

Editorial

Infection and inflammation in the cardiovascular system

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1. Infection and inflammation in the cardiovascular system

Infectious disease is one of the few genuine adventures left in the world.

Hans Zinsser (1878–1940), Rats, Lice and History

Infection and inflammation of the cardiovascular system are a frequent cause of cardiac and/or vascular disease, which represents an enormous clinical burden in adult medicine. Major advances have now occurred in understanding cellular and molecular bases of a wide variety of inflammatory cardiovascular diseases. Some of these (myocarditis) have been recognized as inflammatory disease for a long time. Of others (atherosclerosis), the inflammatory nature of disease and possible involvement of bacterial antigens therein has emerged only recently. In both cases however, new insights in inflammatory mechanisms will have great impact on clinical thinking and management. Therefore, *Cardiovascular Research* has decided to devote a spotlight issue to this topic. This issue contains 10 review articles that provide state-of-the-art knowledge and, in addition, 14 original papers with novel data on the intriguing relationship between infection/inflammation and cardiovascular disease.

2. Inflammation and infection in the myocardium

Historically, myocarditis has been the cause of a great deal of clinical and pathologic confusion and debate. Though the term *myocarditis* goes back to the 1800s, it was only in 1941 that histologic myocarditis was discerned from ischemic heart disease. Until the introduction of the

endomyocardial biptome in 1962, myocarditis was diagnosed during life often presumptive and not always correct, mainly in young patients with heart failure preceded by a febrile illness. Most cases were diagnosed as late as at autopsy. Confusion was further heightened by lack of agreement among clinicians regarding indications for endomyocardial biopsy as well as interpretation of biopsy findings. Histologic criteria for myocarditis are still a matter of debate among pathologists, and it has become now increasingly apparent that more attention should be given to serologic, molecular and immunologic factors in order to fully characterize the disease.

According to the 1995 World Health Organization (WHO)/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathy [1], inflammatory cardiomyopathy is now included as a subtype of specific cardiomyopathies, defined as myocarditis in association with cardiac dysfunction. Infectious, autoimmune, and idiopathic forms of inflammatory heart disease have been recognized. There is reasonable clinical and experimental evidence that dilated cardiomyopathy may occur as a late consequence of myocarditis, thus the two entities may very well represent two stages of the same disease. However, dilated cardiomyopathy represents the end stage of a variety of insults to the myocardium, of which indeed some, but certainly not all evoke an inflammatory response.

There are a large number of agents, infectious and non-infectious, that can cause myocarditis. Since Gore and Saphir demonstrated in 1947 that rheumatic and diphtheritic myocarditis each constituted only 10% of a series of 1402 cases of myocarditis, increasing attention has been paid to other forms of myocarditis. These forms comprise viral myocarditis, e.g. by enteroviruses, adenoviruses or herpes viruses. During the past few years, human immunodeficiency virus (HIV) has fast become the most common cause of myocarditis observed at necropsy. An important parasitic form of myocarditis is caused

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by the protozoan *Trypanosoma cruzi*. It was first described in 1909 by the Brazilian physician Carlos Chagas who also reported the cycle of infection and the pathologic findings in each phase of the disease. The disease is endemic in Latin America with 16 to 18 million infected individuals and 100 million at risk for infection; as a result of modern transportation and immigration, Chagas' heart disease is now a worldwide problem, especially in the United States, where also 500 000 persons are estimated to be infected.

2.1. In this spotlight issue

Major factors that contribute to infectious myocarditis and the various diagnostic modalities with particular emphasis to molecular techniques like PCR and gene sequencing are extensively discussed by Calabrese et al. [2]. Mason provides an overview of multiple pathogenetic mechanisms that play a crucial role in the development and progression of the disease [3]. As underlined by the author, many of these mechanisms that act in a chronological cascade can overlap in some cases, rendering the diagnosis and treatment difficult. Since 1974 when Woodruff first demonstrated a determinant role of T-lymphocytes in the pathogenesis of murine myocarditis, considerable attention has been drawn to determine the role of different T-cell subtypes in the immunopathogenesis of viral myocarditis. The original article of Yndestad et al. [4] deals with the source of T-cells and mechanisms of T-cell activation in chronic heart failure. They conclude that the inflammatory response of T-lymphocytes appears independent of the etiology of the disorder. Different proinflammatory cytokines have a critical role in the development and progression of myocarditis and many of the detrimental effects on myocardium seem to be strictly related to overproduction of nitric oxide (NO). However, in the experimental model of intrauterine infection Rounioja et al. [5] have demonstrated that severe foetal cardiac dysfunction is linked to overproduction of cytokines through mechanisms independent of NO. With the use of an animal model, Tessier et al. [6] demonstrated the occurrence of severe impairment of cardiac glucose metabolism in endotoxin-induced inflammation, thus providing more insight into cardiac function during sepsis or critical illness. Cardiac abnormalities are an important complication of AIDS. Different etiological factors such as primary HIV infection of the myocardium, superinfections, substance abuse, HIV-related neoplasms or the sequelae of drug therapy (highly active antiretroviral therapy—HAART) are reviewed by Barbaro [7]. Due to the adverse effects of HAART, the author emphasizes the importance of careful assessing of HIV infected patients and patients already under antiretroviral treatment. When HIV infection is the only principal etiological factor, the pathogenesis is yet not clear: direct retroviral action and/or focal infiltration of activated immune cells have been mainly postulated. In mice with AIDS-related-cardiomyopathy Chaves et al. [8] demonstrated an increase of cardiac myocyte

protein nitration rather than focal immune cell lesions. Zidovudine (originally called AZT), developed in 1987 in North Carolina for the treatment of AIDS, is an antiviral drug used to reduce the severity of AIDS-related conditions. However, one of the most important adverse effects of the drug is on the cardiovascular system. Hypertrophy of the interventricular septum, modified vascular smooth muscle responsiveness, and a modest increase in systolic blood pressure have been shown by Ruga et al. [9] in rats treated with AZT for 240 days. Among non-viral infections, the present issue also focuses on Chagas' disease. De Lourdes Higuchi et al. [10] provide an in-depth overview of the pathology of the heart in Chagas' disease. The authors emphasize that an inflammatory response with often accentuated exacerbation is most likely responsible for progressive neuronal damage, microcirculatory alterations and changes in extracellular matrix of the heart, ultimately leading to organ failure.

