Implication of microRNA as a potential biomarker of myocarditis

Jin-Hee Oh, MD¹, Gi Beom Kim, MD², Heeyoung Seok, PhD³

¹Department of Pediatrics, St. Vincent’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea; ²Department of Pediatrics, Seoul National University Children’s Hospital, Seoul National University College of Medicine, Seoul, Korea; ³Department of Transdisciplinary Research and Collaboration, Genomics Core Facility, Biomedical Research Institute, Seoul National University Hospital, Seoul, Korea

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Myocarditis was previously attributed to an epidemic viral infection. Additional harmful reagents, in addition to viruses, play a role in its etiology. Coronavirus disease 2019 (COVID-19) vaccine-induced myocarditis has recently been described, drawing attention to vaccine-induced myocarditis in children and adolescents. Its pathology is based on a series of complex immune responses, including initial innate immune responses in response to viral entry, adaptive immune responses leading to the development of antigen-specific antibodies, and autoimmune responses to cellular injury caused by cardiomycocyte rupture that releases antigens. Chronic inflammation and fibrosis in the myocardium eventually result in cardiac failure. Recent advancements in molecular biology have markedly increased our understanding of myocarditis. In particular, microRNAs (miRNAs) are a hot topic in terms of the role of new biomarkers and the pathophysiology of myocarditis. Myocarditis has been linked with microRNA-221/222 (miR-221/222), miR-155, miR-10a, and miR-590. Despite the lack of clinical trials of miRNA intervention in myocarditis yet, multiple clinical trials of miRNAs in other cardiac diseases have been aggressively conducted to help pave the way for future research, which is bolstered by the success of recently U.S. Food and Drug Administration-approved small-RNA medications. This review presents basic information and recent research that focuses on myocarditis and related miRNAs as a potential novel biomarker and the therapeutics.

Key message

- Myocarditis was recently examined quantitatively as inflammation of the heart muscle based on endomyocardial biopsy, and its noninvasive diagnosis remains unsatisfactory.
- Additionally, numerous miRNAs (miR-155, miR-146b, miR-590, miR-221, miR-222, etc.) coupled with inflammation or viral activation have been examined in myocarditis patients or mouse models.
- The recent identification of mmu-miR-721 (has-miR-Chr8:96), a myocarditis-specific microRNA, demonstrated its potential as an acute myocarditis biomarker.

Introduction

Myocarditis is a broad term for inflammatory disorders of the heart muscles. In his work, Traité des Maladies du Coeur (Treatise on Heart Disease) published in 1749, Jean Baptise Senac identified inflammation in the heart. Later, Joseph Freidrich Sobeinheim coined the term myocarditis to describe cardiomyopathy caused by myocyte inflammation, ischemia, and hypertensive heart disease. Various viral infections in the heart, such as coxsackievirus, echovirus, the mumps virus, influenza virus, measles virus, poliovirus, and smallpox, have been reported during epidemic periods, leading to myocarditis becoming a broader term that covers myocardial infarction, chronic ischemic heart disease, and occasionally, pancarditis or myopericarditis. To date, it has been used interchangeably. Recent efforts have been made to clearly describe myocarditis, which is defined as inflammation of the cardiac muscle and recognized as a disease that leads to heart failure.

Endomyocardial biopsy (EMB) with quantitative standards (≥14 lymphocytes/mm², including ≤4 monocytes/mm², with the presence of cluster of differentiation 3–positive T lymphocytes, 7 cells/mm²) and immunohistochemistry assays are used to diagnose myocarditis. However, this approach is only acceptable for isolated inflammatory regions, making it difficult to diagnose fulminant myocarditis (FM), which involves widespread inflammation throughout the heart. Quantitative cardiac troponin analysis combined with cardiac magnetic resonance imaging (MRI) to assess the injured myocardium can be utilized to noninvasively diagnose myocarditis to overcome localized inflammation, spontaneous resolution, and myocardial fibrosis.
Myocarditis etiology

Infection, autoimmune responses, and toxicity are the 3 most common causes of myocarditis. Among them, viral infections are the most common. Several viruses, including coxsackievirus, H1N1 influenza, adenovirus, hepatitis C, cytomegalovirus, echovirus, parvovirus B-19, herpes virus, and Epstein-Barr virus were detected in heart autopsy samples on a regular and local basis. In addition to viral infection-mediated immune responses, bacterial-driven cases such as Lyme disease (Borrelia burgdorferi) and parasite-mediated Chagas disease (Trypanosoma cruzi) have been reported regularly, as have drug- or vaccine-related cases such as ampicillin or tetracycline or smallpox vaccines.

