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Editorial — *Special issue: Heart Failure*

Inflammatory cardiomyopathy: Still many questions await answers ☆

Heart failure represents a major public health problem as it belongs to the most significant causes of morbidity and mortality in developed countries. Dilated cardiomyopathy (DCM) is a common cause of heart failure. DCM is defined by the presence of left ventricular (LV) dilatation and LV systolic dysfunction in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment [1]. The long-term prognosis of the disease has improved remarkably during the past 20 years [2]. However, despite progress in drug treatment and non-pharmacological therapeutic options like cardiac resynchronization therapy, DCM still remains the most frequent reason for heart transplantation in adults and children [3].

DCM is not a single disease but a heterogeneous group of disorders comprising familial and acquired forms. Familial forms of DCM represent about 20% of cases and >40 genes have been implicated in causing disease [4]. Today, myocarditis is thought to be one of the major causes of acquired DCM [5]. The etiologies of myocarditis are manifold and include viral, bacterial, rickettsial, helminthic, fungal, and protozoal infections as well as non-infectious causes like autoimmune, toxic, and allergic forms. Viral infection is regarded as the most common cause of acute myocarditis. The pathophysiology of myocarditis is still not completely understood. Based on data from murine models of enteroviral myocarditis, the course of viral myocarditis may be divided into 3 phases [6]. The early phase of myocarditis is initiated by infection of cardiac myocytes, fibroblasts or endothelial cells through receptor-mediated endocytosis. At this moment, myocyte injury may result from either direct virus-mediated lytic processes or emerging antiviral immune response. Thus acute phase of myocarditis takes only a few days. The second, subacute phase covers several weeks to months and is characterized by (auto)immune reactions arising from activation of virus-specific T-lymphocytes together with antibody and cytokine (tumor necrosis factor α, interleukins 1 and 6) production. All these processes aim to enhance viral clearance, but they may aggravate cardiac damage and contractile dysfunction. In many patients, immune responses declines with successful virus elimination and LV function recovers. However, in some individuals chronic immune stimulation and autoimmune processes may persist due to incompletely cleared virus infection or in response to the virus- and immune-mediated tissue damage. Both these cellular and humeral inflammatory processes contribute to the progression of chronic myocardial injury and represent a third phase characterized by ventricular remodeling and development of DCM.

The increasing knowledge about the pathogenic link between myocardial inflammation and injury lead to the definition of a new and distinct entity, inflammatory cardiomyopathy (ICM) in the 1996 WHO classification of cardiomyopathies. ICM was defined as inflamed myocardium assessed histologically (e.g., myocarditis) in association with cardiac dysfunction [7]. The histopathological criteria at that time were the Dallas criteria, which distinguished active, recurrent, healing, and borderline myocarditis [8]. According to the Dallas criteria, acute myocarditis was defined by lymphocytic infiltrates in association with myocyte necrosis. Borderline myocarditis was then characterized by inflammatory infiltrates without evidence of myocyte necrosis. However, the assessment of myocardial inflammation by Dallas criteria is limited by several factors including low sensitivity, high interobserver variability and sampling error [9]. Importantly, the isolated histopathological evaluation also does not say anything about persistent myocardial infection. The nice example of the limitation of the Dallas criteria represents the Myocarditis Treatment Trial, which failed to show a benefit of immunosuppressive therapy of ICM [10]. The negative results of this trial might have been influenced by a lack of consensus in histopathological interpretation of endomyocardial biopsy (EMB) findings and, maybe more importantly, by the absence of molecular biological analyses of EMB in order to detect persistent (viral) infection. Thereby, patients with viral infection might have been treated with immunosuppressive agents, which could have increased virus replication and damaged the myocardium.

Therefore, more objective and comprehensive immunohistological and microbiological evaluation of myocardial specimens was introduced and gained acceptance [9]. Immunohistochemistry allows the quantitative characterization and localization of mononuclear infiltrating cells. Indeed, with the use of immunohistological methods, the number of EMB revealing myocarditis markedly increased [11]. In a cohort of 299 patients with DCM, who underwent EMB, Kühl et al. found positive Dallas criteria for active or borderline myocarditis in 5.6%; however, immunohistological markers of myocardial

