vs post: 8.73 (SD, 2.24); $p < 0.001$) and in the pulse wave velocity (pre: 8.33 (SD, 1.67) vs post: 7.63 (SD, 1.66) m/s; $p < 0.001$), as well as pulse pressure (pre: 54.81 (SD, 18.73) vs post: 48.52 (SD, 15.74) mm Hg; $p = 0.023$).

Conclusion: Our results demonstrated that a unique session of high-intensity IMT improved hemodynamic indices of LV filling and arterial stiffness in patients with HFpEF.

Keywords: Heart Failure/physiopathology; Stroke Volume; Inspiratory Reserve Volume; Hemodynamic; Echocardiography/methods; Rehabilitation; Pulmonary Medicine; Respiratory System; Dyspnea.

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome of greater prevalence in women, older adults, and patients with hypertension and diabetes.[1,2] Its main mechanism of action is pathophysiological dysfunction in left ventricle (LV) filling. Such dysfunction can result in increased LV filling pressure, left atrial pressure, and pulmonary artery pressure, which can be altered at baseline or during exercise.[3] Dyspnea and fatigue are common symptoms in patients with HFpEF, being one of the main causes of exercise intolerance.[4,5]

Central and peripheral arterial stiffness represents another important mechanism for HFpEF development. Altered pulsatile hemodynamic indices are associated with intolerance to effort, as they indicate worsening of ventriculo-arterial coupling, basically due to excessively increased LV afterload, hindering LV ejection performance.[6-8]

In addition to cardiovascular factors, respiratory muscles strength (RMS) has an additional role in global hemodynamic performance, influencing cardiac output, pulmonary pressure, and pulmonary arterial resistance, which contributes to activation of cardiovascular reflexes, limiting exercise tolerance in patients with HFpEF.[9-12]

Inspiratory muscle training (IMT) at moderate intensity (30% of maximal inspiratory pressure [MIP]) has already shown benefits in functional capacity and quality of life in patients with HFpEF.[13] However, data about the effects of IMT on LV filling function and on behavior of arterial pulsatile hemodynamics have not been properly investigated, especially at intensities greater than 30% of MIP. Therefore, this study aimed to evaluate the immediate effect and after 1 h of IMT at 80% of MIP on LV diastolic function and arterial stiffness in patients with HFpEF.

Methods

Study design and population

This is a quasi-experimental cross-sectional study. Patients from a tertiary hospital in southern Brazil, aged over 45 years,

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who met the European Society of Cardiology criteria for HFpEF at the time the study was designed[14,15] and who were clinically stable without previous hospitalization of 30 days were included. Patients with angina pectoris, atrial fibrillation, or atrial flutter during examination, pericardiopathies and musculoskeletal problems that prevented performance of functional capacity test were excluded.

After initial invitation, patients were informed about the echocardiogram to assess cardiac indexes and confirm the diagnosis; RMS assessment by MIP and maximal expiratory pressure (MEP); 6-minute walk test (6MWT); and assessment of arterial pulsatile hemodynamics. Patients who agreed to participate in the present study signed a free and informed consent form, according to the project approved by the ethics committee of the corresponding institution (39338614.0000.53.49).

Variables evaluation

Echocardiography

The evaluation of LV hemodynamic was performed by a 2-dimensional (2D) M-mode 10 standard Doppler echocardiogram (Siemens Acuson X 300, Siemens Medical Solutions USA Malvern, PA, USA) according to the recommendations of the American Society of Echocardiography.[16] The echocardiograms were performed by the same operator. All echocardiographic recordings were obtained in digital format and recorded with an average of 3 cardiac cycles for analysis. The spectral Doppler recordings of mitral flow were obtained from the apical 4-chamber view to assess LV filling dynamics. The following variables were measured: peak early (E wave) and late (A wave) transmittal filling velocities in centimeters per second; E/A ratio; deceleration time of the E velocity in milliseconds (from the peak of E velocity to baseline). Spectral tissue Doppler was performed in the apical portion of the 4 chambers, the sample volume was set at 5 x 5 mm and placed at the junction of the LV septal and lateral wall with the mitral ring and 3 consecutive cardiac cycles, which were transferred to a workstation and analyzed. Peak velocities during systole, onset of diastole (E') and late diastole (a') were measured and the mean of both sites was analyzed. The non-invasive LV filling pressure index was assessed by early diastolic mitral inflow velocity and mitral annular tissue velocity ratio (E/e'). The test was performed before RMS assessment, immediately after IMT (post-immediate), and 1 hour after IMT (post-late).

Arterial stiffness measured by pulse wave velocity

The assessment of arterial stiffness was performed by analyzing pulse wave velocity (PWV) and pulse pressure (PP) based on the oscillometric method, using data from the brachial artery pressure. The recordings were made at a diastolic pressure level for about 10 s using a conventional adult blood pressure cuff available in 2 sizes (24-34 and 32-42 cm) and a high accuracy pressure sensor (Mobil-O-Graph NG, IEM GmbH, Stolberg, Germany).[17]

Respiratory muscle strength test

RMS was always assessed by the same evaluator measuring MIP and MEP. Measurements were obtained using a pressure analyzer (Globalmed MVD300, Porto Alegre, Brazil). The procedures were repeated 6 times and the 3 greatest measures were considered valid, as long as the variation between them was not greater than 10%, following the guideline for pulmonary function tests.[18] The patients were positioned seated, elbows supported, and a nasal clip was applied. The air passed through a nozzle transmitted the pressure level to the pressure transducer. MIP and MEP were considered to be the highest value of 3 measures selected.[19] IMT intensity was determined by the highest value MIP (80%) for training protocol. The test was conducted after echocardiography and pulsatile hemodynamics.

Six-minute walk test

The 6MWT was always performed by the same evaluator according to recommendations by the American Thoracic Society.[20] The test was conducted in an adapted corridor with markings of 30 meters. Patients were instructed to walk the longest distance possible over 6 minutes, always with encouragement. Pre-effort and post-effort blood pressures were checked, and heart rate was monitored during test.

Intervention protocol

Inspiratory muscle training

Individuals were submitted to an IMT session with an intensity of 80% of MIP. The PowerBreathe Classic light resistance model was used with intensity adjusted from 10 to 90 cm H_20. Three sets of 10 minutes were performed with recovery of 1 minute between each set. After IMT end, patients underwent echocardiogram and pulsatile hemodynamics evaluations again to assess immediate effects. In addition, they waited for 1 hour at rest to repeat the assessments.

Statistical analysis

The variables were described in simple and relative frequency for categorical variables, and mean and standard deviation for continuous variables. To analyze the differences between continuous and categorical variables in the pre-, post-immediate, and post-late periods, the Generalized Estimation Equations method and Bonferroni correlation were used for multiple comparisons. For the sample calculation, expecting to reach a difference of 3.3 in the E/e' index between pre- and post-protocol and considering a power of 80% and an alpha error of 5%, we estimated a sample of 18 participants. The data were analyzed using the SPSS version 18.0 statistical program.

Results

The study population consisted of 18 individuals with predominance of the female gender. The main associated

comorbidities were systemic arterial hypertension, diabetes mellitus and obesity. In addition, drug therapy beta-blockers were the most used.

Despite the sample showed characteristic values for moderate diastolic dysfunction (E/e'), the distance covered in 6MWT demonstrates a good functional capacity, representing absolute average by Weber's class A individuals. In addition, PWV values appear to be within normal range for arterial stiffness, as well as cardiac output (3.94 (SD, 0.17) L/min) and cardiac index (2.05 (SD, 0.09) L/min/m^2). However, PP values are high, identifying possible aortic stiffness with valve regurgitation. The baseline sample characteristics are described in Table 1.

After 1 h of IMT, a significant change in E/e' was observed compared to the initial values (10.33 (SD, 3.15) vs 8.73 (SD, 2.24); $p < 0.001$) and also a reduction between the post-immediate and the post-late periods (10.38 (SD, 3.23) m/s vs 8.73 (SD, 2.24) m/s; $p < 0.011$) (Figure 1).

In relation to arterial stiffness, there were significant changes in PWV between pre- and post-late periods (8.33 (SD, 1.67) vs 7.63 (SD, 1.66) m/s; $p < 0.001$) and between post-immediate and post-late periods (8.24 (SD, 1.78) vs 7.63 (SD, 1.66) m/s; $p < 0.001$) (Figure 2). Similarly, PP showed significant changes between pre- and post-late periods (54.81 (SD, 18.73) mm Hg vs 48.52 (SD, 15.74) mm Hg; $p < 0.001$) and between post-immediate and post-late periods (57.92 (SD, 16.21) mm Hg vs 48.52 (SD, 15.68) mm Hg; $p < 0.001$) (Figure 3).

Discussion

The present study evaluated the immediate effect and 1 hour after IMT on hemodynamic indexes of LV filling, as well as on pulsatile arterial hemodynamic indexes in patients with HFpEF. The main finding of the present study was that IMT modified hemodynamic indexes of LV filling and pulsatile hemodynamics, demonstrating the positive effects of high-intensity training.

Table 1 – Anthropometric, respiratory, echocardiographic, and hemodynamic characteristics

Variables (N = 18)	Values (mean (SD) or %)
Anthropometric data	
Age (years)	61.3 (7.2)
Height (cm)	160 (0.9)
Body mass (kg)	84.1 (16.4)
BMI (kg/m^2)	32 (4.6)
Female (%)	66.7
Drug therapy (%)	
Beta-blocker	76.5
ACEi	47.1
ARB	35.3
CCB	41.2
Furosemide	41.2
Thiazide	52.9
ARA	29.4
Nitrate	23.5
Hydralazine	11,8
Antiplatelet	52.9
Comorbidities (%)	
Systemic hypertension	94.1
Diabetes	41.2
Obesity	47.1
Smoking	5.9
Coronary artery disease	35.3
Chronic obstructive pulmonary disease	5.9
Renal failure	7.3
Stroke	4.7
Rheumatic disease	6.8
Functional capacity	
NYHA I – II (%)	94.4
NYHA III (%)	5.6
6MWT (meters)	431.4 (117.2)
Respiratory variables	
MIP (cm H_2O)	73.6 (17.8)
Predicted MIP (cm H_2O)	115.8 (6.9)
70% of predicted MIP (cm H_2O)	80.8 (4.9)
MEP (cm H_2O)	124 (28.9)
Predicted MEP (cm H_2O)	90.8 (19)
70% of predicted MEP (cm H_2O)	65.6 (14.8)
Inspiratory weakness (%)	61.1
Echocardiographic variables	
Simpson EF (%)	64.2 (11.7)
E/e'	9.8 (3.6)
E/A	1 (0.7)
IRT	103.8 (87)
LAV	73.7 (25.7)
iLAV	39.4 (10.2)
Teicholz iLVM (g/m^2)	119.4 (47.3)
Pulsatile hemodynamics variables	
PWV (m/s)	8.3 (1.7)
CPP	54.8 (4.3)
Aix	32.2 (12.8)

BMI: body mass index; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; ARA: angiotensin receptor antagonists; NYHA: New York Heart Association; 6MWT: 6-minute walk test; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; EF: ejection fraction; IRT: isovolumetric relaxation time; E: peak E-wave velocity; e': peak early diastolic velocity on tissue Doppler; LAV: left atrial volume; iLAV: indexed left atrial volume; iLVM: indexed left ventricular mass; PWV: pulse wave velocity; CPP: central pulse pressure; Aix: augmentation index.

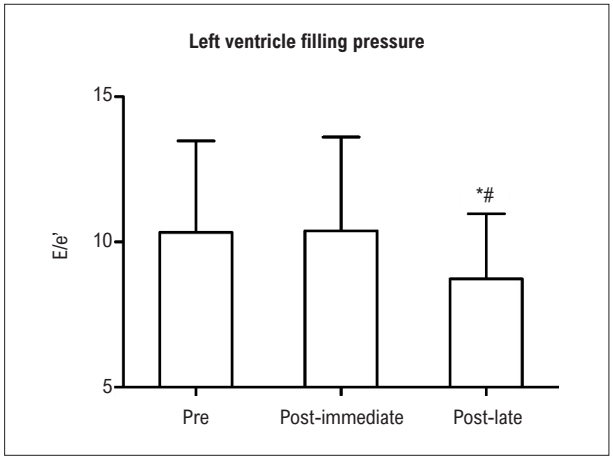

Figure 1 – *Estimation of left ventricle filling pressure pre, post-immediate and post-late. * p < 0.05 between pre- and post-immediate; # p < 0.05 between post-immediate and post-late. E/e': non-invasive index of LV filling.*

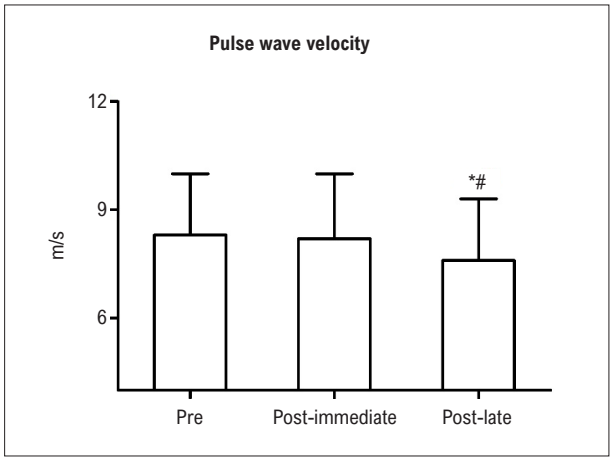

Figure 2 – *Pulse wave velocity pre, post-immediate and post-late. * p < 0.05 between pre- and post-immediate; # p < 0.05 between post-immediate and post-late.*

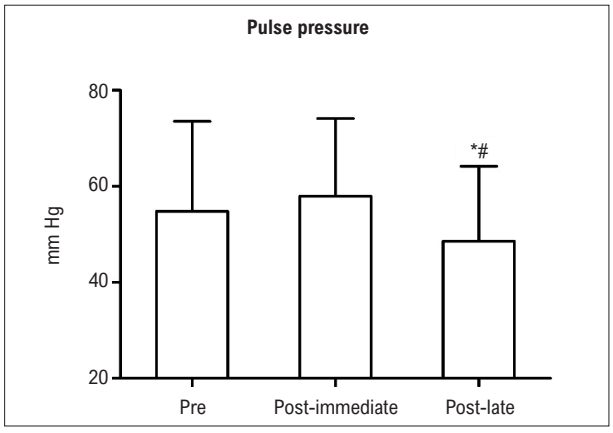

Figure 3 – *Pulse pressure pre, post-immediate and post-late. * p < 0.05 between pre- and post-immediate; # p < 0.05 between post-immediate and post-late.*

There was a significant effect immediately after IMT for E/e' ratio. We also found a significant effect from the post-immediate to the post-late. These results confirm our hypothesis that IMT would promote positive effects on hemodynamic indexes of LV filling. Some evidences suggest that IMT is effective in modifying E/e' ratio; however, when performed at an intensity of 30%.[13] Contrary to the literature, we demonstrated that high-intensity IMT (80% of MIP) is able to modify hemodynamic indexes of LV filling. In addition, it is noteworthy that we conducted only 1 supervised IMT session. We believe that maintaining high-intensity IMT for weeks can promote adequate mechanical action in the respiratory muscles, facilitating the redirection of peripheral blood flow, which can generate a stimulus in the bioavailability of nitric oxide and consequently in vasodilation.[21]

With regard to PWV, we found significant differences in comparison between post-immediate and post-late periods. PWV is an important predictor of cardiovascular disease and mortality.[22] In addition, studies show that PWV is directly related to amendment to ventriculo-arterial coupling leading to exercise intolerance and causing hemodynamic changes in the afterload, with consequent increase in dyspnea to small and moderate efforts.[10,12] Although PWV values are within normal range in our sample, PP is high, identifying possible aortic stiffness and valve regurgitation for these patients. Evidence indicates that a value of 50 mm Hg for PP is related to ventricular hypertrophy and mortality from cardiovascular diseases.[23,24] In the present study, we were able to demonstrate that there was a significant reduction in PP immediately after a high-intensity IMT session ($p = 0.023$).

Another important result that we found in the present study was that 61.1% of the sample presented respiratory muscle weakness, with a cutoff point of < 80 cm H_20 for MIP.[19] We know that BMI > 30 kg/m^2 found for the present individuals is directly related to reductions in MIP, due to distension of diaphragm muscle fibers caused by the mechanical action of abdominal fat.[25] A lower BMI is also associated with greater resistance of the respiratory muscles, demonstrating that the reduction of body mass is fundamental for these patients.[26,27]

It is important to reduce the hemodynamic indexes values of LV filling, arterial stiffness and PP, as well as to increase MIP in patients with HFpEF, since all these factors are integrated for the onset of dyspnea and fatigue during efforts.[9] The reduced performance of this integrative system related to dyspnea and fatigue can be explained by abnormal chemoreflex activity, thus resulting in greater ventilation and greater sympathetic activity, hindering arterial baroreflex adjustments and increasing the time of adrenergic vasoconstriction, which results in increased right ventricular afterload.[11,28] This inadequate hyperventilation during exercise modulates the chemoreflex activity due to a higher production of CO_2, making peripheral O_2 extraction difficult and causing inefficiency of metabolic buffer, thus being able to increase neurohumoral activity.[29] Finally, we can affirm that the metaboreflex activity of the respiratory muscles also influences ventilatory response and exercise intolerance in patients with HFpEF. This metaboreflex overload leads to increased phrenic nerve, ventilation, and sympathetic activity, consequently increasing vasoconstriction and fatigue of peripheral muscles.[30,31]

Therefore, the integration processes related to dyspnea and fatigue can directly influence myocardial work and blood flow redistribution.[29] IMT has the potential to rehabilitate patients with HFpEF, and the rationale is related to improving venous return, increasing cardiac output, reducing ventricular afterload regardless of training mode.[11,28,32,33] In addition, IMT can improve functional capacity and consequently promote a better quality of life for patients with HFpEF, since dyspnea and fatigue are associated with a worse prognosis.

The results of the present study are important to promote new questions about the intensity of IMT, since only 1 session with 80% of MIP promoted significant improvements in hemodynamic indices of LV filling and arterial stiffness, without complications during the protocol. Therefore, our results demonstrate that a high-intensity IMT session is effective for improving the parameters evaluated in patients with HFpEF. Nevertheless, it is worth mentioning that high-intensity IMT seems to be a promising strategy in the rehabilitation scenario.

Limitations

The present study has some limitations, among which we can mention the absence of a control group, which would add important information about the effects of IMT. Another limitation is that only 1 IMT session was conducted, causing a gap in the literature on the chronic effects of high-intensity IMT. Finally, we emphasize the importance of research in the area of IMT for patients with HFpEF. Here, we suggest that future studies assess the effects of different intensities of IMT with comparisons to a control group.

Conclusion

Our results demonstrated that a unique session of high-intensity IMT improved hemodynamic indices of LV filling and arterial stiffness in patients with HFpEF. Future studies should test high-intensity IMT consecutive sessions as a rehabilitation method for patients with HFpEF.