Amid the recent coronavirus disease 2019 (COVID-19) pandemic, cases of myocarditis reported in people vaccinated with the COVID-19 mRNA vaccine and the relationship between myocarditis after COVID-19 infection and vaccination are under investigation. This finding was supported by 2 major cohort studies. One survey in Israel reported 136 cases of definitive or probable myocarditis within one month of receiving one shot of the vaccine. This study included more than 5 million participants who had received immunization. Of these cases, 135 had a mild or moderate clinical course and one was fatal. After the second dose of the vaccination, a 15 in 100,000 chance of developing myocarditis was assessed in adolescents and young men aged 16–19 years. Similar studies in the United States reported a somewhat lower rate of 5 of 10,000 cases (18- to 24-year-old men). However, all of these cases were less severe than myocarditis caused by direct viral infection. Severe acute respiratory syndrome coronavirus 2 infection results in an 18-fold increased risk of myocarditis in the same age group.

Two 10-year studies of Koreans included cases of myocarditis in children. Park et al. studied the incidence of myocarditis in Korean children in 2010–2019. This multicenter study included 142 patients with myocarditis/pericarditis. The patients were a mean 5.4 years of age, with males accounting for 61% of the total. Compared to other age groups ranging from 17 days to 17 years of age, the teen years, defined as ages 12–17 years, had the highest prevalence of 1.25 per 1,000 patients. The frequency of occurrence has increased considerably over the last decade from 0.34 in 2010 to 1.25 in 2019. Among the principal etiologies of infections are Mycoplasma pneumoniae, enterovirus, rhinovirus, adenovirus, respiratory syncytial virus, influenza virus, parainfluenza virus, and parvovirus. On rare occasions, adenoviruses and endemic coronaviruses have been observed simultaneously. However, in 60% of patients, no pathogens were
Myocarditis pathogenesis

Because viral infection is the most common cause of myocarditis, viral infection-mediated pathology is discussed here. These studies are mostly based on the pathophysiological understanding of the murine model. The first step is linked to viral replication in the heart, resulting in cellular rupture, an antigen-independent and innate immune response. Consequently, adaptive immune responses are triggered in antigen-presenting cells, resulting in the production of antigen-specific antibodies. Autoimmune reactions and cellular damage propagate during this stage as cardiac proteins are released through cardiomyocyte rupture. Finally, the replacement of collagen with dead myocardial results in persistent inflammation and fibrosis.

There is also disagreement regarding whether viral infection is a direct pathogenic cause of cardiac injury. It is a situation in which a virus triggers immune responses to cause cardiomyocyte injury, or that cardiomyocyte injury is caused by viral infection. The presence of the viral genome in the myocardium of patients with chronic inflammatory cardiomyopathy, rather than acute myocarditis, is suggested. Reports on FM associated with viral infection frequently adopted nasopharyngeal swabs for the diagnosis of viral infection. The hs-troponin level was also elevated in COVID-19 patients, suggesting that the virus generated aberrant immune-mediated inflammatory responses rather than viral-directed myocyte damage.

Understanding the pathophysiology, whether the virus is directly or indirectly involved, is critical for immunosuppression because its role is also conflicting. The use of immunosuppressive medication should generally be validated by polymerase chain reaction to ensure that the condition is not an active infection in EMB.

Patients with acute myocarditis alone or in combination with autoimmune responses were also identified among those who received immuno-checkpoint inhibitor (ICI) medications. Since many cancer patients have just begun to utilize ICI treatment and its estimated correlation with myocarditis is 1.14%, it may become a subtype of myocarditis with distinct age and inflammatory type in the near future.

Myocardial inflammation and the cellular compartment

Idiopathic, autoimmune, and infectious are the 3 types of myocardial inflammation. Interactions between several cellular compartments causes myocardial inflammation. T, B, and lymphoid-derived cells, such as macrophages, dendritic cells, granulocytes, mast cells, and immature precursor cells, all contribute to the differentiation of inflammatory cells and myofibroblasts. Caspase-1, n-terminal PYRIN PAAD DAPIN and c-terminal caspase-recruitment domain containing, and nucleotide-binding oligomerization domain-like receptor pathways play a role in the production of proinflammatory cytokines during this process. Toll-like receptors (TLRs) have also been implicated in the activation of innate immune responses in the early stages. TLR3 polymorphism have been linked to enteroviral myocarditis. Tumor necrosis factor-α (TNF-α) and interleukin (IL)-1β are also released in the myocardium by the TLR pathway.

