JAFIB EP

Review Article

Journal of Atrial Fibrillation & Electrophysiology

www.jafib-ep.com

Pathophysiology of Myocarditis: State of Art Review

Sri Harsha Kanuri[1], Surya Kiran Aedma[2], Anant Naik [3], Preetham B Kumar[2], Pranav Mahajan[4], Rahul Gupta[4], Jalaj Garg[5], Mohit Thurugam[6], Mehmet Ali Elbey[1], Padmini Varadarajan[2], Ramdas G. Pai[2], Dhanunjaya Lakkireddy[1]

[1]Case Western Reserve University
[2]University of California Riverside, School of Medicine, Riverside, CA, USA
[3]Carle Illinois College of Medicine, Urbana, Illinois, USA
[4]Lehigh Valley Health Network, Cardiology Allentown, PA, USA
[5]Division of Cardiology, Cardiac Arrhythmia Service, Loma Linda University Health, Loma Linda, CA
[6]Mount Sinai School of Medicine, New York, USA

Abstract

Myocarditis refers to inflammation of the myocardium caused by infectious and non-infectious process. It should be considered in any patient presenting with unexplained congestive heart failure, ventricular arrhythmias, atrial fibrillation or dilated cardiomyopathy . Prompt diagnosis and treatment is required, otherwise unrecognized myocarditis can rapidly progress to cardiogenic shock with increase in mortality and morbidity. Although various etiologies such as viruses and autoimmune phenomenon have been proposed, there are many unanswered questions regarding the underlying pathophysiology that initiate and trigger myocardial inflammation. These gaps in knowledge need to addressed by developing appropriate myocarditis disease models for understanding the interaction of initial insult, autoimmunity, and host genetics so as to develop novel therapeutic modalities that can halt the disease progression for better clinical outcomes. This review focuses on etiology, pathophysiology, symptomatology, diagnosis, treatment and directions of myocarditis.

Epidemiology

Myocarditis refers to inflammation of the myocardium caused by infectious and non-infectious process. The prevalence of myocarditis worldwide is estimated at 10.2-105.6 cases per 100,000 population annually[1]. Review of postmortem autopsy reports revealed that myocarditis is often overlooked, and its incidence is around 0.11% and 0.007% for non-specific myocarditis and giant cell myocarditis respectively[2, 3]. The average age for myocarditis is 40 ± 16 yrs[4, 5]. Generally, it is believed that myocarditis is more common in males as compared to females due to the protective effects of hormonal profile (estrogen and progesterone) on autoimmune responses[6-8]. Younger men presenting with myocarditis have rapid clinical progression with higher risk of death whereas females tend to present at older age with ventricular arrhythmias secondary to myocarditis[8].Some of the common etiological factors include infections, toxins, drugs, infiltrative diseases and autoimmune diseases[1]. 1-5% of patients with documented viral infection progress to develop myocarditis[8]. It should be considered in any patient presenting with unexplained congestive heart failure, ventricular arrhythmias, atrial fibrillation or dilated cardiomyopathy[1]. It accounts for up to 46% of cases in young children with sudden cardiac death and dilated cardiomyopathy[9].

Prompt diagnosis and treatment is required, otherwise unrecognized myocarditis can rapidly progress to cardiogenic shock with increase in mortality and morbidity[10]. Although various etiologies such as viruses and autoimmune phenomenon have been proposed, there are many unanswered questions regarding the underlying pathophysiology that initiate and trigger myocardial inflammation[10]. These gaps in knowledge need to be addressed by developing appropriate myocarditis disease models for understanding the interaction of initial insult with myocardial tissue, autoimmunity, and host genetics so as to develop novel diagnostic and therapeutic modalities that can halt the disease progression for better clinical outcomes.

Key Words

Myocarditis, Pericarditis, Inflammation, Autoimmunity, Auto-antibodies, Autoreactive T-cells, Innate immunity.

Corresponding Author
Dhanunjaya Lakkireddy, MD, FACC, FHRS
Executive Medical Director, The Kansas City Heart Rhythm Institute (KCHRI) @ HCA Midwest, Professor of Medicine, University of Missouri – Columbia

Etiology

The aetiology of myocarditis is very much varied and can be summarized as follows: Infectius agents (bacteria, virues, fungi, protozoa and parasites), toxins, drugs, autoimmunity, hypersensitivity,

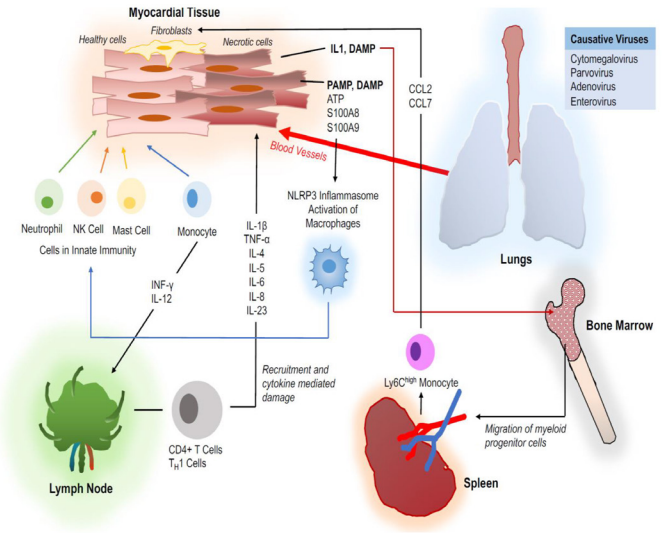

Figure 1: **Phase 1 Pathogenesis of Myocarditis. Infiltration of viral organisms in the lungs leads to hematologic spread of viral tissue to healthy myocardial tissue. An immune response mediated by the innate immune system, via monocytes, neutrophils, NK cells and mast cells, and ultimately the recruitment of the adaptive immune system, via CD4+ T-cells and TH1 cells leads to a cascade of necrosis. This causes a systemic inflammatory response, leading to the production of Ly6C^{high} Monocytes in the spleen.**

systemic inflammatory diseases, chemicals, radiation exposure and idiopathic[11,12].

Viruses

The viruses that had been in implicated in the causation of myocarditis include adenoviruses (Coxsackie A&B, ECHO, influenza, and Polio), enteroviruses, adenoviruses, mumps, measles, rubella, hepatitis C&B, COVID-19 and HIV[11,12].

Bacteria

Bacteria such as Staphylococcus, Streptococcus, Corynebacterium diphtheriae, Ehrlichia, Borrelia, Legionella, Clostridium, Mycoplasma pneumonia, Treponema pallidum, Salmonella and Shigella species etc. are also known to cause myocarditis[11,12].

Fungal

Although fungal myocarditis is rare, the most frequently encountered opportunistic invasive fungal infections of the myocardium are due to Candida, Aspergillus, Cryptococcus, Histoplasma, Blastomyces and Coccidioides[38].

Protozoal

The most common protozoa parasites known to cause infection in the myocardium include Trypanosoma cruzi, Toxoplasma, Plasmodium, Entamoeba, Leishmania, Balantidium and Sarcocystis[12,39].

Parasites

Some of the parasites implicated in myocarditis include larva migrans and schistomiasis[12].

Toxins / drug-induced

Toxin induced cardiomyopathy occurs mostly in individuals with long-term occupational exposure (lead, mercury, arsenic), medically prescribed drugs (tricyclic antidepressants, dobutamine, anthracycline lithium, epinephrine, radiotherapy, catecholamines, doxirubucin and trastuzumab) or with illicit drugs (cocaine, amphetamines, alcohol) and IL-2 [40,12,41]. myocarditis

Hypersensitivity drug reactions

Myocarditis can be secondary to hypersensitivity reaction to administration of drugs such as antibiotics (ampicillin, cephalosporins, tetracycline and sulfasoxazole), diuretics (hydrochlorthiazide and spironolactone), digoxin, dobutamine, tricyclic anti-depressants, lithium and indomethacin[11,12].

Systemic diseases

Systemic inflammatory diseases such as Systemic lupus erythematosus (SLE), Sjogren's syndrome, Chagas disease, Inflammatory bowel disease, Takayasu arteritis, Thyrotoxicosis, Churg-strauss syndrome and Sarcoidosis can be associated with myocarditis as a secondary phenomenon due to molecular mimicry and deposition of antigen-antibody complexes in the myocardium[11,12].

Pathophysiology

Viruses were implicated in up to 69% cases of myocarditis. The pathophysiology of clinical myocarditis can be divided into three phases. Phase I (viral access into myocardium and initiation of adaptive immune response), Phase II (autoimmune phase including role of T-cells, cytokines, and auto-antibodies) and Phase III (chronic myocarditis and dilated cardiomyopathy).

Phase I: Viral infection and initial activation of innate immunity (1-7 days)

Cardiotropic viruses such as Adenovirus and Coxsackie virus are implicated as most important causative factors for myocarditis. Once they enter the body through respiratory tract or gut, they initially get localized into the immune cells of the neighboring lymphoid organs, which provides them temporary shielding against immune clearance. They eventually are transported to the distant target organs such as heart causing myocarditis and cardiomyopathy. These viruses

Table 1: Infectious etiologies of Myopericarditis

Viruses (common)	Bacteria	Fungal	Protozoans
Adenovirus	**Staphylococcus (most common bacterial cause)**	**Candida**	**Trypanosoma (Chaga's disease)**
Enterovirus (Coxsackie A/B)	Streptococcus	Aspergillus	Toxoplasma
Parvovirus	Corynebacterium diphtheria	Cryptococcus	Plasmodium
Ebstein Bar Virus	Ehrlichia	Histoplasma	Entamoeba
Herpesviridae	Borrelia	Blastomyces	Leishmania
Human Immunodeficiency Virus	Mycobacteria	Coccidioides	Balantidinum
Corona virus	Salmonella		Sarcocystis
Hepatitis	Chlamydia		
Influenza			
Varicella			

Table 2: Non-infectious etiologies of Myopericarditis

Drugs & toxins	Autoimmune	Malignancy	Vaccine associated
Occupational exposure to lead, arsenic, mercury	CTDs (SLE, RA, Scleroderma, MCTD)	Lung cancer, breast cancer, melanoma	Smallpox vaccine
Prescription drugs (TCAs, dobutamine, anthracycline, epinephrine, trastuzumab, methyldopa)	Inflammatory Bowel Disease (Crohn's Ulcerative Colitis), Scleroderma, Celiac disease		
Illicit substances (cocaine, amphetamines, alcohol)	Eosinophilic		

CTD= Connective Tissue Disease, SLE=Systemic Lupus erythematous, RA=Rheumatoid Arthritis, MCTD=Mixed Connective Tissue Disease

are predominantly regarded as cardiotropic as they have predilection towards heart and act by binding through transmembrane receptor known as CAR (Coxsackie virus and adenovirus receptor) and decay accelerating receptor (DAR)[10, 12]. Induction of cytokine mRNA, expression of interferons, interleukins, TNF-alpha and induction of cardiac auto-antibodies are some of the findings that can occur during this phase[12].Viral antigens can activate the immune system with the help of major histocompatibility complex (MHC) and T-cell membrane–associated tyrosine kinase p56lck[43]. The various mechanisms by which viral laden cardiomyocytes are killed by cytotoxic lymphocytes in this phase can range from perforins, serine proteases and Fas-ligand pathway[44]. Immune responses during phase I can be considered to be a double-edged sword as they serve a dual purpose by helping in clearing of viral infected cardiomyocytes as well as aggravating virus induced myocardial damage[44]. It is important to understand that if T-cell mediated immune responses were not successful in curtailing, restricting and healing of viral myocarditis in this early phase, then it most likely progresses to phase II[44].

Innate immune response:

Once viral infection occurs, both cardiomyocytes and innate immune cells will be activated by toll like receptors (TLRs), nucleotide binding oligomerization domain like receptors (NOD), pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs) such as ATP, S100A8 and S100A9[45-48]. Their activation leads to secretion of cytokines, chemokines, and interferons as well as inflammasome activation in macrophages thereby resulting in the migration of innate immune cells such as monocytes, mast cells, natural killer cells and neutrophils towards the site of damage in the myocardial tissue[48, 49]. The main purpose of this innate immune response is to eliminate the viruses from the body, to neutralize the viral induced myocardial damage, and prevent the progression to inflammatory cardiomyopathy. Coordinated and synchronized innate immune response is a crucially significant defense mechanism unleashed by the body for clearing the virus from the body and reversing the virus induced myocardial damage.

Unfortunately disjointed and unabated actions of innate immune cells can result in excessive loss of myocardial contractile units which can potentially be exacerbated by effects of adaptive immune system in phase II.

