CHAPTER 1

General introduction and outline of the thesis
INTRODUCTION

Inflammation of the cardiovascular system plays a crucial role in the pathogenesis of a broad range of cardiovascular diseases. Manifestations of cardiovascular inflammation may vary widely, depending on the severity of the disease and the affected part of the cardiovascular system, which may involve the myocardium, pericardium, cardiac valves, conduction system and vasculature. Infectious, auto-immune, systemic, and toxic agents can all elicit cardiovascular inflammation (Figure 1.1). However, many individuals who are exposed to these causative agents will never develop inflammation. Those who do develop inflammation can have clinically silent inflammation or present with symptoms ranging from mild symptoms only to severe heart failure or even sudden cardiac death. Immunogenetic and environmental factors are presumed to be important determinants of this variability in disease susceptibility and outcome.

Recognition of cardiovascular inflammation in clinical practice

Tissue analysis by immunohistochemistry and polymerase chain reaction is considered the gold standard for diagnosing cardiovascular inflammation and its underlying causes. A tissue sample of the myocardium can be obtained safely and effectively by an endomyocardial biopsy (EMB). Despite its potential diagnostic and therapeutic implication, EMB is limited by a low sensitivity due to sampling error, a poor interobserver agreement, and complications such as stroke and cardiac perforation occurring on rare occasions. Furthermore, it is not always possible to obtain tissue samples of affected sites. For these reasons, the diagnosis is often based on a combination of clinical criteria with non-invasive diagnostic test results. In this context, clinical symptoms, electrocardiography, blood biomarkers and echocardiography are relatively unspecific and have a low sensitivity. Cardiovascular magnetic resonance (CMR), on the other hand, allows in-vivo characterization of the myocardial tissue, which can be useful in establishing the diagnosis of myocarditis. However, CMR cannot determine the underlying cause of inflammation and has a relatively poor sensitivity in cases of chronic and low-grade inflammation. As a result of the clinical complexity and the drawbacks of available diagnostic tools, the evaluation of cardiovascular inflammation continues to be a major challenge, which hinders the development of effective preventive and treatment strategies (Figure 1.2).

Myocarditis

Myocarditis is the most impressive and typical example of cardiovascular inflammation, being one of the leading causes of sudden cardiac death and dilated cardiomyopathy.
Figure 1.1: Inflammation of the cardiovascular system can be the result of infectious, auto-immune, systemic, and toxic causes. Immunogenetic and environmental factors are presumed to mediate disease susceptibility and outcomes. Electrocardiography, echocardiography, coronary angiography and blood biomarkers are important diagnostic tests that can help rule out other cardiovascular diseases and to monitor disease processes. To diagnose cardiovascular inflammation, characterization of the affected tissue is required, which can be achieved non-invasively by cardiovascular magnetic resonance or invasively by endomyocardial biopsy. Although both have their own limitations, endomyocardial biopsy is considered the diagnostic gold standard.
in young adults, and an important cause of symptoms such as chest pain, dyspnoea and palpitations\textsuperscript{17-19}. The disease thereby carries a heavy burden in previously healthy individuals. Myocarditis, in most cases, results from an infection of the myocardium by common cough viruses, including adenovirus, enterovirus, Epstein-Barr virus, human herpes virus 4 and 6, parvovirus B19, and cytomegalovirus. Although most people will encounter these cardiotropic viruses during their lifetime, only a small number of patients will actually develop viral myocarditis. As discussed previously, this heterogeneity is most likely due to a complex interplay of immunogenetic susceptibility and environmental factors, leading to an exaggerated inflammatory response against the virus\textsuperscript{20-23}. After the acute phase, the disease follows a relatively benign course in most patients, especially in those who present with chest pain and preserved cardiac function\textsuperscript{24-26}. However, inflammation may persist in a subclinical form, due to a viral-induced auto-immune response or a persisting viral infection\textsuperscript{27-32}. Consequently, the disease may progress to dilated cardiomyopathy in approximately 20% of the patients with viral myocarditis\textsuperscript{33}. It is therefore crucial to detect the disease early in its course and prevent persisting inflammation that may lead to dilated cardiomyopathy and end-stage heart failure.