Inflammatory cell invasion is aided by macrophages. Because Ly6Chi inflammatory macrophages are found in the early stages of cardiac damage, their blockade has been used to treat autoimmune myocarditis. The Ly6Clow M2 macrophage is a critical factor in the transition from acute to pathological remodeling via myofibroblast replacement. Thymic resistance to alpha-myosin heavy chain (MyHC) causes, at least in part, T-cell function to quell autoimmune responses after clearing infections. Overexpressing alpha-MyHC promoter-specific T-cell receptors were designed for a mouse autoimmune
myocarditis model based on this understanding. The release of cytokines by T cells determines myocarditis progression. T-helper (Th) type 1 cells produce interferon gamma, while Th2 cells produce IL-4, -5, and -13. Type 17 helper T (Th17) cells mainly produce IL-17.

While lymphoid-derived cells are involved in adaptive immune responses, endothelial cells act as barriers preventing circulating bone marrow-derived cells from entering the heart. Interstitial cell types, such as fibroblasts, myofibroblasts, and stromal cells, act as a matrix to modify the inflammatory phenotype via local cues. During pathogenesis, the cardiomyocyte compartment is also involved in early infection and adaptive responses such as altered calcium signaling or hypertrophy. Both direct and indirect cross-talk was used to orchestrate these interactions (Table 2).

### Myocarditis and miRNA

There has been research on the posttranscriptional modulation of cardiac immunological responses, including miRNA-mediated controls. MiRNAs are 22-nt single-strand RNAs that complementarily base pair with mRNAs, primarily but not exclusively in the 3’ untranslated region, to govern translation by a minimum 6-mer base-pairing. This is generally a translational repressor.

The importance of miRNAs in myocardial specification and cardiac development, as well as in cardiac disorders such as cardiac hypertrophy, myocardial infarction, arrhythmia, myocarditis, coronary artery disease, and heart failure, has been recognized. Circulating miRNAs in the blood have been used to identify novel biomarkers in addition to their role in the heart. MED13 and miR-208a are 2 of the most notable regulators of metabolic homeostasis via systemic control.

Table 3 summarizes the miRNAs in heart disorders, including myocarditis. Several miRNA profiling studies have been conducted. A total of 107 miRNAs were dysregulated in human right ventricular myocarditis samples. The inhibition of miR-155, miR-21, and miR-146b, for example, reduced cardiac inflammation and myocardial damage in a coxsackievirus B3 (CVB3) animal model and mouse autoimmune studies.

### Table 2. Etiology of myocarditis

| Etiology          | Pathogenesis          | Reference |
|-------------------|-----------------------|-----------|
| Virus             |                       |           |
| Coxsackie         | Viral replication     | 17, 18    |
| H1N1 strains of influenza |               | 19        |
| Hepatitis C       |                       | 21, 22    |
| Adenovirus        |                       | 20        |
| Cytomegalovirus   |                       | 23        |
| Echovirus         |                       | 24        |
| Epstein-Barr virus|                       | 26        |
| Parvovirus B19    |                       | 25        |
| Human herpes virus 6 genome |           | 25        |
| Bacteria          |                       |           |
| Borrelia burgdorferi (Lyme diseases) | | 27        |
| Parasite          |                       |           |
| Trypanosoma cruzi (Chagas diseases) | Inflammatory/oxidative stress | 28        |
| Drug              |                       |           |
| Phenytoin         |                       |           |
| Hydrochlorothiazide|                      |           |
| Furosemide        |                       |           |
| Ampicillin        |                       | 28        |
| Tetracycline      |                       |           |
| Azithromycin      |                       |           |
| Aminophylline     |                       |           |
| Phenytoin         |                       |           |
| Benzodiazepines   |                       |           |
| Tricyclic antidepressants |           |           |
| Tumor necrosis factor antagonists | |           |
| Vaccine           |                       |           |
| Smallpox          |                       | 32, 33    |
| COVID 19          |                       | 30, 31    |

COVID-19, coronavirus 2019.

