Why is diagnosis of infectious myocarditis such a challenge?

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Heinz-Peter Schultheiss

Department of Cardiology and Pneumology, Campus Benjamin Franklin, Charité – University Medicine Berlin, Hindenburgdamm 30, D-12200 Berlin, Germany

Uwe Kühl

Author for correspondence: Department of Cardiology and Pneumology, Campus Benjamin Franklin, Charité – University Medicine Berlin, Hindenburgdamm 30, D-12200 Berlin, Germany
Tel.: +49 30 8445 4219
Fax: +49 30 8445 4219
uwe.kuehl@charite.de

"In the subacute and chronic phase of infectious and noninfectious myocarditis or inflammatory cardiomyopathy … myocardial inflammation cannot be suspected from the clinical profile, since nearly all clinical characteristics suggestive of acute myocarditis are missing."

Etiologies of myocarditis include a number of infectious agents such as viruses, bacteria, protozoa and fungi, but most frequently the myocardial inflammatory processin myocarditis is directed against viral pathogens. Both viruses and the cellular antiviral immune response can injure myocardial tissue [1,2]. Although imaging techniques can provide noninvasive tissue characterization and localize larger inflammatory infiltrates, they are misleading if infectious agents are involved, since they neither detect nor quantify different virus types and loads or inflammatory cell numbers, nor differentiate between cell subtypes of the immune response. Consequently, the underlying infectious etiologies and inflammatory characteristics cannot be clinically identified.

New pathogen-specific quantitative molecular diagnostic tests and histochemical staining procedures have expanded the role for endomyocardial biopsy as the only reliable method to elucidate the true nature of the disease and to specify tailored treatment conditions for subgroups of patients [3]. Biopsy-based treatment decisions demand, however, a complete molecular biological, histological and histochemical work-up of myocardial tissue. Otherwise, an incorrect therapeutic decision may be based on incomplete diagnostic information and jeopardize treated patients, as reported for immunosuppressive treatment of virus-positive patients [4,5].

Clinical phenotypes of infectious & noninfectious myocarditis

Myocarditis can be diagnosed by established histopathological, histochemical, or molecular criteria, but it is challenging to identify it clinically. In acute disease, sudden onset of chest pain and exertional dyspnea, congestive heart failure despite regularly seized ventricles or with enlarged ventricular chambers which may develop rapidly within days or weeks, ventricular arrhythmias and abnormal ST-T segments and changes in the presence of elevated cardiac enzymes (CK/CKMB or TNT) are highly suspicious for an active inflammatory process of the myocardium, if other acute cardiac diseases have been excluded. Without angiography, it cannot clinically be distinguished from an acute coronary syndrome.

In the subacute and chronic phase of infectious and noninfectious myocarditis or inflammatory cardiomyopathy, which by definition is a chronic myocarditis with DCM phenotype, myocardial inflammation cannot be suspected from the clinical profile, since nearly all clinical characteristics suggestive of acute myocarditis are missing. Patients present with uncharacteristic complaints such as angina, dyspnea, fatigue, reduced physical disability or arrhythmias in the presence of a preserved or impaired systolic or diastolic function, or with idiopathic dilated cardiomyopathy.

EXPERT REVIEWS

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The same holds true in early virus-associated disease or if the inflammatory response has failed to clear the infectious pathogen from the myocardium. A virus-specific phenotype of myocarditis does not exist. Viral infections can cause serious human diseases including acute and chronic heart failure. The majority of viral infections, however, are asymptomatic or oligosymptomatic and therefore, such infections are frequently not recognized prematurely as a possible cause of a delayed onset of heart disease [6]. In the past, viral myocarditis and chronic viral heart disease have therefore more often been a clinically derived diagnosis of exclusion, rather than a specifically proven diagnosis.

> "The diagnostic challenge is to uncover this clinically complex situation by unraveling treatable disease entities such as virus or inflammation from conditions with irreversible myocardial injury."

The diagnostic challenge becomes even more complicated by the complex virus profiles of the myocardium with a number of distinct virus species and virus subtypes, different virus loads or reactivated pathogens, all of which may be present in the presence or absence of inflammatory processes [7–9]. These distinct conditions not only influence actual presentation and natural course of the disease, but also possess a deep impact on the clinical phenotype [1,10–16]. Depending on the virus-immanent target cell in the heart, clinical presentation ranges broadly from subclinical disease to fulminant heart failure [17]. Systolic heart failure is often caused by pathogens that infect and injure contractile myocytes, as known for enteroviruses or adenoviruses. Other patients with preserved systolic function complain of chest pain or dyspnea as the leading symptom, despite preserved systolic function. This is a typical condition when parvoviruses or herpesviruses infect the vascular endothelium resulting in endothelial dysfunction.