Monocytes:

Once these viruses enter into the cell, they multiply within the host cell, causing cytoskeletal dismantling and ultimately leading to myocardial tissue degradation[10]. This results in the release of intracellular danger signals including myocyte antigens into the circulation triggering the activation of adaptive immune response[12]. On the other hand, myocardial tissue damage also releases IL-1β, PAMPs and DAMPs into the circulation which triggers emergency hematopoiesis in the bone marrow, resulting in the release of myeloid progenitor cells into the circulation. These myeloid progenitor cells eventually migrate into the spleen triggering extra medullary hematopoiesis leading to the production of pro-inflammatory Ly6C^{high} monocytes (figure 1)[50]. Interferon gamma (IFNγ) produced by inflamed cardiomyocytes induces the fibroblasts within the myocardium to produce chemokines (CCL2 & CCL7) which attracts Ly6C^{high} monocytes towards the myocardium. Accordingly, blockade of these chemokines resulted in decreased migration of these Ly6C^{high} monocytes and attenuation of destructive autoimmune process of myocarditis[51]. The monocytes that are recruited and transformed into macrophages in the myocardium have dual function including secretion of anti-inflammatory cytokines that promote tissue repair as well as secretion of pro-inflammatory cytokines such as TNF-alpha and IL-6 that can provoke myocardial tissue damage[10].

Although main purpose of recruiting monocytes to the myocardium is to mount an immune response for clearing the viral infection, most often it proceeds in an uncontrolled and disjointed manner leading to excessive myocardial damage and loss of myocyte contractile units[51]. In experimental autoimmune myocarditis, IL-17A signals through fibroblasts to inhibit efferocytosis (removal of dead myocytes by macrophages) and promote pro-inflammatory gene expression in Ly6C^{high}monocyte-derived macrophages (MDMs), thereby inciting rapid myocardial damage in viral myocarditis[52]. In the contrary, MDMs with M2 gene expression are known to facilitate the recruitment of regulatory T-cells (Treg) into the myocardium which are preferentially instrumental in halting the myocardial damage by attentuation of

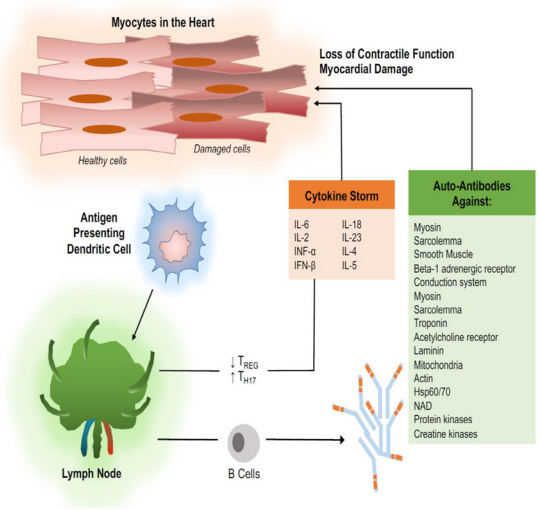

Figure 2: **Phase 2 Pathogenesis of Myocarditis. A cytokine storm, generated by the downregulation of regulatory T cells and upregulation of T_H17 cells in lymph nodes, further causes myocardial damage. The production of autoantibodies against myocardial tissue further potentiates the damage by B-cells.**

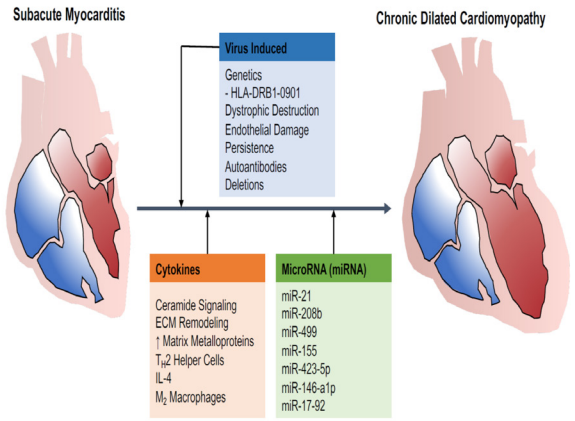

Figure 3: **Transformation of Subacute Myocarditis to Chronic Dilated Cardiomyopathy. A combination of cytokines, miRNA and virally induced damage precipitates the dilation of the heart and the further loss of contractility.**

hyperactive adaptive immune system[51].

Mast cells, Natural Killer cell, Dendritic cells, and Neutrophils

Earliest cell mediated immune response to viral infection of myocardium includes migration and degranulation of mast cells for secretion of cytokines such as TNF-alpha, IL-4 and IL-1β for neutralizing the viruses and confine the myocardial damage[10]. Furthermore, mast cells also secretes matrix metalloproteinases (MMPs) and fibrinogenic mediators (chymases and tryptases) that mainly functions to induce the fibroblasts within the myocardium and thereby producing stem cell factors that can potentially differentiate into more mast cell precursors in the myocardium[53]. It has been shown that, gene expression of mast cell enzymes(chymase and tryptase) increases during the active phase of myocarditis and sub-acute phase of congestive heart failure emphasizing its protective role in myocardial necrosis and fibrosis respectively[53]. To prevent the progression of inflammatory myocarditis and promote the clearance of viral infection, natural killer (NK) cells are usually recruited into the site of myocardial injury. NK-cells have been shown to be protective against coxsackie B virus (CBV) and cytomegalovirus (CMV) induced myocarditis by their inherent lytic effect[54]. Their principal mechanisms of action in myocarditis include formation of perforin induced pores in viral infected cardiomyocytes, limiting viral replication and attenuating the inflammatory response[54]. Furthermore, the protective effects of NK cell include suppression of auto-reactive T-cells and monocyte maturation for myocardial regeneration[51].

Neutrophils

Neutrophils are one of the earliest immune cells that migrate to the myocardium after viral infection for initiating and maintaining myocardial inflammation through a process called NETosis (neutrophil extracellular traps), a process which has been demonstrated in mice with experimental autoimmune myocarditis[55,56]. Downstream signaling events that occurred after neutrophil recruitment to the myocardial tissue include NF-kB activation, upregulation of CD11b, increased adhesion to fibrinogen/fibronectin, secretion of pro-inflammatory mediators (myeloperoxidase, IL-6, IL-8, TNF-alpha & IL-1β)[57]. Increase in neutrophil to lymphocyte ratio (NLR) reflects the extent of myocardial necrosis and is associated with major adverse cardiac complications in patients with myocarditis[58, 59]. Furthermore, it has also been shown that neutrophils can accentuate the progression of myocarditis by sustaining the severity of CD8+ T lymphocyte migration to the injured myocardium which is independent of T-cell migration associated with adaptive immune response [60]. However, in CVB3 viral myocarditis neutrophil migration was shown be beneficial rather than counterproductive where IL-12 mediated protection included upregulation of interferon-gamma (IFN-*y*) and increased neutrophil and macrophage accumulation for clearance of virus from the infected myocardium[61]. Furthermore, neutrophil induced secretion of alarmins (S100A8 and S100A9) also promotes the progression of inflammatory cardiomyopathy[10]. Interestingly, neutrophil induced myocardial necrosis coincides with elevation of alarmins in the plasma of patients with active myocarditis as compared to healthy controls which can be used as biomarkers for flaring of myocardial inflammation [47].

Phase II:Activation of adaptive immune response

Prominent features of this stage include activation of adaptive immune response, T-cell activation, chemokine & cytokine secretion, T-cell mediated clearance of virus, T-cell mediated myocardial injury and accumulation of cardiac specific auto-antibodies (figure 2)[12]. This phase can last from few weeks to few months and result in decrease in viral titers, clearance of virus and improvement of contractile function.

Role of T-cells

Myocardial damage in viral myocarditis, autoimmune myocarditis and autoimmune inflammatory cardiomyopathy is usually mediated by activated T-cell repertoire[10]. Viral antigens processed by Golgi apparatus of cardiomyocytes are presented on the cell surface with the help of major histocompatibility complex (MHC)[43]. Antigen presenting cells (APCs) present these viral antigens to the T-lymphocytes in the neighboring lymphoid organs which leads to activation of T-cells which actively seek viral infected myocytes to destroy and eliminate them by cytokine mediated or perforin based lysis mechanisms[43]. Some of the viruses such as EBV are known to trigger a massive CD8+ T-cell influx towards myocardium thereby amplifying the immune response[10].

Table 3: **Treatment options of non-virus NICM**

Guideline directed medical therapy	**All patients with reduced left ventricular ejection fraction (LVEF)**
Immunosuppressive therapy (prednisone + azathioprine)	Noted to have improved LVEF, decreased mortality, and decreased NYHA class (TMIC study) in conditions like giant cell myocarditis, eosinophilic myocarditis, granulomatous myocarditis, and inflammatory myocarditis associated with sarcoid
IVIG	
Intramyocardial administration of high doses of triamcinolone	To avoid clinical side effects of IST
Combination of monoclonal anti-CD3 antibodies, methylprednisolone, and cyclosporine	Treatment for idiopathic giant cell myocarditis
Trans-endocardial stem cell injection of allogenic human mesenchymal stem cells	Increased EF, improved exercise performance and decreased MLHFQ
IL-1 receptor blockade (Anakinra)	Demonstrated improvement in fulminant myocarditis

IST – Immune suppressive therpy

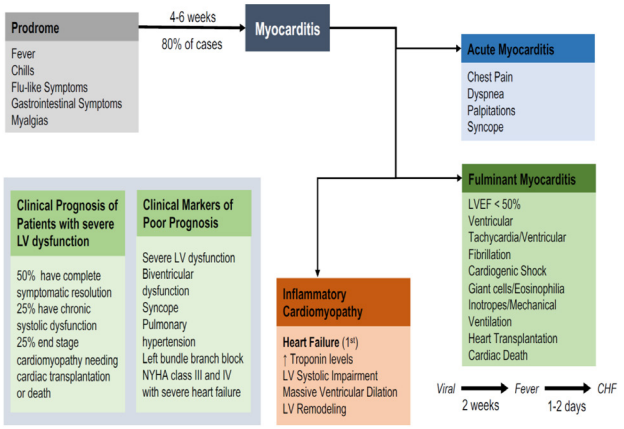

Figure 4: **Symptomology of Myocarditis. Prodrome symptoms present 4-6 weeks prior to the development of myocarditis, followed by the development of acute myocarditis, fulminant myocarditis, or inflammatory cardiomyopathy. Fulminant myocarditis precipitates congestive heart failure (CHF) 1-2 days following febrile symptoms.**

In animal models, there are two subsets of T-lymphocytes namely Th17 and Treg which are involved in the pathogenesis of autoimmune myocarditis[10].

Regulatory Treg cells have a protective function against myocarditis and cardiomyopathy by attenuating the cardiac inflammation[10]. In experimental autoimmune myocarditis, the percentage of Treg cells is inversely correlated with disease severity. Treg cells downregulate the virus induced myocardial inflammation by secreting inhibitory cytokines (TGF-β1&IL-10) or expressing surface molecules(CTLA-4 or glucocorticoid-induced TNF receptor) and thereby halt the progression of myocarditis to dilated cardiomyopathy [62]. One of the important proposed mechanisms for COVID-19 induced myocardial damage include cytokine storm with increased Th17 lymphocytes caused due to imbalance of TH1 and TH2 regulatory cells[63,64].

Th17 cells are elevated in the animal models with viral myocarditis and dilated cardiomyopathy[65]. Viral infection of cardiomyocytes is followed by active replication, myocardial cell death, necrosis, and lysis. Myocardial necrosis leads to extravasation of cardiac myosin into interstitium. This cardiac myosin can act through TLR2 ligands of CD14+ monocytes and stimulate the production of IL-6, TGF-β1and IL-23 resulting in down-regulation of Treg phenotype and up-regulation of Th17 phenotype[65]. Furthermore, cardiac fibroblasts can secrete chemokine (CCL20) to recruit the Th17 cells into the myocardium which amplify the local inflammatory response in active viral myocarditis[66]. Integrin CD11b (expressed by dilated myocardial cells and monocytes) can promote the differentiation of naive CD4+ T-cell precursors to Th17 cells in the spleen and thereby increase the levels of IL-17, IL-23 and STAT-3 expression in the heart tissues in viral myocarditis[67]. Predominance of Th17 phenotype in human myocarditis is associated with dilated cardiomyopathy, cardiac fibrosis and heart failure[65].