### Table 3. MiRNAs correlated with myocarditis

| miRNA       | Expected target                  | Category                          | Reference |
|-------------|----------------------------------|-----------------------------------|-----------|
| miR-221/222 | ETS1/2, irf2, BCL2L1, TOX, BMF, CXCL12 | Activation of CVB3 | 84        |
| miR-203     | ZFP-148                          | Cell survival                      | 1         |
| miR-141     | elf4E                            | Viral translation/cellular translation | 102       |
| miR-10a*    | CVB3 nt6818-6941                 | Viral biosynthesis                 | 103, 104  |
| miR-21      | YOD1, VCL                        | Desmin/desmosome/cadherin          | 79        |
| miR-1       | Connection-43                    | Gap junction                       | 105       |
| miR-126     | LRP6, WRCH1                      | Cell death                         | 106       |
| miR-155     | PU.1                             | Inflammation, virus replication    | 76, 85    |
| miR-146b    | IRAK1, TRAF6                     | Inflammation                       | 79, 107   |
| miR-142     | MBD2, SOCS1                      | Immuno-metabolic turbulence        | 108       |
| miR-590     | NF-κB/p50 subunit                | Inflammation                       | 80        |
| mmu-miR-721/has-miR-Chr8:96 | Ppary, Nos2, Stat3, Tgfβ, and Cd69 | Early response                    | 86        |

CVB3, coxsackievirus B3; miRNA, microRNA.
590-3p overexpression reduced disease by repressing nuclear factor kappa B (NF-κB) expression and turning off IL-6/TNF-α expression by targeting NF-κB.  

Patients with myocarditis were profiled for various CVB3 clearance conditions. Patients with defective cardiac function under protracted viral accumulation (CVB3) had a greater expression of 8 miRNAs, including miR-135b, -155, -190, -422a, -489, -590, -601, and -1290. Circulating miRNAs in the blood have been investigated as a means of diagnosis or prognosis, while myocarditis is present. miR-208 and miR-499 were overexpressed in the blood plasma during acute myocarditis. However, misregulation of these 2 miRNAs has been documented in acute ischemia and hypertensive disorders, implying that other defining factors may be required. Cellular release in response to inflammation could explain the mixed expression of these 2 miRNAs.

In mouse myocarditis model studies involving enterovirus CVB3, the dysregulation of miR-221/222 by targeting ETS1/2, interferon regulatory factor 2, and B-cell lymphoma 2 (Bcl2)-like-11 maintained prolonged cardiac viremic states and activate inflammatory and injury pathways by targeting ETS1/2, interferon regulatory factor 2, and Bcl2-like-11. MiR-155 uses a similar regulatory mechanism to activate immune responses such as T cells and monocytes by targeting PU.1 and suppressor of cytokine signaling 1.

Recent studies using a murine myocarditis model revealed the induction of cardiac myosin-specific Th17 lymphocytes in a myocarditis-specific manner, turning on as early as 3 days after onset, which differs from the response of myocardial infarction, which also showed Th17 cell upregulation later in the disease course. Using a murine model, the authors validated Th17 cell upregulation of mmu-miR-721 from 27 dysregulated miRNAs. The authors stated that dysregulation of the human version of miR-721, has-miR-Chr8:96, was confirmed in a large human cohort study that included 42 myocarditis patients (based on cardiac MRI diagnosis), 90 myocardial infarction patients, and 80 healthy participants, implying that it could be used as a biomarker for acute myocarditis.

A total of 113 miRNAs were differentially expressed in a murine myocarditis model using Trypanosoma cruzi. The authors reported that miR-146b, miR-21, miR-142-3p, miR-142-5p, miR-145-5p, and miR-149-5p were correlated with disease severity.

### MiRNAs as medications for cardiac diseases

Although antisense RNAs as a novel mechanism for medication have been explored since 1978, the success of partisiran, a short RNA drug that mimics siRNAs with pharmacological features to treat polynuropathy, has only recently become beneficial for treatment.

