Biomarkers of Heart Failure in Myocarditis and Dilated Cardiomyopathy

DeLisa Fairweather, Eric D. Abston and Michael J. Coronado
Johns Hopkins University Bloomberg School of Public Health
USA

1. Introduction

There are many reviews that discuss the role of biomarkers in cardiovascular disease (CVD) and heart failure (Braunwald, 2008; Chen et al., 2010; Hochholzer et al., 2010), but little information exists regarding the presence and usefulness of biomarkers for heart failure in myocarditis and dilated cardiomyopathy (DCM) patients. Heart failure (HF) is the end consequence of many CVDs including atherosclerosis, myocardial infarction, myocarditis and DCM. CVD is the leading cause of morbidity and mortality in Western nations (Roger et al., 2011), and a growing concern worldwide (Gaddam et al., 2011). As treatments for CVD prolong survival, the prevalence of chronic HF has increased. It is now estimated that 5.8 million people in the United States live with HF and over 23 million worldwide (Bui et al., 2011). Approximately 550,000 new cases of HF are diagnosed each year, with a lifetime risk for developing disease of one in five (Chen et al., 2010; Krumholz et al., 1997). Hospitalizations for HF have also increased dramatically in the United States from 402,000 in 1979 to 2.4 million in 2007 with the cost of treating HF patients estimated at $39 billion annually (Bui et al., 2011; Chen et al., 2010; Roger et al., 2011). Biomarkers have become an increasingly important clinical tool for assessing CVD and progression to HF. Biomarkers are used in early detection of sub-clinical disease, diagnosis, risk stratification, monitoring disease state, and to determine therapies (Hochholzer et al., 2010). Many biomarkers are also risk factors directly involved in the pathogenesis of disease.

2. Heart failure

In spite of advances in diagnosis and treatment, HF remains a growing medical problem associated with major hospitalization, mortality and poor prognosis. Heart failure is characterized by significantly reduced cardiac output resulting in an inability to meet the metabolic needs of the body. Most cases of HF are caused by systolic dysfunction, or reduced myocardial contractile function, as occurs during ischemic injury, pressure or volume overload and DCM. However, HF can also occur because of an inability to relax, expand or fill the ventricle resulting in diastolic dysfunction as observed during myocardial fibrosis and constrictive pericarditis (Afanasyeva et al., 2004; Kumar et al., 2005). The prevalence of HF is higher in men than women and sex is a major risk factor along with age, hypertension, left ventricular (LV) hypertrophy, valvular heart disease, obesity and diabetes (Bui et al., 2011; Roger et al., 2011) (Table 1). The New York Heart Association (NYHA) has

defined four stages of HF in patients called the NYHA classification: class I) patients who have no symptoms or limitations in ordinary activities; class II) patients who have no symptoms in rest or in mild exercise, but symptoms appear with intense activity resulting in slight or mild limitations; class III) patients who have a marked limitation of activity, but no symptoms at rest; and finally class IV) patients who have symptoms when resting and who are restricted to bed or chair. This classification is still widely used in clinical practice but is not always a reliable guide to evaluate prognosis and therapy of patients with systolic HF (Hebert et al., 2011). Echocardiography is the imaging method most commonly used for the initial clinical assessment of patients with suspected HF because it is widely available, versatile, non-invasive, and has a low cost (Blauwet & Cooper, 2010). However, causative diagnosis cannot be established in a significant number of patients with HF despite significant advancement in echocardiographic techniques. Cardiac magnetic resonance imaging (MRI) is being used with increasing frequently and often provides additional information to echocardiography in patients with suspected or known HF (Blauwet & Cooper, 2010; Karamitsos & Neubauer, 2011; Olimulder et al., 2009). Although echocardiography and MRI are good at defining changes in volume, they do not assess pressure.

Nonmodifiable risk factors	Potentially controllable risk factors
Increasing age	Infections
Male gender	Inflammation
Family history	Obesity
Genetic abnormalities	Alcohol
Left ventricular hypertrophy	Stress
Myocardial infarction	Air pollution
Valvular heart disease	Diabetes mellitus
Hypersensitivity	Hypertension
	Tobacco smoking
	Hyperlipidemia

Table 1. Risk factors for developing heart failure. (Adapted from Bui et al., 2011 and Kumar et al., 2005)

The cardiac myocyte is generally considered to be a terminally differentiated cell that has lost its ability to divide or regenerate. Increased mechanical load causes an increase in the cellular content resulting in an increase in cell size termed hypertrophy (Kumar et al., 2005). The extent of hypertrophy varies depending on the underlying causes (Figure 1). Volume overload hypertrophy is characterized by dilation and an increase in muscle mass and wall thickness. Cardiac hypertrophy is also accompanied by many transcriptional and morphologic changes including generation of myofibroblasts, collagen deposition and fibrosis (Figure 1). Sustained hypertrophy and/or dilation may evolve to HF.

