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Acute Myocarditis – A Trigger of Cardiac Autoimmunity?

Expected Insights from the Etiology, Titre-Course, and Effect on Survival of Cardiac Autoantibodies (ETiCS) Study

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1. Introduction

Progressive cardiac dilatation and pump failure of unknown aetiology - termed “idiopathic” dilated cardiomyopathy (DCM) (Richardson et al., 1996; Maron et al., 2006) - represents one of the main causes of severe heart failure in Western populations with an annual incidence of about 100 and a prevalence of 300-400 patients per year (American Heart Association, 2009). The large majority of cases are thought to arise from an initial (mostly viral) infection leading to acute myocardial inflammation. Acute myocarditis may either heal (about one third of the cases) or progress to a chronic inflammatory process with continued fibrotic repair, subsequent dilatation of the left and/or right ventricle and -finally- severe congestive heart failure (about another third of the patients). Progression to DCM appears to occur particularly, when associated (a) with chronic inflammation of the myocardium due to viral persistence (Kühl et al., 2005) and/or (b) with the development of autoantibodies directed against distinct sarcoplasmatic or myocyte membrane proteins that are essential for cardiac function (Freedman & Lefkowitz, 2004; Jahns et al., 2006). The latter findings are further strengthened by the fact that patients with DCM often have alterations in both, their innate and their adaptive immune system (Limas, 1997; Luppi et al., 1998; Jahns et al., 2006; Mahrholdt et al., 2006). Thus, under certain conditions an initial acute inflammatory reaction may proceed into a kind of low-grade inflammation (MacLellan & Lysis, 2003) facilitating the development of abnormal or misled immune responses to the primary (infectious)

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trigger (MacLellan & Lusis, 2003; Freedman & Lefkowitz, 2004; Kühl et al., 2005; Smulski et al., 2006; Maekawa et al., 2007). More recently, a detailed molecular analysis of T cell infiltrates in human endomyocardial biopsies (EMBs) from both, patients with acute myocarditis and patients with (post-)inflammatory DCM revealed an increased expression of CD3d, CD3z, and T cell receptor beta constant region (TRBC) in both disease entities. However, differential expression of functional T cell markers was found in DCM EMBs only (dominance of Th1 markers, regulatory [FoxP3] T cells, and cytotoxic T cells (CTLs)) and not in acute myocarditis. Additionally, in DCM EMBs some Th2 marker genes were increased, indicating that a Th2 response (required for T/B cell interactions) also participates in the T cell infiltrates in DCM (Noutsias et al., 2011). This might explain, why a substantial number of DCM patients have been found to develop cross-reacting antibodies and/or autoantibodies to different cardiac self-antigens, including mitochondrial proteins (e.g., adenine nucleotide translocator, lipoamide and pyruvate dehydrogenase (Schultheiss & Bolte, 1985; Schultheiss et al., 1988; Pohlner et al., 1997; Schulze et al., 1999)), sarcoplasmatic proteins (e.g., actin, laminin, myosin, troponin (Neumann et al., 1990; Caforio et al., 2002; Okazaki et al., 2003; Göser et al., 2006; Li et al., 2006)), and membrane proteins (e.g., cell surface adrenergic or muscarinergic receptors (Fu, L.X.M. et al., 1993; Magnusson et al., 1994; Jahns et al., 1999; Christ et al., 2006)).

Irrespective of whether development of DCM is primarily due to chronic myocardial infection (Kühl et al., 1996) or to abnormalities in the adaptive or innate immune system (Luppi et al., 1998; Eriksson et al., 2003), in both cases cardiac tissue injury is believed to be mediated mainly by cytokines and/or heart-specific autoantibodies (Caforio et al., 1995; Limas, 1997; Eriksson et al., 2003). However, the pathophysiological relevance of each of the aforementioned cardiac autoantibodies (aabs) is far from clear. Low titers of autoantibodies to various house-keeping antigens can also be detected in healthy subjects as a part of the natural immunological repertoire (Rose, 2001).