Author Contributions

Conception and design of the research and Acquisition of data: Menezes MG, Garcia EL, Grings V, Danzmann LC; Analysis and interpretation of the data: Menezes MG, Grings V, Danzmann LC; Statistical analysis: Menezes MG, Franzoni LT, Danzmann LC; Obtaining financing: Menezes MG, Danzmann LC; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Menezes MG, Garcia EL, Franzoni LT, Grings V, Danzmann LC.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Luterana do Brasil under the protocol number 393386.14.1.0000.5349. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

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Review Article

Possible Mechanisms of Action of SGLT2 Inhibitors in Heart Failure

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Abstract

In mid-2013, sodium-glucose co-transporter 2 (SGLT2) inhibitors such as canagliflozin, dapagliflozin, and empagliflozin were introduced as possible treatments for type 2 diabetes mellitus (DM2). Cardiovascular safety studies demonstrated that not only were SGLT2 inhibitors safe, but they were also associated with a significant reduction in cardiovascular mortality and heart failure (HF) outcomes including hospitalizations. These findings encouraged the development of clinical trials aimed specifically at investigating the effects of this new drug class on HF with reduced ejection fraction (EF), including the DAPA-HF and EMPEROR-reduced studies. The demonstration of beneficial effects of SGLT2 inhibitors on the reduction of cardiovascular events in treated patients with symptomatic HF and reduced left ventricular EF (LVEF < 40 %) resulted in the extension of SGLT2 inhibitor indication to patients with symptomatic HF with reduced EF. The mechanisms behind these beneficial effects of SGLT2 inhibitors are not entirely known. In this review, we analyze several current hypotheses for the cardioprotective effects of SGLT2 inhibitors, including reduced blood pressure, increased natriuresis, improved energy metabolism, prevention of inflammation, weight loss, improved glycemic control, inhibition of the sympathetic nervous system, prevention of myocardial remodeling, prevention of ischemia/reperfusion injury, inhibition of Na+/H+ channels, increased autophagy and lysosomal degradation, SGLT1 inhibition, reduced hyperuricemia, reduced epicardial fat, increased erythropoietin levels, increased progenitor/precursor cells, reduced oxidative stress, and improved vascular function.

Introduction

As the global number of patients with type 2 diabetes mellitus (DM2) approaches 500 million, that of patients with heart failure (HF) reaches 64 million.[1-3] HF and DM2 often co-occur, resulting in a worse prognosis for both conditions. Records suggest that DM2 can be present in up to 40% of patients with HF and reduced ejection fraction (EF) and up to 45% of those with preserved EF. Additionally, patients with DM2 are 2.5 to 5 times more likely to develop HF and 30% more likely to require hospitalization for HF.[4] The mechanisms involved in the association of DM2 and HF are multifactorial and include diastolic left ventricular (LV) dysfunction, metabolic alterations such as lipotoxicity, renin-angiotensin-aldosterone system activation, oxidative stress, microcirculatory dysfunction, endothelial dysfunction, dysautonomia, and altered myocardial calcium cycling.[4,5] Most treatments for DM2 involve increasing the activity of beta cells, insulin reposition, and the restoration of insulin sensitivity; pharmacological treatments for HF with reduced EF, on the other hand, involve the use of beta-blockers, renin-angiotensin-aldosterone system inhibitors, neprilysin inhibitors, and mineralocorticoid receptor antagonists.[2-4,6] In mid-2013, sodium-glucose co-transporter 2 (SGLT2) inhibitors such as canagliflozin, dapagliflozin, and empagliflozin were introduced as possible treatments for DM2. Surprisingly, the cardiovascular safety studies originally proposed by North-American and European regulatory agencies to ensure the safety of new antidiabetic drugs found that not only were SGLT2 inhibitors safe, but they were also associated with a significant reduction in cardiovascular mortality, and especially with HF outcomes.[7-9] The cardiovascular safety studies of SGLT2 inhibitors and their findings on the reduction of HF outcomes, specifically hospitalization for HF, encouraged the initiation of clinical trials dedicated to the effects of this new drug class on HF with reduced EF.[10,11] More recently, the beneficial effects of SGLT2 inhibitors on the reduction of cardiovascular events in adequately treated patients with symptomatic HF (New York Heart Association [NYHA] functional class >/= II) with reduced EF (< 40%) led the United States Food and Drug Administration (FDA) and the Brazilian Health Regulatory Agency (*Agência Nacional de Vigilância Sanitária*; Anvisa) to extend the indication of SGLT2 inhibitors to the treatment of symptomatic HF with reduced EF.[1,4,6] SGLT2 receptors are present in the proximal convoluted tubules of the kidney and mediate glucose uptake, accounting for 90% of renal glucose reabsorption. The inhibition of SGLT2 receptors leads to a reduction in their ability to reabsorb glucose, promoting its excretion in urine and leading to a reduction in plasma glucose levels. This effect is independent of insulin secretion so that this drug class is unlikely to cause hypoglycemia.[12] Although the reduction in cardiovascular events in patients with symptomatic HF and reduced EF after adjunctive treatment with dapaglifozin[10] and empaglifozin[11] has been demonstrated in rigorous clinical trials, the mechanism of action of this drug class in the treatment of HF has not been fully elucidated. This review aims to discuss the main possible mechanisms of action of SGLT2 inhibitors in HF.

Historical background

The need for cardiovascular safety testing of the three main SGLT2 inhibitors was especially emphasized by the

Keywords

Heart Failure; Diabetes Mellitus; Sodium-Glucose Transporter 2 Inhibitors.

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FDA after studies showed that thiazolidinediones[13-15] and saxagliptin[16,17] could increase the risk of HF outcomes and especially hospitalization. The first clinical trial to establish the cardiovascular safety of SGLT2 inhibitors was the EMPA-REG OUTCOME study, published in 2015.[9] This was a randomized, double-blind, placebo-controlled clinical trial of patients with established cardiovascular disease and DM2, who were randomly allocated to empagliflozin or placebo. The study involved 7020 patients, 4687 in the treatment group and 2333 in the placebo group, followed for a mean period of 3.1 years. The primary outcomes were cardiovascular death, nonfatal myocardial infarction (MI), and nonfatal stroke. The study yielded statistically significant findings on the safety and superiority of empagliflozin, with a 32% relative risk reduction for all-cause mortality and a 35% relative risk reduction in hospitalization for HF, although the rates of atherothrombotic events such as MI and stroke did not differ between groups.[9] The CANVAS[8] study published in 2017 had the same objective, and included 10142 patients with DM2 and high cardiovascular risk randomly allocated to canagliflozin or placebo and followed for a mean of 3.9 years. Primary outcome rates (all-cause cardiovascular mortality, non-fatal MI, or stroke) were significantly lower in the canagliflozin group, occurring in 26.9 participants per 1000 patient-years as compared to 31.5 per 1000 patient-years in the placebo group. The study also identified possible renal benefits such as reduced albuminuria progression, improved glomerular filtration rates, and reduced renal replacement therapy and renal mortality.[8]

The year 2019 saw the publication of the largest and longest follow-up study of cardiovascular outcomes in this drug class: the DECLARE-TIMI 58,[7] which investigated the effects of dapagliflozin on cardiovascular events. This was also a randomized clinical trial involving 17160 patients with DM2 and established atherosclerotic disease or multiple risk factors for its development. Patients were randomly allocated to 10 mg/day dapagliflozin or placebo and followed for a mean period of 4.2 years. The two primary effectiveness outcomes were MACE (a composite of cardiovascular death, MI, or ischemic stroke) and a composite of cardiovascular death and hospitalization for HF. The use of dapagliflozin resulted in lower rates of hospitalization for HF.[7] The publication of the three aforementioned studies clarified the benefits of SGLT2 inhibitors on cardiovascular outcomes in patients with DM2. However, since few patients in the EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 studies had a diagnosis of HF at the start of these investigations, dedicated studies were developed to evaluate the possible benefits of these drugs in patients with established HF. A randomized, double-blind clinical trial on patients with chronic HF with reduced EF with or without DM2 was developed to evaluate the effects of 10mg dapagliflozin once daily relative to placebo addition to standard treatment for HF. The primary outcome was a composite of cardiovascular death, hospitalization for HF, or urgent-care visits for HF. The study revealed a significant reduction in the occurrence of the primary outcome, which was reported in 16.2% of the dapagliflozin group and 21.2% of the placebo group.[7] Similar findings were obtained with empagliflozin,[11] which also led to a significant reduction in the occurrence of major cardiovascular events in a population of patients with symptomatic HF and reduced EF, corroborating the benefits of this class of medications in the treatment of symptomatic HF with reduced EF.

Possible mechanisms of action of SGLT2 inhibitors in heart failure

As previously mentioned, SGLT2 inhibitors, though initially developed for the treatment of DM2, have demonstrated clear benefits on cardiovascular outcomes, especially those related to HF with reduced EF, in addition to kidney outcomes in patients with or without diabetes.[18] Though the mechanisms through which SGLT2 inhibitors affect HF with reduced EF have not been completely elucidated, experimental studies have suggested several possible explanations for this association (Figure 1). These include the following: 1) reduced blood pressure; 2) increased natriuresis; 3) improved energy metabolism; 4) prevention of inflammation; 5) weight loss; 6) improved glycemic control; 7) inhibition of the sympathetic nervous system; 8) prevention of myocardial remodeling; 9) prevention of ischemia/reperfusion injury; 10) inhibition of Na+/H+ channels; 11) increased autophagy and lysosomal degradation, SGLT1 inhibition; 12) reduced hyperuricemia; 13) reduced epicardial fat; 14) increased erythropoietin (EPO) levels; 15) increased progenitor/precursor cells; 16) reduced oxidative stress; and 17) improved vascular function. Therefore, several hypotheses have been put forward to explain the effects of these drugs. The main ones will be discussed in the following sections.

Weight loss

Renal glucose excretion during treatment with SGLT2 inhibitors results in a substantial caloric loss. This results in a significant loss of body weight as fatty acids are mobilized from adipose tissue.[18-20] Clinical trials have demonstrated a significant reduction in body weight in patients treated with SGLT2 inhibitors.[21] While this weight loss may contribute to the beneficial effects of SGLT2 inhibitors, other mechanisms must also be involved since the effects of weight loss measures on HF severity have been far smaller than those observed with SGLT2 inhibitors. Therefore, weight loss is unlikely to be the main mechanism through which SGLT2 inhibitors affect HF outcomes. Furthermore, the effects of SGLT2 inhibitors on weight loss are moderate and tend to decrease over time due to counterregulatory mechanisms such as increased energy intake triggered to maintain body weight.[22]

Improved glucose control

Although SGLT2 inhibitors are effective at reducing glucose levels, this is unlikely to be directly associated with the benefits of this medication class on HF. Hyperglycemia alone is a weak risk factor for cardiovascular illness.[23] Additionally, the rapid efficacy of these investigations (observed days after treatment initiation) speaks against an association between glucose reduction and improved cardiovascular outcomes. The differences in glycemic control and cardiovascular outcomes reported in previous clinical

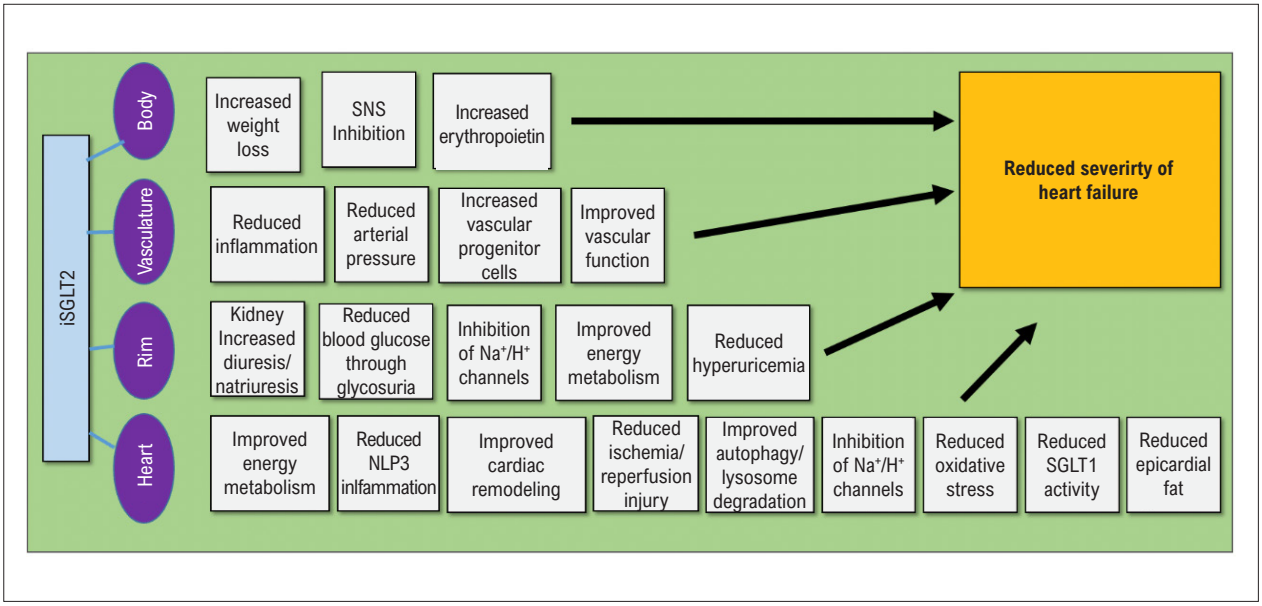

Figure 1 – *Possible mechanisms through which SGLT2 inhibitors improve heart failure outcomes. iSGLT2: sodium-glucose co-transporter 2 inhibitors; SNS: sympathetic nervous system; NLRP3: nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing; SGLT1: sodium-glucose co-transporter 1.*

trials have been small, and post hoc analyses of these studies suggest that baseline glycated hemoglobin and changes in HbA1c are not necessarily associated with the effects of treatment with SGLT2 inhibitors.[23] This was confirmed in the DAPA-HF study, which found that dapagliflozin was similarly effective in individuals with and without diabetes.[10] In patients without diabetes, its effectiveness was similar to that observed in individuals with prediabetes or reduced glucose tolerance relative to normoglycemic participants. Similar findings were obtained in a study of empagliflozin, another SGLT2 inhibitor, which proved effective in the treatment of HF with reduced EF regardless of the presence of DM2.[11] Polynomial analyses in the DAPA-HF study demonstrated that baseline glycated hemoglobin was unrelated to the positive effects of dapagliflozin on HF and mortality.[10] Additionally, in experimental models of HF, benefits of SGLT2 inhibition have been observed regardless of whether diabetes or hyperglycemia is present.[24,25]

Blood pressure reduction

Hypertension is an important modifiable risk factor for HF. As such, it has been suggested that some of the beneficial effects of SGLT2 inhibitors on HF may be explained by their effects on blood pressure since SGLT2 inhibitors are known to reduce these values.[26] Although the mechanisms behind the antihypertensive activity of SGLT2 inhibition are not entirely clear, these effects are likely mediated by the osmotic and diuretic effects of SGLT2 inhibitors caused by the inhibition of sodium reabsorption in the proximal tubules of the kidney. SGLT2 inhibition may increase urinary sodium excretion by 30 to 60%.[26,27] The anti-hypertensive effects of SGLT2 inhibitors are larger than those of thiazide diuretics when used in combination with beta-blockers or calcium antagonists.[28,29] By decreasing blood pressure, SGLT2 inhibitors may decrease the cardiac post-load, reducing cardiac overload and improving efficiency. This could be the mechanism through which SGLT2 inhibitors affect HF outcomes. However, the effects of SGLT2 inhibition on blood pressure reduction are modest and unlikely to entirely explain the beneficial effects of this drug on cardiovascular and kidney function. Additionally, reduced blood pressure is expected to have a greater effect on stroke rates relative to other cardiovascular outcomes, which was not observed in the EMPA-REG OUTCOME study.[9] Lastly, in the DAPA-HF trial, blood pressure reductions were modest and unlikely to be related to a significant reduction in cardiovascular events.[10]

Increased natriuresis

SGLT2 inhibitors promote natriuresis and glycosuria, and it has been suggested that osmotic diuresis may improve HF outcomes. Analyses from the EMPA-REG OUTCOME study suggested that hemoconcentration (presumably secondary to volume contraction) was responsible for nearly 50% of the cardiovascular benefits observed in this investigation.[9] Yet the benefits of SGLT2 inhibitors are unlikely to be explained by diuresis alone since other diuretic measures have not been associated with a reduction of cardiovascular events in HF studies. It has been suggested that SGLT2 inhibitors may differ from classical diuretics given their peculiar mechanism of action and, especially, their effects on the reduction of interstitial fluid. In a study comparing dapagliflozin and hydrochlorothiazide, for instance, reduced plasma volume and increased erythrocyte mass were observed with the former but not the latter.[30] When compared to a loop diuretic (bumetanide), dapagliflozin was associated with a greater

reduction in interstitial fluid rather than blood volume.[31] It has therefore been suggested that SGLT2 inhibition may have differential effects on interstitial fluid (vs. intravascular volume) which can limit the neurohumoral stimulation that occurs in response to the contraction of intravascular volume caused by traditional diuretics.

Reduced sympathetic stimulus

SGLT2 acts by stimulating the sympathetic nervous system. The effects of hyperstimulation of this system can include arterial stiffening and, consequently, chronic elevation of blood pressure, ultimately leading to vascular and kidney damage. Both effects are directly related to poorer HF outcomes.[32] SGLT2 inhibitors are associated with a reduced sympathetic tone, and the ability to induce vasodilation by activating voltage-gated potassium channels and protein kinase G, which are crucial for the regulation of vascular tone. Additionally, they improve endothelial function and arterial stiffness.[12] The sympathetic nervous system,[33,34] in turn, plays a crucial role in blood pressure control and the physiopathology of hypertension, and its activation may be related to the development of HF.[35,36] Several experimental[37] and clinical[38] studies have suggested that SGLT2 inhibitors reduce the activation of the sympathetic nervous system. Though the exact mechanisms behind HF risk reduction and the beneficial effects of SGLT2 inhibitors are not fully known, some hypotheses are supported by stronger evidence, such as the effects of sympathetic tone, as illustrated in Figure 2.

Interestingly, the reduction in sympathetic tone caused by SGLT2 inhibitors contributes to the reduction in HF hospitalizations.[32] In older patients with HF refractory to clinical treatment, ipragliflozin improved sympathetic activity as assessed by 123 I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy, suggesting that this may contribute to the cardioprotective activity of SGLT2 inhibitors.[39] Additionally, hyperactivation of the sympathetic nervous system is associated with poor prognosis, ventricular arrhythmia or even sudden death. In the EMPA-REG OUTCOME study, empagliflozin was associated with a reduced incidence of sudden death.[9] Though the precise mechanisms underlying this association have not been fully elucidated, the attenuation of sympathetic hyperactivation caused by SGLT2 inhibitors may reduce the risk of complex arrhythmia and sudden death. The EMBODY[40] study, which is still ongoing, is investigating whether the effects of SGLT2 on sympathetic tone, through the re-establishment of the balance between sympathetic and parasympathetic tone, could improve survival and reduce the rates of cardiovascular events and sudden death. In this interesting study, patients with diabetes and HF will be randomized to empagliflozin or placebo. The findings from this investigation may provide novel evidence of the effects of this drug class on the reduction of electrical events of the heart. While the exacerbated activation of sympathetic tone is associated with unfavorable vascular remodeling several studies have reported significant reductions in arterial stiffness in patients with DM2 treated with dapagliflozin,[41] canagliflozin,[42] or empagliflozin.[43] This effect is accompanied by improved endothelial function,[41] promoting reductions in arterial and central pressure with possible effects on the prevention of cardiovascular events. More recently, in a study of 97 patients with DM2, Sposito et al. showed that treatment with dapagliflozin improved endothelial function relative to glibenclamide as determined by Doppler-recorded reactive vasodilation.[44] These findings indicate that the effect of SGLT1 inhibitors on sympathetic tone and vascular remodeling can contribute to their benefits for patients with HF.