Cytokine activation and storm

T-cell derived cytokines can be helpful in promoting the recovery of the disease process as well as accelerating the progression of myocarditis from phase II to phase III[44]. Recruitment and activation of T-lymphocytes in myocardium sets in motion a cascade of events by secretion of pro-inflammatory mediators such as TNF, IL-1a, IL-1b and IFN-gamma leading to myocardial damage, destruction of myocyte contractile units and interstitial matrix[12,43]. Moreover, predominance of Th17 immuno-phenotype in myocarditis was associated with elevated pro-inflammatory cytokines such as IL-6, IL1-β, TGF-β1& IL-23 which play a major role in pathogenesis of heart failure and dilated cardiomyopathy in myocarditis[65]. According to Roseet al, the inflammatory phase of autoimmune myocarditis is mediated by Th17 cell induced cytokines such as IL-17A, IL-17F, and IL-22[68]. IL-1 beta and TNF-alpha are the cytokines that are present in the earlier stages whereas IFN-gamma and IL-2 are the cytokines that predominate in the later stages of the viral myocarditis[69].IL-4, IL-5, IL-23 and IL-12 are responsible for progression of phase II to phase III of myocarditis[68]. In the contrary, IL-10, IL-13 and IFN-gamma offer protection against decreasing the severity of auto-immune phase of myocarditis[68]. Furthermore, viral induced necrosis of cardiomyocytes can release IL-1, TNFα into the interstitium which can stimulate the macrophages leading to production of pro-inflammatory cytokine IL-1 beta which can in turn precipitate the migration of more inflammatory cells into the myocardium perpetuating the cycle of cardiomyocyte destruction, cardiomyopathy and heart failure[70]. Regulatory T cells such as Th2 can secrete cytokines such as IL-10 and IL-13 which can have immunomodulatory properties such as inhibition of pro-inflammatory cytokines and macrophage function[68,69]. Administration of antibodies against cytokines offered protection by attenuating the severity of murine myocarditis[44]. Suppression of Toll-like receptor signaling, and cytokine mediated signaling which are important in the development of innate and adaptive immunity offered protection against autoimmune myocarditis and dilated cardiomyopathy in animal models[71].

Auto-antibodies (Role of B-cells)

The presence of viral antigens in the cardiomyocytes or circulation can activate the CD4+ lymphocytes leading to B-cell proliferation and resultant antibody production[43]. Previous studies indicate that heart specific antibodies are present in at least 60% of the patients with viral inflammatory cardiomyopathy[10]. The presence of auto-antibodies against the components of myocardium in the patients with chronic myocarditis can promote the disease progression[44]. In patients with myocarditis, numerous antibodies have been detected including anti-sarcolemma antibody, anti-myosin alpha and beta heavy chains, anti-troponin antibodies, anti-acetylcholine receptor antibodies, anti-beta-1 adrenergic antibodies, anti-cytoskeleton antibodies (actin, laminin and desmin), anti-mitochondrial antibodies (NAD, Creatine kinase and pyruvate kinase), anti-heat shock protein (60&70) antibodies and anti-membrane antibodies[44,48]. Passive transfer of these auto-antibodies developed in rats immunized with cardiac myosin heavy chain, cardiac troponin, muscarinic receptor M2 and beta1-adrenergic receptor into normal rats resulted in cardiomyocyte necrosis and inflammatory cardiomyopathy[10].

Gene-environment interactions

Previous studies had revealed that risk of developing dilated cardiomyopathy is related to the presence of mutant loci on HLA1 and HLA II class proteins[10]. Moreover, gut bacteria such as bacteroides can precipitate the immune response as well as development of auto-

antibodies against myocardial tissue due to cross reactivity between myosin 6 antigen and myosin peptide[10].

Phase III: Chronic myocarditis and dilated cardiomyopathy

The third phase is chronic myocarditis which includes chronic inflammation, cardiac remodeling and dilated cardiomyopathy which can last weeks to months[10, 12]. Although speculative, some of the mechanisms proposed for the progression into chronic myocarditis (phase III) include viral persistence, viral gene expression, virus induced remodeling, autoimmune mechanism, exaggerated inflammatory response and post injury adverse remodeling[44, 72]. The pathophysiology of phase III myocarditis is summarized in figure 3.

Viral persistence

A characteristic feature common to adenoviruses, enteroviruses and parvoviruses is that they tend to persist in low levels in the myocardial tissue thereby perpetuating chronic inflammation and LV dysfunction[10, 43]. In few cases of dilated cardiomyopathy, the latent viruses can be localized to dead and degenerating myocytes, inflammatory cells and endothelial cells which can be identified by in -situ hybridization technique[44]. One of the important mechanisms through which viruses persist within the myocardium include 5' terminal deletions in genomic RNA so that they can trigger chronic inflammatory state and dilated cardiomyopathy[10]. The presence of gene loci such as HLA-DRB1*0901 and HLA-DRB1*1201are also associated with chronic persistence of hepatitis C viruses in the myocardium[10, 73]. Viral persistence causes development of auto-antibodies against cardiac myosin which can cross react with viral and myosin epitopes due to molecular mimicry, thereby resulting in autoimmune myocarditis and dilated cardiomyopathy. The most probable cause suggested for progression to dilated cardiomyopathy is latent coxsackie virus protease 2A induced destruction of sarcolemma membrane and dystrophin[43, 74, 75]. The underlying mechanisms that are speculated in parvovirus induced cardiomyopathy include endothelial dysfunction, upregulation of E-selectin, T-cell recruitment, coronary vasospasm, cardiac ischemia, myocyte necrosis and systolic dysfunction[12, 76].

Cytokine mediated changes

Th17, Th9 and Th22 phenotypes of T cells are mainly implicated for the casuation of autoimmune myocarditis and its progression to dilated cardiomyopathy[51]. Initial remodeling changes begins in earlier stages of myocarditis due to pro-fibrotic effects of T-cell secreted cytokines (IL-1beta, TNF-alpha, IL-4 & IL-17) which progresses to cardiac fibrosis in later stages, leading to dilated cardiomyopathy[72]. In this regard, extracellular matrix remodeling (a critical step for progression of acute myocarditis into dilated cardiomyopathy) is precipitated by pro-inflammatory cytokines (TNF-alpha& IL-1 beta) that are elevated in phase I of myocarditis[72]. Cytokines activate matrix metalloproteinases (collagenase, elastase and gelatinase) that can initiate extracellular matrix remodeling for disease progression to chronic myocarditis[43, 77]. In animal models, TH2 helper cells, IL-4 and M2 macrophages were responsible for progression of acute myocarditis to dilated cardiomyopathy through low level inflammation, necrosis and fibrosis[72]. It has been hypothesized that, cytokines mediated death signaling mechanisms will result in adverse cardiac remodeling and progressive heart failure leading to dilated cardiomyopathy[43, 78]. Patients with myocarditis who progress to dilated cardiomyopathy usually have imbalance in the ratio of cytotoxic T-cells (Killer T-cells) to regulatory T-cells (Treg) with associated downregulation of regulatory Treg cells leading to increased activation of cytotoxic T-cells with associated increased production of pro-inflammatory cytokines leading to deleterious consequences in this regard[51].

Role of miRNAs

MiRNAs such as miR-21, miR-208b and miR-499 have been speculated to be involved in progression of viral myocarditis to dilated cardiomyopathy[79]. Furthermore miR-21, miR-146a/b, -155, -423-5p, and the miR-17-92 cluster have been implicated in NICM and LV systolic dysfunction[79].

Histopathology

The histopathological findings can depend on the etiology, duration of myocardial injury and stage of myocarditis. Endomyocardial biopsy might reveal different histological patterns ranging from eosinophils, granulomatous changes, giant cells, mono-nuclear cells, histiocytes along with varying degrees of myocardial necrosis and fibrosis[80-82]. Myocarditis can also be classified based on cellular infiltrate present such as lymphocytic myocarditis, lympho-histiocytic myocarditis, neutrophilic myocarditis, giant cell myocarditis, eosinophilic myocarditis, and granulomatous myocarditis[80, 83]. In few cases, the cellular infiltrate is associated with vasculitis component which might complicate the clinical scenario[83]. In myocarditis associated with Kawasaki disease, the inflammatory infiltrate is usually localized to epicardial layer at the base of the heart after 10 days of infection[84]. Involvement of myocardium in systemic sarcoidosis is usually characterized by presence of non-necrotizing epithelioid cell granulomas composed of lymphocytes, epithelioid histiocytes and multinucleated giant cells[85]. Fulminant myocarditis is characterized by multiple foci of active inflammation and myocyte necrosis and is fatal unless patients are promptly diagnosed and aggressively treated. In COVID-19 induced myocarditis, the predominant cellular infiltrate include lymphocytes, macrophages and granulomas (giant cells and eosinophils)[86]. In some cases, COVID-19 induced myocarditis can be associated with involvement of endothelial cells (endothelitis) and lead to micro or macrothrombi, inflammation and intraluminal megakaryocytes in microvasculature[10, 86, 87]. Systemic sarcoidosis may be associated with presence of non-caseating granulomas in the pericardium[88].

Symptomatology

Most of the patients of myocarditis have a prior viral prodrome comprising of fever, chills, flu like symptoms [9, 10, 12]. After few weeks of viral prodrome, the clinical manifestations of acute myocarditis can range from chest pain, shortness of breath, syncope, cardiogenic shock, ventricular arrhythmias to sudden cardiac death[9, 10, 12]. In some cases, patients can have fulminant myocarditis presenting with cardiogenic shock and severe LV dysfunction requiring inotropes, mechanical ventilation and cardiac transplantation. Patients with acute myocarditis can be asymptomatic or present with EEG changes ranging from premature-ventricular complexes, irregular / polymorphic ventricular tachycardia and ventricular fibrillation[89]. In young and middle aged patients, acute fulminant myocarditis has presented with sudden cardiac death[89]. Healed myocarditis on the other hand can present with regular

ventricular tachycardia[89].

Furthermore, patients can present with significant conduction disturbances or fatal ventricular arrhythmias raising the possibility of giant cell myocarditis, cardiac sarcoidosis or borrelia burgdorferi infection[9]. Most commonly, patients with arrhythmias secondary to myocarditis present with syncope, palpitations, shortness of breath, and dizziness thus alerting the clinician to perform relevant diagnostic workup[9].

It is not uncommon to find myocarditis in postmortem autopsy of patients who developed sudden cardiac death secondary to malignant ventricular arrhythmia[9]. The clinical course of myocarditis is quite variable and depends on the etiological factors, risk factor profile and treatment response. Most of the patients (50%) with myocarditis who present with mild LV dysfunction recover with no clinical sequelae[12]. However, at least 25% of the patients progress to develop end stage cardiomyopathy needing heart transplantation[12]. Previous studies indicate that the mortality rate in viral myocarditis has been estimated to be 20% and 56% at 1 year and 5 years respectively[12]. It is important to note that one of the important prognostic factors for recovery of LV function in myocarditis is the extent of myocardial damage in acute phase I[9]. The symptomatology and prognostic factors of myocarditis is summarized in figure 4.

Inflammatory cardiomyopathy is associated with atrial and ventricular tachyarrhythmias[89]. The pathophysiology of arrhythmias in inflammatory cardiomyopathy involves direct myocardial injury, microvascular ischemia, broken intercellular gap junctions and fibroblast remodeling[89].

Inflammation can initiate AF through modification of atrial electrical circuit and structural remodeling thereby altering the atrial electrophysiology[90]. Electrophysiological changes that can be attributed to inflammation induced atrial electrical remodeling include decreased action potential duration, dysfunctioning of gap junctions and alteration of intercellular connections between atrial myocytes[89-91]. TNF-alpha which is upregulated in inflammation can induce atrial fibrosis via activation of smad-2,3 / TGF-beta signaling pathway[90, 92]. Some of the systemic inflammatory diseases which have increased propensity to AF include Rheumatoid Arthritis (RA), collagen induced arthritis, Psoriasis, Inflammatory bowel disease (IBD) and Ankylosing Spondylitis (AS)[93-96].