In addition, under physiological conditions at least the intracellularly localized cardiac antigens are not easily accessible for the immune system. Thus, the mechanisms by which autoimmune-mediated myocardial injury is initiated are mostly based on indirect or circumstantial evidence (Limas, 1997). The potential pathophysiological - and thus clinical - relevance of a heart-specific autoantibody depends on its disease-inducing or -aggravating potential, which in turn is supposed to be associated with both the *accessibility* and the *functional relevance* of its target. Therefore, autoantibodies directed against cell surface key constituents, and in particular aabs that have the potential to affect myocardial contraction and relaxation (e.g., by interaction with the cardiac beta1-adrenoceptor (beta1-AR)) and/or the M2-muscarinic acetylcholine receptor (M2-AchR)) represent key candidates involved in the initiation and/or progression of DCM (Fu et al. 1993, 2008; Magnusson et al., 1996; Limas, 1997; Engelhardt et al., 2004; Jahns et al., 2004; Freedman & Lefkowitz, 2004). Whereas anti-muscarinic antibodies (exhibiting an agonist-like effect on cardiac M2-AchR) have been associated with negative chronotropic effects at the sinuatrial level (e.g., sinus node dysfunction, atrial fibrillation (Wang et al., 1996; Baba et al., 2004)), functionally activating anti-beta1-AR antibodies have been associated with both the occurrence of severe arrhythmias at the ventricular level, and the development of (maladaptive) left ventricular hypertrophy, finally switching to left ventricular enlargement and progressive heart failure (Jahns et al., 1999, 2006; Iwata et al., 2001; Engelhardt et al., 2004; Störk et al., 2006). In addition, both autoantibodies seem to target the (easily accessible) second extracellular loop of the respective receptors.

To generate an autoimmune response, myocyte membrane proteins (including receptors) must be degraded to small oligopeptides able to form a complex with a major histocompatibility (MHC) class II or human leukocyte antigen (HLA) molecule of the host (Hoebeke et al., 1996). In previous clinical studies autoimmunity has been found to be associated with certain HLA- and MHC class II-phenotypes (Limas, 1996), and also with the expression and/or activity of the T-lymphocyte antigen 4 (CTLA-4) - known as a potent (indirect) suppressor of the immune system (Golden et al., 2005). Therefore, another important point to consider in the development of (human) post-inflammatory and/or post-ischemic cardiomyopathy is the patients' genetic pre-disposition, which will determine both, the susceptibility to self-directed immune reactions and the phenotypic expression of the myocardial disease (MacLellan & Lusic, 2003; Limas et al., 2004).

On this background the following book-chapter will review current knowledge and recent experimental and clinical evidence for the potential role of cardiac autoantibodies in the pathogenesis of DCM focussing on the rationale and expected insights from the prospective diagnostic multicentre Etiology, Titre-Course, and (effect on) Survival of cardiac autoantibodies (ETiCS) study.

2. Rationale and scope of the ETiCS study

Evidence for a pathophysiologic role of autoimmunity in human heart disease has substantially increased during the past two decades, but the true prevalence and clinical impact of cardiac autoantibodies (aabs) in human heart disease are still unclear, as are the events leading to their formation, their frequency of appearance, and their kinetics (that is, their patterns of clearance and/or persistence).

In this regard, the investigator-initiated diagnostic multicentre ETiCS study will prospectively address the hypothesis that a first inflammatory (i.e., acute myocarditis (AMiitis)) or ischemic injury of the myocardium (i.e., first acute myocardial infarction (FAMI)) may trigger the development of heart-directed autoimmune reactions (**Fig. 1**).