Reduced inflammation

Inflammation is a major contributor to HF severity. Inflammatory markers are increased in patients with HF and correlate with disease severity[45,46] in HF with reduced and preserved EF.[47] Inflammatory cytokines are known to cause endothelial dysfunction and increase fibrosis and extracellular matrix turnover. SGLT2 inhibitors have the potential to decrease inflammation-associated molecular processes such as extracellular matrix turnover and fibrosis.[48] This can be illustrated by the fact that dapagliflozin suppresses collagen synthesis in the rat myocardium, demonstrating its antifibrotic effects through the modulation of inflammatory responses.[48] Despite these findings, it is still not entirely clear how SGLT2 inhibitors modify and modulate the inflammatory process. It is thought that SGLT2 inhibitors initially dampen the macrophage inflammatory response by decreasing the availability of glucose, the preferred energy source for these cells.[49] The nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing (NLRP3) inflammasome plays an important role in inflammatory mediation. The inflammasome is a complex of interacting proteins that trigger the maturation of pro-inflammatory cytokines to initiate the inflammatory response. This response is amplified by the production of tumor necrosis factor-alpha (TNF-alpha) and the activation of inducible nitric-oxide synthase. Therefore, the inflammasome, or the NLPR3 inflammasome, specifically, may play a central role in the modulation of chronic inflammation, affecting HF progression.[50] Recent data suggest that SGLT2 inhibitors can reduce NRLP3 inflammasome activation in the heart[51,52] and that this effect is independent of glucose reduction. It is unclear whether the effects of SGLT2 inhibitors on the NRLP3 inflammasome are direct or indirect. Beta-hydroxybutyrate is an effective blocker of the NLRP3 inflammasome,[53] and SGLT2 inhibitors increase circulating beta-hydroxybutyrate levels, which may contribute to their mechanism of action.

Prevention of cardiac remodeling

Cardiac remodeling refers to several structural alterations of the heart muscle, including cardiac hypertrophy, cardiomyocyte inflammation, and fibrosis. These alterations result in increased HR severity. SGLT2 inhibitors have beneficial effects on cardiac remodeling, as documented in several studies.[24,30,54-58] A randomized trial investigated the effects of a 6-month treatment with empagliflozin or placebo on myocardial modeling in patients with diabetes and coronary artery disease using cardiac magnetic resonance imaging. The study showed that patients treated with empagliflozin exhibited a significant reduction in LV mass relative to those in the placebo group, despite the brevity of the treatment intervention.[59] This result

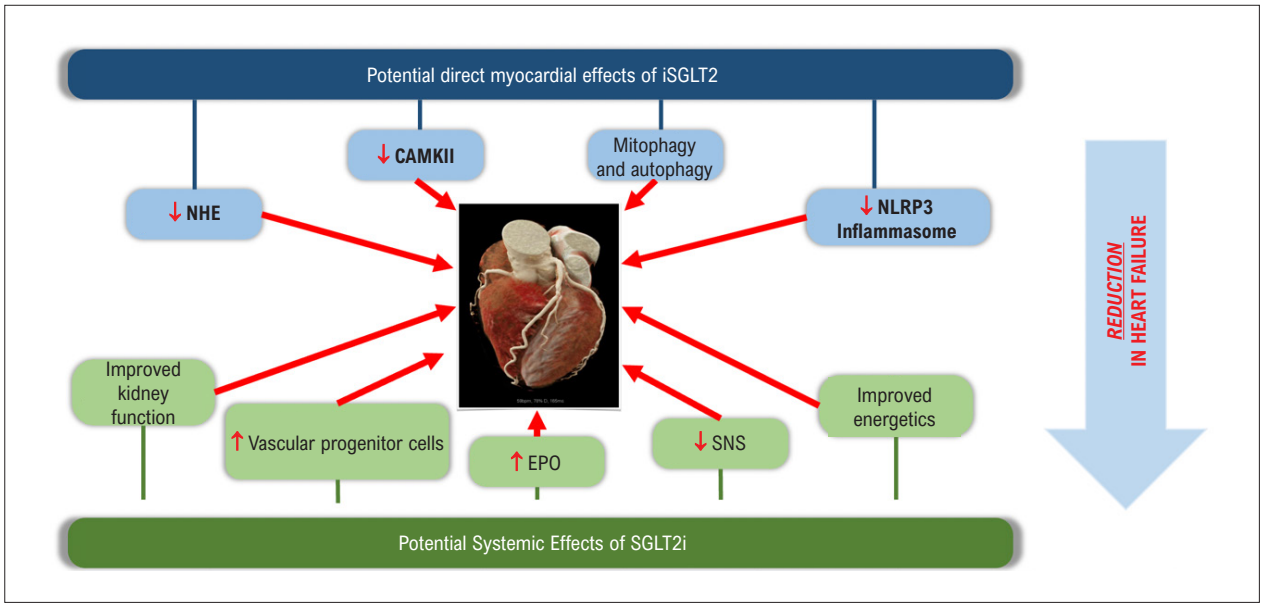

Figure 2 – *Possible systemic, direct, and indirect effects of iSGLT2. CAMKII: calmodulin-dependent protein kinase; EPO: erythropoietin; NHE: sodium/hydrogen exchange; NLRP3: nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing; iSGLT2: sodium-glucose co-transporter 2 inhibitor; SNS: sympathetic nervous system.*

suggests that SGLT2 inhibitors can promote the reverse remodeling of the heart muscle. Although we do not clearly know how SGLT2 inhibitors prevent remodeling, part of this mechanism can be explained by their anti-inflammatory effects, which can reduce fibrosis[60,61] and, consequently, cardiac remodeling. The inhibition of SGLT2 receptors can therefore reverse the cardiac remodeling observed in HF, reducing the stress on the LV and improving ventricular function.

Suppression of myocardial fibrosis

As previously mentioned, SGLT2 inhibitors play an important role in the attenuation of myocardial fibrosis, a form of irreversible myocardial damage associated with ventricular dysfunction. HF is accompanied by cardiac remodeling due to the deposition of the extracellular matrix, composed of fibrosis and collagen deposition by cardiac fibroblasts. In patients with DM2, even a 3% increase in the extracellular volume of the myocardium can lead to a highly significant increase of up to 52% in the risk of death or hospitalization for HF. It has been proposed that SGLT2 inhibitors may suppress collagen synthesis, activating M2 macrophages and inhibiting myofibroblast differentiation.[12,18,19] M2 macrophages secrete interleukin-10 (IL-10), an anti-inflammatory cytokine that plays a crucial role in tissue healing and homeostasis. The reduction in myocardial fibrosis can be demonstrated noninvasively by the assessment of the extracellular volume through advanced imaging methods such as cardiac magnetic resonance, a method that is widely used in contemporary clinical studies. In a study by Mason et al., where patients with diabetes and coronary artery disease were randomized to empagliflozin or placebo for 6 months (Figure 3), the SGLT2 inhibitor led to a 1.4% reduction in extracellular volume (Figure 4) which was associated with a reduction in LV mass.[58]

Reduced ventricular overload

Another mechanism that may explain the benefits of SGLT2 inhibitors on all-cause mortality in patients with HF and reduced EF could be the reduction in pre- and post-load, and the ensuing improvement in ventricular functioning.[12,18,19] This occurs because the inhibition of SGLT2 in the proximal tubule promotes natriuresis and glycosuria, resulting in osmotic diuresis,[18,60] and ultimately reducing ventricular filling pressure and myocardial work.[19] The natriuretic response, through a tubuloglomerular feedback system, also leads to afferent arteriole vasoconstriction, reducing intraglomerular pressure and possibly explaining the renal preservation associated with the use of SGLT2 inhibitors.[18] The variation in plasma volume leads to an increase in hematocrit, which was likely responsible for over 50% of the benefits of these drugs on cardiovascular mortality according to the EMPA-REG OUTCOME[19] study. Another mechanism that may complement the change in plasma volume and hematocrit is increased erythropoiesis observed in some studies after the start of treatment with SGLT2 inhibitors. Additionally, unlike conventional diuretics, the uricosuric effect that may promote differences in cardiovascular outcomes since serum uric acid is associated with an increased risk of cardiovascular death was present in those using SGLT2 inhibitors.[19]

Repairing vascular function

Endothelial and smooth vascular muscle dysfunctions contribute to the physiopathology of HF[62] and contribute to increased morbidity and mortality rates. SGTL2 inhibitors improve vascular function by decreasing the activation of endothelial cells, inducing direct vascular relaxation. Additionally, SGLT2 inhibition reduces endothelial dysfunction

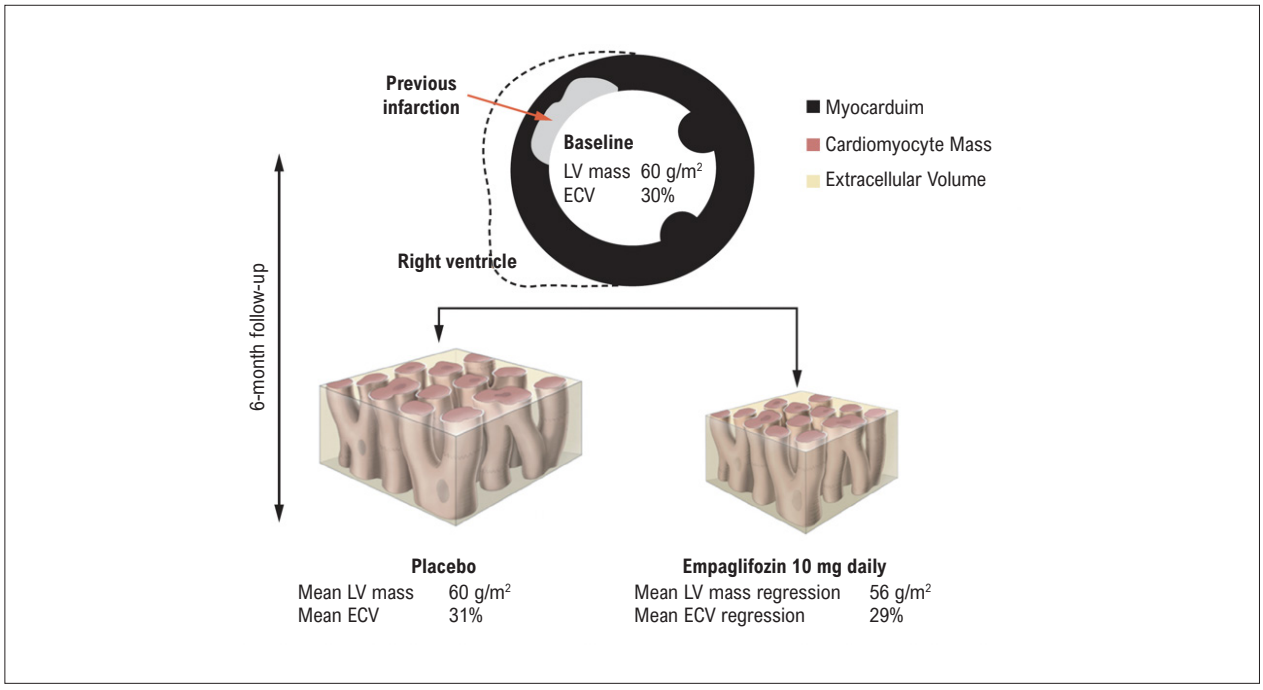

Figure 3 – *A 6-month blinded, randomized trial of the effects of empagliflozin vs placebo in patients with type 2 diabetes mellitus (DM2) and coronary artery disease (reproduced with permission from the authors).[58] LV: left ventricular; ECV: extracellular volume.*

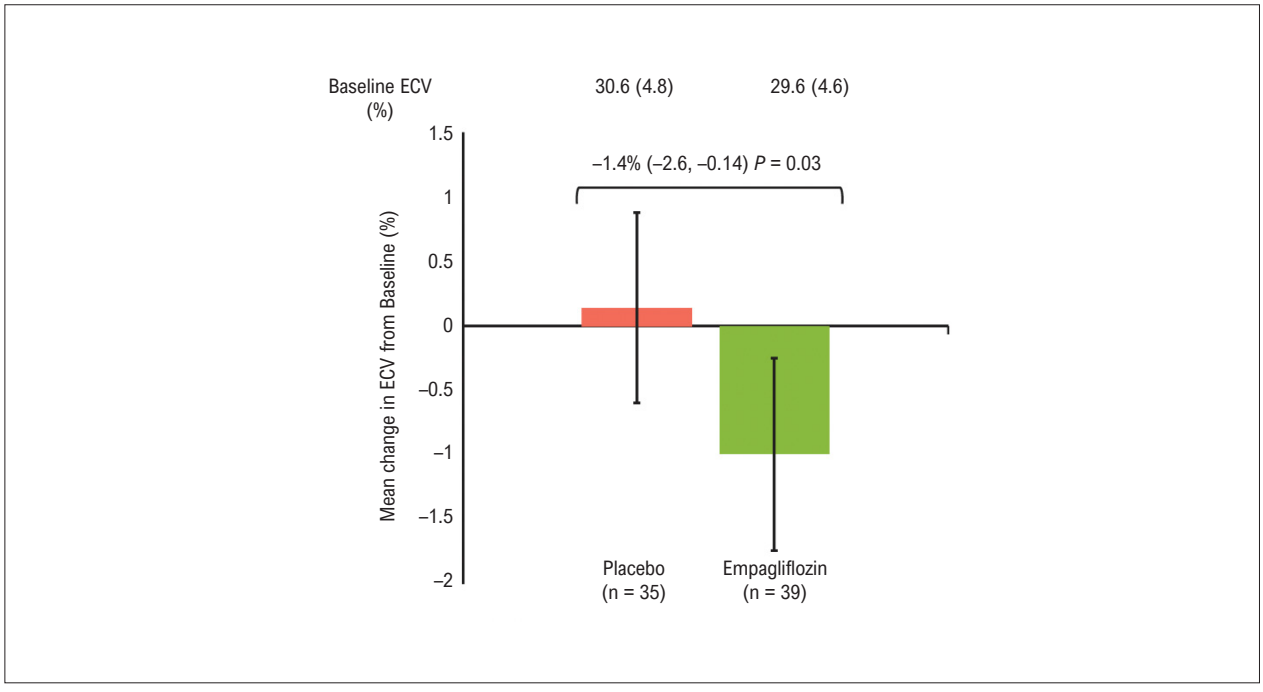

Figure 4 – *After 6 months of treatment with empagliflozin, there was a significant reduction in the myocardial extracellular volume of patients with diabetes and coronary artery disease (reproduced with permission from the authors).[58] ECV: extracellular volume.*

and molecular alterations associated with early atherogenesis, decreasing arterial stiffness and vascular resistance.[63,64] Additional benefits of SGLT2 inhibitors include the induction of vasodilation through the activation of protein kinase-G and voltage-gated potassium channels. Together with natriuresis and osmotic diuresis, the direct effects of SGLT2 inhibitors on the vascular system contribute to improved hemodynamic function in patients with HF.

Increasing erythropoietin (EPO) levels

The increase in hematocrit observed with the use of SGLT2 inhibitors, even in individuals without diabetes, suggests that these medications can increase EPO secretion by the kidneys and ultimately promote erythropoiesis.[65] This increase in EPO contributes to improvements in cardiomyocyte mitochondrial function, angiogenesis, cell proliferation, and inflammation, in addition to increasing oxygen supply to myocardial tissue.[65] The EMPA-Heart Cardio Link-6 randomized clinical trial demonstrated that one month of treatment with empagliflozin led to significant increases in EPO levels in patients with diabetes and coronary artery disease.[65] These patients also exhibited a significant increase in hematocrit and reductions in ferritin and hemoglobin concentration.

Reducing epicardial fat

Epicardial adipose tissue is the visceral fat that surrounds the heart and comes into direct contact with the coronary tunica. The attenuation of epicardial adipose tissue as demonstrated on computed tomography can indicate the presence of inflammatory alterations and coronary neovascularization and is therefore associated with an increased risk of cardiovascular events.[20] SGLT2 inhibitors reduce the accumulation of adipose tissue and perivascular inflammation, minimizing the secretion of leptin and its effects on cardiac fibrosis.[66] In patients with both diabetes and coronary artery disease, SGLT2 inhibition reduces the mass of epicardial adipose tissue and bioactive molecules such as TNF-alpha and the type 1 plasminogen activator inhibitor. This can therefore attenuate inflammation and even the remodeling associated with HF.[67]

Increased vascular progenitor cells

Another mechanism that could explain the cardioprotective effect of SGLT2 inhibitors is the restoration of vascular repair through the mobilization of vascular progenitor cells in the bone marrow. Tissue revascularization requires a network of circulating cells to work together to mediate microvascular growth. There is evidence to suggest that SGLT2 inhibition may affect the balance of circulating progenitor vascular cells, monocytes, and inflammatory cells in patients with diabetes and established cardiovascular disease.[18] In a previous study, Hess et al.[68] observed that treatment with empagliflozin was associated with a reduction in M1 proinflammatory macrophages, and a subsequent increase in the number of polarized M2 macrophages which are associated with an anti-inflammatory response (Th2). Previous studies have demonstrated that phlorizin-induced SGLT2 inhibition increases antioxidant production, and the administration of empagliflozin reduces the production of NOX1, an important component of oxidative stress in the peripheral vasculature of rats with diabetes.[69] Systemic reductions in oxidative stress promote the maturation of progenitor cells in the bone marrow.[70] It has been proposed that the administration of SGLT2 inhibitors leads to an increase in the release of angiogenic progenitor cells from the bone marrow.[68]

Improved metabolism and cardiac bioenergetics

Fatty acids are an important energy source for healthy heart tissue; however, HF is associated with impaired cardiac fatty acid oxidation. In these cases, the heart utilizes ketone bodies as an alternative energy source through enzymes such as beta-hydroxybutyrate dehydrogenase (BHD1). SGLT2 inhibitors can increase the production of ketone bodies, especially beta-hydroxybutyrate, increasing the energy supply to the heart muscle.[18] In this way, the change in metabolic substrate contributes to increased efficiency and myocardial contractility. The increased ketone production is also believed to reduce acetyl CoA levels, which, in turn, reduce the hyperacetylation of mitochondrial enzymes, improving mitochondrial energy production.[12]

Inhibition of sodium/hydrogen exchangers

Another explanation for the effects of SGLT2 inhibitors on HF involves their interaction with type 1 (NHE1) and 3 (NHE3) sodium/hydrogen exchangers. NHE1 is found in myocardial and vascular tissues, and when activated, increases intracellular sodium and calcium levels, the first of which is associated with HF and cardiomyocyte injury. NHE3 is found in the kidneys and promotes sodium reabsorption and subsequent water retention.[12] SGLT2 inhibitors are believed to directly inhibit NHE1 and promote natriuresis by reducing NHE3 expression. This pathway may contribute to the explanation of the close link between diabetes and HF. They are stimulated by elevated glucose and insulin levels in diabetes and by the exacerbated neurohumoral activation in HF. Therefore, patients with decompensated HF can also experience an exacerbation of diabetes.[12,46] In conclusion, the inhibition of NHE1 and NHE3 may be an important part of the cardiac and renal mechanisms through which SGLT2 inhibitors treat HF.[18]

Reduced leptin levels

Leptin, a protein associated with energy homeostasis, is a major contributor to the development of HF in individuals with diabetes. This protein stimulates SGLT2 receptors in the kidneys, causing sodium retention and influencing inflammation and cardiac fibrosis. SGLT2 inhibitors can suppress the effects of leptin in several ways. The reduction in visceral adipose tissue lowers leptin levels, while the inhibition of SGLT2 receptors in the kidneys reduces sodium absorption.[18] SGLT2 inhibitors also increase overall adiponectin levels, decreasing inflammatory action through TNF-alpha inhibition. Adiponectin is associated with reductions in body fat, which it promotes by inhibiting SGLT2.