Small RNA therapies, either inhibiting or activating, are likely to be actively developed for the medical intervention of

| Table 4. Clinical trials of miRNAs and cardiac diseases |
|--------------------------------------------------------|
| **NCT No.** | **Conditions** | **Outcome measures** | **Phases** | **Enrollment** | **Status** |
|-----------------|-----------------|---------------------|------------|----------------|-----------|
| NCT02850627 | Coronary heart disease | miRNAs spectrum, Major adverse cardiac event | Phase 4 | 100 | Unknown status |
| | Acute myocardial infarction | Renin predicts cardiovascular homeostasis and ventricular remodeling | | | |
| | | Ang II predicts cardiovascular homeostasis and ventricular remodeling | | | |
| | | Serum E inflammatory mediators | | | |
| | | Brain natriuretic peptide | | | |
| | | Echocardiography measure of left ventricular systolic function | | | |
| | | Echocardiography measure of left ventricular diastolic function | | | |
| | | New York Heart Association functional classification | | | |
| | | Coronary angiography | | | |
| | | Seattle Angina Questionnaire score | | | |
| | | The traditional Chinese medicine syndrome scale | | | |
| NCT01615003 | Coronary heart disease | The change of cycle threshold of relational microRNA in coronary artery disease with unstable angina | Phase 2 | 70 | Unknown status |
| | Unstable angina | Blood stasis syndrome | | | |
| | | | | | |
| NCT04950569 | Heart failure | NT-proBNP, miR-660-3p, miR-665 and miR-1285-3p | Phase 4 | 136 | Recruiting |
| | | Left ventricular ejection fraction | | | |
| | | NYHA 6 Minutes walking distance | | | |
| NCT03083119 | Coronary heart disease | Major adverse cardiovascular events | Phase 2 | 70 | Unknown status |
| | Unstable angina | Seattle Angina Questionnaire | | | |
| | | Blood stasis syndrome scale of coronary heart disease angina pectoris | | | |
| | | Lipid | | | |
| NCT02447809 | Coronary artery disease | The expressions of miRNAs profile | Phase 4 | 400 | Unknown status |
| | | Clinical efficacy | | | |
| NCT02071966 | Non-ST segment elevation | MicroRNA and microparticles | Phase 4 | 55 | Terminated |
| | Acute coronary syndrome | | | | |

NCT, the national clinical trial; miRNA, microRNA; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.
heart disorders. In the pharmaceutical industry, there are 2 primary types of antitechnologies that repress miRNAs. The first is antagonim, a cholesterol-based modified RNA, while the second is locked nucleic acid (LNA)-modified RNA. Anti-

miR-92a, also known as MRG-110, is an LNA/DNA mixed, phosphorothioate linkage, and 16-nucleic acid medication that was administered intravenously and had a repressive efficacy of up to 2 weeks with a single dose in healthy humans. Taubel et al. used an antisense LNA method to block miR-132-3p in patients with heart failure. This group previously demonstrated that LNA-based chemical modification approaches effectively lowered miRNA levels while maintaining Watson-Crick base-pairing.

Furthermore, scientists demonstrated that miR-132-3p repression clearly improved the heart failure mouse model, which was then expanded into a large animal setting as a preclinical trial to determine the dosage with enhanced cardiac functions. With this excellent research background, the authors assessed the efficacy of LNA-miR-132-3p (CDR132L) for the first time by examining heart failure biomarkers, cardiac fibrosis, QRS narrowing, and left ventricular ejection fraction. For 28 patients, 4 dosage groups with a maximum dose of 10 mg/kg administered every 4 weeks were created. Efficacy assessments were underpowered in the phase 1b trial due to the research design and small patient cohort, but this study clearly demonstrated the safety of a dose-dependent reduction of plasma miR-132-3p expression level and encouraged the next stage in the development of this innovative drug.

### MiRNAs as biomarkers for cardiac diseases

In both experimental animals and humans, miRNA expression profiling has been shown to reflect disease status and/or progression. Misregulation of miR-195 and miR-21 was observed for the first time in mouse models of heart hypertrophy. Since then, a large amount of miRNA profiling data has been amassed in various cardiovascular disease models and patients, leading to current active clinical trials. In heart failure patients, for example, profiling miRNA expression as biomarkers from patients receiving U.S. Food and Drug Administration (FDA)-approved medications has been described. Table 4 contains detailed information on miRNA investigations in clinical trials.

### Conclusion

Myocarditis remains a challenge, and the recent COVID-19 outbreak has brought it back to the forefront. Although its exact pathophysiology remains unknown, new research is seeking to improve our understanding and lay the groundwork for newer treatment methods. MiRNAs offer further insights into this understanding.