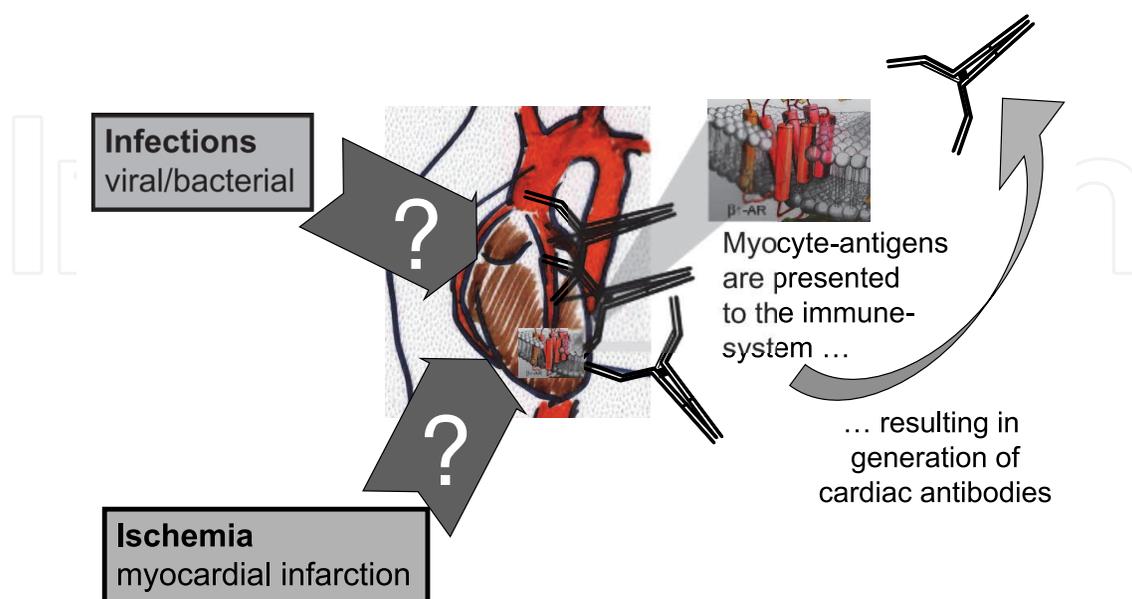


Fig. 1. Formation of autoantibodies against myocardial self-antigens.

Immunogenicity is defined as the property of a molecule to induce an immune response (Hoebeke, 1996). To serve as a potential antigen, myocyte constituents (e.g., cardiac membrane receptors) must be degraded by proteolysis into small fragments (oligopeptides), and one or several of the generated fragments must be able to form a complex with one of the major histocompatibility complexes (class II-MHCs) or human leukocyte antigen (HLA) molecules of the host. When presented to T cells (Harding et al., 1990; Mobini et al., 1999) antigenic parts of such myocyte-derived (self) peptides may engender an immunological response. Acute inflammatory processes are supposed to enhance the occurrence of self-directed immune responses (e.g., acute viral or bacterial myocarditis and/or acute ischemic events (Borda et al., 1984; Latif et al., 1993; Köhl et al., 1996; Limas, 1997; Noutsias et al., 1999; Liu & Mason, 2001; Rose, 2001; Caforio et al., 2002)).

Therefore, we assume that a first substantial inflammatory or ischemic myocyte damage – through liberation of a “critical amount” of cardiac self-antigens previously hidden to the immune system – might induce and perpetuate a disease-causing and/or -modulating autoimmune reaction that deteriorates cardiac function and ultimately results in progressive heart failure.

As a consequence, the ETiCS study has been designed to provide a maximum of sequential clinical and serological data from patients after a first inflammatory or ischemic cardiac event. The development/prevalence and titre-course (clearance/persistence) of distinct cardiac aabs after 0, 3, 6, and 12 months of either event will be prospectively assessed and correlated with the corresponding cardiac functional parameters, cardiac imaging (echocardiography, cardiac magnetic resonance imaging), and clinical outcome. A limited number of ETiCS sub-studies will focus on components of the patients’ immune system potentially involved in the generation of cardiac receptor-aabs – including a search for pre-disposing genotypes (Limas et al., 2004; Caforio & Iliceto, 2008) – and on the possible impact of conformational adrenoceptor-aabs on renal function (Boivin et al., 2001).

Expanding the scope of ETiCS beyond adrenoceptor-directed autoimmunity other known cardiac aabs will be investigated by the respective expert core centres, including aabs against the muscarinic acetylcholine receptor 2 (Fu, L.X.M. et al., 1993), against troponin I (Göser et al., 2006), organ-specific and skeletal muscle cross-reactive anti-heart-aabs (Caforio et al., 2007), and cardio-depressant aabs (Felix et al., 2002). This joint venture will enable a comprehensive characterisation of heart-directed autoimmunity after inflammatory or ischemic disruption of myocardial integrity, and allow for cross-correlations of the titre-course and prognostic impact of all cardiac aabs prospectively analyzed.

3. Design of the ETiCS study

The prospective ETiCS study complies with the standards of Good Clinical Practice (GCP) and has been approved by the Ethics committees of all participating institutions. Within a two years-period ETiCS will include 400 patients with a first cardiac event, 200 of them with acute myocarditis (AMiitis), and 200 patients with a first myocardial infarction (FAMI; acute ST-elevation MI only, without any history or signs of previous myocardial infarction). After inclusion and baseline assessment, the patients will undergo three follow-up visits after 3, 6, and 12 months (Fig. 2). Diagnosis of acute myocarditis is based on at least one major and two minor clinical criteria and/or symptoms (see table 1) and must be confirmed by endomyocardial biopsy (EMB) using either the WHO/ISFC (Richardson et al., 1996; Elliott et al., 2008) or the Dallas criteria (Aretz et al., 1987). This proceeding is in full accordance

with the actual AHA/ACC/ESC scientific statement on the role of EMB in the management of cardiovascular disease (Cooper et al., 2007), which strongly recommends EMB in acute myocarditis because of its potential relevance for outcome and therapeutic decisions (Kindermann et al., 2008; Frustaci et al., 2009). In addition, immunohistology and molecular analysis of the EMBs may also significantly contribute to further elucidate the clinical impact of heart-directed autoimmune reactions.