Systemic inflammation which is frequently associated with increased thrombin formation and hypercoagulation causes fibrotic changes in the atrial wall and increased propensity to AF generation[90]. Local myocardial inflammation such as pericarditis and myocarditis which are highly associated with occurrence of AF have evidence of inflammatory sequelae in the atrial myocardial tissue such as higher CD45+ and CD68 lymphocytes, increased cardiac MCP-1 (Monocyte chemoattractant protein-1), upregulated Toll-like receptors (TLR-4 & TLR-2) and NLRP3 inflammasome activation (NACHT, LRR, and PYD domains-containing protein 3)[90]. The clinical spectrum of inflammatory myocarditis can range from asymptomatic LV failure to fulminant myocarditis presenting with atrio-ventricular block, atrio-ventricular tachyarrhythmias, left ventricular dysfunction with and without heart failure and sudden cardiac death[89, 90]. Giant-cell myocarditis and Lyme myocarditis can present clinically with AV block with or without LV systolic dysfunction in younger population due to direct compression of conduction system[97, 98]. Unexplained sudden cardiac death might be the initial presentation in young and middle aged adults with inflammatory cardiomyopathies[99]. Inflammatory cardiomyopathies can clinically present with ventricular arrhythmias such as premature ventricular complexes (PVCs), ventricular tachycardia and ventricular fibrillation due to automaticity or re-entry mechanisms[100]. Specifically, acute myocarditis presents with irregular and polymorphic ventricular tachycardia whereas burnout or healed myocarditis presents with regular or monomorphic ventricular tachycardia [100]. COVID-19 myocarditis can present with symptoms ranging from fatigue, dyspnea, tachycardia, chest pain, chest tightness, acute-onset heart failure and cardiogenic shock[101]. Sometimes, it can also present as fulminant myocarditis with ventricular dysfunction and heart failure within 2-3 weeks of viral exposure[29, 101]. In Lyme myocarditis, involvement of atrio-ventricular node is common with patient presenting with partial or complete heart block necessitating immediate diagnosis and antibiotic treatment[102]. Moreover, myocardial involvement with mild-moderate LV dysfunction which is self-limiting in few weeks has also been reported in few clinical case reports [103, 104]. In the typical clinical presentation of Giant-cell myocarditis, there is a rapid progression to fulminant form with symptoms and signs of severe LV dysfunction and cardiogenic shock[105]. Other forms of presentation with giant-cell myocarditis include AV block, ventricular arrhythmias and indolent form where clinical symptoms are absent and diagnosis is confirmed at autopsy or transplantation[106, 107].

Diagnosis

Diagnosis of myocarditis does not depend on clinical presentation alone due to wide array of symptoms. As a clinician, it is always prudent to have a high level of suspicion because of atypical presentation and rapid progression to fulminant myocarditis in few cases which necessitates prompt confirmation and tailored therapy to prevent morbidity and mortality. Biomarkers such as troponins or creatinine kinase (CK) lack specificity. Checking troponin levels during acute cardiomyopathy due to suspected myocarditis is a class 1C recommendation[108, 109]. Serum markers of inflammation like leukocyte count and C reactive protein can be elevated, however, normal values do not exclude myocarditis. The utility of viral serology is limited e.g., for PVB19 myocarditis, majority of patients are already positive for PVB19 immunoglobulin G antibodies due to its high prevalence. Every patient with cardiac symptoms should get an EKG as a screening tool, although it has very low sensitivity for myocarditis[110]. The EKG findings vary from nonspecific ST segment and T wave changes, heart blocks, Q waves or left bundle branch block. Presence of Q waves during acute myocarditis has been associated with higher CK levels, significantly lower LV ejection fraction (EF), higher incidence of cardiogenic shock and conduction abnormalities[111]. Studies which have evaluated ECG recording at the time of myocardial biopsy have shown that the presence of QTc prolongation greater than 440 milliseconds, QRS duration greater than 120 milliseconds and abnormal QRS axis are associated with worse outcomes[112].

There are no pathognomonic features specific for myocarditis on echocardiogram. Studies have been done to evaluate echocardiographic

parameters in fulminant versus acute myocarditis. This has prognostic implication because patients with fulminant myocarditis show substantial improvement in LV function after six months compared with those of acute myocarditis[113]. In patients with fulminant myocarditis, LV is not dilated but the walls are thickened when compared to acute myocarditis, where there is marked LV dilation with normal wall thickness[113]. The severe inflammation in fulminant myocarditis is known to cause interstitial edema and myocardial wall thickening with decreased LV contractility. The utility of echocardiography in myocarditis is more relevant particularly in patients who initially present with cardiomyopathy, LV dysfunction and full blown heart failure[114].

Cardiac magnetic resonance imaging (cMRI) has evolved over the years as an important non-invasive diagnostic tool for myocarditis. cMRI is sensitive to changes in the tissue that occur during myocardial inflammation. cMRI is particularly useful in diagnosing myocarditis in hemodynamically stable patients, thereby avoiding invasive procedures like coronary angiography and endomyocardial biopsy (EMB)[115]. Role of cMRI is minimal in hemodynamically unstable patients due to irregular heart rate, tachycardia and mechanical ventilation interfering with adequate imaging. The pattern of late gadolinium enhancement (LGE) in myocarditis is usually epicardial or in the myocardial wall[116]. cMRI is also used to stratification of high-risk patients based on their scar pattern in the myocardial wall. In acute myocarditis, presence of myocardial edema but absence of LGE on cMRI has been associated with better clinical outcomes in terms of recovery[117]. Lake Louise criteria 2009 proposed cMRI findings consistent with myocarditis if at least 2 criteria are present – 1) T2W imaging with edema, hyperemia, necrosis, or scar; 2) Global early gadolinium enhancement ratio between myocardium and skeletal muscle on T1W; 3) Non-ischemic LGE pattern. In 2018, latest criteria requires 2 of 2 to be positive for a strong MRI diagnosis of acute myocardial inflammation: 1) Myocardial edema in T2 mapping or T2W images; 2) non-ischemic myocardial injury (abnormal troponin, LGE)[118]. Ferreira et al. reported that, native T1 mapping detects inflammation and myocarditis without the need for gadolinium enhancement agents[119]. MyoRacer trial compared T1, T2 mapping with gold standard EMB, concluding that in acute myocarditis (symptom duration <14 days), T1 mapping was superior in detecting myocardial inflammation (Area under curve (AUC) - 0.82) whereas in chronic myocarditis (symptom duration >14 days), T2 mapping showed acceptable results (AUC – 0.77)[120]. Positive T1 and T2 mapping together increases the specificity for diagnosing acute myocardial inflammation. These findings show that T1 and T2 based measurements complement each other and need to be included in the CMR protocols. Currently, cMRI is a class IC recommendation as per 2012 ESC (European Society of Cardiology) guidelines[5,121]. Few MRI images showing late gadolinium enhancement (LGE) indicating the myocardial inflammation in transmural, epicardial, mid-myocardial and sub-epicardial layers are included in this manuscript as well.

Although EMB is a gold standard for diagnosis, it is rarely performed for diagnosis and management of myocarditis due to its invasive nature and associated local complications. However, according to ESC (European Society of Cardiology) and ACC (American College of Cardiology), EMB is performed in sudden onset of severe heart failure within 2 weeks of viral infection as well as in fulminant myocarditis associated with ventricular fibrillation or high degree heart block unresponsive to standard heart failure treatment[122]. The use of EMB has been growing as a diagnostic tool for patients presenting with systolic or diastolic dysfunction to diagnose myocarditis. ESC working group on myocardial and pericardial diseases identifies acute myocarditis from EMB by evidence of myocyte necrosis and myocardial inflammation based on immuno-histochemical finding of ≥ 14 infiltrating immune cells/mm2 (CD3+T-lymphocytes and/or CD68+ macrophages). In case of chronic myocarditis, there is no finding of acute myocyte injury, but inflammation and interstitial fibrosis are evident [123]. In 1986, a formal criterion for diagnosis of myocarditis, called the Dallas criteria, was established[124]. However, questions associated with sampling error, variation in observer interpretation, and lack of correlation between Dallas criteria myocarditis and demonstration of viral genomes in heart tissue have rendered the criteria inadequate[125]. EMB can be used to identify individual types of myocarditis, such as lymphocytic or eosinophilic myocarditis, which can be of prognostic value. In addition, EMB can also improve our understanding of the cellular and molecular pathophysiology of cardiovascular disease. Inspite of having all these pitfalls, EMB should be recommended as a supplementary diagnostic tool for aiding in diagnosis of unexplained, idiopathic and rapid onset myocarditis for delivering personalized and focused therapy based on the clinical scenario.

Fulminant myocarditis: workup

The lab workup of the patient presenting with fulminant myocarditis (FM) should include echocardiography, cardiac CT, cardiac MRI, nuclear imaging, endomyocardial biopsy and coronary angiography[126, 127]. Some of the frequently encountered features with FM in echocardiography can range from bi-ventricular dysfunction, increased LV diameter, increased septal wall thickness, increased interstitial edema and pericardial effusion. Identification of diffuse late gadolinium enhancement (LGE) with cardiac MRI is diagnostic of fulminant myocarditis which should be managed with appropriate therapy. In cardiac sarcoidosis and inflammatory cardiomyopathies like fulminant myocarditis, focused or diffused uptake of 18FDG on PET scan is indication of active inflammation and should be followed by initiation of anti-inflammatory therapy[89, 128]. It is important to note that, FDG-PET scan is not only used for diagnosis but also for monitoring response to anti-inflammatory therapy in fulminant myocarditis as well as cardiac sarcoidosis[89, 128]. Although endomyocardial biopsy is rarely used in the diagnosis of fulminant myocarditis, it should be considered in the following clinical scenarios as per the AHA (American Heart Association) guidelines namely new onset clinical heart failure (2 weeks to 3 months) with ventricular arrhythmias, II/III degree AV block and refractory to standard heart failure therapy [129]. Endomyocardial biopsy and pathological examination revealed lymphocytic myocarditis (72%), giant-cell myocarditis (14%) and eosinophilic myocarditis (12%) in patients with fulminant myocarditis [126].

Current and future therapeutic interventions

Myocarditis that occurs secondary to infections, toxins and systemic diseases will usually subside with treatment of underlying condition. In the contrary, the treatment of non-infectious myocarditis is challenging and there are currently wide array of treatment options that can be explored. Previous studies have demonstrated that in patients with virus free NICM, immunosuppressive therapy (IST) will have at least 90%

efficacy in resolution of myocardial inflammation[130]. The benefits of IST in NICM can be explained by increased myocardial proliferation, upregulated synthesis of contractile proteins and inhibition of cardiomyocyte death[130]. Accordingly, usage of IST is justified in giant cell myocarditis, eosinophilic myocarditis, granulomatous myocarditis and inflammatory myocarditis associated with sarcoidosis[130]. The response to IST can depend on many factors but most importantly, upregulation of HLA has been demonstrated to be positive indicator for response to IST. The combination of prednisolone and azathioprine has been associated with favorable improvement in LVEF and reduction in LV chamber dilation in 88% of NICM as compared to patients receiving placebo therapy[130]. In eosinophilic myocarditis, the usage of prednisolone and azathioprine combination resulted in improvement of mean survival of 8.4% on 90% of the patients[48,131]. In TIMIC study, the patients with auto-reactive myocarditis who were treated with prednisolone and azathioprine combination had decrease in New York Heart Association class status, LV end-diastolic diameter & LV end-diastolic volume along with drastic improvement in LVEF[48,132]. Prior studies had investigated the use of intravenous immunoglobulin therapy (IVIG) in NICM due to its anti-inflammatory effect, upregulation of anti-inflammatory cytokines, down-regulation of complement cascade, increased FC-gamma receptor saturation and inhibitory action on dendritic cells, leukocyte adhesion, apoptosis & metalloproteinases[48,133].

To avoid systemic side effects of IST, some researchers have tried loco-regional approach with intra-myocardial administration of high doses of triamcinolone with favorable clinical outcomes. Another approach used in NICM is immune adsorption which involves removal of anti-cardiac antibodies along with pro-inflammatory cytokines with better patient outcomes [48,134,135]. The proposed treatment for idiopathic giant cell myocarditis include, monoclonal anti-CD3 antibodies, methylprednisolone and cyclosporine[48]. In rat model of dilated cardiomyopathy, intra-myocardial injection of mesenchymal stromal cells from bone marrow or adipose tissue resulted in improvement of EF (Ejection Fraction), LV end-systolic diameter (LVESD), systolic volume & LV function along with reorganization of myocardial tissue due to increased angiogenesis and anti-fibrotic effects[136]. In NICM, trans-endocardial stem cell injection of allogenic human mesenchymal stem cells (hMSCs) resulted in increased EF, improved exercise performance and decreased MLHFQ (Minnesota living and heart failure questionnaire) score[137]. In fatal myocarditis with end-stage heart failure, treatment with IL-1 receptor blockade or IL-1 inhibition resulted in amelioration of cardiac function, weaning from extra-corporeal membrane oxygenation and removal of left ventricular assist device & respiratory support[138]. Newer therapies such as IL-1 beta inhibitors (Anakinra) have been found to be efficacious in fulminant myocarditis although their toxic profile is not entirely known[139]. In acute myocarditis and experimental autoimmune myocarditis, HMGB1 (high mobility group box protein 1) inhibitors have been proven to be a novel therapeutic strategy in improving LV pump function and long-term prognosis[140]. In NICM and autoimmune dilated cardiomyopathy, intra-myocardial injection of mesenchymal stromal cells (autologous or allogenic) were found to be associated with improvement in LV systolic function and myocardial regeneration[136,137].