Prevention of ischemia/reperfusion injury

Cell injury, necrosis, and programmed cell death (apoptosis, necroptosis, autophagy) are important physiopathological characteristics of several maladaptive processes in the heart, including myocardial ischemia and HF.[71] Recent experimental evidence suggests that SGLT2 inhibition has cardioprotective effects against ischemia/reperfusion injuries. The authors of these studies hypothesize that the improved cardiovascular survival observed after treatment with SGLT2 inhibitors is associated with their direct cytoprotective effects which include protection against myocardial ischemia/reperfusion injury. The first demonstration of the cardioprotective effects of canagliflozin against ischemia/reperfusion injury in diabetic and non-diabetic animals was obtained in a study of Langendorff-perfused hearts from diabetic and non-diabetic rats treated with canagliflozin for a 4-week period, who showed smaller infarcts than those in comparison conditions.[61] These results also suggest that SGLT2 inhibitors may be introduced as a cardioprotective intervention in high-risk cardiovascular patients, irrespective of diabetes status.[61] The beneficial effect of SGLT2 on ischemia/reperfusion injury is associated with a reduction in the activity of calmodulin kinase II, resulting in increased calcium flux in the sarcoplasmic reticulum and increased contractility. However, it is not yet clear if this effect occurs in humans.

Reducing hyperuricemia

Plasma uric acid has a negative effect on the prognosis of HF.[72] Uric acid serum levels are intimately related to insulin resistance markers. Patients with DM2 are known to have lower serum uric acid levels than the general population, and to date, this has been attributed to the osmotic diuresis caused by elevated serum glucose. Slight reductions in plasma uric acid have been observed after treatment with SGLT2 inhibitors.[73] This can be attributed to the increase in glycosuria in the proximal tubules since SGLT2 inhibitors promote uric acid secretion.[74] However, the issue of whether reduced hyperuricemia due to SGLT2 inhibition is a marker or cause of its effects remains open for discussion.

Conclusions

Several studies have demonstrated the benefits of SGLT2 inhibitors on cardiovascular outcomes. Yet the precise mechanisms behind the cardioprotective effects of SGLT2 inhibitors have not been entirely established. Several such mechanisms have been proposed, including reduced sympathetic activity, improved cardiovascular hemodynamics, and bioenergetic availability. These are all complex, interdependent factors that potentiate one another. As such, further studies are needed to shed light on the effects of SGLT2 inhibitors in the context of HF. SGLT2 inhibitors are promising drugs with proven effectiveness in the treatment of several chronic illnesses, starting with DM2 and extending to HF with reduced EF in 2019, and, as recently established by the DAPA-CKD study, consistent benefits on kidney function.

Author Contributions

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This article does not contain any studies with human participants or animals performed by any of the authors.

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Review Article

Acute Myocarditis in Childhood and Adolescence in the Covid-19 Era

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Abstract

Myocarditis in children and adolescents is an inflammatory myocardial disease with a heterogeneous presentation ranging from oligosymptomatic, with no impaired ejection fraction to catastrophic clinical presentation with cardiogenic shock (fulminant myocarditis) or sudden death. Thus, this condition remains a major challenge from the diagnostic and therapeutic points of view. Despite the different etiologies listed, the most frequent form may be related to viral diseases, and new forms of myocarditis, such allergic ones (eosinophilic and use of medications, particularly cancer immunotherapy), have been currently described. Increasing the rate of suspicion is crucial. Measurement of serum levels of troponin and N-terminal B-type natriuretic peptide, as well as the use of advanced methods of cardiac imaging, such as strain echocardiogram, positron emission tomography, and cardiac magnetic resonance, are integral part of multimodal assessment in suspected patients. Although endomyocardial biopsy remains is still the gold standard for disease diagnosis, currently it tends to be performed in specific situations, such as fulminant clinical presentation and chronic or recurrent myocarditis. The management of this condition includes general supportive care, treatment of heart failure, control of arrhythmias when present, assessment of mechanical support and cardiac transplantation. Treatments based on immunosuppression and immunotherapy are still controversial. In this article, we propose a broad review of diagnostic and treatment methods, as well as the different etiologies in the pediatric population.

Introduction

Myocarditis represents a heterogeneous group of myocardial inflammatory diseases in terms of etiology, inflammatory response, clinical course, and response to treatment. Additionally, it shows high morbidity and mortality rates in the pediatric population[1] and is considered the most common cause of heart failure (HF) in previously healthy children.[1,2] Furthermore, its clinical presentation has a spectrum of signs and symptoms ranging from oligosymptomatic cases to cardiogenic shock and sudden death, which represents a diagnostic challenge in pediatrics.[3] Dilated cardiomyopathy (DCM), a severe complication of myocarditis, is a common cause of heart transplantation in childhood.[1,2,4]

This article aims to present the advances in the field of diagnosis and treatment, in order to propose an algorithm to aid pediatricians, family physicians, and pediatric cardiologists in approaching patients with myocarditis.

Keywords

Myocarditis; Cardiomyopathy; Heart Failure; Children; Adolescents.

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Definition

Myocarditis is characterized by myocardial inflammation associated with a process of myocyte degeneration and necrosis, may be focal or diffuse, and may cause cardiac dysfunction and/or arrhythmias.[1] In 1995, myocarditis was classified as an inflammatory cardiomyopathy by the World Health Organization, and its diagnosis is established based on histopathological, immunological and immunohistochemical criteria. Moreover, infectious causes, toxic agents, autoimmune and autoinflammatory conditions, allergic reactions, or idiopathic causes may be involved,[5] thus characterizing the heterogeneous nature of the disease.

Epidemiology

The incidence and prevalence of myocarditis are difficult to determine, due to its varied clinical presentation.[1,6,7] A population-based registry study conducted by Arola et al.[8] in Finland observed an incidence of myocarditis of 1.95:100 000 people/year (considering children and adolescents from 0 to 15 year old).

Despite its rarity, myocarditis is significant,[3] since most patients require admission at intensive care unit, as well and ventilatory and circulatory supports.[6] This condition is responsible for 0.5 cases for each 10 000 consultations in pediatric emergency;[1] however, the actual frequency is probably higher than that reported, due to undiagnosed or asymptomatic cases.[8]

In international studies not including Latin American countries, the age distribution of disease diagnosis is bimodal, with a peak in the first year of life and another at 16 years of age. In adolescents, the disease is more frequent in the male sex (81%) than in the female.[8,9] Also according to the work performed by Arola et al.,[8] the incidence of myocarditis among male adolescents may be as high as 18.1:100 000 people/year. This increased incidence among male adolescents may be justified by the presence of testosterone.

Although outcome is favorable in nearly 50% of patients, morbidity and mortality rates remain significant. Sequelae and chronic evolution occur in approximately 30% of the cases, with 80% of cases of chronic cardiomyopathy leading to cardiac transplantation or death.[5] An autopsy study with

pediatric patients observed that 2% of deaths were caused by myocarditis.[10] In a recent autopsy pediatric study, 1.8% of patients had histological evidence compatible with myocarditis; of these, 57% had sudden death and 54% were younger than 1 year of age.[11]

Myocarditis accounts for 30% to 35% of children with a phenotype of DCM in registers from Australia and North America and for 22% of new-onset left ventricular dysfunction in the United Kingdom.[12-14]

Myocarditis in children is associated with higher rates of HF, hospitalization, length of stay at intensive care unit, and use of inotropic support at the time of diagnosis compared to children with idiopathic DCM. A recent study of hospitalized patients in the United States showed that almost a half of patients required inotropic support, 37.5% required mechanical ventilation, and 7.4% required extracorporeal membrane oxygenation (ECMO) support.[15,16]

Mortality at the acute phase ranges from 7 to 15% of the cases, and myocarditis is an important cause of DCM and cardiac transplantation in children without congenital heart disease, which account for 80% of the cases.[6]

Pathophysiology

Although the pathogenesis of myocarditis will depend on its etiology, much of our understanding on the disease is based on experimental models of guinea pigs infected with coxsackievirus.[17] In viral myocarditis, the existence of three phases has been proposed. Initially, there is a period of viral replication, leading to acute myocyte injury and consequently evolving to DCM, which is associated with changes in the extracellular matrix of the myocardial tissue.[1]

Etiology

A wide spectrum of infectious and immunomediated causes, as well as hypersensitivity to medications, drugs, and toxins, are involved in the etiology of myocarditis.[1,18-20] Most cases in the pediatric population are caused by viral infections, mainly with adenovirus, cytomegalovirus, Epstein-Barr virus, and enterovirus, the main of which being coxsackie virus type B. However, with the emergence of new diagnostic modalities, other pathogens were also detected, including polymerase chain reaction (PCR) and endomyocardial biopsy (EMB), parvovirus B19, human herpes virus 6, in several patients with myocarditis confirmed by biopsy in European studies.[18] Arboviruses, such as Chikungunya, dengue, and Zika virus, may also be involved.[21] Recently, cases of myocarditis due to H1N1 infection were documented.[1]

Thus, infectious exposures, especially to viruses, are responsible for most cases of pediatric myocarditis in Canada and in the United States;[19] whereas the most common cause of this condition worldwide is *Trypanosoma cruzi*. It is worth emphasizing that, in Latin America, chagasic myocarditis may affect children and adolescents in endemic areas and, due to migration, patients from these areas may be diagnosed in North America, Europe, and Asia.[5,19]

Currently, in view of the pandemic caused by the coronavirus disease 2019 (COVID-1), cases of myocarditis related to the severe acute respiratory syndrome virus 2 (SARS-CoV-2) have been described.[22,23] In pediatrics, myocarditis has shown to be related to cases of multi-systemic inflammatory syndrome and associated with clinical signs of Kawasaki disease.[22] In this cases, troponin elevation is one of main markers of myocardial involvement.[23,24] Dolhnikof et al.[25] showed the presence of particles of SARS-CoV-2 in the myocardial tissue through an electronic microscopic study and detection of viral RNA with reverse transcriptase PCR (RT-PCR). Multisystem inflammatory syndrome in children occurs some weeks after SARS-CoV-2 infection; therefore, patients may present with signs of acute HF and negative RT-PCR for SARS-CoV-2, associated with a significant elevation of troponin levels and inflammatory markers.[26]

Autoimmune myocarditis may be an isolated condition, such as in giant cell eosinophilic myocarditis and, or be part of a systemic disease, such as systemic lupus eritematosus, Sjögren syndrome, vasculitis, and polymyositis.[27] In scenarios of autoimmune myocarditis, there is lymphocytic infiltrate, suggesting important participation of T cells.[27] Simpson et al.[28] showed evidence of autoimmune mechanism in children with clinical picture of myocarditis through the presence of significant elevation of human cardiac anti-myosin antibodies.[28]

In addition to chemotherapy and radiation therapy used in the treatment of childhood cancer, new therapies with immunotherapy – checkpoint inhibitors – characterize potential risks for cardiac toxicity and are related to cases of myocarditis.[29-31] These patients should receive special attention, because they may initially present with normal echocardiogram, and more complex diagnostic methods are needed to confirm myocardial inflammation.[31] The Table 1 shows the different causes of myocarditis.

Clinical presentation

The diagnosis of pediatric myocarditis remains a challenge, due to its varied clinical presentation, which ranges from asymptomatic patients with only subtle findings on electrocardiogram (ECG) to fulminant HF and sudden death (MAY 2011). Thus, initial clinical suspicion is necessary for the diagnosis to be confirmed, especially in oligosymptomatic cases.

Studies such as those by Rodrigues-Gonzales et al.[6] and Durani et al.[4] showed that, in most patients (59 to 83%), the diagnosis of myocarditis was not made on the initial assessment; thus, more than one medical assessment were required before the diagnosis of myocarditis or DCM was made.[18] In the studies, children often received an initial diagnosis of respiratory disease (bronchiolitis, asthma, or pneumonia) or gastrointestinal infection.[1]

Clinical presentation also varies according to patient's age. Neonates and infants may present with unspecific symptoms suggestive of infection, including fever, hypoactivity, and suction difficulty, or may severe signs, such apneia, cyanosis, and cardiogenic shock.[2,7]

In older children and in adolescents, clinical manifestations may also be different. Most children present with unspecific respiratory or gastrointestinal complaints; only a minority of

Table 1 – Etiology of myocarditis in childhood and adolescence

Etiology		Examples
Infectious	Viruses	Adenovirus, echovirus, enterovirus (coxsackie), herpes (cytomegalovirus, Epstein-Barr virus, human herpes virus type 6, hepatitis C, HIV, H1N1, parvovirus B19, arboviruses (dengue, Chikungunya, and Zika), SARS-CoV-2
	Bacteria	Clamidia, *Corynebacterium diphtheriae*, *Klebsiella, Salmonella*, *Legionella, Mycobacterium tuberculosis, micoplasma*, *Staphylococcus*, *Streptococcus A*, *Streptococcus pneumonia*, *Tryponema pallidum*, *Haemophilus influenzae*
	Fungi	Actinomyces, Aspergillus, Candida, Cryptococcus
	Protozoa	Toxoplasma gondii, Trypanosoma cruzi
Autoimmune	Celiac disease, Churg-Strauss syndrome, dermatomyositis, giant cell myocarditis, hypereosinophilic syndrome, Kawasaki disease, systemic lupus eritematosus, lymphofollicular myocarditis, rheumatoid arthritis, sarcoidosis, ulcerative colitis, scleroderma	
Hypersensitivity reactions	Penicillin, ampicillin, cephaloesporin, tetracyclines, sulfonamides, benzodiazepines, clozapine, thiazide and loop diuretics, methyldopa, tetanus toxin, varicella vaccine, antidepressants	
	Anphetamines, anthracyclines, catecholamine, cocaine, cyclophosphamide, phenytoin, transtuzumab, toxic amitriptyline, amphotericin B, *cannabis*, carbon monoxide, electric shock, ethanol, Hymenoptera, isoniazid, lidocaine, methyldopa, spider and scorpion venoms	

HIV: human immunodeficiency virus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

them report chest pain. The most frequently reported signs of myocarditis are unspecific symptoms, such as shortness of breath (69%), vomiting (48%), or feeding difficulties (40%). Sudden death may occur in some cases of myocarditis.[2] Every patient with new-onset HF or arrhythmia should have myocarditis considered as a possible diagnosis.

The presentation of myocarditis may be categorized into clinical syndromes such as: chest pain, HF with phenotype of DCM or fulminant myocarditis, arrhythmias, and sudden death.

Chest pain: intense chest pain, similar to that of acute myocardial infarction, associated with typical electrocardiographic changes and increase in biomarkers such as troponin and brain natriuretic peptide (BNP).[1] It is usually associated with pericardial impairment, but cardiac function is normal.[32] In these patients, it is necessary to ensure that coronaries do not have congenital or acquired anatomical abnormalities through imaging tests such as echocardiogram and coronary computed tomography angiography.

Sudden death: despite being a rare event, sudden death in the pediatric population is commonly associated with myocarditis[16] and may be the initial presentation of the disease. In these cases, diagnosis is made histologically, in which an infiltrative inflammatory process becomes an arrhythmogenic focus generating fatal arrhythmia, or through cardiac imaging after an event of aborted sudden death. Myocarditis accounts for approximately 9% of sudden deaths in young athletes in the United States with confirmed cardiovascular event was documented.[28]

1. Arrhythmias

Symptoms such as palpitations and syncope occur in pediatric patients with myocarditis even in the absence of HF or of overt reduction of left ventricular a function.

Resting sinus tachycardia is also an important subtle characteristic and, despite not being a consistent finding, it may be the only finding in mild forms.

The presence of ventricular arrhythmias in structurally normal hearts and ventricular tachyarrhythmias in athletes has been associated with myocarditis.[30,31] Myocarditis should also be considered in children with acquired complete heart block. Lyme carditits and Chagas disease have been associated with complete heart block. Although most children may recover atrioventricular conduction, some patients may require permanent. Although most children may recover atrioventricular conduction, some patients may require permanent pacemaker implantation.[32-34]

2. HF with phenotype of DCM

The most classical presentation of myocarditis is the onset of symptoms of HF in a phenotype of DCM some weeks after a history compatible with viral disease. Respiratory and gastrointestinal symptoms, as well as myalgia, are characteristic of this phase, and fever may be present or not.[19,35]

Signs of congestive HF are observed in most patients[18] varying in severity of symptoms according to the degree of myocardial inflammation.[1] Tachydyspnea, tachycardia, changes in cardiac and respiratory auscultation, and hepatomegaly are usually observed, followed by signs of low cardiac output.

3. Fulminant acute myocarditis

Is a different subset of acute myocarditis characterized by HF with severe hemodynamic involvement requiring mechanical or inotropic circulatory support and meeting at least two of the following criteria: fever, onset with symptoms different from those of HF within 1 or 2 days, and history of viral disease in the 2 weeks before hospitalization. Fulminant myocarditis is associated with symptoms of major left ventricular dysfunction and unexpected HF from 2 to 3 weeks after the onset of viral infection.[14,36] Fulminant myocarditis accounts for 10 to 38% of all

cases of myocarditis,[37] and has been described in children with mortality rates ranging from 48.4% in Japan to 9% in France. Despite the severe presentation, results are significantly better that those of adults with acute myocarditis. In children presenting with cardiogenic shock, ventricular arrhythmia, or atrioventricular block stabilization with mechanical circulatory support (MCS) will be required, such as extracorporeal membrane oxygenation (ECMO). In patients who do not respond after a period of 1 to 2 weeks, an endomyocardial biopsy (EMB) should be considered in order to rule out giant cell myocarditis that responds to treatment with immunosuppression, despite having a poor prognosis.[38]

Diagnosis

The diagnosis of myocarditis is especially challenging due to its varied clinical presentation, which encompasses from asymptomatic patients with only subtle findings on ECG to fulminant HF and sudden death. Diagnosis remains mostly based on high degree of clinical suspicion, supported by biomarkers, such as cardiac troponin and BNP, and advanced techniques of cardiac imaging, such as tissue Doppler echocardiography and cardiac magnetic resonance, with EMB being considered the gold standard of diagnosis. Clinical characteristics of myocarditis are usually similar to that of HF, and this condition is the most common cause of new-onset HF in healthy children. Patients with mild symptoms are at risk of worsening and, thus, early diagnosis is important in the establishment of appropriate monitoring and support care.[5,39]

After clinical suspicion, based on medical history taking and physical examination, investigation begins with supplementary tests. Table 2 and Figure 1 summarize the main diagnostic tools and possible findings.

ECG

In children with myocarditis, ECG is altered in at least 93% of patients,[20] although normal results do not exclude the diagnosis of this condition. Changes are unspecific and range from sinus tachycardia to ventricular arrhythmias, and there may be low QRS complex voltage, atrioventricular block, changes in ST segment and QT interval.[15,19,20]

Biomarkers

The levels of inflammatory activity markers, such as hemosedimentation velocity and reactive C protein, are often elevated, and leukocytosis may be present, although normal results do not rule out the diagnosis of myocarditis.[11,19]

Abnormal troponin levels may support the diagnosis of myocarditis. Troponin T may have greater sensitivity to detect micronecrosis in myocarditis, due to the proportionally higher and longer increase in its serum levels compared with creatine kinase.[11,35] It is believed that EMB should be performed when troponin levels are elevated, because there is a greater likelihood of showing myocardial inflammatory infiltrate.[15]

Soongswang et al.[40] found that troponin T has good sensitivity (71%) and specificity (86%) to diagnose acute myocarditis in children and that troponin T levels were higher in patients with myocarditis compared to those with DCM.[40] However, it is important to highlight that, in clinical practice, values of troponin T and I are measured by different methods; therefore, it is essential to know the cutoff values for the test kits used in the institution where the patient was treated.