Suspicion of acute myocarditis (One major and two minor criteria fulfilled)	
Major criteria	ST/T wave changes in the electrocardiograms (ECG) Ventricular arrhythmia (ECG) Pericardial effusion on echocardiography Impairment of LVEF on echocardiography with CAD excluded by coronary angiography (no stenosis >50%)
Minor criteria	Dyspnea, new onset within the past 30 days Chest pain, new onset within the past 30 days Palpitations, new onset within the past 30 days History of infection within the past 30 days Fever >38.0° C within the past 30 days

Table 1. Diagnostic criteria for suspicion of acute myocarditis.

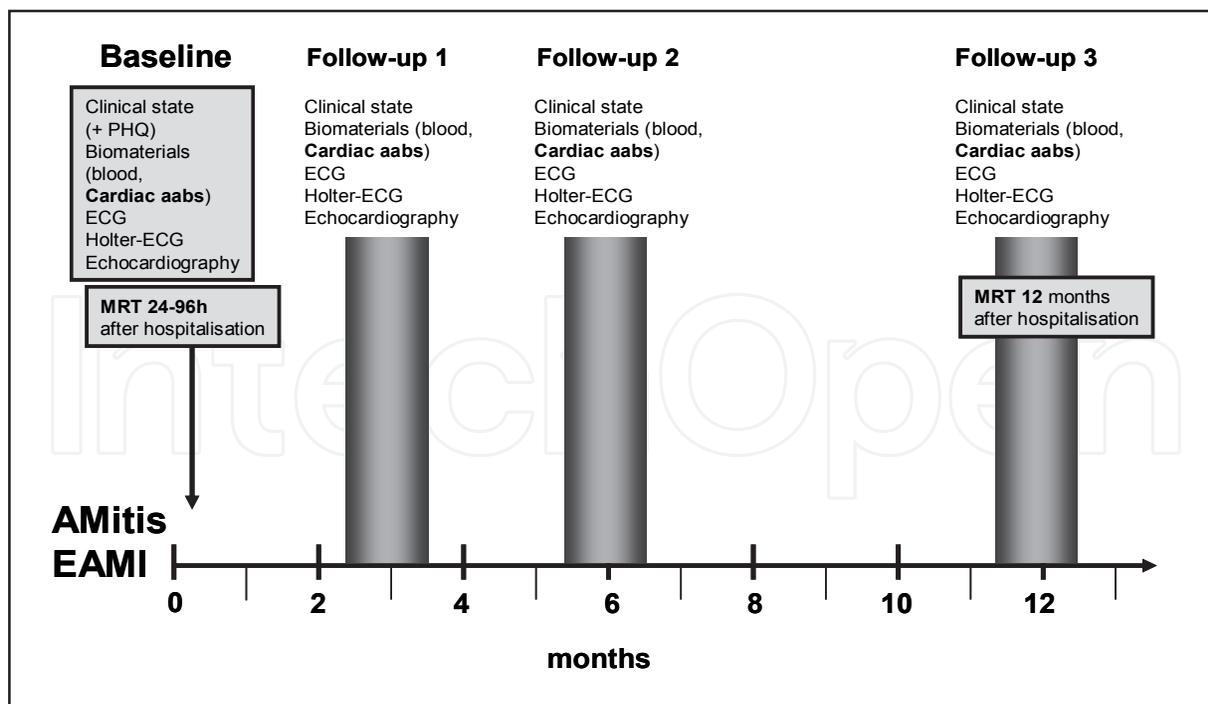


Fig. 2. Time schedule of the follow-up examinations in the ETiCS study.

Echocardiography and cardiac magnetic resonance imaging (cMRI) will be carried out in all patients within 24 to 96 hours of hospitalisation and one year after the respective cardiac

event. Follow-up visits at 3, 6, and 12 months comprise a detailed patient history including medication, physical examination, a standardized health questionnaire, echocardiography, ECG, Holter-ECG, and blood sampling (**Fig. 2**). The sequentially obtained blood samples will serve to determine the time course of formation and the titre-course (clearance/persistence) of distinct cardiac aabs at 0, 3, 6, and 12 months after inflammatory or ischemic cardiac injury (AMitis, FAMI). Three-hundred healthy subjects with normal blood pressure, ECG, and exercise-stress test will serve as a control collective (male to female ratio 1:1, n=50 per five-years age range, no history of myocardial infarction, diabetes, or peripheral vascular disease). The primary endpoint of the planned cross-sectional analyses is the association of a specific cardiac aab status at diagnosis (aab-positive/aab-negative) with (a) the change in cardiac function as derived from sequential echocardiograms and cMRI (baseline *versus* 12 months), and (b) the severity and clinical course of the index disease. Longitudinal primary endpoints are titre-changes of a given cardiac aab over time, conversion rates (persistence/clearance), and the “time to first cardiovascular event” (see table 2 for definition of composite endpoints). Pre-specified secondary endpoints for each of the different cardiac aabs at diagnosis are time to cardiovascular death and time to all-cause death (table 2).