Fulminant myocarditis: Current treatment guidelines

Cardiogenic shock in patients with fulminant myocarditis who present with can be managed with inotropic agents, vasopressors, mechanical ventilation, intra-aortic balloon counter pulsation and extracorporeal membrane oxygenation (ECMO)[127]. The diagnosis of cardiac sarcoidosis by MRI warrants treatment with corticosteroids along with azathioprine / methotrexate / cyclophosphamide[126,127]. Giant cell myocarditis is treated with corticosteroids, thymoglobulins and cyclosporine[126,127]. In lymphocytic myocarditis with the presence of LV dysfunction, administration of interferon-gamma for 24 weeks resulted in substantial clinical benefit and clearance of viral genomes from the tissues[141]. Indications of implantable cardioverter defibrillator (ICD) is indicated in fulminant myocarditis with sustained ventricular arrhythmias, LVEF < 35%, LGE on cardiac MRI, inducible ventricular arrhythmias, syncope/near syncope and IIIrd degree AV block as these patients are more prone to sudden cardiac death (SCD)[89,142]. According to the European heart association guidelines, CRT-D (Cardiac resynchronization therapy) is indicated whenever there is LBBB (Left Bundle Branch Block) in NYHA (New York Heart Association) functional heart failure II-IV and LVEF < 35%[143]. Catheter ablation is contemplated in patients with fulminant myocarditis who are refractory to immunosuppressive / anti-arrhythmic therapy, who have atrial arrhythmias, electrical storm and sustained ventricular tachycardia[89,144]. Although transcatheter endocardial radiofrequency ablation approach is used for controlling ventricular arrhythmias refractory to anti-arrhythmic medications, combining it with an epicardial approach has been suggested for complete elimination of arrhythmogenic foci in myocarditis induced rhythm disturbances[145-147]. Treatment options for patients with fulminant myocarditis who are refractory to anti-arrhythmic therapy and catheter ablation include cardiac sympathectomy, LV assist device and finally cardiac transplantation[89,148].

Burned out or recovered myocarditis - role of EP study / ablation / ICD

Burned out hypertrophic myocarditis (BO-HCM) occurs during the late phases of hypertrophic cardiomyopathy when myocardial tissue is replaced by overgrowth of fibrotic tissue[149]. The underlying mechanism of this phenomenon can be explained by ischemia of small intramural coronary arteries, excessive alcohol intake and genetic factors[149]. Morphologically, there is LV dilation, ventricular wall thinning and systolic dysfunction developing the late phases of hypertrophic cardiomyopathy[149]. It is a diagnosis of exclusion and more likely to be diagnosed at the time of heart transplantation or at autopsy[149]. The clinical progression of this clinical entity is usually slow, unpredictable with potential to develop atrial fibrillation (AF) [150]. It is always prudent to administer a cardioverter-defibrillator for monitoring of any arrhythmias. The mortality of burnt out myocarditis is around 11%[150]. AF associated with BO-HCM is usually associated with cardiac decompensation, LV dysfunction, thromboembolic events and higher chances of hospitalization[151]. In apical hypertrophic cardiomyopathy progressing into burnout stage, indications for radiofrequency ablation are VT storm and ventricular fibrillation that are unresponsive to medications and defibrillator implantation[152]. Currently, the efficacy of atrioventricular (AV) node ablation and biventricular pacing in the management of refractory AF associated with BO-HCM is not clearly established[153].

In the patients with previous myocarditis, presence of active

inflammation by CMR / FDG-PET scan warrants immunosuppressive therapy which is clinically efficacious in reducing the risk of ventricular arrhythmias including ventricular fibrillation, ventricular tachycardia and premature ventricular contractions (PVCs) [154]. Some of important sites of origin in VT in non-ischemic inflammatory cardiomyopathy (NICM) include RV (endocardium & epicardium) and LV endocardium (basal septum, anterior wall and peri-valvular regions)[155]. In some cases of previous or recovered myocarditis, VT ablation is only indicated in patients experiencing recurrent VT despite immunosuppressive therapy after confirming the chronic active inflammation with FDG-PET scan with or without CMR and EMB [156]. Although VT ablation therapy reduced inducible VT, VT storm and ICD burden in patients with arrhythmogenic inflammatory cardiomyopathy (AIC), it was not completely successful in completely terminating VT recurrences arising due to intramural circuits from scar as well as ongoing inflammation[155]. The indicators for successful ablation of ventricular arrhythmias arising from papillary muscles in healed myocarditis include presence of action potentials in purkinje potentials and smaller size of papillary muscles[157]. In case of PVCs due to recovered myocarditis, ablation is only indicated in those arising from right ventricular outflow tract (RVOT) rather than those arising from pericardium and left ventricle because it is associated with higher complications, lower success rate[158]. Administration of catheter ablation should be considered in patients with PVC burden > 24-30% even if the patient is asymptomatic and LVEF is preserved to prevent the onset of tachycardia induced cardiomyopathy[159]. Alternatively, if the LVEF dysfunction is secondary to PVCs then catheter ablation should be first line therapeutic option for reducing the symptom burden, improving the exercise capacity and optimizing the lifestyle in patients with healed myocarditis[159]. In a single center prospective study, the success of catheter ablation performed for PVCs associated with previous myocarditis is modest (45%) as these patients had recurrent PVCs arising from other locations at three months follow up[160]. In a meta-analysis of prospective and retrospective cohort studies, it was found that catheter ablation is an effective strategy for reducing VT recurrence in post-myocarditis patients with less relapse rate and low complications[161]. This meta-analysis also concludes that, catheter ablation is a very useful adjuvant to medical therapy in managing VT recurrences in post-myocarditis patients. Future large randomized clinical control trials with long term follow up with standard immunosuppressive therapy, catheter ablation and combination are warranted to effectively determine the efficacy of catheter ablation in post-myocarditis patients[161].

A Special note on COVID-19 myocarditis and mRNA COVID-19 vaccine induced myocarditis

COVID-19 induced myocarditis

Coronavirus disease 2019 (COVID-19) is a pandemic caused by coronaviruses which are a family of single stranded, positive sense, enveloped RNA viruses. ACE2 (angiotensin converting enzyme 2) pathway is used by virus to attack lungs[23]. Since ACE2 is expressed in heart, kidneys, brain and the gut, the virus is known to affect these tissues also. Virus binds to ACE2 by a protein on the surface called SPIKE (S protein)[24]. There are several mechanisms by which COVID-19 virus is thought to cause myocarditis. Initially it was thought to cause direct destruction of cardiomyocytes. A study done in Germany on 39 consecutive autopsy cases has shown that virus was present in interstitial cells rather than myocytes[25]. Another mechanism postulated was that virus can enter into the endothelial cells via the ACE2 pathway and cause damage. The most widely accepted mechanism is hyperactivation of the immune system causing a cytokine storm[27]. These circulating cytokines cause collateral damage via direct myocardial injury, microvascular and macro-vascular thrombus formation[28]. Thrombus induced ischemia, inflammatory cell infiltration, cytokines and hypoxemia are other underlying mechanisms postulated to be main reasons for COVID-19 induced myocarditis [29].

In a multicenter multinational retrospective study, which was performed to characterize the COVID-19 myocarditis in 54 PCR positive patients, it was revealed to be more prevalent in females and non-hispanic whites with a median age of presentation around 38 years[162]. COVID-19 myocarditis presented most commonly with dyspnea, chest pain, fever, cough, and GI symptoms. The prevalence of COVID-19 induced acute myocarditis in young athletes and older adults by cardiac MRI was 3% and 26-60% respectively [162-165]. Although COVID-19 induced myocardial injury occurs in mild form in young adults and resolves within few weeks without any sequelae in most cases, sometimes its progression to full blown myocardial syndrome with cardiac decompensation in rare cases requires extensive workup for confirming diagnosis and designing personalized cardioprotective therapy[166]. COVID inflamed myocardial tissue can form a viable breeding ground for generation of atrial arrhythmias particularly in severely ill patients and these patients should be frequently monitored and considered for anticoagulant therapy to prevent thromboembolic episodes[166, 167]. Earlier detection and management of fulminant myocarditis secondary to COVID-19 infection is warranted because there is risk of fatal ventricular arrhythmias and sudden cardiac death in these patients[166]. Cardiac MRI in these patients can demonstrate myocardial edema, non-ischemic myocardial injury, LGE in inferolateral LV chamber, LVEF (44-62%) and pericardial effusion. Relevant findings in endomyocardial biopsy in these patients include presence of CD3+ T-lymphocytes and CD68+ macrophages. COVID-19 is implicated in lymphocytic myocarditis with predominant lymphocytic infiltrates in 30-40% cases [126]. Diffuse inflammatory infiltrates are more likely associated with non-COVID-19 myocarditis as compared to COVID-19 myocarditis[87,168]. Out of the patients who succumbed to COVID-19, histopathology examination in the autopsy series revealed small inflammatory foci scattered in the myocardium in most the cases whereas multifocal inflammatory infiltrates with cardiomyocyte injury were recognized only in 1.4% cases[169]. The underlying pathophysiological mechanisms that are proposed for COVID-19 induced myocarditis include direct myocardial injury by direct infection of cardiomyocytes, pericytes and fibroblasts through angiotensin pathway [162]. Alternatively, COVID-19 induced auto-antibodies against viral proteins during the infection can indirectly cross-react with myocardial tissue due to molecular mimicry and thereby initiating myocardial inflammation[126,162]. Interestingly, isolation of COVID-19 virus from myocardium from patients presenting with signs and symptoms of myocarditis was demonstrated only in 26.7% of cases [170,171]. Fulminant myocarditis is more common in COVID-19 induced myocarditis (38.9%) as compared to non-COVID-19 induced myocarditis (8.3%)[162]. Accordingly, patients with COVID-19 induced myocarditis had more severe reduction of LV systolic function (LVEF 40% vs 55%) requiring temporary circulatory support and experienced increased mortality (20.4% vs 5.4%) as compared to patients with

non-COVID-19 myocarditis[162]. Immune mediated cardiac injury as well as hyperinflammation might contribute to cardiogenic shock and hemodynamic instability in COVID-19 induced myocarditis [172-175]. In this clinical scenario, it is always prudent to supplement advanced mechanical circulatory support along with medical management using remdesivir, dexamethasone and convalescent plasma[166, 176]. Estimated overall mortality in COVID-19 induced myocarditis at 120 days is around 6.6% and 15.5% with and without presence of pneumonia [162]. The in-hospital mortality of COVID-19 induced acute myocarditis is higher (15.5%) as compared to that of non-COVID-19 induced myocarditis (1.2%) in multi-center Lombardy registry [162, 177]. The higher incidence of mortality can be attributed to presence of risk factors such as acute respiratory distress syndrome, septic shock, hypoxia and higher lactate levels [162]. Periodic clinical follow up of COVID-19 infected patients for 2 months after sero-positivity with cardiac MRI revealed that the percentage of patients with chronic myocardial involvement and those presenting with overt myocarditis is 78% and 60% respectively[178]. In these patients, the COVID-19 induced immunological changes in myocardial tissue can result in fibrotic changes as well as microangiopathy leading to cardiomyopathy and chronic heart failure thereby warranting periodic follow up for initiation of cardioprotective therapy at the earliest time point for better clinical outcomes [166]. Moreover, these patients should also be scheduled for periodic follow up to monitor development of cardiac arrhythmias with the possible implantation of cardioverter-defibrillators and ablation in case by case basis depending on the clinical scenario for optimal clinical outcomes[169].