High levels of natriuretic peptide (BNP and N-terminal B-type natriuretic peptide [NT-pro-BNP]) may be present in myocarditis and are useful to determine cardiac etiology in children with respiratory symptoms.[19] Rodriguez-Gonzalez et al.[6] showed that NT-proBNP levels > 5,000 pg/mL are associated with worse prognosis in children with myocarditis.

Chest X-RAY

Findings on chest x-ray usually include increased cardiac area on account of increased left ventricular (LV) diameter and/or pericardial effusion[7,20] and may reveal pulmonary congestion and edema, infiltrates, or pleural effusion.[7]

Table 2 – Main diagnostic tools in acute myocarditis in children and adolescents

Investigation tools	Possible findings
Medical history taking	Typical symptoms of cold/influenza, gastroenteritis, insect bites, family history of cardiomyopathy, and precordial pain. Signs of new-onset heart failure or arrhythmia in previously healthy children.
Physical examination	Resting tachycardia and clinical signs of heart failure.
Biomarkers	Troponin and BNP elevation.
Chest x-ray	Image suggestive of increased cardiac area, pulmonary congestion, pleural effusion, and pulmonary infiltrate.
Electrocardiogram	Sinus tachycardia, ventricular hypertrophy, abnormalities in ST segment and in T wave, arrhythmias, AVB, QT segment prolongation, low QRS complex voltage.
Echocardiogram	Increased telesystolic and diastolic ventricular volume, wall motion abnormalities, septal or ventricular thickening, reduced ejection fraction, valvular regurgitation, and presence of thrombi.
Gallium scintigraphy	Capture of gallium
Nuclear magnetic resonance	Edema, cardiac tissue inflammation and necrosis/fibrosis.
Myocardial biopsy	Presence of lymphocytic infiltrate, edema, and necrosis of cardiac muscle cells, viral PCR.

AVB: atrioventricular block; BNP: brain natriuretic peptide.

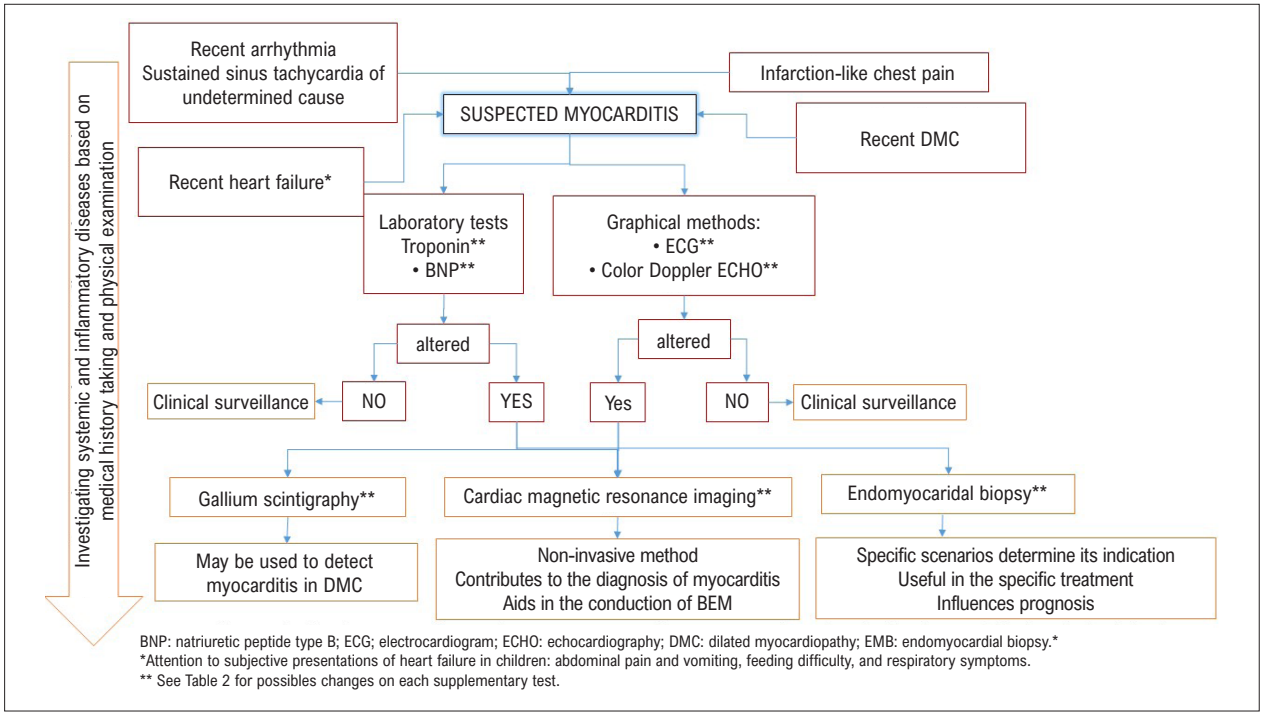

Figure 1 – *Diagnostic flowchart for pediatric patients with suspected myocarditis.*

Echocardiography

Echocardiographic findings typical of myocarditis are increased LV systolic and diastolic diameters and reduced LV shortening and ejection fractions, characterizing the phenotype of DCM.[19,41] Atrioventricular valvular regurgitation and segmental abnormalities of ventricular wall motion, as well as pericardial effusion, may also be observed.[7,19,41] Changes in right ventricular function may be associated with greater likelihood of adverse outcomes, including cardiac transplantation or death.[7]

Fulminant myocarditis may be characterized by increased intraventricular septal thickness due to interstitial edema and LV dimensions close to normal.[19,41] Patients with this condition have better prognosis in recovering LV function.[19] Phenotypes of hypertrophic and restrictive cardiomyopathy have already been described in patients with diagnosis of myocarditis confirmed by histopathology.[7,19]

The use of tissue Doppler and ventricular strain may also contribute in the diagnosis of myocarditis.[32,41] However, the diagnostic value of ECHO is limited, because many patients with mild myocarditis may present with normal echocardiographic results.[42] Echocardiography is also important to rule out other causes of HF, especially coronary abnormalities.[7]

Nuclear medicine

The presence of cardiac inflammation may be demonstrated scintigraphy studies.[16,38] In children with DCM, gallium-67 scintigraphy may be used to detect myocarditis, showing high sensitivity (87%) and specificity (81%) compared with EMB.[43] However, this technique is not frequently used in children with suspected myocarditis.[1,38]

Cardiac magnetic resonance

Cardiovascular magnetic resonance is a tool widely accepted to investigate patients with suspected myocarditis and became the non-invasive diagnostic method of choice in the diagnosis of myocarditis.[2,44,46] In pediatrics, in addition to contributing to diagnosis, cardiovascular magnetic resonance is able to contribute in prognosis, especially in cases of fulminant myocarditis.[47] Martinez-Villar et al.[45] showed the contribution of resonance in the diagnosis of myocarditis in adolescents with infarction-like presentation.

This technique allows for a detailed assessment of ventricular wall dimensions and thickness and of cardiac function; moreover, it provides data on myocardial tissue, showing the presence of edema, inflammation, and fibrosis.[13] Edema is seen through enhancement of T2-weigthed image, early enhancement on T-1 weighted image is related to hyperemia. Conversely, late gadolinium enhancement translates the presence of fibrosis, which is typically not restricted to a vascular territory, being usually mesomural and subepicardial.[2,13,32] Figures 2 and 3 illustrate these changes. Cardiac resonance is also able to identify segmental changes in ventricular walls, more commonly in inferolateral and basal walls.[34]

Friedrich et al. published in 2009 the Consensus on cardiovascular magnetic resonance for inflammatory cardiomyopathies, the Lake Louise criteria, which establish

that the presence of edema, hyperemia, and necrosis/fibrosis are assessed through T2-weighted images, early enhancement, and late gadolinium enhancement; likewise, the presence of 2 or more of these criteria strongly suggest the presence of myocarditis,[42] with a sensitivity of 67% and a specificity of 91%.[13] Diagnostic accuracy may be improved with myocardial assessment on T1-weighted images.[47] Therefore, the use of T-1 mapping together with T2-weighted images and late gadolinium enhancement increases diagnostic accuracy to 96%.[45,46]

Others unspecific findings of myocarditis include: regional changes in ventricular wall motion, reduced myocardial function, and pericardial effusion.[45]

In addition to the diagnosis of myocarditis, magnetic resonance may provide information on disease progression and resolution.[45]

EMB

The histopathological demonstration defined by the Dallas criteria, proposed in 1986.[14] Is still necessary for the definite diagnosis of myocarditis; thus, EMB is still the gold standard.[2,16,19] EMB shows the etiology of myocarditis, because infectious, inflammatory, toxic, infiltrative, and autoimmune changes occur at the cell level, and non-invasive methods are not able to demonstrate them.[49] Although some factors limit its routine use,[1,6,38] the indication of EMB is justified by the fact that specific inflammatory diseases of the myocardium have an unique treatment, impacting on prognosis.[16,48,49-51] For example, the treatment of myocarditis mediated by immune processes differs from that of viral myocarditis, and it is difficult to diagnose them by non-invasive methods.[1,49]

The EMB procedure may rarely be related to some complications such as cardiac tamponade and atrioventricular block requiring temporary pacemaker.[7,13,16] In pediatric patients, the overall risk of complications is relatively low, ranging from 1 to 6 %,[1] and is directly related to patient's clinical condition, to the experience of the medical team in performing the procedure, and to the availability of cardiac surgery if needed.[38] Mortality rates range from 0 to 0.4%.[1] Therefore, the risk/benefit of biopsy should be individually assessed.

The sensitivity of Dallas criteria for the diagnosis of myocarditis is around 55%; however, the use of immunohistochemistry and polymerase chain reaction (PCR) for viral research increases the diagnostic sensitivity of EMB,[13,38] since some studies showed the presence of virus in the absence of Dallas criteria.[14,36,48] The collection EMB samples from both ventricles increases sensitivity for the diagnosis of myocarditis.[43] The diagnosis may be improved with the combined use of EMB and magnetic resonance improve diagnosis, because magnetic resonance can guide the better site for the collection of EMB samples when focal lesions are present in the right or in the left ventricle.[3,16,50]

In 2007, a joint publication by the American Heart Association, the American College of Cardiology Foundation, and the European Society of Cardiology defined as class I recommendation for EMB two scenarios out of 14: unexplained new-onset HF of less than 2 weeks' duration associated with hemodynamic compromise; or unexplained new-onset HF of 2 weeks' to 3 months' duration associated with ventricular dilatation or arrhythmias or conduction disease.[49] However, the European Society of Cardiology recently included the presence of pseudoinfarction as recommendation for EMB, after exclusion of coronary disease.[48] In the pediatric population, the presence of unexplained cardiomyopathy receives recommendation IIa for EMB.[49]

According to the Dallas criteria, acute myocarditis is defined by lymphocytic infiltrates in association with myocyte necrosis, whereas borderline myocarditis is characterized by inflammatory infiltrate without evidence of necrosis.[51]

Treatment

The therapeutic approach of myocarditis in childhood and adolescence is still controversial and mainly based on support treatment.[1,12,20] However, specific treatment may be required, according to results from EMB, clinical presentation, and disease prognosis.[48]

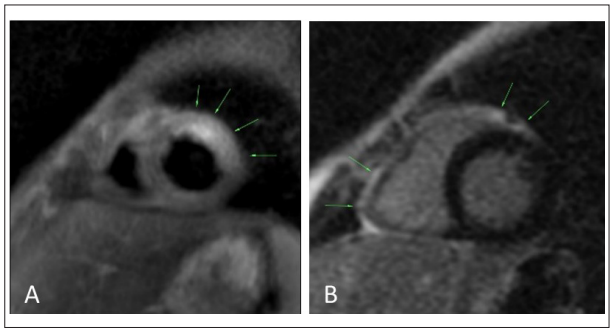

Figure 2 – *Cardiac magnetic resonance showed myocardial edema at anterolateral mid-basal walls. (A) Effusion, thickening, and pericardial enhancement more evident near the right and left ventricular basal segments. (B) Aspect suggestive of recent or active myopericarditis.*

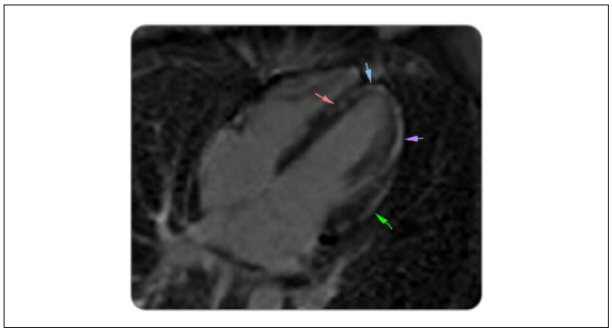

Figure 3 – *Presence of atypical late enhancement for coronary disease with heterogeneous pattern, sparing the endocardium located in the anterior, anteroseptal, and inferior segments. Compatible with non-ischemic necrosis/fibrosis (myocarditis).*

General measures

These measures consist of treating HF and arrhythmias and of preventing sudden death by reducing myocardial oxygen consumption, treating anemia, and adhering to water and salt restriction with strict control of water balance.[2,12]

1. Physical activity limitation/rest: competitive activities should be suspended for 6 months, as long as ventricular function is normal and there is no evidence of clinically relevant arrhythmias.[12,19]
2. Treatment of HF: stabilizing children with hemodynamic compromise is crucial, admission to the pediatric intensive care unit for hemodynamic and ventilatory supports is required in cases presenting with HF.[1,11,12] Infusion of inotropics, use of afterload reducers, and use of diuretics help improve cardiac function.

   The administration of diuretics should be made with caution, because rapid reduction in volemia may worsen hypotension and compromise tissue perfusion in a patient with an already reduced cardiac output.[2,11] The use of inotropics such as dobutamine, dopamine, noradrenaline, and adrenaline will be necessary in patients with hypotension, low cardiac output, and reduced cardiac function; their infusion may increase the risk for arrhythmias. The use of milrinone (phosphodiesterase inhibitor) is very useful in afterload reduction, improves cardiac function, and has a lower risk of predisposing to arrhythmias.[2,11,19]

   The use de angiotensin-converting enzyme inhibitors (ACEI) and beta blockers in adult patients is associated with good prognosis.[19] However, beta blockers should not be administered to children in the acute phase of myocarditis, when there is low cardiac output. After stabilization and transition to the use of an oral diuretic, the use of beta blockers such as carvedilol is recommended, as well as the use of ACEI, which is associated with reduced reverse remodeling and improved functional class.[2] Digoxin should be used with extreme caution in patients in the acute phase of disease, since its administration may trigger arrhythmias and increase the production of inflammatory cytokines.[11]
3. Arrhythmias: in patients with myocarditis, arrhythmias are usually transient and occur during the acute phase of disease. However, changes in cardiac rhythm may be associated with greater mortality and should be managed conventionally. Despite that, some patients will require peacemaker implantation for total atrioventricular block, and those with sustained ventricular arrhythmia will require amiodarone and, in selected cases, implantable cardioverter defibrillator.[11,49]
4. Advance life support: mechanical circulatory support (MCS) is required in patients with refractory cardiogenic shock. MCS devices are able to replace heart's pumping function until myocardial function is recovered (rescue therapy) or until cardiac transplantation is possible (bridge therapy for transplantation).[2,11,43]

   Pediatric patients with fulminant myocarditis benefit from ECMO support, because recovery of ventricular function may occur within some weeks.[1,7,52]

Specific measures

1. Intravenous immunoglobulin (IVIG): the use of immunoglobulin in pediatric patients with new-onset myocarditis or DCM is still controversial, since there are no available controlled studies showing its benefit.[1,2,53-55] The use of immunoglobulin is based on its antiviral and immunomodulatory potential, which reduces the cytokine production and inflammation.[1,7] Robinson et al.[56] conducted a Cochrane review with several databases and concluded that IVIG may be useful in children with myocarditis associated encephalitis and that more controlled clinical trials are needed to demonstrate the benefit of IVIG in pediatric myocarditis. However, studies with series of pediatric cases show that the use of immunoglobulin improves ventricular function and survival in this population, suggesting that immunoglobulin has a beneficial role in pediatric myocarditis.[1,7,49,54] In a meta-analysis study, Huang et al.[53] demonstrated that patients with fulminant myocarditis showed better survival at follow-up and that the use of IVIG showed to be superior compared with conventional treatment in reducing in-hospital mortality rates.[53] However, a systematic review with meta-analysis conducted by Yen et al.[55] found that immunoglobulin did not change survival rates, and thus should not be routinely administered for acute pediatric myocarditis.

   In the I Brazilian guideline on HF and cardiac transplantation in fetuses, children and adults with congenital heart disease, developed by the Brazilian Society of Cardiology (*Sociedade Brasileira de Cardiologia*, SBC), the use of IVIG is considered recommendation IIb, with level of evidence B, for the following conditions: idiopathic DCM (optimized clinical treatment, more than 1 year with symptoms of HF) with presence of high titers of parvovirus B19 genome for in the myocardial tissue confirmed by EMB and molecular biology; myocarditis confirmed by EMB through immunohistochemistry and presence of viral genome in the myocardial tissue on molecular biology.[43]
2. Immunosuppression: the role of immunosuppression is still discussed in the treatment of myocarditis, with the purpose of suppressing inflammatory response and autoimmune activity in order to improve clinical status and ventricular function and reduce mortality.[12,16,44,57] It may be considered adjuvant therapy when EMB is performed, and the presence of viral activity is ruled out through PCR study and documentation of inflammatory activity.[11] The Tailored Immunosuppression in Inflammatory Cardiomyopathy (TIMIC) study confirms the efficacy of immunosuppressive therapy in this situation.[57]

   In giant cell myocarditis confirmed by EMB, immunosuppression received class I recommendation I, level of evidence B. Conversely, in inflammatory cardiomyopathy confirmed by EMB through immunohistochemistry with optimized clinical treatment and more than 6 months of symptoms of HF, in the absence of viral genome by molecular biology, immunosuppression received class recommendation IIb and level of evidence B.[43] This therapy is also indicated in eosinophilic myocarditis.[19]

Camargo el al.[58] showed that immunosuppressive therapy is beneficial in pediatric patients with inflammation on EMB, regardless of the presence of viral genome. However, their study did not use a control group of active patients with myocarditis treated conventionally.[58]

Therapy may be based on the association of prednisone and azathioprine or corticosteroids associated or not with cyclosporine.[16,19,43]

3. Antiviral therapy: the presence of viral genome in EMB samples has guided antiviral therapy. Interferon-β (IFN-β) and IVIG are the main therapeutic options, whose objective is to interrupt viral replication by eliminating them. It is necessary to confirm inflammatory activity associated with viral replication documented by EMB.[16,49] Patients with DCM and persistent viral genome show improved cardiac function after using subcutaneous IFN-β.[7,49] The use of antiviral therapy is more effective in the earlier stages of myocarditis.[19]

   Infections with cytomegalovirus, herpes simplex, and human immunodeficiency virus (HIV) should receive their predefined therapies.[12]

Prognosis

The prognosis of myocarditis is as variable as its clinical presentation. The patients may recover and subsequently evolve to DCM or death.[44,59,60] Patients with normal cardiac function usually have good prognosis, unlike those with DCM.[1,44] In general, nearly 50% of patients will improve after 2 to 4 weeks of disease onset, nearly 30% will develop DCM, and the remaining 20% may evolve to clinical worsening, requirement for cardiac transplantation, or death.[17]

Ejection fraction below 30% and shortening fraction bellow 15%, LV dilatation, and moderate to severe mitral regurgitation are considered predictors of poor prognosis.[1] In a study conducted by Kim et al.,[60] LV dilatation was the main factor associated with mortality in children with acute myocarditis. Transplantation-free survival in children with acute viral myocarditis ranges from 70 to 75%.[54] However, neonates and infants have significant mortality rates in up to 45% of the cases.[1]

Patients with fulminant myocarditis are more likely to recover ventricular function after surviving the acute phase with cardiogenic shock.[1,44]

New horizons

New models of pathogen identification through metagenomic next-generation sequencing (mNGS) have contributed in the approach of myocarditis in large centers. In most studies with mNGS, it was observed that the identified viruses were not included in the routine viral panels.[61,62] These studies also reinforce the need of population research fronts specific for epidemiology and etiology of myocardites. The pursuit of etiopathogenic diagnosis will contribute to characterize outcomes and prognosis in specific populations, thus enabling to include investigations with vaccines and appropriate antiviral therapeutics.