Primary endpoint: prospective ETiCS study
Titre course of conformational cardiac aabs
Secondary endpoints: prospective ETiCS study
Change in left ventricular enddiastolic diameter
Change in left ventricular ejection fraction
Occurrence of ventricular arrhythmias
Change of clinical NYHA classification
Severity of inflammation as assessed by EMB/cMRI
Time to cardiovascular death/all-cause death
Composite endpoints
Cardiovascular Death
Myocardial infarction
Resuscitation (successful or not successful)
ICD discharge, if appropriate
Cardiac transplantation
Sudden cardiac death
Death due to progressive heart failure
Death due to myocardial infarction

Table 2. Pre-defined endpoints of the ETiCS study.

4. ETiCS substudies

4.1 Immunobiology of heart-directed autoreactivity

This substudy attempts to unravel the step-by-step changes occurring in a patients' immune system whilst autoantibody-mediated immune cardiomyopathy develops after inflammatory or ischemic myocardial injury, including the time course and cell types (T and B cell subpopulations) involved in the generation of cardiac aabs. The reactivity and prevalence of receptor (auto)antigen-specific T and B cell populations will be assessed by

antigenic recall assays as well as FACS and Elispot analyses. In addition, the respectively activated immunologic paths will be derived from the Th1/Th2/Th17 cytokine profiles determined in the sera from cardiac autoantibody-positive patients with acute myocarditis (including an analysis of the corresponding EMBs (Noutsias et al, 2011)) or acute transmural myocardial infarction. Since the cytotoxic T-lymphocyte antigen 4 (CTLA-4) is a potent (indirect) suppressor of the immune system, its mutation or hampered expression might promote hyperreactivity to autoantigens (Golden et al., 2005). Thus, in all ETiCS patients CTLA-4 expression and CTLA-4 alleles will be determined by FACS and by PCR, respectively. In addition, in all patients the HLA-DR/DQ and MHC class II haplotypes (Limas et al., 2004; Caforio & Iliceto, 2008) will be determined and correlated with the formation and titre-course of distinct cardiac aabs in order to unravel the individual genetic susceptibility for heart-directed autoimmune reactions.

4.2 Adrenoceptor-autoantibodies and their impact on kidney function

The possible clinical implications of adrenoceptor-directed autoimmunity have gained increasing interest in human heart disease. By contrast, the renal effects of functionally active adrenoceptor-aabs have been almost neglected. Previous immuno-histologic studies on the rat kidney strongly suggest that functionally stimulating adrenoceptor aabs are capable of modulating the secretion of renin from the juxtaglomerular cells *via* renal beta1-AR and, also, to increase the sodium-reabsorption in the distal tubulus (Boivin et al., 2001). Thus, through renal beta1-AR-mediated activation of the renin-angiotensin-aldosterone-system (RAAS) and/or augmentation of the circulating blood volume such aabs might contribute to further worsening of the prognosis of antibody-positive heart failure patients. To assess the impact of adrenoceptor-aabs on kidney function (and clinical outcome), a number of pre-specified renal functional parameters will be sequentially determined in all ETiCS patients (e.g. serum *versus* urine creatinine/sodium/pH; glomerular filtration rate (GFR), urinary protein excretion). Primary endpoints are the relationship between antibody-titres and renal function at baseline and the “time to first cardiovascular event”, adjusted for renal function. Secondary endpoints include the change in renal function dependent on the formation and conversion rates (clearance/persistence) of adrenoceptor-aabs. These data might furnish a rationale for the development of novel therapeutic strategies to protect the kidney(s) from functional adrenoceptor-aabs in aab-positive heart failure patients.

5. Conclusion and expected insights from the ETiCS study

In the last two decades, much knowledge has accumulated with respect to the possible pathophysiologic and clinical implications of heart-directed aabs (Jahns et al., 2006; Fu, M., 2008).