Vaccine induced myocarditis

COVID-vaccine induced myocarditis is demonstrated to be very milder as compared to COVID-19 induced myocarditis. According to CDC vaccine adverse reporting system, there were only 399 reported cases of myocarditis from 128 million vaccinated individuals with either BNT162b2 or mRNA-1273[179]. In another study, incidence of acute myocarditis was 28 cases from administration of 28 million COVID-19 vaccine doses (1 case per 100,000 mRNA COVID-19 vaccine doses)[180]. Another observational follow up study described 8 patients with acute myocarditis following BNT162b2 mRNA (Pfizer-BioNTech) and mRNA-1273 (Moderna) coronavirus disease 2019 (COVID-19) vaccines[181]. As per the current literature, the important risk factor for suspecting myocarditis is young adults presenting with chest pain within a week of COVID-19 vaccination[166]. Specifically, most of these patients presented with chest pain 48-96 hr following vaccine administration[181]. Pertinent abnormalities with echocardiography include reduced LVEF (51.5%), regional wall motion abnormalities and hypokinesis. Cardiac MRI revealed patchy delayed gadolinium enhancement (DGE) with myocardial edema[181]. Majority of these patient experienced full uneventful recovery and were discharged from the hospital in stable condition with no further deterioration upon follow up[181]. In a matched case control study, the incidence of myocarditis following BNT162b2 mRNA vaccine is particularly more in males in age groups > 30 years[182]. It is important to note that, the incidence of COVID-19 mRNA vaccine induced myocarditis is 1000 times less as compared to the incidence of COVID-19 induced myocarditis[183]. The average incidence of myocarditis following COVID-19 vaccination is around 2.13 cases per 100,000 persons and it is more prevalent in age group 16-29 years according to a retrospective cohort study performed in a large Israel health care system[184]. The average incidence of myocarditis after administration of 2.8 million COVID-19 vaccine doses in US military is around 1-10 cases per 100,000 persons-years[185]. In the previous Israeli health care study, the risk ratio of developing myocarditis following COVID-19 vaccine is approximately 3.24 as compared to 18.24 with COVID-19 infection [184, 186]. The underlying mechanisms by which mRNA COVID-19 vaccines induce myocarditis include immune reactivity, cross reactivity of COVID-19 spike glycoprotein antibodies with myocardium and hormonal differences[187]. COVID-19 spike glycoprotein antibodies specifically cross react with myocardial myosin alpha-heavy chain particularly in patients in certain genetic background that predisposes them to abnormal innate and acquired immune responses in heart tissues[187]. Accordingly, this results in the activation of inflammatory pathways in the myocardial tissues leading to development of myocarditis following COVID-19 vaccination[187]. This happens more likely in males as compared to females as testosterone hormones have a tendency to potentiate T1 helper induced cell response via attenuating anti-inflammatory cell recruitment [187]. The onset of myocarditis happens within 7 days after COVID-19 vaccination and after brief hospitalization (3-5 days) most of these patients had uneventful recovery to baseline cardiac function within 1-5 weeks [187]. In a systemic review and meta-analysis study, the median hospital stay of COVID-19 vaccine induced myocarditis is around 3.91 days and 99.7% of the patients recovered without any sequelae[188]. In this regard, the survival rate of COVID-19 mRNA vaccine induced myocarditis is around >99% as compared to 30-80% with COVID-19 induced myocarditis. Clinical follow up study of children with COVID-19 induced myocarditis revealed that, immunization substantially reduced hospitalizations, ICU admissions and deaths from COVID-19 infection in these children with a remote possibility of myocarditis which runs a short term benign clinical course with no long term sequelae[189]. Based on these findings, it is plausible to conclude that the risk-benefit ratio of COVID-19 vaccines in regard to myocarditis is very encouraging and it would be prudent to recommend the administration of COVID-19 vaccines in all age groups. Unnecessary media coverage and scrutiny is seeding needless public apprehensiveness regarding myocarditis post mRNA COVID-19 vaccination and discouraging them from getting vaccinated. The results of evidence based clinical research studies demonstrating the safety and efficacy of these vaccines should be widely circulated among the general population so that they get vaccinated to prevent the spread of COVID-19 and associated morbidity and mortality. According to CDC guidelines, if the patients develops myocarditis after 1st dose of COVID-19 then it is imperative to wait until the patient had fully recovered to baseline cardiac function and subsequently proceed to 2nd dose after having discussion with their health care provider[190].

Summary and Future directions

Prompt diagnosis of myocarditis is the most critical step for timely administration of immunosuppressive therapy. Current diagnostic modalities employed for myocarditis include FDG-PET scan and cardiac MRI. These imaging modalities are very expensive, and they present a challenge particularly in patients who do not have a better insurance coverage. Moreover, there are no optimized non-invasive screening serum biomarkers currently for patients with myocarditis which can provide appropriate risk stratification guidelines for timely management. Despite novel imaging methods and immunosuppressive

therapy, myocarditis is still associated with complications such as arrhythmias, congestive heart failure, cardiomyopathy, and LV dysfunction. Currently, there is still a wide knowledge gap in understanding the downstream signaling events that are responsible for progression of myocarditis into dilated cardiomyopathy. Specifically, the role of viruses, immune response, genetic makeup in the disease progression and prognosis is not very well understood so far. Understanding pathophysiology of individual phases of myocarditis is very important so that identification and validation of novel diagnostic and therapeutic modalities can be done in a systematic manner. These gaps in knowledge can be addressed by employing better animal models and cell culture systems that can assess initial myocardial insult, model immune responses, and better understand the immune cell interactions with cardiomyocytes. More importantly, there should be standardization of non-invasive and invasive diagnostic methods so that a better risk stratification of patients can be made in a case-by-case basis. There is also an urgent need to design novel therapeutic interventions which are more effective and at the same be less toxic for patients with contraindications to immunosuppressive medications. This review gives insight into the underlying step by step downstream signaling events that are responsible for myocarditis along with etiology, diagnostic modalities, and current treatment guidelines. We hope to address at least some of the knowledge gap in the understanding of pathophysiology of myocarditis and thus paving way for new research on this disease process. Accordingly, single, and multi-center randomized clinical control trials are the need of the hour and most pressing need in this regard so that novel non-invasive and effective diagnostic and therapeutic modalities for myocarditis can be developed and evaluated for better clinical outcomes to reduce morbidity and mortality for this clinical entity.

Conflicts of Interest

None of the authors have any conflict of interest.

References

1. Golpour, A., et al., Epidemiological Impact of Myocarditis. J Clin Med, 2021. 10(4).
2. Wakafuji, S. and R. Okada, Twenty year autopsy statistics of myocarditis incidence in Japan. Jpn Circ J, 1986. 50(12): p. 1288-93.
3. Passarino, G., et al., Prevalence of myocarditis at autopsy in Turin, Italy. Arch Pathol Lab Med, 1997. 121(6): p. 619-22.
4. Patriki, D., et al., Clinical Presentation and Laboratory Findings in Men Versus Women with Myocarditis. J Womens Health (Larchmt), 2020. 29(2): p. 193-199.
5. Caforio, A.L., et al., Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J, 2013. 34(33): p. 2636-48, 2648a-2648d.
6. Caforio, A.L., et al., A prospective study of biopsy-proven myocarditis: prognostic relevance of clinical and aetiopathogenetic features at diagnosis. Eur Heart J, 2007. 28(11): p. 1326-33.
7. Magnani, J.W., et al., Survival in biopsy-proven myocarditis: a long-term retrospective analysis of the histopathologic, clinical, and hemodynamic predictors. Am Heart J, 2006. 151(2): p. 463-70.
8. Fung, G., et al., Myocarditis. Circulation Research, 2016. 118(3): p. 496-514.
9. Krejci, J., et al., Inflammatory Cardiomyopathy: A Current View on the Pathophysiology, Diagnosis, and Treatment. Biomed Res Int, 2016. 2016: p. 4087632.
10. Tschöpe, C., et al., Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. Nature Reviews Cardiology, 2021. 18(3): p. 169-193.
11. Haas, G.J., Etiology, Evaluation, and Management of Acute Myocarditis. Cardiology in Review, 2001. 9(2): p. 88-95.
12. Pollack, A., et al., Viral myocarditis—diagnosis, treatment options, and current controversies. Nature Reviews Cardiology, 2015. 12(11): p. 670-680.
13. Kindermann, I., et al., Update on myocarditis. J Am Coll Cardiol, 2012. 59(9): p. 779-92.
14. Noutsias, M., et al., Human coxsackie-adenovirus receptor is colocalized with integrins alpha(v)beta(3) and alpha(v)beta(5) on the cardiomyocyte sarcolemma and upregulated in dilated cardiomyopathy: implications for cardiotropic viral infections. Circulation, 2001. 104(3): p. 275-80.
15. Kindermann, I., et al., Predictors of outcome in patients with suspected myocarditis. Circulation, 2008. 118(6): p. 639-48.
16. Klingel, K., et al., Molecular pathology of inflammatory cardiomyopathy. Medical Microbiology and Immunology, 2004. 193(2): p. 101-107.
17. Bültmann, B.D., et al., Fatal parvovirus B19–associated myocarditis clinically mimicking ischemic heart disease: An endothelial cell–mediated disease. Human Pathology, 2003. 34(1): p. 92-95.
18. Macsween, K.F. and D.H. Crawford, Epstein-Barr virus-recent advances. Lancet Infect Dis, 2003. 3(3): p. 131-40.
19. Richter, J., et al., An unusual presentation of a common infection. Infection, 2013. 41(2): p. 565-9.
20. Kytö, V., et al., Cytomegalovirus Infection of the Heart Is Common in Patients with Fatal Myocarditis. Clinical Infectious Diseases, 2005. 40(5): p. 683-688.
21. Barbaro, G., et al., Cardiac involvement in the acquired immunodeficiency syndrome: a multicenter clinical-pathological study. Gruppo Italiano per lo Studio Cardiologico dei pazienti affetti da AIDS Investigators. AIDS Res Hum Retroviruses, 1998. 14(12): p. 1071-7.
22. Barbarini, G. and G. Barbaro, Incidence of the involvement of the cardiovascular system in HIV infection. AIDS, 2003. 17.
23. Hoffmann, M., et al., SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell, 2020. 181(2): p. 271-280.e8.
24. Glowacka, I., et al., Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. Journal of virology, 2011. 85(9): p. 4122-4134.
25. Lindner, D., et al., Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases. JAMA Cardiology, 2020. 5(11): p. 1281-1285.
26. Kawakami, R., et al., Pathological Evidence for SARS-CoV-2 as a Cause of Myocarditis: JACC Review Topic of the Week. Journal of the American College of Cardiology, 2021. 77(3): p. 314-325.
27. Tang, Y., et al., Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies. Frontiers in Immunology, 2020. 11(1708).
28. Bikdeli, B., et al., COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up. Journal of the American College of Cardiology, 2020. 75(23): p. 2950-2973.
29. Ali, M., et al., COVID-19 and myocarditis: a review of literature. The Egyptian Heart Journal, 2022. 74(1): p. 23.
30. Flaxman, N., MYOCARDIAL ABSCESS. Journal of the American Medical Association, 1943. 122(12): p. 804-806.
31. McGee, M., et al., Staphylococcus aureus Myocarditis with Associated Left Ventricular Apical Thrombus. Case reports in cardiology, 2018. 2018: p. 7017286-7017286.
32. Krause, P.J. and L.K. Bockenstedt, Lyme Disease and the Heart. Circulation, 2013. 127(7): p. e451-e454.
33. Klein, J., et al., Lyme borreliosis as a cause of myocarditis and heart muscle disease. European Heart Journal, 1991. 12(suppl_D): p. 73-75.
34. Varghese, M.J., et al., Complete heart block due to diphtheritic myocarditis in the present era. Annals of pediatric cardiology, 2013. 6(1): p. 34-38.