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inflammation were present in 43% [12]. According to the World Health Federation consensus meeting from 1999, EMB is currently considered to be inflamed by immunohistochemical detection of focal or diffuse mononuclear infiltrates (T lymphocytes and macrophages) with >14 cells/mm^2 [13]. These infiltrating cells could include T- and B-lymphocytes, their activated forms, and up to 4 monocytes or macrophages/mm^2. At the same time, a causative microbial agent had to be identified or excluded by molecular biological methods covering polymerase chain reaction (PCR) or in situ hybridization [14]. Based on the results of such comprehensively evaluated EMB, several subtypes of DCM may be distinguished: (1) dilated cardiomyopathy with negative EMB (presumably due to the healed inflammation and virus elimination or due to other non-infectious causes), (2) ICM or autoreactive ICM, which is characterized by persistent inflammation as demonstrated by immunohistochemistry and no detectable infectious agent, and (3) chronic viral heart disease or viral ICM defined by the presence of chronic viral infection that may be (or not) accompanied by myocardial inflammation [15]. Therefore, despite the progress in noninvasive diagnostics of myocarditis, mainly in the field of magnetic resonance imaging, EMB still represents a gold standard in the diagnosis of various types ICM as it is the most sensitive method for detection of myocardial inflammation and the only tool to demonstrate the presence or absence of persistent myocardial infection, mostly of viral origin. Importantly, only such complex EMB evaluation allows tailoring the therapy of DCM in more detail [16]. The patients with ICM and negative PCR for infectious agent may benefit from combined immunosuppressive therapy as was shown in TIMIC trial [17]. If *Borrelia burgdorferi* or other non-viral infectious agent is found in EMB, antibiotic treatment may lead to improvement in LV size and function [18]. The most difficult situation represents viral ICM. Antivirotics would be effective in the very early stages of myocarditis, but, unfortunately, most adult patients present in the chronic phases of disease. Immunomodulatory therapy using interferon beta has been tested for treatment of chronic viral cardiomyopathy [19]; however, results of randomized, placebo-controlled trials are lacking.

In recent years, the prognostic value of complex evaluation of EMB specimens also gained attention. In the study by Caforio et al., 174 patients with immunohistologicaly defined myocarditis were followed for 24 months [20]. A presence of viral genome in EMB was shown to be a significant predictor of adverse prognosis with respect to survival free from heart transplantation or death. Similarly, Kühl et al. demonstrated that viral persistence in the myocardium is associated with progressive cardiac dysfunction, whereas the clearance of viral genomes in control EMB at 7 months follow-up was accompanied by significant improvement in LV ejection fraction [21]. The importance of viral genome persistence, specifically enteroviral RNA, for adverse clinical outcome of patients with DCM was demonstrated also by Why et al. [22]. Immunohistological evidence of myocardial inflammation (with or without evidence of viral genome) was demonstrated to predict cardiovascular death and the need for heart transplantation in the study of Kindermann et al., in which 181 consecutive patients with clinically suspected viral myocarditis were followed up for a mean of 59 months [23]. Interestingly, neither the histopathological criteria nor the detection of viral genome was a predictor of poor outcome.

In this issue of the journal, Krejčí et al. present very interesting results of a prospective study focused on the evolution of echocardiographic parameters and clinical status of patients with recently diagnosed symptomatic DCM [24]. Seventy patients with recently occurred DCM with LV ejection fraction $<40\%$ and the history of heart failure symptoms less than 12 months underwent comprehensively evaluated EMB. In agreement with previous studies, immunohistochemically defined myocardial inflammation was found in half of the study population and viral genome was detected in 61% of patients with parvovirus B19 being far the most common agent. All patients were treated only by standard heart failure medication according to current recommendations; it means, none of the subjects was treated by immunosuppression or immunomodulatory approaches. At 6 months follow-up, LV ejection fraction, as well as other LV echocardiographic parameters, significantly improved in patients with positive EMB findings of myocardial inflammation, but remained unchanged in subjects with negative immunohistochemistry. A significant improvement of LV ejection fraction was found regardless of viral genome presence or absence. All patients improved in clinical status as assessed by NYHA classification.

These results may seem rather controversial with respect to data cited above; however, they are not entirely surprising. There is solid evidence in recently published literature that simple finding of viral genome(s) in the myocardium, at least the DNA of parvovirus B19, cannot be simply put into causative pathogenic relationship with the development of DCM. Kuethe et al. studied samples of left-atrium tissues from 100 patients who underwent open-heart surgery because of valve replacement of coronary artery bypass grafting [25]. In 85% of these individuals, the genome of parvovirus B19 was detected. In another study, Lotze et al. found similar frequency (50% vs. 45%) of parvovirus B19 genomes in EMB samples taken from 24 patients with DCM and in tissue of right atrial appendages of 10 control subjects undergoing bypass surgery with normal LV ejection fraction [26]. In agreement with the results of Krejčí et al., Kuethe et al. demonstrated in another study similar improvement in LV ejection fraction in patients acute DCM regardless the presence or absence of viral genome in baseline EMB [27]. Therefore, intensive research is aimed to improve diagnostics of clinical relevance of the viral presence in the myocardium; simply said: how to distinguish when the virus is responsible for the development of LV dysfunction and DCM, respectively, and it is still worth to fight with him by specific treatment approaches, and when the virus sitting in the myocardium is just an "innocent bystander". In this context, main attention is currently paid to quantification of viral load and replication [28].