Homologies between cardiomyocyte surface molecules (in particular membrane receptors) and viral or bacterial proteins have been proposed as a mechanism for the elaboration of endogenous cardiac autoantibodies by antigen mimicry (Elies et al., 1996; Hoebeke et al., 1996). Chagas' heart disease, a slowly evolving inflammatory cardiomyopathy, is one of the best investigated examples to highlight this mechanism. The disease is induced by the protozoon *Trypanosoma cruzi*. About 30% of the Chagas' patients develop antibodies that cross-react between the ribosomal P2beta-protein of *T. cruzi* and some specific amino acids present in the second extracellular loop of the human beta1-adrenoceptor (Elies et al., 1996).

Because the large majority of functionally active beta1-aabs detected in DCM patients seem to be directed against the same receptor loop, it was speculated that these antibodies might also originate from molecular mimicry between the beta1-adrenoceptor and hitherto non-identified viral pathogen (Hoebeke, 1996). Another example is Chlamydia-associated heart disease, which in BALBc mice appears to be induced by antigen mimicry between Chlamydia antigens and the alpha-myosin heavy chain molecule, resulting in activation of autoreactive T- and B-cells (Bachmaier et al., 1999).

However, irrespective of (potentially occurring) immunologic cross-reactions, to date no prospective clinical study has ever addressed the key question, whether structural damage to the heart muscle (e.g., necrosis or apoptosis) is a mandatory pre-requisite for the formation of heart-directed aabs.

In general, the immune system will not attack cardiac self-proteins. On a susceptible genetic background, however, this self-inhibition of immune effector cells after cardiac injury may be hampered. It is presently unclear, whether this autoreactivity depends on the kind and extent of injury, the kind and amount (or "dose") of self-antigens presented, or the kind and quality of the subsequently engaged immunologic paths. Regarding the latter aspect, a recent analysis of the expression of functional T cell markers in EMBs from patients with acute myocarditis and patients with chronic (post-inflammatory) DCM found an increased expression of CD3d, CD3z, and TRBC in both disease entities, whereas Th1 (more than) Th2 marker-genes as well as regulatory and cytotoxic T cells were differentially up-regulated in DCM EMBs only (Noutsias et al., 2011). Interestingly, in human DCM biopsies any clues for a Th17 response were lacking, which is in sharp contrast to findings in murine models of (experimental) autoimmune myocarditis (Valaperti et al., 2008). Nevertheless, from these recent molecular data it seems clear now that in human DCM a Th2 response also participates in the myocardial T cell infiltrates and serves as a pre-requisite for the stimulation (that is, maturation) of autoreactive B cells that, e.g., produce cardiac autoantibodies.

In acute myocarditis diffuse and/or focal inflammation causes structural damage to the heart. If myocardial inflammation persists, in a majority of cases cardiac function does not recover and finally may result in severe DCM. Acute ischemia also causes structural damage to the heart and to date represents the most common aetiology of heart failure. Thus, a structured follow up of patients with either disease is both pathophysiologically and clinically relevant.

The ETiCS study will follow such patients 3, 6, and 12 months after their index events, because the formation of autoreactive immunoglobulin G (IgG) is supposed to take place within the first 6 weeks (up to three months) after the index event.

A variety of autoreactive IgG have been identified, but only few of them have been investigated more in detail. Because myocyte surface receptors are easily accessible to circulating autoantibodies, the cardiac beta1-adrenergic receptor (which is the predominant adrenoceptor subtype in the heart) and the M2-muscarinic acetylcholine receptor represent key targets for autoreactive antibodies that might affect heart function to some extent.

To generate an autoimmune response, membrane receptors must be degraded to small oligopeptides able to form a complex with a MHC class II or HLA molecule of the host (Hoebeke, 1996). In case of the human beta1-adrenoceptor, a computer-based search for potential immunogenic amino-acid stretches within this (seven) transmembrane spanning protein revealed, that the only portion of the molecule containing B- and T-cell epitopes (and accessible to antibodies) was in fact the predicted second extracellular receptor loop

(beta1-ECII). This might explain the successful use of ECII-mimicking peptides for the induction of specific anti-beta1-ECII antibodies in different animal-models (Magnusson et al., 1996; Jahns et al., 2004, 2006). Finally, by isogenic transfer of anti-beta1-ECII antibodies in a human-analogous rat model the (autoimmune-)attack against the hearts of healthy recipients by activating anti-beta1-antibodies has been identified as a possible cause of heart failure (Jahns et al., 2004).