Postinfectious disease

A persisting viral infection or a persisting postinfectious autoimmune myocarditis cannot be distinguished from a post-myocarditic condition, in which remnants of the infectious disease but not a persisting viral infection or a chronic inflammatory process are responsible for symptoms and progression of the heart failure. The diagnostic challenge is to uncover this clinically complex situation by unraveling treatable disease entities such as virus or inflammation from conditions with irreversible myocardial injury [18]. This is clinically important since the latter may partially improve upon symptomatic heart failure medication but will not respond to specific anti-infectious or immunosuppressive treatment effectively.

Diagnosis

Since the pathological conditions in myocarditis take place at the cellular level, tissue analysis and not clinical tests are necessary to elucidate the nature of the underlying acquired disease [19]. Despite well known limitations giving rise to false-negative results (sampling error), endomyocardial biopsy is the gold standard for unequivocally establishing the diagnosis, particularly if histology is complemented by sensitive histochemical and molecular methods [20]. No other clinical diagnostic tool can prove the loads and types of different viruses or nonviral infectious pathogens, elucidate and quantify inflammatory cell subtypes, detect minor myocardial necroses, newly developing fibrosis, or circumscribed early scar formation characteristic of active infective disease. All of this information is needed for successful management of patients [2].

Why is the pathogen-specific diagnosis so important?

In acute heart failure, biopsy-based information is mandatory to recognize virus-negative inflammation that requires immediate and tailored immunosuppression in order to reduce early mortality and improve long-term outcome. Typical conditions are giant cell myocarditis, necrotizing eosinophilic myocarditis, or decompensating sarcoidosis [4,21,22]. Fulminant lymphocytic myocarditis may resolve spontaneously with a good long-term outcome for those 60% of patients who survive the early critical phase while nonfulminant but acute myocarditis has a more adverse prognosis with a mortality of 25–56% within 6–8 years [23–25]. The histological and immunohistological recognition of cellular inflammation can thus facilitate and improve symptomatic management of afflicted patients. Application of a permanent device (e.g., pacemaker, ICD) may become unnecessary after clinical stabilization following fading inflammation. A postponed decision for treatment may even prevent hasty acute heart transplantation.

In chronic inflammation, immunosuppression demands biopsy-based exclusion of virus from treated patients because virus-positive patients do not improve or even deteriorate upon anti-inflammatory treatment [21]. Virus-negative patients with postinfectious or autoimmune inflammatory processes responded well to imunosuppression in early clinical trials [4,21,26].

Antiviral treatment can only be successful if it is started in time, before the virus has caused irreversible myocardial injury [11]. Patients with chronic heart failure due to persistent enterovirus and adenovirus infections of the myocardium responded well to a 6-month IFN-β course [27]. Complete elimination of viral genome was proven by follow-up biopsies taken 3 months after termination of the antiviral therapy. Virus clearance was paralleled by an improvement of mean left ventricular function, a decrease in ventricular size, an amelioration of heart failure symptoms. Other viruses, for example, parvovirus B19 or human herpesvirus 6, respond less well upon IFN-β treatment with respect to virus clearance, although these patients did improve clinically despite incomplete virus clearance following reduction of viral load and improvement of endothelial dysfunction [28].

Conclusion

To recognize whether an infectious disease may hide behind uncharacteristic cardiac symptoms and consequently to prove a myocarditis unambiguously poses an important clinical challenge. A reliable diagnostic differentiation between virus-positive or virus-negative myocarditis and a postinfectious state, which permits discrimination between treatable and nontreatable diseases, has to be accomplished in order to allow successful administration of a pathogen-tailored treatment strategy [4,21,26,27,29,30]. This approach cannot be reached by routine clinical diagnoses but

demands biopsy-based information with complete histological, histochemical and molecular work-up of tissue samples.

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References

1 Liu PP, Schultheiss HP. Myocarditis. In: *Heart Disease (8th Edition).* Baunwald (Ed.). W B Saunders co, PA, USA 1775–1792 (2008).

2 Cooper LT, Kuehl U, Schultheiss HP. Myocarditis management. *Eur. Heart J.* 32, 2616–2625 (2011).

3 Cooper LT, Baughman KL, Feldman AM *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. *Circulation* 116, 2216–2233 (2007).

4 Frustaci A, Chimenti C, Calabrese F *et al.* Immunosuppressive therapy for active lymphocytic myocarditis: virological and immunologic profile of responders versus nonresponders. *Circulation* 107, 857–863 (2003).

5 Heim A, Stille-Siegener M, Kandolf R, Kreuzer H, Figulla HR. Enterovirus-induced myocarditis: hemodynamic deterioration with immunosuppressive therapy and successful application of interferon-α. *Clin. Cardiol.* 17, 563–565 (1994).

6 Modlin FJ. Picornaviridae. In: *Principles and Practice of Infectious Diseases.* Mandell GL, Douglas RG Jr, Bennett JE (Eds). Churchill Livingstone, NY, USA, 721–732 (1990).