3. Inflammation and infection in the vascular system

Infectious disease and inflammation have been the focus of attention for the last two decades. The observation that inflammatory cells not only play a role in the pathogenesis of the atherosclerotic plaque, but may also determine the progression from a stable vascular lesion to an unstable (ruptured) plaque and ensuing acute vascular event has sparked the interest in the interaction between inflammation and vascular disease. In fact, even low grade inflammation (for example as reflected by slightly elevated levels of C-reactive protein) seems to predict the clinical outcome of patients with atherosclerosis, in terms of developing acute thrombotic events as a result of atherosclerotic plaque rupture. There are many areas of interest where inflammation meets vascular biology, from vascular remodelling as a response to inflammatory processes, inflammation as part of ischemia–reperfusion syndromes, extensive cross-talk between inflammation and coagulation, and modulation of vascular cell and lipoprotein metabolism by inflammatory mediators. Conversely, pharmacological agents known to interfere in vascular disease often display additional effects that interfere with inflammatory mechanisms.

It is a matter of debate whether the inflammatory response is merely a matter of host-response upon developing vascular abnormalities and toxic agents or should be viewed as an underlying independent process in the pathogenesis of vascular disease. In that respect the hypotheses that infectious agents, eliciting inflammatory responses, may initiate or amplify atherosclerotic changes is of interest. Although there are many infectious agents, such as *Mycoplasma*, *Chlamydia* species or *Cytomegalovirus*, that have been implicated in the pathogenesis of vascular disease and (remnants of) these agents sometimes are identified in atherosclerotic lesions, it is still

unclear whether these microorganisms are truly etiologic factors rather than innocent bystanders.

3.1. In this spotlight issue

Keller et al. [11] present a review on the effect of various infections on endothelial cells, describing a number of effects various pathogens may have on endothelial functions. Infections with *Chlamydia pneumoniae* and vascular disease are further highlighted in two original contributions. One of these manuscripts focuses on placental infection with *Chlamydia pneumoniae* and intrauterine growth restriction [12] and the other deals with *Chlamydia*-induced atherosclerosis by modulation of inducible nitric oxide synthase [13]. The link between infectious agents and cardiovascular disease is further outlined in the overview by de Kleijn et al. [14] focused on the participation of the recently characterized family of Toll-like receptors in the process of neointima formation and atherosclerotic plaque formation. Another immunological pathway involved in atherosclerosis is antigen-specific T-cell activation, in which a myriad of antigens appears to play a role, as explained in the review by de Boer et al. [15]. Besides the important role of inflammatory cytokines as mediators of these inflammatory processes, other regulators of the immune response have recently been identified. Phospholipase A2 represent one of these mediatory pathways, as evidenced in the contribution of Niessen et al. [16]. Two original papers on the role of chronic inhibition of cyclooxygenase-2 and the effect of reactive oxygen species thereon further highlight the involvement of such pathways [17,18]. Another original manuscript in this series deals with components of the complement cascade secreted by another type of inflammatory cell inside the atherosclerotic plaque: the dendritic cell [19]. The clinical relevance of inflammatory mediators and acute phase reactants in patients undergoing percutaneous coronary interventions is underlined by the original article of Rahel et al. [20]. Lastly, Levi et al. [21] discuss the differential effects of infectious agents and inflammatory responses on various pathways of the coagulation system. This is further elaborated in the review by Peters et al. [22], dealing with the molecular basis of endothelial dysfunction in sepsis. The intricate relationship between infection, host-response, mediatory pathways, coagulation and fibrinolysis is the subject of two other original articles in this spotlight issue, one dealing with the relationship between inhibition of intervention in the kinin–angiotensin system and coagulation [23] and the other regarding the involvement of fibrinolytic and extracellular matrix proteins and vascular remodelling [24].

4. Future perspectives

As evidenced by the reviews as well as by the original articles of this special issue, many new insights have been

made in the field of cardiovascular infection and inflammation. The application of molecular techniques on myocardial tissue has improved the sensitivity to detect viral inflammatory cardiomyopathy. Numerous studies of patients with myocarditis have demonstrated the usefulness of PCR analysis for etiologic diagnosis. These new diagnostic tools in the future will enable a tailored therapy. The molecular determinants of cardiac viral infections are now under intense investigation because an understanding of these determinants may lead to an explanation for the highly variable clinical course. In the modern molecular era the complex infective agents–host interaction will be clarified which will lead to a better knowledge of inflammatory cardiomyopathy and will significantly change our management of this disease in the near future.

Similarly, in vascular disease, more knowledge on the various mechanisms that play a role in atherogenesis and other types of vascular disorders will likely provide new therapeutic targets for prevention and treatment of disease. Since infection and inflammation are intricately involved in the pathogenesis of vascular disorders, it is likely that new therapeutic strategies, aimed at components or pathways of inflammatory responses will find a place in the therapeutic armoury to prevent or treat vascular disease.

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