Conclusions

Myocarditis is characterized as a multifaceted disease able to promote different clinical pictures and outcomes. Numeral diagnostic and therapeutic technological advances have changed its natural history; however, epidemiological studies of clinical registries are essential to characterize the population in each country.

The Children and Adolescents Myocarditis and Cardiomyopathy Registry (ChARisMa), conducted by Universidade Federal Fluminense (UFF) in Niterói, state of Rio de Janeiro, Brazil, with partner institutions and the support from the SBC Department of Heart Failure (*Departamento de Insuficiência Cardíaca da Sociedade Brasileira de Cardiologia*, DEIC-SBC), aims to map and characterize pediatric and adolescent population with suspected or diagnosed myocarditis and cardiomyopathy. The obtained population data will contribute in guiding and developing protocols with educational, diagnostic, therapeutic, and follow-up measures.

Promoting research guidelines in diagnostic suspicion in childhood may contribute to better outcomes, not only in this population but also in the adult population with DCM of unknown etiology.

Author Contributions

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Review Article

Diuretics and Clinical Management of Congestion in Heart Failure: A Review

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Abstract

Heart failure is a syndrome with variable presentations; congestion is the most common form in acutely decompensated patients. In this scenario, the main drug to resolve congestion is a loop diuretic. However, a portion of the population has diuretic resistance. In this context, adjuvant diuretic therapies are needed to resolve congestion in patients with heart failure. The main strategies studied so far are thiazide diuretics, mineralocorticoid receptors antagonists, vasopressin antagonists, nesiritide, sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors, hypertonic saline, and fluid and salt restriction. The purpose of this article is to review pharmacological modalities for management of congestion, associated or not with diuretic resistance, their positive and negative points, and the current state of knowledge about each drug.

Introduction

Heart failure (HF) is a syndrome in which variable cardiovascular or systemic diseases with cardiovascular involvement converge to similar signs and symptoms. However, even within the same syndrome, patients may have different presentations. For example, symptoms may range from dyspnea during high-intensity sports in an elite athlete who suffered an infarction up to a cardiogenic shock in a post-infarction patient or in an 80-year-old patient with longstanding hypertension. Furthermore, the presentation of HF may be chronic, acute, or acutely decompensated. The treatment of chronic HF has undergone very significant advances, which has, in clinical practice, changed its natural history, especially from the 1980s onwards. Acutely decompensated HF (ADHF) is the central theme of the present article.

ADHF is the leading cause of hospitalizations in patients older than 65 years of age,[1] accounting for around 1 million hospitalizations in the United States per year, having an impact both on morbidity and mortality. It is estimated that one out of two patients are readmitted within 6 months, with an in-hospital mortality rate from 4 to 12%. Even after hospital discharge, it is estimated that 35% of patients with ADHF evolve to death within 1 year.[2,3] This is a serious situation both from the individual point of view, due to worsened quality of life and reduced survival, and in terms of public health, due to the high costs involved.

Similar to chronic presentations, ADHF is very heterogeneous, with regard to both patient care demand and disease clinical presentation.[3] One of the most common of these is clinical congestion.[4] In patients with presentations, decision-making is simple; however, many patients have subtle signs of congestion on physical examination, thus hampering accurate diagnosis. Moreover, the process of congested patient is dynamic, since variations in intracardiac pressures may change within a short time,[5] depending on a cascade of events, such as ventricular and atrial end-diastolic pressure, pulmonary capillary wedge pressure, pulmonary arterial wedge pressure, right chamber pressures, hemodynamic variations depending on patient's ventilation mode, among other factors.[6,7]

New tools have helped understand and improve the definition of congestion; some of them are well-established, others are still in the establishment stage. The use of natriuretic peptides,[8] in addition to pulmonary echography[9] and point-of-care echocardiography, has become increasingly common for a better analysis of patient's hemodynamic profile, with potential improvements in outcomes.[10,11] Furthermore, "congested" patients often have poor distribution of intravascular volume with but do not necessarily have increased total volume, which may also impact their therapy.[5]

Several therapies have been implemented in congested patients. With regard to therapeutic advances in chronic HF over the last 30 years, the most used drugs still belong to one class: diuretics.

Use of diuretics in congested patients

"The clamour for diuretics dates back many centuries to the earliest association of dropsy with impairment of renal function, but until twenty years ago these drugs were chiefly remarkable for the mediocrity of their therapeutic achievements". This sentence, retrieved from an article published in Lancet[12] in the 1940s, shows how the advent of diuretics occurred over the last 100 years, although dropsy dated back before Christ.[13]

The first diuretics used in the treatment of HF, were based on mercurial diuretics, and its form of use with sustained efficacy was an incidental finding, as well as many great medical discoveries. The hypothesis of using mercury as a diuretic was grounded nearly 500 years ago, but, for 4 centuries, it had successively similar results, all of them

Keywords

Heart Failure; Diuretics.

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frustrating. However, in the transition from the 1910s to the 1920s, sustained diuretic properties were found in mercurial compounds originally developed to treat syphilis.[12] The great limitation for their use was mercurial toxicity, which led to the development of progressively less toxic forms tested in oral, intravenous, intramuscular, and rectal routes of administration, with acceptable diuretic responses, especial the intravenous route.[12] Its mechanism of action is possibly related to sodium excretion in proximal convoluted tubule.[14]

Later, other diuretics were developed, such as carbonic anhydrase inhibitors, in 1937; a sulfanilamide, in 1949;[15] and thiazides. The clinical use of loop diuretics, especially furosemide and etacrynic acid,[16–18] initiated in the early 1960s and is indicated today for the treatment of patients with HF.

Loop diuretics

Loop diuretics, represented by furosemide, bumetanide, and torsemide (Table 1) are undoubtedly the main tool for decongestioning patients with ADHF, being used in more than 90% of patients hospitalized with HF.[19] These diuretics act on the Na-K-2Cl pump of the thick segment of Henle's loop, promoting diuresis through sodium excretion. Loop diuretics are possibly the most study class within this context, although evidence in this field is still considerably limited. In addition to their diuretic effect, loop diuretics have a vasodilatory action on smooth muscle cells of vessel walls. There is also an effect on renin–angiotensin–aldosterone system activation, which has both positive aspects, such as modulation of glomerular flow in the nephron, and negative aspects, such as neurohumoral activation leading to the perpetuation of detrimental effects in patients with HF.[20] The efficacy of loop diuretics for decongestion depends on several factors, such as route administration, chronic use by the patients, dose, comorbidities (especially renal dysfunction), and dietary salt intake, among others.[20]

The largest study involving diuretics in HF was the DOSE study.[22] A total of 308 patients were randomized in a 2-by-2 factorial design to receive intravenous furosemide either continuously or intermittently, to maintain their outpatient dose (low-dose strategy) or to receive a 2.5-time higher dose (high-dose strategy), both applied intravenously. There was no difference in the overall assessment of symptoms by the patient and in the change in creatinine levels after 72 h, which were the primary study outcomes. In a post hoc analysis adjusted for decongestion parameters, the effect of the high dose apparently improved resolution of congestion: the higher the dose of diuretics, the greater the decongestion, and the greater the response.[23] Moreover, there was a higher number of patients with worsened renal function in the group that used higher doses of furosemide.

Diuretic resistance

Compared with healthy patients, those with HF already using loop diuretics have an attenuated response to diuretics.[24] Several mechanisms have been proposed to explain this process, such as reduced diuretic efficacy, salt retention, rebound effect, and nephron remodeling.[2,20] This process generates diuretic resistance, in which diuretics do not achieve the desired decongestion, manifested by low urine sodium concentrations, despite the recommended maximum doses.[20] Some adjuvant treatments have been proposed to overcome the problem by maximizing diuretic response and promoting decongestion in patients with HF.

Thiazide diuretics

A strategy to "overcome" diuretic resistance is using thiazides, a class of medications that acts in the distal convoluted tubule, a site different from that where loop diuretics act, suggesting synergy in the diuretic action in the nephron and producing distal blockade of sodium reabsorption.

The most used medications in this context are hydrochlorothiazide e metolazone (considering that metolazone is not available in our setting), in addition to chlorothiazide. Studies conducted so far are promising, with increased diuresis and reduced congestion, but methodology was very limited[2] and there was remarkable heterogeneity, including with regard to clinical outcomes.[25] The doses and medications have been different (in the case of hydrochlorothiazide, the doses used in the studies range from 25 to 200 mg; in the case of metolazone, from 1.25 to 10 mg).

In patients with diuretic resistance, a study comparing metolazone, chlorothiazide, and tolvaptan (a vasopressin antagonist) identified increased diuresis with the addition of any of the three medications, with no difference between the groups, in patients receiving a high-dose of diuretics.[26] There was no placebo group in the trial. In a retrospective unicenter study with patients receiving intravenous furosemide, diuresis was greater in those using intravenous chlorothiazide compared to those using oral hydrochlorothiazide.[27]

Resuming the analysis of the DOSE trial, with regard to the use of thiazides, there was a trend of higher use of thiazides in the low-dose group (23% vs 13%, $p = 0.06$), which may somehow have contributed to study neutrality.[22] Furthermore, the largest study in the history of hypertension (ALLHAT) found a reduction in the incidence of HF with use of chlorthalidone,[28] there are no studies with the addition of chlorthalidone to loop diuretics in congested patients with HF.

In summary, thiazide diuretics are promising in the treatment of congestion in patients with HF. However, there is scarcity of more robust studies to better

Table 1 – Equipotency between loop diuretics and route of administration[20,21]

Medication	Furosemide	Torsemide	Bumetanide
Intravenous dose	40 mg	20 mg	1 mg
Intravenous/oral conversion	1:2	1:1	1:1

define effect magnitude. Two clinical trials are currently in progress (ClinicalTrials NCT01647932[29] and ReBEC RBR-5qkn8h[30]), and their results may possibly be published in the near future.

Vasopressin antagonists

The mechanism of action of vasopressin antagonists, especially of the most studied in HF, namely tolvaptan, which was developed in Japan in the 1990s, may be mainly explained by their affinity with V2 receptors located in the collecting duct, thus inhibiting free water resorption[31] and producing aquaresis, with no electrolyte elimination. With a well defined and innovative mechanism and animal tests with favorable results, randomized clinical trials started to be conducted.[32] The first multicenter study on the topic was the ACTIV in CHF,[33] a phase 2 randomized clinical trial that tested different doses of tolvaptan (30 mg, 60 mg e 90 mg) vs placebo in 319 patients with ejection fraction below 40% and decompensated HF. In the three groups, there was a weight reduction compared to the placebo group, with no worsening of renal function or electrolytic disorders. Moreover, in a post hoc analysis, there was greater benefit in more congested patients and with worse renal function. A safety analysis showed that there was a higher number of sudden deaths in the tolvaptan 60 mg group compared with placebo (6% vs 1.3%, $p < 0.01$).

Since tolvaptan passed its initial test, the EVEREST[34,35] studies were published 3 years later, in which 4133 patients with a profile very similar to those of the previous study, ie, ejection fraction below 40%, functional class III/IV, and decompensation within the last 48 hours, were randomized to tolvaptan 30 mg or placebo. There was no difference between the groups with regard to the primary outcome of hospitalization due to HF or cardiovascular mortality (tolvaptan 42% vs placebo 40.2%, $p = 0.55$).

In summary, these were two more neutral studies that belonged to an era when pharmacological treatment of HF seemed stagnant, with no significant advances.

In relation to diuretic resistance, however, some findings were interesting for patient's compensation: there was greater body weight reduction in 1 (-1.76 vs -0.97 kg; $p < 0.001$) and 7 days, less dyspnea, less edema and, in hyponatremic patients, greater sodium increase in the tolvaptan group. In a subsequent sub-analysis, there was reduced cardiovascular mortality or hospitalization in patients with sodium concentration below 130 mEq/L (hazard ratio: 0.6 [0.37-0.98]); $p = 0.04$), in addition to greater weight loss (0.7 kg on day 1). In another study of a population with HF in an intensive care unit, the amount of continuous furosemide was lower, the urine volume was higher, and the number of patients with worsening kidney injury was lower in the tolvaptan group than in placebo group.[36] Furthermore, a clinical trial of 217 patients with renal dysfunction stages 3 and 4 observed-that tolvaptan resulted in higher 48-h urine volume (6464.4±3173.0 vs 4997.2±2101.4 mL, $p < 0.001$), with no worsening of renal function compared with placebo, in addition to greater weight loss.[37]

However, more recently, in the TACTICS-HF[38] study of a population with decompensated HF, 257 patients were randomized to tolvaptan or placebo. There was worsening of renal function with tolvaptan (39% vs 27%; $p = 0.037$) and there was no greater relief of dyspnea, thus persisting the findings from previous studies of greater negative water balance. These two similar findings were reproduced in a subsequent study, in which patients with diuretic resistance were randomized,[39] but no worsening of renal function was observed.

With regard to diuretic resistance specifically, data are scarce: in addition to the aforementioned study, with 60 patients divided into three groups,[26] an open randomized study of 81 patients with HF and renal dysfunction (glomerular filtration rate < 45 mL/min/1.73 m^2) showed grater urine output with tolvaptan (in agreement with previous studies in other settings), with no weight loss and with less worsening of renal function. It is worth emphasizing that the concept of diuretic resistance was not strict in this study, being defined as signs of congestion regardless of using a daily dose equal to or greater than 40 mg of furosemide.[40]

In short, vasopressin antagonists did not show benefits in clinical outcomes. Is there room for their use in chronic HF? Absolutely not. Is there room for their use in acute HF? Maybe, in the scenario of patients with significant congestion, hyponatremia, loss of renal function, and actual diuretic resistance.

Nesiritide

One of the responses to situations of myocute distention (similar to congestive presentations) is secretion of natriuretic peptides – particularly, B-type natriuretic peptide (BNP). As a consequent, there are vasodilatation, neurohumoral modulation and, in addition to other responses, natriuresis.[41]

Considering the vasodilatory and diuretic properties, nesiritide, a recombinant BNP, was developed. The proposal seemed interesting, which led to clinical trials. In comparison to nitroglycerin and placebo, there was a favorable hemodynamic response with nesiritide in the VMAC study, which randomized decompensated patients.[42] However, in outpatient patients with ejection fraction below 40%, hospitalizations for HF and functional class III-IV, there was no reduction in the composite outcome of overall mortality, cardiovascular hospitalization, or hospitalization due to renal causes; thus, the ideia of nesiritide was abandoned for this use.[43]

Initially, results with nesiritide seemed favorable. Nonetheless, subsequent evidence suggested worsening of renal function and increased mortality, which led to a gradual reduction in the use of this medication in the mid-2000s.[44] As a result, larger and better-designed studies on the topic were subsequently conducted.

The first large clinical trial on nesiritide in acute patients was ASCEND-HF, in which 7141 patients with HF were randomized.[45] The result was a neutral study, with no effect on mortality or new hospitalization for HF, but perhaps with a better response with regard to dyspnea. As a furosemide

potentiator, a mechanism that could be interesting in the case of patients with diuretic resistance, the result was also neutral.[46]

The next study on the topic focused on patients with renal dysfunction stages 3 and 4. The ROSE-AHF study compared low-dose dopamine, nesiritide, and placebo.[47] There was no difference in decongestion or in improvement of renal function between the groups. In 2018, the production of nesiritide was discontinued in the United States.

Mineralocorticoid receptor antagonists

Spironolactone and eplerenone are representative of aldosterone antagonists and of the path of diuretics in HF, promoting reduced mortality in combination with other well-established therapies.[48-50] They act on the distal convoluted tubule, and thus have both neurohumoral and diuretic actions. Based on the latter action, it was possible to build the rationale for the use of these antagonists in patients with ADHF.

In ADHF, the first data on the use of de spironolactone in diuretic dose were favorable: less signs of congestion and lower levels of natriuretic peptides.[51] Subsequently, the ATHENA-HF study was published, which involved 460 patients and compared spironolactone 100mg vs placebo.[52] The results were neutral, thus failing to show the benefit of spironolactone in ADHF.

Therefore, mineralocorticoid receptor antagonists still have a major role in the treatment of chronic HF, but with no apparent benefit in the context of ADHF.

Sacubitril/valsartan

Sacubitril/valsartan, a combination of an angiotensin blocker with a neprilysin inhibitor, had its effect compared with that of enalapril in the largest study ever performed in patients with chronic HF, the PARADIGM-HF.[53] In this study, sacubitril/valsartan promoted a 20% reduction in a primary composite outcome of cardiovascular death or hospitalization for HF (relative risk [RR] 0.80; confidence interval [CI] 0.73-0.87; p = 0.0000002). There was also a statistically significant reduction of similar magnitude in cardiovascular mortality (RR 0.80 CI 0.71-0.89; p = 0.00004) and overall mortality (RR 0.84 CI 0.76-0.93; p = 0.0001). The mechanism of action of this drug may be explained by inhibition of BNP degradation, promoted by neprilysin, associated with renin-angiotensin-aldosterone system blockade, promoted by valsartan. As a result, there is an increase in BNP serum levels and, respectively, in its endogenous effects of vasodilatation and natriuresis, both of which are desirable in the treatment of patients with HF.

Based on the foregoing, we may consider sacubitril/valsartan as another medication that may potentially add knowledge in the study of diuretics. In a sub-analysis of the PARADIGM-HF study, there was a decrease in the use of furosemide (or equivalent) in the sacubitril/valsartan arm compared with the enalapril arm: around 2% in 6 months, 4.1% in 12 months, and 6.1% in 24 months.[54] There are controversies whether reduced diuretic requirement results from improvement in clinical-hemodynamic parameters in patients with HF or from a direct diuretic effect.[55]

In the context of ADHF, the sacubitril/valsartan was again compared with enalapril in the PIONEER-HF study.[56] Patients hospitalized with ADHF were followed for up to 8weeks. There was a statistically significant decrease in the primary outcome of serum levels of NT-ProBNP, an outcome replacing clinical improvement in this population. Additionally, there was a 44% decrease in the relative risk of hospitalization for HF.

Furthermore, an additional finding may suggest a clinically relevant diuretic effect: a higher level of hypotension was observed in patients receiving sacubitril/valsartan compared with those receiving enalapril, which may have been caused by a diuretic effect.[57] However, there is still scarcity of larger studies for a better understanding de um eventual diuretic effect of sacubitril/valsartan.