Over the past several years, miRNA studies on cardiac diseases have been ongoing. There are 6 records of miRNAs in coronary heart disorders, myocardial infarction, heart failure, and unstable angina on the clinical trial list, spanning early phases 1–4. There were 40 studies on miRNAs in heart disorders if the searches were widened to include non-FDA-defined phase trials. To date, no direct clinical studies have investigated miRNAs in myocarditis; nevertheless, the role of miRNAs has been investigated and specific miRNAs have been identified, paving the way for future innovative interventions and/or diagnostics.

### Footnotes

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ORCID:

Jin-Hee Oh https://orcid.org/0000-0002-2893-0563
Gi Beom Kim https://orcid.org/0000-0002-7880-280X
Heeyoung Seok https://orcid.org/0000-0003-2699-9935

### References

1. Fung G, Luo H, Qiu Y, Yang D, McManus B. Myocarditis. Circ Res 2016;118:496-514.
2. D'Ambrosio A, Patti G, Manzoli A, Sinagra G, Di Lenarda A, Silvestri F, 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;34:2636-48, 2648a-2648d.
3. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. Myocarditis: the Dallas criteria. Hum Pathol 1987;18:619-24.
4. Aretz HT. Myocarditis: the Dallas criteria. Hum Pathol 1987;18:619-24.
5. Aretz HT. Myocarditis: the Dallas criteria. Hum Pathol 1987;18:619-24.
6. Kociol RD, Cooper LT, Fang JC, Moslehi J, Sabe MA, et al. Recognition and initial management of fulminant myocarditis: a scientific statement from the American Heart Association. Circulation 2020;141:e69-92.
7. Chow LH, Radio SJ, Sears TD, McManus BM. Insensitivity of right ventricular endomyocardial biopsy in the diagnosis of myocarditis. J Am Coll Cardiol 1989;14:915-20.
8. Anzini M, Merlo M, Sabbadini G, Barbati G, Finocchiaro G, Pinamonti B, et al. Long-term evolution and prognostic stratification of biopsy-proven active myocarditis. Circulation 2013;128:2384-94.
9. Kindermann I, Kindermann M, Kandolf R, Klingel K, Bultmann B, Muller T, et al. Predictors of outcome in patients with suspected myocarditis. Circulation 2009;118:639-48.
10. Heeyoung Seok et al. Recognition and initial management of fulminant myocarditis: a scientific statement from the American Heart Association. Circulation 2020;141:e69-92.
11. Vaidya VR, Abudan AA, Vasudevan K, Shantha G, Cooper LT, Kapa S, et al. The efficacy and safety of electroanatomic mapping-guided endomyocardial biopsy: a systematic review. J Interv Card Electrophysiol
12. Global Burden of Disease Study C, Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386:743-800.

13. Cooper LT Jr, Keren A, Sliwa K, Matsumori A, Mensah GA. The global burden of myocarditis: part 1: a systematic literature review for the Global Burden of Diseases, Injuries, and Risk Factors 2010 study. Glob Heart 2014;9:121-9.

14. Ammirati E, Cipriani M, Moro C, Raineri C, Pini D, Sormani P, et al. Clinical presentation and outcome in a contemporary cohort of patients with acute myocarditis: multicenter Lombardy registry. Circulation 2018;138:1088-99.

15. Ammirati E, Veronese G, Brambatti M, Merlo M, Cipriani M, Potena L, et al. Fulminant versus acute nonfulminant myocarditis in patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2019;74:299-311.

16. Maron BJ, Udelson JE, Bonow RO, Nishimura RA, Ackerman MJ, Estes NA 3rd, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 3: hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and other cardiomyopathies, and myocarditis: a scientific statement from the American Heart Association and American College of Cardiology. Circulation 2015;132:e273-80.

17. Pauschinger M, Phan MD, Doerner A, Kuehl U, Schwimmelck PL, Peller W, et al. Enteroviral RNA replication in the myocardium of patients with left ventricular dysfunction and clinically suspected myocarditis. Circulation 1999;99:889-95.

18. Andreoletti L, Leveque N, Boulagou C, Brasselet C, Fornes P. Viral causes of human myocarditis. Arch Cardiovasc Dis 2009;102:539-68.

19. Baratelli AE, Boimond N, Ramful D. Myocarditis associated with 2009 influenza A (H1N1) virus in children. Cardiol Young 2010;20:351-2.

20. Bowles NE, NJ, Kearney DL, Pauschinger M, Schulteis HE McCarthy R, et al. Detection of viruses in myocardial tissues by polymerase chain reaction. evidence of adenovirus as a common cause of myocarditis in children and adults. J Am Coll Cardiol 2003;42:466-72.