**Cardiovascular inflammation in ankylosing spondylitis**

Cardiovascular inflammation may also occur in the setting of rheumatic autoimmune disease, of which systemic sclerosis, systemic lupus erythematosus, and rheumatoid arthritis
are the most well-known and most extensively studied. Little is however known about cardiovascular involvement in ankylosing spondylitis (AS). AS is a relatively common inflammatory rheumatic disease, characterized by arthritis of the spine and sacro-iliac joints. Several epidemiological studies have reported higher rates of cardiovascular death in patients with AS compared to the general population, which remained after correcting for traditional cardiovascular risk factors, suggesting a contributing role for inflammation. To evaluate cardiovascular involvement in AS, two autopsy studies have examined post-mortem heart of patients with AS and found aortic root thickening and interstitial myocardial fibrosis. Cardiovascular involvement in AS has been further clarified by studies that used echocardiography, demonstrating increased prevalence of left ventricular (LV) diastolic dysfunction, aortic root dilation, and aortic valve regurgitation. Furthermore, two studies have reported increased aortic stiffening in AS, although this was not found by others. No studies so far have used CMR to evaluate cardiovascular involvement in AS, although this will likely provide incremental insights into its morphology and pathophysiology.

Cardiovascular inflammation in acute myocardial infarction

Inflammation appears to be major factor in predisposing atherosclerotic plaques to rupture and produce thrombosis, which is the most common cause of acute myocardial infarction (AMI). Multiple clinical studies, in both patients and healthy subjects, have demonstrated an association between high levels of inflammatory markers and future cardiovascular events. Furthermore, autopsy studies in patients who died of AMI have found widespread inflammation of the coronary artery tree. Although the underlying trigger of this inflammation is still largely unknown, a viral infection, either coronary or noncoronary, might be one of the factors. This is supported by the observation that the incidence of AMI and respiratory infections both follow a seasonal pattern, being highest during winter. Furthermore, influenza infection has been consistently associated with a greater risk of AMI, while vaccination against influenza is associated with a reduced risk. Inflammation, besides implicated in the development of AMI, is also the result of the disease. Following AMI, cardiomyocyte death and extracellular matrix degradation activates an extensive inflammatory cascade, both locally at the site of infarction, as well as systemically in the blood and remote sites. This post-AMI inflammation is an extremely complex process that, on the one hand, is crucial for effective cardiac repair, but on the other, may contribute to adverse remodelling. Better knowledge of the inflammatory processes involved in the development of and recovery from AMI, together with improved imaging techniques to characterize this inflammation, may help identify patients at increased risk.
OUTLINE OF THE THESIS

The aim of this thesis was to improve the detection, characterization and staging of cardiovascular inflammation and its pathophysiological features in patients with suspected myocarditis (Part I), patients with ankylosing spondylitis (Part II), and patients with AMI (Part III), by using new CMR and immunohistochemical methods.

Part I

Chapter 2 provides a comprehensive overview of current diagnostic tools for assessing myocarditis, including electrocardiography, blood biomarkers, echocardiography, CMR, and EMB. In addition, several promising new techniques that may help improve the diagnostic work-up are discussed, including CMR T1 and T2 mapping, microRNA profiling and a skeletal muscle biopsy. In Chapter 3, the diagnostic yield of CMR was evaluated in a large clinical population with suspected acute myocarditis, and its additional value above non-CMR diagnostic methods was determined. Chapter 4 reports a proof-of-principle study in which the diagnostic potential of a skeletal muscle biopsy was investigated. It was hypothesized that skeletal muscle may reflect the pathology of the heart in myocarditis and, as such, a skeletal muscle biopsy might have diagnostic value. In Chapter 5, the sensitivity of two different immunohistochemical lymphocyte markers to diagnose myocarditis were compared. To do so, heart tissues were analysed from post-mortem patients with myocarditis and from mice with acute viral myocarditis.

Part II

Chapter 6 reports a prospective study in which we evaluated cardiac involvement in AS by using a comprehensive CMR protocol that included cine imaging, late gadolinium enhancement, T1 mapping, and T2 mapping. In Chapter 7, aortic stiffness was assessed in patients with AS by velocity-encoded and anatomical CMR imaging, which allowed measuring pulse wave velocity (PWV) in the aortic arch. Aortic arch PWV measurements of the AS cohort were compared to a matched control group of healthy individuals. In addition, the association of aortic stiffness with AS characteristics and LV remodelling was determined.

Part III

Chapter 8 concerns the assessment of tissue changes in remote myocardium after AMI and its association with inflammatory markers and LV remodelling. For this purpose, CMR with
cine imaging, late gadolinium enhancement, and T1 mapping was performed in patients with AMI in both the acute and subacute phase. In Chapter 9, it was hypothesized that myocarditis may facilitate the development of AMI through coronary inflammation and atherosclerotic plaque destabilization. For this purpose, an autopsy study was performed in which coronary inflammation and plaque vulnerability was evaluated in patients with both myocarditis and AMI and in patients with myocarditis only. These two groups were then compared to patients with AMI only and controls who died of non-cardiac causes.

Finally, Chapter 10 provides a summary of the thesis and discusses future perspectives.

REFERENCES

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