35. Dung, N.M., et al., Treatment of Severe Diphtheritic Myocarditis by Temporary Insertion of a Cardiac Pacemaker. Clinical Infectious Diseases, 2002. 35(11): p. 1425-1429.
36. Nosanchuk, J.D., Fungal myocarditis. Front Biosci, 2002. 7: p. d1423-38.
37. Brown, G.D., D.W. Denning, and S.M. Levitz, Tackling human fungal infections. Science, 2012. 336(6082): p. 647.
38. A, A., Fungal cardiomyopathy: A review and pooled analysis of pathophysiology, diagnosis and clinical management. . Res Rev Insights, 2019. 3.
39. A, A., Parasitic (Protozoan) cardiomyopathy: A review and pooled analysis of pathophysiology, diagnosis and clinical management. Res Rev Insights, 2019. 3.
40. Ansari, A., B.J. Maron, and D.G. Berntson, Drug-induced toxic myocarditis. Texas Heart Institute journal, 2003. 30(1): p. 76-79.
41. A, A., Toxin-induced cardiomyopathy: A review and pooled analysis of pathophysiology, diagnosis and clinical management. Res Rev Insights, 2019.
42. Aretz, H.T., et al., Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol, 1987. 1(1): p. 3-14.
43. Liu Peter, P. and W. Mason Jay, Advances in the Understanding of Myocarditis. Circulation, 2001. 104(9): p. 1076-1082.
44. Mason, J.W., Myocarditis and dilated cardiomyopathy: an inflammatory link. Cardiovasc Res, 2003. 60(1): p. 5-10.
45. Alexopoulou, L., et al., Recognition of double-stranded RNA and activation of NF-κB by Toll-like receptor 3. Nature, 2001. 413(6857): p. 732-738.
46. Tschöpe, C., et al., NOD2 (Nucleotide-Binding Oligomerization Domain 2) Is a Major Pathogenic Mediator of Coxsackievirus B3-Induced Myocarditis. Circ Heart Fail, 2017. 10(9).
47. Müller, I., et al., Serum alarmin S100A8/S100A9 levels and its potential role as biomarker in myocarditis. ESC heart failure, 2020. 7(4): p. 1442-1451.
48. Maisch, B., Cardio-Immunology of Myocarditis: Focus on Immune Mechanisms and Treatment Options. Frontiers in cardiovascular medicine, 2019. 6: p. 48-48.
49. Heymans, S., et al., The Quest for New Approaches in Myocarditis and Inflammatory Cardiomyopathy. J Am Coll Cardiol, 2016. 68(21): p. 2348-2364.
50. Leuschner, F., et al., Rapid monocyte kinetics in acute myocardial infarction are sustained by extramedullary monocytopoiesis. J Exp Med, 2012. 209(1): p. 123-37.
51. Bruestle, K., et al., Autoimmunity in Acute Myocarditis: How Immunopathogenesis Steers New Directions for Diagnosis and Treatment. Current Cardiology Reports, 2020. 22(5): p. 28.
52. Hou, X., et al., The Cardiac Microenvironment Instructs Divergent Monocyte Fates and Functions in Myocarditis. Cell Rep, 2019. 28(1): p. 172-189.e7.
53. Higuchi, H., et al., Mast Cells Play a Critical Role in the Pathogenesis of Viral Myocarditis. Circulation, 2008. 118(4): p. 363-372.
54. Ong, S., N.R. Rose, and D. Čiháková, Natural killer cells in inflammatory heart disease. Clinical immunology (Orlando, Fla.), 2017. 175: p. 26-33.
55. Xu, D., et al., Gr-1+ Cells Other Than Ly6G+ Neutrophils Limit Virus Replication and Promote Myocardial Inflammation and Fibrosis Following Coxsackievirus B3 Infection of Mice. Frontiers in cellular and infection microbiology, 2018. 8: p. 157-157.
56. Weckbach, L.T., et al., Midkine drives cardiac inflammation by promoting neutrophil trafficking and NETosis in myocarditis. J Exp Med, 2019. 216(2): p. 350-368.
57. Rivadeneyra, L., et al., Role of neutrophils in CVB3 infection and viral myocarditis. J Mol Cell Cardiol, 2018. 125: p. 149-161.
58. Drobni Zsofia, D., et al., Decreased Absolute Lymphocyte Count and Increased Neutrophil/Lymphocyte Ratio With Immune Checkpoint Inhibitor–Associated Myocarditis. Journal of the American Heart Association, 2020. 9(23): p. e018306.
59. Vinco, G., et al., P868Neutrophil-to-lymphocyte ratio at the onset of acute myocarditis reflects the extent of myocardial necrosis. European Heart Journal, 2018. 39(suppl_1).
60. Grabie, N., et al., Neutrophils sustain pathogenic CD8+ T cell responses in the heart. Am J Pathol, 2003. 163(6): p. 2413-20.
61. Fairweather, D., et al., IL-12 protects against coxsackievirus B3-induced myocarditis by increasing IFN-gamma and macrophage and neutrophil populations in the heart. J Immunol, 2005. 174(1): p. 261-9.
62. Vdovenko, D. and U. Eriksson, Regulatory Role of CD4⁺ T Cells in Myocarditis. Journal of Immunology Research, 2018. 2018: p. 4396351.
63. Huang, C., et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet, 2020. 395.
64. Moore, J.B. and C.H. June, Cytokine release syndrome in severe COVID-19. Science, 2020. 368(6490): p. 473.
65. Myers, J.M., et al., Cardiac myosin-Th17 responses promote heart failure in human myocarditis. JCI insight, 2016. 1 9.
66. Yu, M., et al., Cardiac Fibroblasts Recruit Th17 Cells Infiltration Into Myocardium by Secreting CCL20 in CVB3-Induced acute Viral Myocarditis. Cellular Physiology and Biochemistry, 2013. 32(5): p. 1437-1450.
67. Wei, H., et al., CD11b is involved in coxsackievirus B3-induced viral myocarditis in mice by inducing Th17 cells. Open Life Sciences, 2020. 15(1): p. 1024-1032.
68. Rose, N.R., Critical cytokine pathways to cardiac inflammation. Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research, 2011. 31(10): p. 705-710.
69. Matsumori, A., Cytokines in myocarditis and cardiomyopathies. Curr Opin Cardiol, 1996. 11(3): p. 302-9.
70. De Luca, G., et al., Myocarditis: An Interleukin-1-Mediated Disease? Frontiers in immunology, 2018. 9: p. 1335-1335.
71. Tajiri, K., et al., Suppressor of cytokine signaling 1 DNA administration inhibits inflammatory and pathogenic responses in autoimmune myocarditis. J Immunol, 2012. 189(4): p. 2043-53.
72. Elamm, C., D. Fairweather, and L.T. Cooper, Republished: pathogenesis and diagnosis of myocarditis. Postgraduate medical journal, 2012. 88(1043): p. 539-544.
73. Sanchez, M.J. and N.V. Bergasa, Hepatitis C associated cardiomyopathy: potential pathogenic mechanisms and clinical implications. Med Sci Monit, 2008. 14(5): p. Ra55-63.
74. Wang, Q. and X.H.T. Wehrens, Connecting enterovirus infection to dystrophin dysfunction in dilated cardiomyopathy. Annals of translational medicine, 2016. 4(Suppl 1): p. S23-S23.
75. Badorff, C., et al., Enteroviral protease 2A cleaves dystrophin: Evidence of cytoskeletal disruption in an acquired cardiomyopathy. Nature Medicine, 1999. 5(3): p. 320-326.
76. Bültmann, B.D., et al., Fatal parvovirus B19-associated myocarditis clinically mimicking ischemic heart disease: an endothelial cell-mediated disease. Hum Pathol, 2003. 34(1): p. 92-5.
77. Ono, K., et al., Cytokine Gene Expression After Myocardial Infarction in Rat Hearts. Circulation, 1998. 98(2): p. 149-156.
78. Liu, P. and M.J. Sole, What is the relevance of apoptosis to the myocardium? Can J Cardiol, 1999. 15 Suppl B: p. 8b-10b.
79. van den Hoogen, P., et al., Heart Failure in Chronic Myocarditis: A Role for microRNAs? Current genomics, 2015. 16(2): p. 88-94.
80. Kang M, A.J., Viral Myocarditis. StatPearls Publishing, 2020
81. Tschöpe, C., et al., Management of Myocarditis-Related Cardiomyopathy in Adults. Circulation Research, 2019. 124(11): p. 1568-1583.
82. Mattsson, G. and P. Magnusson, Electrical storm in the inflamed heart: ventricular tachycardia due to myocarditis. Clinical case reports, 2017. 5(8): p. 1327-1332.
83. Leone, O., et al., The spectrum of myocarditis: from pathology to the clinics. Virchows Arch, 2019. 475(3): p. 279-301.
84. Harada, M., et al., Histopathological characteristics of myocarditis in acute-phase Kawasaki disease. Histopathology, 2012. 61(6): p. 1156-1167.
85. Arava, S., et al., Myocarditis: Pathologist's perspective. Journal of the Practice of Cardiovascular Sciences, 2015. 1(2): p. 161-167.
86. Bearse, M., et al., Factors associated with myocardial SARS-CoV-2 infection,

myocarditis, and cardiac inflammation in patients with COVID-19. Modern Pathology, 2021.
87. Halushka, M.K. and R.S. Vander Heide, Myocarditis is rare in COVID-19 autopsies: cardiovascular findings across 277 postmortem examinations. Cardiovascular Pathology, 2021. 50: p. 107300.
88. Roberts, W.C., Pericardial heart disease: its morphologic features and its causes. Proceedings (Baylor University. Medical Center), 2005. 18(1): p. 38-55.
89. Karki, R., C. Janga, and A.J. Deshmukh, Arrhythmias Associated with Inflammatory Cardiomyopathies. Curr Treat Options Cardiovasc Med, 2020. 22(12): p. 76.
90. Zhou, X. and S.C. Dudley, Evidence for Inflammation as a Driver of Atrial Fibrillation. Frontiers in Cardiovascular Medicine, 2020. 7.
91. Ryu, K., et al., Effects of sterile pericarditis on connexins 40 and 43 in the atria: correlation with abnormal conduction and atrial arrhythmias. American Journal of Physiology-Heart and Circulatory Physiology, 2007. 293(2): p. H1231-H1241.
92. Liew, R., et al., Role of tumor necrosis factor-κ in the pathogenesis of atrial fibrosis and development of an arrhythmogenic substrate. Circulation Journal, 2013: p. CJ-12-1155.
93. Bandyopadhyay, D., et al., Trends of cardiac complications in patients with rheumatoid arthritis: analysis of the United States national inpatient sample; 2005-2014. Current problems in cardiology, 2021. 46(3): p. 100455.
94. Ahlehoff, O., et al., Psoriasis and risk of atrial fibrillation and ischaemic stroke: a Danish Nationwide Cohort Study. European heart journal, 2012. 33(16): p. 2054-2064.
95. Dogan, Y., et al., Evaluation of QT and P wave dispersion and mean platelet volume among inflammatory bowel disease patients. International Journal of Medical Sciences, 2011. 8(7): p. 540.
96. Szabo, S.M., et al., Increased risk of cardiovascular and cerebrovascular diseases in individuals with ankylosing spondylitis: A population-based study. Arthritis & Rheumatism, 2011. 63(11): p. 3294-3304.
97. Kandolin, R., J. Lehtonen, and M. Kupari, Cardiac sarcoidosis and giant cell myocarditis as causes of atrioventricular block in young and middle-aged adults. Circulation: Arrhythmia and Electrophysiology, 2011. 4(3): p. 303-309.
98. Yeung, C. and A. Baranchuk, Diagnosis and treatment of Lyme carditis: JACC review topic of the week. Journal of the American College of Cardiology, 2019. 73(6): p. 717-726.
99. Fabre, A. and M.N. Sheppard, Sudden adult death syndrome and other non-ischaemic causes of sudden cardiac death. Heart, 2006. 92(3): p. 316-20.
100. Peretto, G., et al., Ventricular arrhythmias in myocarditis: characterization and relationships with myocardial inflammation. Journal of the American College of Cardiology, 2020. 75(9): p. 1046-1057.
101. Siripanthong, B., et al., Recognizing COVID-19-related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm, 2020. 17(9): p. 1463-1471.
102. Samarendra, P. and S. Kapoor, Diagnosing Lyme Carditis Presenting With Complete Heart Block. J Med Cases, 2020. 11(7): p. 224-227.
103. Van der Linde, M., Lyme carditis: clinical characteristics of 105 cases. Scand J Infect Dis Suppl, 1991. 77: p. 81-4.
104. Horowitz, H.W. and R.N. Belkin, Acute myopericarditis resulting from Lyme disease. American Heart Journal, 1995. 130(1): p. 176-178.
105. Fine, N.M., Giant Cell Myocarditis: Still the Deadly Giant. JACC Case Rep, 2020. 2(10): p. 1489-1491.
106. Ekström, K., et al., Incidence, risk factors, and outcome of life-threatening ventricular arrhythmias in giant cell myocarditis. Circulation: Arrhythmia and Electrophysiology, 2016. 9(12): p. e004559.
107. Kandolin, R., et al., Diagnosis, Treatment, and Outcome of Giant-Cell Myocarditis in the Era of Combined Immunosuppression. Circulation: Heart Failure, 2013. 6(1): p. 15-22.
108. Caforio, A.L.P., et al., Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. European Heart Journal, 2013. 34(33): p. 2636-2648.
109. Bozkurt, B., et al., Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies: A Scientific Statement From the American Heart Association. Circulation, 2016. 134(23): p. e579-e646.
110. Morgera, T., et al., Electrocardiography of myocarditis revisited: Clinical and prognostic significance of electrocardiographic changes. American Heart Journal, 1992. 124(2): p. 455-467.
111. Nakashima, H., et al., Q Wave and Non-Q Wave Myocarditis with Special Reference to Clinical Significance. Japanese Heart Journal, 1998. 39(6): p. 763-774.
112. Ukena, C., et al., Prognostic electrocardiographic parameters in patients with suspected myocarditis. European Journal of Heart Failure, 2011. 13(4): p. 398-405.
113. Felker, G.M., et al., Echocardiographic findings in fulminant and acute myocarditis. J Am Coll Cardiol, 2000. 36(1): p. 227-32.
114. Felker, G.M., et al., Echocardiographic findings in fulminant and acute myocarditis. Journal of the American College of Cardiology, 2000. 36(1): p. 227-232.
115. Lin, L.Q., et al., Impact of Cardiovascular Magnetic Resonance Imaging on Identifying the Etiology of Cardiomyopathy in Patients Undergoing Cardiac Transplantation. Scientific Reports, 2018. 8(1): p. 16212.
116. Friedrich Matthias, G., et al., Cardiovascular Magnetic Resonance in Myocarditis: A JACC White Paper. Journal of the American College of Cardiology, 2009. 53(17): p. 1475-1487.
117. Vermes, E., et al., Predictive value of CMR criteria for LV functional improvement in patients with acute myocarditis. Eur Heart J Cardiovasc Imaging, 2014. 15(10): p. 1140-4.
118. Ferreira Vanessa, M., et al., Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation. Journal of the American College of Cardiology, 2018. 72(24): p. 3158-3176.
119. Ferreira, V.M., et al., Native T1-mapping detects the location, extent and patterns of acute myocarditis without the need for gadolinium contrast agents. Journal of Cardiovascular Magnetic Resonance, 2014. 16(1): p. 36.
120. Lurz, P., et al., Comprehensive Cardiac Magnetic Resonance Imaging in Patients With Suspected Myocarditis: The MyoRacer-Trial. Journal of the American College of Cardiology, 2016. 67(15): p. 1800-1811.
121. Kim, P.K., et al., Myocardial T1 and T2 Mapping: Techniques and Clinical Applications. Korean journal of radiology, 2017. 18(1): p. 113-131.
122. Cooper, L.T., et al., The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. J Am Coll Cardiol, 2007. 50(19): p. 1914-31.
123. Stiermaier, T., et al., Biventricular endomyocardial biopsy in patients with suspected myocarditis: Feasibility, complication rate and additional diagnostic value. Int J Cardiol, 2017. 230: p. 364-370.
124. Mason, J.W., et al., A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. N Engl J Med, 1995. 333(5): p. 269-75.
125. Baughman, K.L., Diagnosis of myocarditis: death of Dallas criteria. Circulation, 2006. 113(4): p. 593-5.
126. Kociol, R.D., et al., Recognition and Initial Management of Fulminant Myocarditis. Circulation, 2020. 141(6): p. e69-e92.
127. Veronese, G., et al., Fulminant myocarditis: Characteristics, treatment, and outcomes. Anatol J Cardiol, 2018. 19(4): p. 279-286.
128. Vita, T., et al., Complementary value of cardiac magnetic resonance imaging and positron emission tomography/computed tomography in the assessment of cardiac sarcoidosis. Circulation: Cardiovascular Imaging, 2018. 11(1): p. e007030.
129. Cooper, L., et al., Heart Failure Association of the European Society of Cardiology