21. Matsumori A, Yutani C, Ikeda Y, Kawai S, Sasayama S. Hepatitis C virus from the hearts of patients with myocarditis and cardiomyopathy. Lab Invest 2000;80:1137-42.

22. Omura T, Yoshiyama M, Hayashi T, Nishiguchi S, Kaito M, Horiike S, et al. Core protein of hepatitis C virus induces cardiomyopathy. Circ Res 2000;86:148-50.

23. Wink K, Schmitz H. Cytomegalovirus myocarditis. Am Heart J 1980;100:667-72.

24. Chen J, Han Z, Hu W, Xu W, Yu D, Zhang Y. A large-scale outbreak of echovirus 30 in Gansu Province of China in 2015 and its phylodynamic characterization. Front Microbiol 2020;11:1137.

25. Rohayem J, Dinger J, Fischer R, Klingel K, Kandolf R, Rethwilm A. Fatal fulminant myocarditis patients rescued by mechanical circulatory support. Outcomes, long-term quality of life, and psychologic assessment of fulminant myocarditis patients rescued by mechanical circulatory support. Eur J Heart Fail 2020;22:911-5.

26. Tischop C, Cooper LT, Torre-Amione G, van Lintshout S. Management of myocarditis-related cardiomyopathy in adults. Circ Res 2019;124:1568-83.

27. Mahmood SS, Bradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzinger LM, et al. Myocarditis in patients treated with immune checkpoint inhibitors. J Am Coll Cardiol 2018;71:1753-64.

28. Haslam A, Prasad V. Estimation of the percentage of US patients with cancer who are eligible for and respond to checkpoint inhibitor immunotherapy drugs. JAMA Netw Open 2019;2:e192355.

29. Costanzo-Nordin MR, Reap EA, O'Connell JB, Robinson JA, Scanlon PJ. A nonsteroidal anti-inflammatory drug exacerbates Coxsackie B3 murine myocarditis. J Am Coll Cardiol 1983;6:1078-82.

30. Semmler D, Blank R, Rupprecht H. Complete AV block in Lyme carditis: an important differential diagnosis. Clin Res Cardiol 2010;99:519-26.