SGLT-2 inhibitors

More than 150 years have gone from the discovery of the first non-selective sodium-glucose cotransporter inhibitors up to the emergence of current medications. The sodium-glucose cotransporter 2 (SGLT-2) is predominantly located on proximal convoluted tubule and is responsible for absorbing nearly 90% of the glucose filtered by the kidney through a sodium-dependent channel. Natriuresis induced by transporter blockade leads to greater sodium load to the macula densa and, through glomerular feedback, causes afferent arteriole constriction, reducing intraglomerular pressure and proteinuria. Osmotic natriuresis promoted by SGLT-2 inhibitors reduces blood pressure and blood volume, leading to lower pre- and afterload, with consequent reduction in ventricular filling pressures.[58,59]

The exact mechanism responsible for the beneficial effect of SGLT-2 inhibitors in HF is unknown; however, several of their effects may have a positive impact on this condition, such as blood pressure reduction, blood volume reduction, renin–angiotensin–aldosterone axis blockade, and weight loss.

The decrease of "hard" cardiovascular outcomes (cardiovascular death, infarction, and stroke) related to atherosclerosis in clinical trials was small and limited to patients with established disease, whereas the reduction in hospitalizations for HF and in renal disease progression was robust and not limited to patients with atherosclerotic disease or history of HF.[60]

It is believed that the benefit of SGLT-2 inhibitors in reducing rates of hospitalization for HF results predominantly from their diuretic effect, since patients in clinical trials showed fewer hospitalizations during the first months after randomization.[61,62] Furthermore, a sub-analysis found a decrease in mortality and in hospitalizations for HF in patients with diabetes and HF, with no phenotypical distinction.[63] It is unlikely that the effect on death, HF, and nephroprotection may result from better glycemic control, since the decrease in glycated hemoglobin was slight compared with placebo.[59] Moreover, SGLT-2 inhibitors have the advantage of not activating neurohumoral mechanisms.[64]

In the DAPA-HF study,[65] 4744 patients with class III-IV HF and an ejection fraction of 40% or less were assessed. There was

a significant reduction in worsening HF (hospitalization or need for intravenous diuretics), regardless of the presence or absence of diabetes. These results represent an advance in the treatment of HF, being the first clearly demonstrated a reduced mortality in HF with the use of an antidiabetic drug.

Empagliflozin was tested in the EMPEROR-Reduced study,[66] which randomized 3730 patients with class III-IV HF and an ejection fraction of 40% or less. In this study, there was a reduction in the composite outcome of cardiovascular mortality or hospitalization due to HF worsening on account of reduced hospitalizations.

More recently, sotagliflozin was assessed in patients with diabetes and recent hospitalization due to worsening HF. In the SOLOIST-WHF study,[67] 1222 patients were evaluated, of which nearly 79% had an ejection fraction below 50% — median 35%. Similar to what was observed in the EMPEROR-Reduced study,[66] the primary composite outcome of cardiovascular mortality or hospitalizations for IC was lower in the intervention group on account of reduced hospitalizations. The study ended early because of loss of funding from the sponsor. In short, SGLT-2 inhibitors are a promising class in the treatment of HF, with a decrease in hospitalizations and possibly in cardiovascular mortality, without definite data so far in patients with ADHF.

Hypertonic saline

Over the last 20 years, hypertonic saline has been studied with greater interest in the management of congestion in patients with ADHF. Its main rationale is based on the concept of relative hypovolemia, relative to IC, or absolute, due to the use of diuretics. As a response, glomerulus causes a decrease in glomerular filtration rate; by administering hypertonic saline, this glomerular effect may be attenuated or even eliminated, leading to greater diuresis when used in association with furosemide.[68]

First data on hypertonic saline showed increased diuresis, reduced length of hospital stay and BNP levels, improved renal function, and reduced mortality, thus encouraging the continuity of studies.[69-73] However, there is considerable heterogeneity between the studies,[74,75] and an episode of duplicate data in publications, leading to the retraction of one meta-analysis on the topic.[76] Furthermore, despite body weight reduction, doubts remain with regard to the actual benefit of hypertonic saline in the resolution of pulmonary congestion.[77]

Finally, a systematic review and meta-analysis about hypertonic saline that assessed studies with 2.4 to 4.6% saline associated with 500 mg of furosemide administered intravenously twice a day showed that saline improved weight loss, preserved renal function, and decreased hospitalizations for HF, length of hospital stay, and mortality.[78]

Fluid and sodium restriction

Fluid and sodium restriction in congested patients with HF is a very ancient practice, being recommended in the main HF guidelines. However, evidence supporting this recommendation is scarce.[79] Moreover, there is considerable heterogeneity both in the tested interventions and in the recommended interventions. Generally speaking, the results of the best studies so far in patients with ADHF were neutral and failed to show the benefits of fluid and sodium restriction on weight loss and clinical stability; furthermore, they showed that this restriction increased thirst perception in patients randomized to fluid and sodium restriction.[80-82] Hence, there is no evidence recommending routine fluid and sodium restriction in congested patients hospitalized with ADHF and receiving contemporary treatment.

Conclusion

There have been many advances in the study of diuretics, especially during the last 50 years. In possession of current knowledge, clinical physicians can choose from a wide range of options for the best management of congestion in patients with ADHF. There are several open knowledge gaps on the best strategy for congest patients with ADHF, especially with regard to the study of thiazide diuretics, sacubitril/valsartan, and SGLT-2 inhibitors. This may be interpreted as an opportunity window in knowledge, with the combination of diuretics being a reality as an effective therapy in the management of congestion in ADHF, which may occur as evidence advances.

Author Contributions

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Brief Communication

The Challenge of HFpEF Diagnosis in Brazil

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is highly prevalent in Brazil and worldwide. However, the recent diagnostic criteria for this condition are complex and difficult to apply in the Brazilian health system. This review proposes adapting the modern diagnostic criteria to the needs of each patient, from the primary care to the most complex one, using a system of three steps of complexity and highlighting the importance of searching specific disease etiology.

Heart failure with preserved ejection fraction (HFpEF) remains a major public health problem worldwide and also in Brazil.[1] The recognition and diagnosis of this syndrome remain a challenge, due to its physiopathological complexity and phenotypic diversity.

The current scientific evidence on etiopathogenesis provided more accurate diagnostic recommendations but requires comprehensive echocardiographic analysis.[2,3] A recently published recommendation from the Heart Failure Association of the European Society of Cardiology (HFA-ESC) brought a comprehensive overview and an algorithm for the diagnosis of HFpEF.[4]

Four basic elements for the diagnosis of HFpEF are:

1) Recognition of typical signs and symptoms (e.g. dyspnea, fatigue, reduced exercise tolerance, and signs of congestion) and comorbidities related to HF;[5]
2) Preserved left ventricular systolic function, i.e., ejection fraction (LVEF) ≥ 50%;
3) Left atrium and left ventricle (LV) remodeling;
4) Direct or indirect evidence of high left ventricular filling pressure.

Keywords

Heart Failure/ophysiopathology; Stroke Volume; Diagnostic Imaging; Echocardiography/methods; Dyspmea; Fatigue; Vascular Stiffness; Comorbidity.

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Diagnosis based on three steps

In a recently published article,[6] we propose a compilation of the Brazilian Society of Cardiology (SBC) Guidelines, Mayo Clinic, and HFA-ESC criteria adapted to the national health system. It recommends an approach in three degrees of complexity, adapting the use of resources from primary care (step 1) to the high complexity health centers (steps 2 and 3) (Figure 1).

Step 1: Pre-test clinical approach.

- Anamnesis: identification of signs and symptoms that offer the possibility of HF;
- Comorbidities: diagnosis of the clinical characteristics and major morbidities associated with risk of HFpEF, such as age > 60 years, female sex, obesity, hypertension, diabetes, ischemic heart disease, and atrial fibrillation.
- Agonist or competing comorbidities of HF: agonists to decreased functional capacity, or are a differential diagnosis, such as anemia, chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, peripheral arterial disease, sarcopenia, thyroid diseases, nephropathies, and electrolyte imbalance.
- Basic tests: blood cell count, creatinine, urea, glycemia, lipid profile, electrocardiogram (EKG), and chest X-ray.
- Natriuretic peptides (NPs): have a consolidated role in HF diagnosis. In patients with atrial fibrillation, serum values can rise 3 to 3.5 times, but in obese patients, this may significantly decrease. The following are accepted cutoff points: B-type natriuretic peptide (BNP) ≤ 35 pg/mL and/or N-terminal-pro-BNP (NT-proBNP) ≤ 125 pg/mL make a diagnosis of HFpEF less likely.[3]
- Noninvasive cardiac tests: EKG, echocardiography (ECHO) to estimate LVEF and, in case of suspected myocardial ischemia, provocative tests as the treadmill test.
- Functional capacity tests: the 6-minute walk test, cardiopulmonary tests, and spirometry offer practical information on functional capacity. Ergospirometry-derived indices are the gold standards on functional capacity but are rarely available outside high complexity health units.

In this step, if the clinical, biomarkers and echocardiographic indices are unmistakably altered, HFpEF should be confirmed; however, a normal resting EKG and normal serum levels of NPs make the diagnosis of HFpEF less likely, although normal levels of NPs do not exclude HFpEF.

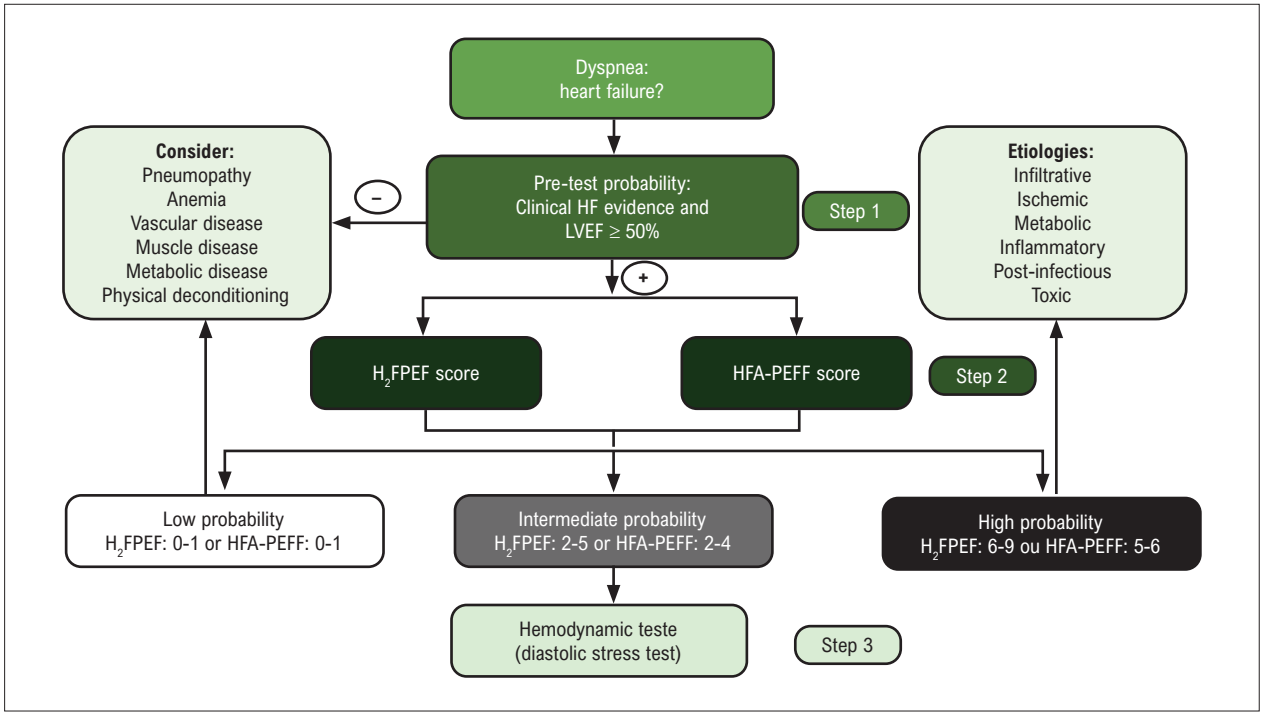

Figure 1 – *Diagnostic algorithm for HFpEF. HF: heart failure; LVEF: left ventricular ejection fraction.*

Step 2 - Confirmatory scores

If there is still doubt on the diagnosis of the syndrome, the next proposal is to confirm it with scoring. The H_2FPEF and HFA-PEFF have recently been developed to establish the probable diagnosis of HFpEF.[4,5] They were validated in retrospective cohorts and demonstrated a higher diagnostic accuracy.[5,7] These scores are offered in parallel, depending on their availability. The H_2FPEF score was derived from clinical and echocardiographic variables that were independently associated with the invasive diagnosis of HFpEF in a population-based cohort. Each criterion generate a score that will estimate the probability of diagnosing the syndrome (Figure 2).

The other available score, HFA-PEFF, is composed of morphological and functional parameters, derived from a comprehensive ECHO, along with serum levels of NPs. A model of major and minor criteria is used to score and estimate the diagnostic probability (Figure 3).

In this strategy, using any of two scores, HFpEF can be ruled out in patients with low scores (0 or 1) and confirmed with higher scores (H_2FPEF ≥ 6 or HFA-PEFF ≥ 5). Conversely, in patients with intermediate scores (H_2FPEF 2-5 or HFA-PEFF 2-4), an invasive or either a non-invasive hemodynamic exercise test is necessary (Figure 1).

Step 3: Diastolic stress test or invasive investigation

A diastolic stress test should be added to the preceding approach of HFpEF if measurements of diastolic function are inconclusive at rest, like when H_2FPEF score sums 2-5 points and HFA-PEFF score sums 2-4 points, respectively. Stress ECHO (SE) is capable of studying diastole, along with systolic function based on E/e' ratio, which estimates the LV filling pressure plus the tricuspid valve regurgitation velocity (TRV), thus allowing for the estimation of the pulmonary artery systolic pressure.

According to the HFA-PEFF consensus,[4] an additional score is added to the one of step 2 (2 points if E/e´ ratio ≥ 15;, 3 points if E/e´ ratio ≥ 15 and TRV > 3.4 m/s). If the final sum is ≥ 5, diagnostic criteria for HFpEF are reached. Diastolic SE is positive for diagnosing if the average peak E/e´ ratio is ≥ 15, with or without a peak TRV ≥ 3.4 m/s.

If diastolic SE does not provide confirmation, an invasive measurement of pulmonary capillary wedge pressure at rest or during SE is indicated. Invasive strategy, although more expensive and less available, is still the gold standard diagnostic method.

Etiological investigation

Once the diagnosis is confirmed, focus should be directed to the systematic search for etiology, which can be divided into primary and secondary.[6] The primary form combines common metabolic and hemodynamic characteristics, such as obesity, diabetes, and hypertension. The secondary form, which is less common, has specific etiologies such as ischemic, infiltrative, restrictive, inflammatory, infectious, toxic, or genetic, and should be actively sought. Mimics of HFpEF have diagnostic clues to aid early identification of phenocopies comprising constrictive pericarditis, primary valvular heart disease, or high-output syndrome, which should not be considered as

Score label	Clinical variable	Characteristics	Points
H_2	**H**eavy	IMC > 30 kg/m^2	**2**
	Hypertension	2 or more anti-hypertensive drugs	**1**
F	Atrial **f**ibrilation	Paroxistic or persistent	**3**
P	**P**ulmonary hypertension	PSAP > 35 mmHg (measured on Doppler ECHO)	**1**
E	**E**lderly	Age > 60 years	**1**
F	**F**illing pressures	E/e´ ratio > 9 (measured on Doppler ECHO)	**1**

Figure 2 – *H_2FPEF score. BMI: body mass index; PASP: pulmonary artery systolic pressure; ECHO: echocardiography; E/e': left ventricular filling pressure non-invasive index.*
Ref. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. Circulation. 2018;138(9):861-870.

	Domain	Major criteria (2 points)	Minor criteria (1 points)
HFA PEFF SCORE	**Functional**	e´ septal < 7 or e´ lateral < 10 or E/e´ > 15 or TRV > 2.8 m/s (PSAP > 35 mmHg)	E/e´: 9-14 or GLS < 16%
	Morphological	LAVI > 34 mL/m^2 or LVMI > 149/122 g/m^2 (M/W) and RWT > 0.42	LAVI: 29-34 mL/m^2 or LVMI > 115/95 g/m^2 (M/W) or RWT > 0.42 or Left ventricle wall tchickness ≥ 12 mm
	Biomarker (sinus rythm)	BNP > 80 pg/mL or NT-proBNP > 220 pg/mL	BNP: 35-80 pg/mL or NT-proBNP: 125 - 220 pg/mL
	Biomarker (atrial fibrillation)	BNP > 240 pg/mL or NT-proBNP > 660 pg/mL	BNP: 105-240 pg/mL or NT-proBNP: 365 - 660 pg/mL

Figure 3 – *HFA-PEFF score. TRV: tricuspid valve regurgitation velocity; PASP: pulmonary artery systolic pressure; LAVI: left atrial volume; LVMI: left ventricular mass index; M: men / W: women; RWT: relative wall thickness; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro–B-type natriuretic peptide; GLS: global longitudinal strain; e': early diatolic myocardial velocity.*
Ref. Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur J Heart Fail. 2020;22(3):391-412.

the HFpEF syndrome, since the latter can determine different clinical outcomes; therefore, a definitive diagnosis is necessary. The big challenge is to adapt the diagnostic strategy for each health system, without unfocusing on the best practice of evidence-based medicine.

Author Contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Danzmann LC, Belyavskiy E, Jorge AJL, Mesquita ET, Torres MAR; Acquisition of data and Analysis and interpretation of the data: Danzmann LC, Jorge AJL, Mesquita ET; Statistical analysis and Obtaining financing: Danzmann LC.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Potential Conflict of Interest

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Brief Communication

Lessons Learned by a Multidisciplinary Heart Failure Clinic In The Midst Of A Pandemic

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Abstract

In addition to the deaths caused by coronavirus disease (COVID-19), several countries also observed an increase in the overall number of cardiovascular deaths during the pandemics compared with the same period in previous years. The presence of heart failure (HF) in the context of COVID-19 identifies a subgroup with complex management and may represent both a risk factor for worse infection outcomes and a severe cardiovascular complication caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Patients with advanced HF require regular rigorous multidisciplinary medical follow-up, performed ideally through face-to-face consultation. However, due to the reallocation of health care professionals and the implementation of measures of isolation and social distancing, telemedicine strategies have strengthened as important allies in the management of HF patients. In the present document, we report the brief experience of the unit of advanced HF and heart transplant of Hospital de Messejana, a reference center in the confrontation of COVID-19 in the state of Ceará, Brazil, with the primarily remote monitoring rather than face-to-face consultation from March to July 2020.

Article

One year after the first case of the new coronavirus disease (COVID-19) was reported in Brazil, on February 26, 2020, there has been the alarming record of 10 517 232 cases and almost 255 thousand deaths in the country.[1] In addition to the deaths caused by COVID-19, several countries also observed an increase in the overall number of cardiovascular deaths during the pandemic compared with the same period in previous years. According to a recent study conducted by researchers from Universidade Federal de Minas Gerais, Universidade Federal do Rio de Janeiro, Hospital Alberto Urquiza Wanderley, and the Brazilian Society of Cardiology, the number of cardiovascular deaths increased up to 132% in Brazil during the pandemic.[2]

Keywords

Heart Failure; Telemedicine; Coronavirus.