7 Kühl U, Lassner D, Pauschinger M *et al.* Detection and prevalence of erythrovirus genotypes in the myocardium of patients with dilated cardiomyopathy. *J. Med. Virol.* 80, 1243–1251 (2008).

8 Kühl U, Pauschinger M, Noutsias M *et al.* High prevalence of viral genomes and multiple viral infections in the myocardium of adults with "idiopathic" left ventricular dysfunction. *Circulation* 111, 887–893 (2005).

9 Pellet PE, Ablashi DV, Ambros PF *et al.* Chromosomally integrated human herpesvirus 6: questions and answers. *Rev. Med. Virol.* (2011) (In Press).

10 Dec GW Jr, Waldman H, Southern J *et al.* Viral myocarditis mimicking acute myocardial infarction. *J. Am. Coll. Cardiol.* 20, 85–89 (1992).

11 Why HJ, Meany BT, Richardson PJ *et al.* Clinical and prognostic significance of detection of enteroviral RNA in the myocardium of patients with myocarditis or dilated cardiomyopathy. *Circulation* 89, 2582–2589 (1994).

12 Badorff C, Lee GH, Lamphear BJ *et al.* Enteroviral protease 2A cleaves dystrophin: evidence of cytoskeletal disruption in an acquired cardiomyopathy. *Nat. Med.* 5, 320–326 (1999).

13 Gorbea C, Makar KA, Pauschinger M *et al.* A role for Toll-like receptor 3 variants in host susceptibility to enteroviral myocarditis and dilated cardiomyopathy. *J. Biol. Chem.* 285(30), 23208–23223 (2010).

14 Kindermann I, Kindermann M, Kandolf R *et al.* Predictors of outcome in patients with suspected myocarditis. *Circulation* 118, 639–648 (2008).

15 Baboonian C, Treasure T. Meta-analysis of the association of enteroviruses with human heart disease. *Heart* 78, 539–543 (1997).

16 Magnani JW, Danik HJ, Dec GW Jr, DiSalvo TG. Survival in biopsy-proven myocarditis: a long-term retrospective analysis of the histopathologic, clinical, and hemodynamic predictors. *Am. Heart J.* 151, 463–470 (2006).

17 Schultheiss HP, Kuehl U. Cardiovascular viral infections. In: *Lennette's Laboratory Diagnosis of Viral Infections (4 Edition).* Lennette EH (Ed.). 304–318 (2010).

18 Fairweather D, Kaya Z, Shellam GR, Lawson CM, Rose NR. From infection to autoimmunity. *J. Autoimmun.* 16, 175–186 (2001).

19 Mangnani JW, Dec GW. Myocarditis: current trends in diagnosis and treatment. *Circulation* 113, 876–890 (2006).

20 Baughman KL. Diagnosis of myocarditis: death of dallas criteria. *Circulation* 113, 593–595 (2006).

21 Frustaci A, Russo MA, Chimenti C. Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. *Eur. Heart J.* 30(16), 1995–2002 (2009).

22 Cooper L, Hare JM, Tazelaar HD *et al.* Usefulness of immunosuppression for giant cell myocarditis. *Am. J. Cardiol.* 102, 1535–1539 (2008).

23 McCarthy RE 3rd, Boehmer JP, Hruban RH *et al.* Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. *N. Engl. J. Med.* 342, 690–695 (2000).

24 Amabile N, Fraisse A, Bouvenot J, Chetaille P, Ovaert C. Outcome of acute fulminant myocarditis in children. *Heart* 92, 1269–1273 (2006).

25 Caforio AL, Calabrese F, Angelini A *et al.* A prospective study of biopsy-proven myocarditis: prognostic relevance of clinical and aetiopathogenetic features at diagnosis. *Eur. Heart J.* 28, 1326–1333 (2007).

26 Stanton C, Mookadam F, Cha S *et al.* Greater symptom duration predicts response to immunomodulatory therapy in dilated cardiomyopathy. *Int. J. Cardiol.* 128, 38–41 (2008).

27 Kuhl U, Pauschinger M, Schwimmbeck PL *et al.* Interferon-β treatment eliminates cardiotropic viruses and improves left ventricular function in patients with myocardial persistence of viral genomes and left ventricular dysfunction. *Circulation* 107, 2793–2798 (2003).

28 Schmidt-Lucke C, Spillmann F, Bock T *et al.* Interferon β modulates endothelial damage in patients with cardiac persistence of human parvovirus B19 infection. *J. Infect. Dis.* 201(6), 936–945 (2010).

29 Parrillo JE, Cunnion RE, Epstein SE *et al.* A prospective, randomized, controlled trial of prednisone for dilated cardiomyopathy. *N. Engl. J. Med.* 321, 1061–1068 (1989).

30 Mason JW, O'Connell JB, Herskowitz A *et al.* A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis treatment trial investigators. *N. Engl. J. Med.* 333, 269–275 (1995).