31. Barba D, Dagan N, Balicer RD. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. Reply. N Engl J Med 2021;384: 236-7.
79. McNamara DM, Holubkow R, Starling RC,Dec GW, Loh E, Torre-Amione G, et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. Circulation 2001;103:2254-9.
83. Drucker NA, Colan SD, Lewis AB, Beiser AS, Wessel DL, Takahashi M, et al. Gamma-globulin treatment of acute myocarditis in the pediatric population. Circulation 1994;89:252-7.
87. Bulut D, Scheeler M, Wichmann T, Borge A, Miebach J, Mbugi A. Effect of protein A immunoadsorption on T cell activation in patients with inflammatory dilated cardiomyopathy. Clin Res Cardiol 2010;99:633-8.
91. Wójcik R, Nowalany-Koziełska E, Wojciechowska C, Głąbczewska G, Wilczewski P, Niklewski T, et al. Randomized, placebo-controlled study for immunosuppressive treatment of inflammatory dilated cardiomyopathy: two-year follow-up results. Circulation 2001;104:39-45.
95. Fairweather D, Kaya Z, Shellam GR, Lawson CM, Rose NR. From infection to autoimmunity. J Autoimmun 2001;16:175-86.
99. Lv H, Havari E, Pinto S, Gottumukkala RV, Cornivelli L, Raddassi K, et al. Impaired thymic tolerance to alpha-myosin directs autoimmunity to the heart in mice and humans. J Clin Invest 2011;121:1561-73.
103. Miric M, Vasićević J, Bojić M, Popovic Z, Kresoriv N, Pesić M. Long-term follow up of patients with dilated heart muscle disease treated with human leucocytic interferon alpha or thymic hormones initial results. Heart 1996;75:596-601.
107. Gullestad L, Aass H, Andreassen AK, Ihlén H, Simonsen S, Kjekshus J, et al. Immunomodulating treatment in advanced heart failure—effect of intravenous immunoglobulin. Tidsskr Nor Laegeforen 2001;121:1902-7.
111. Frustaci A, Chimenti C, Calabrese F, Pieroni M, Thiene G, Maseri A. Immunosuppressive therapy for active lymphocytic myocarditis: virological and immunologic profile of responders versus nonresponders. Circulation 2003;107:857-63.
115. Dennen R, Veltius H, Schalla S, Eurlings L, van Suylen RJ, van Paassen HP, et al. Intravenous immunoglobulin therapy for patients with idiopathic cardiomyopathy and endomyocardial biopsy-proven high PVB19 viral load. Antivir Ther 2010;15:193-201.
119. Bughman KL. Diagnosis of myocarditis: death of Dallas criteria. Circulation 2006;113:593-5.
123. Matsumori A, Igata H, Ono K, Iwasaki A, Miyamoto T, Nishio R, et al. Diagnosis of myocarditis: death of Dallas criteria. Circulation 2001;104:39-45.
127. Dennen R, Veltius H, Schalla S, Eurlings L, van Suylen RJ, van Paassen HP, et al. Intravenous immunoglobulin therapy for patients with idiopathic cardiomyopathy and endomyocardial biopsy-proven high PVB19 viral load. Antivir Ther 2010;15:193-201.
96. Abplanalp WT, Fischer A, John D, Zeiher AM, Gosgnach W, Darville H, et al. Efficiency and target derepression of anti-miR-92a: results of a first in human study. Nucleic Acid Ther 2020;30:335-45.
97. Taubel J, Hauke W, Rump S, Vierreck J, Batkai S, Poetzsch J, et al. Novel antisense therapy targeting microRNA-132 in patients with heart failure: results of a first-in-human Phase 1b randomized, double-blind, placebo-controlled study. Eur Heart J 2021;42:178-88.
98. Li T, Ding ZL, Zheng YL, Wang W. MiR-484 promotes non-small-cell lung cancer (NSCLC) progression through inhibiting Apaf-1 associated with the suppression of apoptosis. Biomed Pharmacother 2017;96:153-64.
99. Kumarswamy R, Volkmann I, Beermann J, Napp I-C, Jabs O, Bhayadia R, et al. Vascular importance of the miR-212/132 cluster. Eur Heart J 2014;35:3224-31.
100. Foinquinos A, Batkai S, Genschel C, Vierreck J, Rump S, Gyongyosi M, et al. Preclinical development of a miR-132 inhibitor for heart failure treatment. Nat Commun 2020;11:633.
101. van Rooij E, Sutherland LB, Liu N, Williams AH, McAnally J, Gerard RD, et al. A signature pattern of stress-responsive microRNAs that can evoke cardiac hypertrophy and heart failure. Proc Natl Acad Sci U S A 2006;103:18255-60.
102. Ho BC, Yu SL, Chen JJ, Chang SY, Yan BS, Hong QS, et al. Enterovirus-induced miR-141 contributes to shutoff of host protein translation by targeting the translation initiation factor eIF4E. Cell Host Microbe 2011;9:58-69.
103. Tong L, Lin L, Wu S, Guo Z, Wang T, Qin Y, et al. MiR-10a* up-regulates coxsackievirus B3 biosynthesis by targeting the 3D-coding sequence. Nucleic Acids Res 2013;41:3760-71.
104. Liao Y, Chen KH, Dong XM, Fang Y, Li WG, Huang FY, et al. A role of pre-mir-10a coding region variant in host susceptibility to coxsackievirus-induced myocarditis. Eur Rev Med Pharmacol Sci 2015;19:3500-7.
105. Xu HF, Ding YJ, Shen YW, Xue AM, Xu HM, Luo CL, et al. MicroRNA-1 represses Cx43 expression in viral myocarditis. Mol Cell Biochem 2012;362:141-8.
106. Ye X, Hemida MG, Qiu Y, Hanson PJ, Zhang HM, Yang D. MiR-126 promotes coxsackievirus replication by mediating cross-talk of ERK1/2 and Wnt/beta-catenin signal pathways. Cell Mol Life Sci 2013;70:4631-44.
107. Wu J, Shen L, Chen J, Xu H, Mao L. The role of microRNAs in enteroviral infections. Braz J Infect Dis 2015;19:510-6.
108. Sun B, Wang N, Zhao P, Wang C, Li H, Chen Q, et al. Circulating exosomes control CD4(+) T cell immunometabolic functions via the transfer of mir-142 as a novel mediator in myocarditis. Mol Ther 2020;28:2605-20.

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