Furthermore, the patients followed in previously mentioned studies were diagnosed within the first or at the beginning of the second decade of this century and thus were not treated with the whole pharmacological armamentarium available at current era. In the study of Kindermann et al., 85% of patients took ACE inhibitors or angiotensin receptor antagonist, but only 57% of were treated with betablockers and 38% with aldosterone antagonists, respectively; similar numbers may be found in the study of Kühl et al. [9,10]. On the other hand, all patients in the study of Krejčí et al. were treated with

the same heart failure medication based on current recommendations and the difference between evolutions of LV ejection fraction of patients with positive and negative EMB evidence for myocardial inflammation was noted. In almost similarly conducted study, Zimermann et al. followed 82 patients with DCM for 7 months after EMB and found significant improvement in functional status and LV echocardiographic parameters in both patients with and without immunohistochemical signs of inflammation treated by standard heart failure medication; however, significantly better outcome concerning echocardiographic parameters and NYHA classification was observed in subjects with baseline EMB positivity for myocardial inflammation [29]. Of note, almost all patients in both groups were treated by ACE inhibitors/angiotensin receptor blockers and betablockers. One may thus hypothesize that EMB positivity of myocardial inflammation might represent a good prognostic indicator for positive LV response to modern heart failure medical therapy and higher probability of at least partial LV reversal remodeling and functional recovery. Of course, further studies investigating this issue are needed. Nevertheless, it is clear that in considerable number of patients with recent-onset DCM a significant improvement of initially severely depressed LV ejection fraction will occur as was also documented in some other recent studies [30,31]. Therefore, as already stated in current European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure, a primary preventive implantation of the implantable cardioverter-defibrillator in patients with newly diagnosed DCM should be considered only after a sufficient period of optimal medical therapy (at least 3 months) after which LV ejection fraction remains below 35% [32].

To conclude, there are many questions left unanswered concerning the diagnostics, prognosis and treatment of ICM. Some were already mentioned above: more precise definition of clinical and prognostic relevance of persistent viral genome in the myocardium as well as myocardial inflammation, accurate identification of the individuals with newly diagnosed DCM whose LV systolic function will considerably improve or even normalize with standard heart failure medication and those who's LV will not be able to reverse remodeling. Together with these issues, more work is needed to determine who and when will benefit from tailored antiviral, immunomodulatory or immunosuppressive therapy. The fascinating story on better understanding ICM goes on!

REFERENCES

[1] P. Elliott, B. Andersson, E. Arbustini, et al., Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases, European Heart Journal 29 (2008) 270–276.

[2] A. Aleksova, G. Sabbadini, M. Merlo, et al., Natural history of dilated cardiomyopathy: from asymptomatic left ventricular dysfunction to heart failure—a subgroup analysis from the Trieste Cardiomyopathy Registry, Journal of Cardiovascular Medicine 10 (2009) 699–705.

[3] J. Stehlik, L.B. Edwards, A.Y. Kucheryavaya, et al., The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult heart transplant report—2010, Journal of Heart and Lung Transplantation 29 (2010) 1089–1103.

[4] N.K. Lakdawala, B.H. Funke, S. Baxter, et al., Genetic testing for dilated cardiomyopathy in clinical practice, Journal of Cardiac Failure 18 (2012) 296–303.

[5] A.M. Feldman, D. McNamara, Myocarditis, New England Journal of Medicine 343 (2000) 1388–1398.

[6] I. Kindermann, C. Barth, F. Mahfoud, et al., Update on myocarditis, Journal of the American College of Cardiology 59 (2012) 779–792.

[7] P. Richardson, W. McKenna, M. Bristow, et al., Report of the 1995 World Health Organization/international society and federation of cardiology task force on the definition and classification of cardiomyopathies, Circulation 93 (1996) 841–842.

[8] H.T. Aretz, M. Billingham, E. Olsen, et al., Myocarditis: the Dallas criteria, Human Pathology 18 (1987) 619–624.

[9] K.L. Baughman, Diagnosis of myocarditis: death of Dallas criteria, Circulation 113 (2006) 593–595.

[10] J.W. Mason, J.B. O'Connell, A. Herskowitz, et al., A clinical trial of immunosuppressive therapy for myocarditis, New England Journal of Medicine 333 (1995) 269–275.

[11] H.P. Schultheiss, Dilated cardiomyopathy—a chronic myocarditis? New aspects on diagnosis and therapy, Zeitschrift für Kardiologie 82 (Suppl. 4) (1993) S25–S32.