In the last decade several research groups have independently shown that anti-beta1-ECII-antibodies preferentially recognize native membrane beta1-receptors in various immunological assays (cell-ELISA, immunoprecipitation, immunofluorescence), indicating that such antibodies or autoantibodies are conformational (Jahns et al., 1999, 2006; Fu 2008). In addition, functional tests revealed that such anti-beta1-ECII may also act as allosteric regulators of beta1-adrenoceptor activity through modulation of cellular cAMP-production and/or cAMP-dependent protein kinase (PKA) activity (Wallukat et al., 1991; Limas et al., 1992; Jahns et al., 1999; Nikolaev et al., 2007). The use of different screening-techniques renders direct comparisons of the available data difficult, however. Hence, so far reported prevalences should be always interpreted in the context of the detection method utilised. Nevertheless, taken all these reports together, there is wide consent that a substantial fraction of patients with DCM and ICM, but only very few healthy subjects have circulating functionally active adrenoceptor-aabs (Wallukat et al., 1991; Magnusson et al., 1994; Jahns et al., 1999). An association of such aabs with impaired cardiac function (Jahns et al., 1999), a higher incidence of ventricular arrhythmias (Iwata et al., 2001; Störk et al., 2006), and a higher incidence of sudden cardiac death (Iwata et al., 2001) have been demonstrated. In addition, a previous clinical follow-up study also implies an increased risk for (cardiovascular) mortality in adrenoceptor aab-positive DCM patients (Störk et al., 2006).

To further analyse the time-course and sequentially engaged immunologic processes in autoimmune-mediated heart disease, the ETiCS study will prospectively follow the evolution of cardiac morphology and function after a first inflammatory or ischemic myocyte damage. In total 400 patients will benefit from a structured follow-up and best standard available medical care. The central hypothesis of ETiCS is that both inflammatory and ischemic myocardial injury may trigger a sequence of immunologic reactions which result in the formation of functionally active cardiac receptor-aabs (Jahns et al., 2006). Thus, the pre-specified primary endpoint is the titre of receptor-aabs at diagnosis compared to 3, 6, and 12 months after the index event. Since these aabs are thought to confer additional risk, pre-specified secondary endpoints of the ETiCS study comprise occurrence of life-threatening arrhythmias, changes in cardiac diameters and function, changes in clinical status, time to cardiovascular death, and time to all-cause death.

Endomyocardial biopsies will allow for a correlation of cardiac aab-titres with the severity of myocardial inflammation (Aretz et al., 1987; Elliott et al., 2008; Kindermann et al., 2008), with the kind of T cells engaged (Th1 vs. Th2-response, Treg, CTLs (Noutias et al. 2011)), and with the presence and/or activity of infective agents detected (that is, the type and load of pre-specified viral/microbial pathogens, as determined by PCR (Kühl et al., 2005)).

Once available, the results of the ETiCS study will significantly contribute to a number of important diagnostic, pathophysiologic and prognostic issues in autoantibody-mediated heart disease (Fu, M., 2008). We expect insights on the role of inflammatory (and ischemic) cardiac damage in triggering autoimmune processes (including the involved immunologic paths), and on the relevance of heart-directed autoimmune reactions for the initiation or progression of heart failure (Jahns et al., 2006). In particular, we might learn and better

understand whether –and if so, then to which extent– the specific target of a heart-directed autoantibody, but also its respective titre and biological activity and –last not least– its respective kinetics (that is, antibody-persistence or -clearance over time) relate to the complex process of cardiac wounding and healing. Different cardiac aabs might have distinct propensities to induce a certain cardiac phenotype, and the ETiCS study will allow for a differentiation of such features in a prospective manner. Thereby, additional prognostic markers for patients with an unfavourable course of autoimmune heart failure might be recognised and, as a consequence, conventional treatment modalities could be optimized earlier and/or novel -more specific- treatment strategies could be developed.

6. Future perspectives and therapeutic implications

Despite available treatment guidelines, the recent progress in conventional pharmacotherapy, and promising novel device-based therapeutic approaches, the outcome of patients suffering from heart failure remains unsatisfactory. This has stimulated the search for causal treatment strategies aiming to block or neutralize factors thought to play a role in heart failure progression.

In a large number of neurologic, rheumatologic, and endocrine disorders autoimmune phenomena have been recognised as main disease-causing factors. Their relevance in human heart disease and failure, however, still need to be substantiated (Jahns et al., 2006; Fu, M., 2008) although preliminary clinical data suggest that the presence of certain cardiac aabs clearly worsens the prognosis of patients with idiopathic DCM (Störk et al., 2006). Therapeutic strategies known from other autoimmune disorders, such as application of peptide-ligands (for multiple sclerosis (Warren et al., 2006)) or immunoadsorption of disease-causing aabs (for myasthenia gravis (Tzartos et al., 2008)) might thus also offer treatment options for a variety of human cardiac disorders.