The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. J Am Coll Cardiol, 2007. 50(19): p. 1914-1931.
130. Frustaci, A. and C. Chimenti, Immunosuppressive therapy in myocarditis. Circ J, 2015. 79(1): p. 4-7.
131. Maisch, B. and S. Pankuweit, Current treatment options in (peri)myocarditis and inflammatory cardiomyopathy. Herz, 2012. 37(6): p. 644-56.
132. Frustaci, A., M.A. Russo, and C. Chimenti, Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. Eur Heart J, 2009. 30(16): p. 1995-2002.
133. Maisch, B., et al., Treatment of inflammatory dilated cardiomyopathy and (peri) myocarditis with immunosuppression and i.v. immunoglobulins. Herz, 2004. 29(6): p. 624-36.
134. Müller, J., et al., Immunoglobulin adsorption in patients with idiopathic dilated cardiomyopathy. Circulation, 2000. 101(4): p. 385-91.
135. Wallukat, G., J. Müller, and R. Hetzer, Specific removal of beta1-adrenergic autoantibodies from patients with idiopathic dilated cardiomyopathy. N Engl J Med, 2002. 347(22): p. 1806.
136. Carmona, M.D., et al., Intramyocardial bone marrow mononuclear cells versus bone marrow-derived and adipose mesenchymal cells in a rat model of dilated cardiomyopathy. Cytotherapy, 2017. 19(8): p. 947-961.
137. Hare, J.M., et al., Randomized Comparison of Allogeneic Versus Autologous Mesenchymal Stem Cells for Nonischemic Dilated Cardiomyopathy: POSEIDON-DCM Trial. J Am Coll Cardiol, 2017. 69(5): p. 526-537.
138. Cavalli, G., et al., Interleukin-1 Receptor Blockade Rescues Myocarditis-Associated End-Stage Heart Failure. Frontiers in immunology, 2017. 8: p. 131-131.
139. Tschöpe, C., et al., Management of Myocarditis-Related Cardiomyopathy in Adults. Circulation Research, 2019. 124(11): p. 1568-1583.
140. Bangert, A., et al., Critical role of RAGE and HMGB1 in inflammatory heart disease. Proc Natl Acad Sci U S A, 2016. 113(2): p. E155-64.
141. Schultheiss, H.-P., et al., Betaferon in chronic viral cardiomyopathy (BICC) trial: Effects of interferon-κ treatment in patients with chronic viral cardiomyopathy. Clinical Research in Cardiology, 2016. 105(9): p. 763-773.
142. Birnie, D.H., et al., HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart rhythm, 2014. 11(7): p. 1304-1323.
143. Members, A.T.F., et al., 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). EP Europace, 2015. 17(11): p. 1601-1687.
144. Willner, J.M., et al., Catheter ablation of atrial arrhythmias in cardiac sarcoidosis. Journal of cardiovascular electrophysiology, 2014. 25(9): p. 958-963.
145. Peretto, G., et al., Arrhythmias in myocarditis: State of the art. Heart Rhythm, 2019. 16(5): p. 793-801.
146. Mazzone, P., D. Tsiachris, and P. Della Bella, Epicardial management of myocarditis-related ventricular tachycardia. European heart journal, 2013. 34(3): p. 244-244.
147. Members, A.T.F., et al., 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Ep Europace, 2015. 17(11): p. 1601-1687.
148. Koplan, B.A., et al., Refractory ventricular tachycardia secondary to cardiac sarcoid: electrophysiologic characteristics, mapping, and ablation. Heart Rhythm, 2006. 3(8): p. 924-929.
149. Rahmani, G., G. Kraushaar, and P. Dehghani, Diagnosing burned-out hypertrophic cardiomyopathy: Daughter's phenotype solidifies father's diagnosis. Journal of Cardiology Cases, 2015. 11(3): p. 78-80.
150. Harris, K.M., et al., Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. Circulation, 2006. 114(3): p. 216-225.
151. Buckley, B.J.R., et al., Atrial Fibrillation in Patients With Cardiomyopathy: Prevalence and Clinical Outcomes From Real‐World Data. Journal of the American Heart Association, 2021. 10(23): p. e021970.
152. Park, J.S. and Y. Choi, Stereotactic Cardiac Radiation to Control Ventricular Tachycardia and Fibrillation Storm in a Patient with Apical Hypertrophic Cardiomyopathy at Burnout Stage: Case Report. J Korean Med Sci, 2020. 35(27): p. e200.
153. Brinkley, D.M., S. Wells Quinn, and W. Stevenson Lynne, Avoiding Burnout From Hypertrophic Cardiomyopathyκ. Journal of the American College of Cardiology, 2020. 75(24): p. 3044-3047.
154. Shivkumar, K. and D.H. Do, Catheter Ablation of Ventricular Tachycardia. Journal of the American College of Cardiology, 2020. 76(14): p. 1657-1659.
155. Bauer, B.S., A.C. Li, and J.S. Bradfield, Arrhythmogenic Inflammatory Cardiomyopathy: A Review. Arrhythmia & Electrophysiology Review 2018;7(3):181–6., 2018.
156. Peretto, G., et al., Inflammation as a Predictor of Recurrent Ventricular Tachycardia After Ablation in Patients With Myocarditis. Journal of the American College of Cardiology, 2020. 76(14): p. 1644-1656.
157. Yokokawa, M., et al., Predictors of successful catheter ablation of ventricular arrhythmias arising from the papillary muscles. Heart Rhythm, 2010. 7(11): p. 1654-1659.
158. Wang, J.-s., et al., The safety of catheter ablation for premature ventricular contractions in patients without structural heart disease. BMC Cardiovascular Disorders, 2018. 18(1): p. 177.
159. Rillig, A., et al., Which Is The Appropriate Arrhythmia Burden To Offer RF Ablation For RVOT Tachycardias? J Atr Fibrillation, 2014. 7(4): p. 1157.
160. Lakkireddy, D., et al., Myocarditis Causing Premature Ventricular Contractions. Circulation: Arrhythmia and Electrophysiology, 2019. 12(12): p. e007520.
161. Androulakis, E., et al., Long-term Outcomes of Catheter Ablation for Ventricular Arrhythmias in Post-Myocarditis Patients: Insights from a Meta-Analysis of Current Data. SN Compr Clin Med, 2022. 4(1): p. 62.
162. Ammirati, E., et al., Prevalence, Characteristics, and Outcomes of COVID-19–Associated Acute Myocarditis. Circulation, 2022. 145(15): p. 1123-1139.
163. Kotecha, T., et al., Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. European heart journal, 2021. 42(19): p. 1866-1878.
164. Puntmann, V.O., et al., Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA cardiology, 2020. 5(11): p. 1265-1273.
165. Moulson, N., et al., SARS-CoV-2 cardiac involvement in young competitive athletes. Circulation, 2021. 144(4): p. 256-266.
166. Kornowski, R. and G. Witberg, Acute myocarditis caused by COVID-19 disease and following COVID-19 vaccination. Open Heart, 2022. 9(1): p. e001957.
167. Liu, P.P., et al., The science underlying COVID-19: implications for the cardiovascular system. Circulation, 2020. 142(1): p. 68-78.
168. Basso, C., et al., Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study. European heart journal, 2020. 41(39): p. 3827-3835.
169. Satterfield, B.A., D.L. Bhatt, and B.J. Gersh, Cardiac involvement in the long-term implications of COVID-19. Nature Reviews Cardiology, 2022. 19(5): p. 332-341.

170. Bearse, M., et al., Factors associated with myocardial SARS-CoV-2 infection, myocarditis, and cardiac inflammation in patients with COVID-19. Modern Pathology, 2021. 34(7): p. 1345-1357.
171. Lindner, D., et al., Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. JAMA cardiology, 2020. 5(11): p. 1281-1285.
172. Ammirati, E., et al., Management of acute myocarditis and chronic inflammatory cardiomyopathy: an expert consensus document. Circulation: Heart Failure, 2020. 13(11): p. e007405.
173. Tschöpe, C., et al., Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. Nature reviews cardiology, 2021. 18(3): p. 169-193.
174. Hékimian, G., et al., Coronavirus disease 2019 acute myocarditis and multisystem inflammatory syndrome in adult intensive and cardiac care units. Chest, 2021. 159(2): p. 657-662.
175. Chau, V.Q., et al., Cardiogenic shock and hyperinflammatory syndrome in young males with COVID-19. Circulation: Heart Failure, 2020. 13(10): p. e007485.
176. Agdamag, A.C.C., et al., Update on COVID-19 myocarditis. Medicina, 2020. 56(12): p. 678.
177. Ammirati, E., et al., Clinical presentation and outcome in a contemporary cohort of patients with acute myocarditis: multicenter Lombardy registry. Circulation, 2018. 138(11): p. 1088-1099.
178. Puntmann, V.O., et al., Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiology, 2020. 5(11): p. 1265-1273.
179. CDC Vaccine adverse event reporting system. Available from: www.wonder.cdc.gov/vaers.html.
180. Bozkurt, B., I. Kamat, and P.J. Hotez, Myocarditis with COVID-19 mRNA vaccines. Circulation, 2021. 144(6): p. 471-484.
181. Larson, K.F., et al., Myocarditis after BNT162b2 and mRNA-1273 vaccination. Circulation, 2021. 144(6): p. 506-508.
182. Le Vu, S., et al., Age and sex-specific risks of myocarditis and pericarditis following Covid-19 messenger RNA vaccines. Nature Communications, 2022. 13(1): p. 3633.
183. Maiese, A., et al., Myocardial pathology in COVID-19-associated cardiac injury: A systematic review. Diagnostics, 2021. 11(9): p. 1647.
184. Witberg, G., et al., Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. New England Journal of Medicine, 2021. 385(23): p. 2132-2139.
185. Montgomery, J., et al., Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military. JAMA Cardiology, 2021. 6(10): p. 1202-1206.
186. Witberg, G., et al., Myocarditis after Covid-19 vaccination in a large health care organization. New England Journal of Medicine, 2021.
187. Heymans, S. and L.T. Cooper, Myocarditis after COVID-19 mRNA vaccination: clinical observations and potential mechanisms. Nature Reviews Cardiology, 2022. 19(2): p. 75-77.
188. Chou, O.H.I., et al., COVID-19 vaccination and carditis in children and adolescents: a systematic review and meta-analysis. Clinical Research in Cardiology, 2022.
189. Dionne, A., et al., Association of Myocarditis With BNT162b2 Messenger RNA COVID-19 Vaccine in a Case Series of Children. JAMA Cardiology, 2021. 6(12): p. 1446-1450.
190. Wallace, M., Oliver, Sara E. COVID-19 mRNA vaccines in adolescents and young adults : benefit-risk discussion.