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Approximately 20 to 30% of patients hospitalized with COVID-19 have some form of myocardial injury, as shown by increased troponin concentrations.[3] This group of individuals have worse prognosis, even after adjusting for relevant risk factors and disease severity. Important etiologies of myocardial injury in COVID-19 include myocardial infarction, stress cardiomyopathy, myocarditis, and direct injury by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in addition to non-cardiac conditions such as pulmonary embolism and sepsis.[4] The presence of heart failure (HF) in this context identifies a subgroup with complex management and may represent both a risk factor for worse infection outcomes and a severe cardiovascular complication caused by SARS-CoV-2.[5]

In the field of heart transplant, there is also evidence of worse COVID-19 prognosis in transplant recipients,[6] although this difference was not observed in a small Brazilian case series.[7] The Committee on Infection in Transplants of the Brazilian Association of Organ Transplants (*Comissão de Infecção em Transplantes da Associação Brasileira de Transplantes de Órgãos,* COINT/ABTO) authorizes the use of all vaccines approved by the Brazil's National Health Surveillance Agency in solid organ transplant recipients; however, there are no data on the efficacy of the vaccines in this population, since immunocompromised individuals were excluded from the existing clinical trials.

According to the recommendations of the Brazilian Guideline on Chronic and Acute Hearth Failure, patients with advanced HF require regular rigorous multidisciplinary medical follow-up, performed ideally through face-to-face education, with reinforcements, delivery of written material, and regular follow-up.[8] However, in view of measures of isolation and social distancing determined by the World Health Organization (WHO), telemedicine strategies, including telemonitoring and virtual consultations, have been strengthened as important allies in the management of HF.[9,10] In addition to reducing risks of unnecessary exposure to the virus, these programs aid in preventive recommendations, identification of patients at risk for decompensation, diffusion of accurate information through teaching platforms and access to specialists' opinion at remote sites.

Since the beginning of the pandemic, Hospital de Messejana became one of the reference centers in the confrontation of the COVID-19 pandemic in the state of Ceará, Brazil. The increased rate of admissions for COVID-19 throughout 2020 was associated with reallocation of beds directed exclusively to infected patients and also to the emergence of new attributions to health care professionals. Normally, our service of advanced HF and

heart transplant has a team comprising six cardiologists, six surgeons, and six nurses, in addition to a multidisciplinary team that includes a psychologist, a social worker, a dietitian, and physical therapists exclusively dedicated to the care of patients with HF and heart transplant. Due to the reallocation of beds and of the team of health care professionals for the care of patients with COVID-19, we implemented a primarily remote follow-up via telephone for patients with HF and transplant patients from March 26 to July 3 2020. This follow-up occurred from Monday to Friday, from 7 a.m. to 1 p.m., and was conducted by two of the six nurses, who worked in rotating shifts. During this period, our nurses performed the follow-up of 361 patients with HF and 143 transplant recipients. For comparative purposes, during the same period of 2019, we had seen 972 patients, with a mean of 322 (standard deviation, 29) patients per month throughout the year. During phone calls, patients were questioned on their clinical status and on treatment adherence, in addition to receiving guidance on non-pharmacological measures such as water and salt restriction, diet, time of medications, among others. If any sign of decompensation was identified, the medical team was then consulted so that due measures were taken. All patients were encouraged to call the outpatient clinic if they had any question or if they experienced any new symptom.

During remote follow-up, we observed a decrease in the proportion of admissions of patients in outpatient follow-up for HF, from 24% in 2019 to 12% in 2020. Conversely, there was a relative increase from 10 to 20% in the hospitalization rate of transplant recipients in outpatient follow-up during the same period. This finding may be explained by the great number of procedures that recent transplant patients have to undergo during the first months and years after transplantation, including endomyocardial biopsies and rescue immunosuppressive therapies, which are unlikely to be performed outside hospital. We did not observe any difference in the percentage of reported deaths between 2019 and 2020; however, when exclusively analyzing individuals who were hospitalized, we found a 2.6-fold increase in the percentage of deaths in 2020, especially among patients with HF, who had an increase from 4% in 2019 to 19% in 2020. We believe that this increased mortality among hospitalized patients may be explained by the prioritization of individuals with more severe disease for hospitalization and, thus, with worse prognosis.

Although telephone follow-up has already been part of the care and research routine in most HF units in Brazil for a long time, this is the first time in more than 20 years that our multidisciplinary team relied primarily on remote monitoring rather than a face-to-face consultation. We believe that the benefits of telemonitoring cannot be judged only on the basis of its impact on morbidity and mortality rates but should also aim to improve the follow-up of non-pharmacological measures, which involve practice of physical activity, weight loss, and control of water and salt intake. Obviously, there are still many technical barriers for the implementation of other telemedicine services in Ceará, including appropriate internet access (both by health care providers and patients), patients' cognitive capacity to handle the appropriate applications, memory capacity and image quality in older devices etc.

Nevertheless, despite the seriousness of the current context, perspectives with regard to telemedicine in Brazil are positive, since it has become a critical tool in the confrontation of the pandemic and in the enhancement of health service coverage. However, it is worth noting that the telemedicine activity in Brazil was regulated through Law n. 13.989/20 in an exceptional manner, with validity only during the pandemic.[9,11] Despite that, considering the favorable results in Brazil and worldwide, we believe that the definitive regulation of telemedicine is only a matter of time.

Author Contributions

Conception and design of the research: Vieira JL, Mejia JAC, Souza Neto JD; Acquisition of data: Vieira JL, Sobral MGV, Florêncio RS, Alves VM, Vasconcelos GG, Almeida GPL, Marinho LLE, Fernandes JR, Souza Neto JD; Analysis and interpretation of the data: Vieira JL, Sobral MGV, Florêncio RS; Writing of the manuscript: Vieira JL; Critical revision of the manuscript for intellectual content: Vieira JL, Alves VM, Vasconcelos GG, Almeida GPL, Marinho LLE, Fernandes JR, Mejia JAC, Souza Neto JD.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Potential Conflict of Interest

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Heart Failure Due to Anomalous Pulmonary Vein Connection Associated with Atrial Septal Defect

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Introduction

Anomalous pulmonary vein dreinage (APVD) is a rare disease, accounting for nearly 1 to 3% of congenital heart diseases.[1] It may be total, when all PVs are involved, or partial, when only some PVs drain anomalously into one or more systemic veins or directly into the right atrium (RA).[1,2] This condition occurs alone or in association with an interatrial septal defect, more often sinus venosus interatrial communication (IAC) (which accounts for nearly 5% of all IAC cases).[3]

Patients with this condition may remain asymptomatic until adulthood. However, overload of right chambers may trigger symptoms, especially reduced functional capacity and progressive dyspnea, in addition to the development of pulmonary hypertension (PH) and ventricular dysfunction, which is the most severe disease scenario.[3] Recognizing these symptoms and establishing early diagnosis and treatment is crucial to avoid disease progression and its prognostic implications.

We present a case of heart failure (HF) due to partial anomalous pulmonary vein dreinage (PAPVD) associated with IAC with reverse remodeling after surgical correction in adulthood.

Clinical case

A previously healthy 36-year-old patient was admitted to the emergency department with dyspnea that started nearly 15 days before and progressively worsened with time, evolving to dyspnea at rest, associated lower limb (LL) edema and orthopnea. On admission, the patient presented with tachydyspnea, blood pressure of 100x60 mm Hg, heart rate of 96 bpm, respiratory rate of 26 irpm, saturation of 93% on oxygen 4 L/min via a nasal cannula. Examination revealed the presence of pathological jugular vein engorgement and hepatojugular reflux. Pulmonary auscultation showed crackles up to the bilateral middle third. Furthermore, we observed propulsive apex beat and palpable right ventricle (RV) by means of hooking palpation, with systolic murmur 3+/6+ more evident in the left paraesternal region (accessory aortic focus) irradiating to the entire precordium, as well as rhythmic heart sounds with loud B2. Abdominal assessment revealed painful and palpable liver located 4 cm below the right costal margin, presence of bowel sounds, and no peritoneal signs. Finally, the patient presented with LL edema 3+/4+.

Chest X-ray showed significant cardiomegaly, with increased apex beat and increased pulmonary artery trunk (PT), enlarged pulmonary hilum, and changes in vascular network, suggestive of congestion (Figure 1A). Electrocardiogram revealed sinus rhythm with right axis deviation, right bundle branch block, signs of biventricular and right atrium (RA) overload (Figure 1B). Laboratory tests did not show relevant changes.

Transthoracic echocardiogram showed PH (pulmonary artery systolic pressure [PASP] of 85 mmHg), major right chamber dilatation with RV dysfunction, left ventricle (LV) systolic dysfunction, grade 2 diastolic dysfunction, moderate pulmonary insufficiency, and major tricuspid insufficiency (Table 1). These findings were confirmed by transesophageal echocardiogram, which also revealed the presence of wide sinus venosus IAC, measuring 38 mm in its greatest diameter.

Chest computed tomography angiography (CTA) was requested to investigate the possible causes of PH, showing cardiomegaly involving the right chambers, negative results for pulmonary thromboembolism but with signs of pulmonary artery hypertension (dilated PA trunk measuring 5.2 cm) (Figure 1C).

On cardiac magnetic resonance, significant biventricular dilation and dysfunction (LV ejection fraction [EF] of 19% and RVEF of 20%) were found, as well as dilated RA and possible right inferior APVD for RA and PT dilatation (Figure 1D).

Initial clinical measures were taken to compensate the patient using intravenous diuretics and oral vasodilators. Subsequently, right heart catheterization was conducted, revealing wide sinus venosus IAC, right superior pulmonary vein with drainage in the superior vena cava, and right inferior pulmonary vein with drainage in the RA roof, RA oxymetric jump, HP (PASP 53 mmHg, pulmonary vascular resistance [PVR]: 3.04 woods), pulmonary-systemic flow ratio (Qp/Qs): 3.79/1, and PVR/systemic vascular resistance (SVR) 0,11.

The patient underwent surgical correction consisting of atrioseptoplasty with redirection of pulmonary vein blood flow,

Keywords

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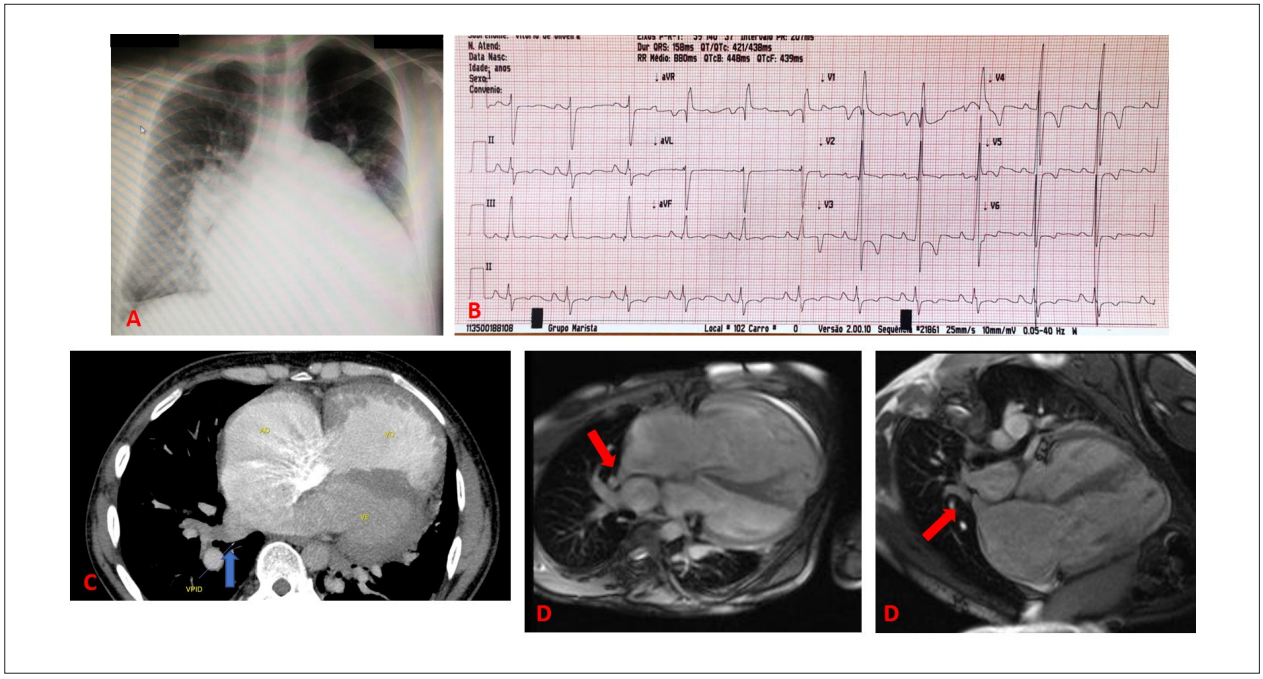

Figure 1 – *Complementary tests. A: Chest X-ray. B: Electrocardiogram. C: Chest computed tomography angiography (blue arrow: entrance of the right pulmonary vein into the right atrium). D: Magnetic resonance imaging (red arrow: entrance of the pulmonary vein into the right atrium).*

Table 1 – Evolution of echocardiographic and magnetic resonance findings before the procedure and 4 months and 1 year after treatment

	Magnetic resonance imaging	Baseline echocardiogram	Echocardiogram 4 months after correction	Echocardiogram 1 year after correction
Right atrium	Dilated	143 mL/m²	Increased	36 mL/m²
Left atrium	27 mm	39 mm	39 mm	39 mm
Left ventricle	739x591 mL	46 mm	42 mm	44 mm
RV functional assessment	EF 19%	FAC 25%	FAC 31%	FAC 24%
Left ventricle	178x141 mL	50x44 mm	50x37 mm	50x36 mm
LVEF	20%	26%	51%	54%
Pulmonary insufficiency	Unvalued	Moderate	Moderate	Moderate
Tricuspid insufficiency	Unvalued	Massive	Moderate	Mild to moderate
Pulmonary trunk	52 mm	39 mm	40 mm	43 mm
PASP	CIA	85 mmHg	57 mmHg	46 mmHg
Other findings	Possible right inferior APVC to RA	IAC 38 mm		

VD: ventrículo direito; FEVE: fração de ejeção do ventrículo esquerdo; PSAP: pressão sistólica da artéria pulmonar; FE: fração de ejeção; DAVP: drenagem anômala da veia pulmonar; AD: átrio direito; FAC: fração de alteração da área do ventrículo direito; CIA: comunicação interatrial.

with good evolution. He received hospital discharge and was prescribed with enalapril 5 mg 12/12 h (maximum tolerated due to hypotension), bisoprolol 10 mg/d, spironolactone 25 mg/d, and furosemide 40 mg/d. The patient returned to the outpatient clinic 4 months after the procedure, asymptomatic, with follow-up echocardiogram showing reverse remodeling (LVEF of 51%) and moderate pulmonary and tricuspid insufficiency. These findings were maintained at late follow-up with a new echocardiogram 1 year after the procedure, with LVEF of 54%, moderate pulmonary insufficiency, and mild to moderate tricuspid insufficiency.

Discussion

PAPVD usually occurs during fetal development, secondary to failure of one or more pulmonary veins of right lung upper lobe in connecting to the left atrium.[2,4] Physiologically, it produce a shunt from left to right, similar to an atrial septal

defect, allowing for the already oxygenated blood to circulate again to the lungs, resulting in excessive pulmonary blood flow. In 80 to 90% of the cases, drainage occurs to the right and is associated with atrial septal defects, more commonly sinus-venosus IAC.[2,3,5]

Many adults with PAPVD are accidentally diagnosed by chest images taken for any other indication, either with CTA in an emergency service to rule out pulmonary embolism, during cardiac catheterization for coronary intervention, or as part of an assessment of post-radiofrequency catheter ablation.[6,7] Most patients with isolated PAPVD are asymptomatic.[2,5,8] However, when this condition is associated with IAC, left-to-right (L-R) shunt occurs, which is responsible for increased right chamber flow and pressure leading to the remodeling of these chambers and of pulmonary vasculature and culminating in symptoms and in PH.[5,8] Since many patients remain asymptomatic up to adulthood, early diagnoses eventually occur as an incidental finding in less than 1% of the cases.[2,5,8] In the remaining cases, diagnostic suspicion based symptoms directs the investigation.

The presence of IAC alone may not be responsible for the onset of symptoms. The magnitude and direction of flow depend on defect size and on the filling pressure of each ventricle.[9] As a rule, the septal orifice needs to measure at least 10 mm, have a Qp/Qs > 1.5/1.0, or promote right chamber dilatation in order to be considered a hemodinamically-significant L-R shunt.[9]

The main diagnostic test for PAPVD is transthoracic echocardiogram.[3,5] However, in cases when this condition is associated with IAC, transesophageal echocardiogram, magnetic resonance imaging, or even right heart catheterization, may be required to elucidate the diagnosis. In addition to diagnosis, invasive hemodynamic assessment allows to calculate Qp/Qs ratio, an important information for therapeutic planning.[2,3]

The treatment of most PAPVD cases consists of clinical follow-up.[2,3,8] Conversely, there is an increase in morbidity and mortality rates when cases of significant IAC do not receive early treatment. Patient's age and pulmonary pressures at the time of correction are the main outcome predictors.[9,10] In both conditions, when there are symptoms, enlarged RV, or significant increase in L-R shunt (Qp/Qs > 1.5), surgical correction is mandatory and may be responsible not only of symptom resolution[2,3,8] but also of reducing the likelihood of late arrhythmia, HF, and PH complications. The risk of arrhythmias increases after the age of 40 in non-operated patients, with atrial flutter, being more frequent up to the age of 60 years, and atrial fibrillation becomes predominant after this age.[6,7]

The short- and long-term results after surgical repair of PAPVD are excellent, and the reported complications rates are low.[6,7] The association between reverse remodeling and improved clinical outcomes is well established in the literature. Therapies capable of promoting EF increase and reducing ventricle sizes are associated with lower mortality in HF.[11]

In the correction of heart diseases with L-R shunt, remodeling is expected after shunt surgical correction. The reduction in RA and ventricle volumes may occur as early as 24 hours after the procedure, but is generally more evident after 6 month and may extend to up to 18 months after the procedure. There is an expected reduction in right chambers, in tricuspid reflux, and in pulmonary pressures, as well as in improvement in LVEF, as observed in the present clinical case. However, the magnitude of remodeling is inversely proportional to patient's age at the time of closure, which reinforces the need for urgently starting treatment soon after symptom onset and diagnosis.[9,12]

Potential complications include stenosis or obstruction of pulmonary or systemic veins, residual IACs, or new atrial arrhythmias.[6,7] Although rare, PH represents a special situation and, if present in an adult patient with PAPVC, may not undergo remission after repair. Advanced cases with RVP > 8 woods or inversion of right-to-left shunt are contraindicated for surgical treatment.[2,3,6-8]

In the present report, the patient started to present with HF symptoms in adulthood, few days before admission. An etiologic investigation found APVD and IAC with important hemodynamic repercussion showing a significant increase in right chambers and in left-to-right shunt (Qp/Qs of 3.79), in addition to PH (PASP of 85 mmHg) and bilateral dysfunction. Surgical correction and pharmacological treatment of HF promoted clinical and echocardiographic improvement in an early and sustained fashion, reinforcing the importance of investigation and treatment of patients with this condition.

Author Contributions

Conception and design of the research: Bonatto MG; Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Bonatto MG, Freitas AKE; Critical revision of the manuscript for intellectual content: Bonatto MG, Freitas AKE, Rocha LSO, Moura LAZ; Doctor responsible for the patient: Collatusso C; Assistance in imaging methods: Torres RA, Blume GG.

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Notes

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