In this regard, recent *in vitro* experiments with functionally active receptor-aabs isolated from a smaller number of DCM-patients indicate, that aab-induced adrenoceptor activation might be abrogated by incubation with epitope-mimicking peptides (Nikolaev et al., 2007; Jahns et al. 2010). Although clinical *in vivo* data with epitope-derived antibody-scavengers are still lacking, the latter *in vitro* findings together with the results from the ETiCS study should stimulate further research in the field of specifically antibody-directed therapeutic strategies.

In addition to established anti-adrenergic drugs like cardioselective beta-blockers such strategies might comprise (a) the aforementioned epitope-derived peptides as antibody-scavengers (Jahns et al., 2010), (b) an elimination of functionally active cardiac aabs by selective or non-selective immunoadsorption (studies currently under way (Felix & Staudt, 2008; Müller et al., 2008)), or (c) the direct targeting/suppression of autoantibody-producing B cells and/or plasma-cells themselves (Neubert et al., 2008).

At least in animal models of antibody-induced immune-cardiomyopathy and -nephropathy some of these novel therapeutic approaches have already been successfully applied (Jahns et al., 2005; Matsui et al., 2006; Neubert et al., 2008; Jahns et al., 2010). Hence, the results from the clinical (diagnostic) ETiCS study might also furnish a basis for and accelerate further pre-clinical development of such novel therapeutic approaches and agents targeting at cardio-noxious aabs, and –hopefully– for a faster transfer into clinical practice. Moreover, by initiating a joint venture of the leading European research institutes in the field of cardiac autoimmunity, ETiCS could equally serve as a starting point for future common efforts to

further understand and therapeutically modulate the immune system with respect to immune-mediated (post-inflammatory) human cardiac disorders.

7. Acknowledgements

The investigator-initiated ETiCS study receives public funding from the German Ministry for Education and Research (Bundesministerium für Bildung und Forschung, BMBF Project number 01ES0816). The ETiCS study has been acknowledged by the German Competence Network Heart Failure (CNHF, subproject 6b), and has equally been associated to the BMBF-funded Comprehensive Heart Failure Centre, University Hospital of Würzburg (CHFC, associated project C4). All authors had full access to the data and have read and approved the final article and have declared no conflicts of interest.

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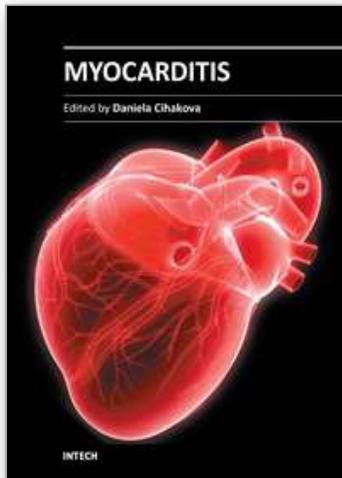
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Myocarditis

Edited by Dr. Daniela Cihakova

ISBN 978-953-307-289-0

Hard cover, 428 pages

Publisher InTech

Published online 19, October, 2011

Published in print edition October, 2011

Myocarditis, the inflammation of the heart muscle, could be in some cases serious and potentially fatal disease. This book is a comprehensive compilation of studies from leading international experts on various aspects of myocarditis. The first section of the book provides a clinical perspective on the disease. It contains comprehensive reviews of the causes of myocarditis, its classification, diagnosis, and treatment. It also includes reviews of Perimyocarditis; Chagas's™ chronic myocarditis, and myocarditis in HIV-positive patients. The second section of the book focuses on the pathogenesis of myocarditis, discussing pathways and mechanisms activated during viral infection and host immune response during myocarditis. The third, and final, section discusses new findings in the pathogenesis that may lead to new directions for clinical diagnosis, including use of new biomarkers, and new treatments of myocarditis.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Roland Jahns, Nikolas Deubner, Valérie Biovin, Alida L.P. Caforio, Stephan B. Felix, Michael Fu, Martin J. Lohse, and Georg Ertl (2011). Acute Myocarditis – A Trigger of Cardiac Autoimmunity? Expected Insights from the Etiology, Titre-Course, and Effect on Survival of Cardiac Autoantibodies (ETiCS) Study, Myocarditis, Dr. Daniela Cihakova (Ed.), ISBN: 978-953-307-289-0, InTech, Available from:
<http://www.intechopen.com/books/myocarditis/acute-myocarditis-a-trigger-of-cardiac-autoimmunity-expected-insights-from-the-etiology-titre-course>

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