[12] U. Kühl, M. Pauschinger, H.P. Schultheiss, Etiopathogenetic differentiation of inflammatory cardiomyopathy. Immunosuppression and immunomodulation, Internist 38 (1997) 590–601.

[13] B. Maisch, B. Bultman, S. Factor, et al., World Heart Federation consensus conference's definition of inflammatory cardiomyopathy (myocarditis): report from two expert committees on histology and viral cardiomyopathy, Heartbeat 4 (1999) 3–4.

[14] B. Maisch, S. Pankuweit, Current treatment options in (peri) myocarditis and inflammatory cardiomyopathy, Herz 37 (2012) 644–656.

[15] H.P. Schultheiss, U. Kühl, L.T. Cooper, The management of myocarditis, European Heart Journal 32 (2011) 2616–2625.

[16] P. Kuchynka, T. Paleček, S. Šimek, et al., Inflammatory cardiomyopathy: current concepts regarding its diagnosis and treatment, Cor et Vasa 51 (2009) 32–37.

[17] A. Frustaci, M.A. Russo, C. Chimenti, Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study, European Heart Journal 30 (2009) 1995–2002.

[18] T. Paleček, P. Kuchynka, D. Hulínska, et al., Presence of *Borrelia burgdorferi* in endomyocardial biopsies in patients with new-onset unexplained dilated cardiomyopathy, Medical Microbiology and Immunology 199 (2010) 139–143.

[19] U. Kühl, M. Pauschinger, P.L. Schwimmbeck, et al., Interferon-beta treatment eliminates cardiotropic viruses and improves left ventricular function in patients with myocardial persistence of viral genomes and left ventricular dysfunction, Circulation 107 (2003) 2793–2798.

[20] A.L. Caforio, F. Calabrese, A. Angelini, et al., A prospective study of biopsy-proven myocarditis: prognostic relevance of clinical and aetiopathogenetic features at diagnosis, European Heart Journal 28 (2007) 1326–1333.

[21] U. Kühl, M. Pauschinger, B. Seeberg, et al., Viral persistence in the myocardium is associated with progressive cardiac dysfunction, Circulation 112 (2005) 1965–1970.

[22] H.J. Why, B.T. Meany, P.J. Richardson, et al., Clinical and prognostic significance of detection of enteroviral RNA in the myocardium of patients with myocarditis or dilated cardiomyopathy, Circulation 89 (1994) 2582–2589.

[23] I. Kindermann, M. Kindermann, R. Kandolf, et al., Predictors of outcome in patients with suspected myocarditis, Circulation 118 (2008) 639–648.
[24] J. Krejčí, H. Poloczková, P. Hude, et al., Impact of inflammatory infiltration and viral genome presence in myocardium on the changes of echocardiographic parameters, Cor et Vasa (2013).
[25] F. Kuethe, J. Lindner, K. Matschke, et al., Prevalence of parvovirus B19 and human bocavirus DNA in the heart of patients with no evidence of dilated cardiomyopathy or myocarditis, Clinical Infectious Diseases 49 (2009) 1660–1666.
[26] U. Lotze, R. Egerer, B. Glück, et al., Low level myocardial parvovirus B19 persistence is a frequent finding in patients with heart disease but unrelated to ongoing myocardial injury, Journal of Medical Virology 82 (2010) 1449–1457.
[27] F. Kuethe, H.H. Sigusch, K. Hilbig, et al., Detection of viral genome in the myocardium: lack of prognostic and functional relevance in patients with acute dilated cardiomyopathy, American Heart Journal 153 (2007) 850–858.
[28] C.T. Bock, K. Klingel, R. Kandolf, Human parvovirus B19-associated myocarditis, New England Journal of Medicine 362 (2010) 1248–1249.
[29] O. Zimmermann, M. Kochs, T.P. Zwaka, et al., Myocardial biopsy based classification and treatment in patients with dilated cardiomyopathy, International Journal of Cardiology 104 (2005) 92–100.
[30] W.A. Teeter, J.T. Thibodeau, K. Rao, et al., The natural history of new-onset heart failure with a severely depressed left ventricular ejection fraction: implications for timing of implantable cardioverter-defibrillator implantation, American Heart Journal 164 (2012) 358–364.
[31] R. Sheppard, P.J. Mather, J.D. Alexis, et al., Implantable cardiac defibrillators and sudden death in recent onset nonischemic cardiomyopathy: results from IMAC2, Journal of Cardiac Failure 18 (2012) 675–681.
[32] J.J. McMurray, S. Adamopoulos, S.D. Anker, et al., ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC, European Heart Journal 33 (2012) 1787–1847.

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