2.1 Myocarditis, dilated cardiomyopathy and heart failure

Myocarditis, or inflammation of the myocardium, leads to around half of all DCM cases in the United States (Roger et al., 2011). DCM is the most common form of cardiomyopathy requiring a heart transplant (Cooper, 2009, Wexler et al., 2009). Additionally, DCM contributes to approximately one third of all congestive HF cases (Jameson et al., 2005). The
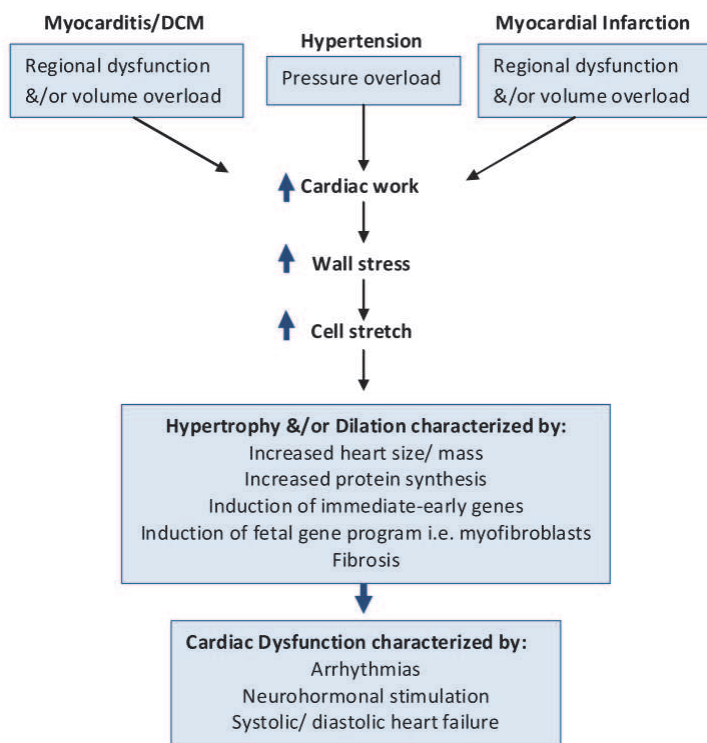
Myocarditis/DCM | Hypertension | Myocardial Infarction

| Regional dysfunction &/or volume overload | Pressure overload | Regional dysfunction &/or volume overload |

↑ **Cardiac work**

↑ **Wall stress**

↑ **Cell stretch**

Hypertrophy &/or Dilation characterized by:
Increased heart size/ mass
Increased protein synthesis
Induction of immediate-early genes
Induction of fetal gene program i.e. myofibroblasts
Fibrosis

Cardiac Dysfunction characterized by:
Arrhythmias
Neurohormonal stimulation
Systolic/ diastolic heart failure

Fig. 1. Representation of the sequence of events leading to the development of heart failure. Viral infection or other causes of myocarditis lead to cardiac dysfunction resulting in increased cardiac work. Adapted from Kumar et al., 2005.

prognosis for patients with acute myocarditis varies but depends on ejection fraction (EF), clinical presentation and pulmonary artery pressure (Schultz et al., 2009). The life expectancy after diagnosis of myocarditis is 50% at 10 years and only 50% at 4 years after diagnosis of DCM (Grzybowski et al., 1996; Gupta et al., 2008). Over 20% of sudden deaths among young adults, the military, and athletes are due to myocarditis (Gupta et al., 2008). Similar to coronary artery disease and HF, myocarditis and DCM occur more frequently in men than women (Cooper, 2009; Roger et al., 2011). The clinical presentation of acute myocarditis in adults is highly variable often presenting as myocardial infarction or angina with nonspecific symptoms. Symptoms suggesting a viral infection including fever, rash, myalgias, arthralgias, fatigue, and respiratory or gastrointestinal symptoms frequently occur several days to weeks before the onset of myocarditis (Blauwet & Cooper, 2010). Electrocardiogram is widely used as a screening tool for myocarditis, but only detects about 47% of cases (Morgera et al., 1992). Echocardiography is useful for evaluating cardiac chamber size, wall thickness, systolic and diastolic function, and the presence of intramural thrombi in suspected myocarditis patients (Blauwet & Cooper, 2010). However, there is no specific echocardiographic feature for myocarditis, and patterns consistent with hypertrophy, DCM and/or ischemic heart disease can be observed in myocarditis patients. Cardiac MRI is an important noninvasive method to assess patients suspected to have acute

myocarditis. Unique features of myocarditis including myocardial edema, hyperemia, increased capillary permeability due to inflammation, and fibrosis can be identified using a combination of T1 and T2-weighted images (Blauwet & Cooper, 2010; Karamitsos & Neubauer, 2011). Endomyocardial biopsy is used to verify inflammation in the heart and to assess whether certain cell populations such as eosinophils or giant cells are present in the myocardium for diagnostic purposes (i.e. eosinophilic or giant cell myocarditis). Due to the focal nature of myocarditis and the fact that foci are frequently located in the peri/myocardium, endomyocardial biopsies often miss inflammation and so often do not aid in diagnosis (Maisch, 1994; Olimulder et al., 2009). Although the complication rate is low, patients are at a risk of death from the procedure.

3. Biomarkers in heart failure

Biomarkers are frequently used in cardiovascular medicine where they provide valuable information regarding diagnosis, treatment, identification of individuals at risk for HF, and potentially the pathogenesis of disease. For a biomarker to be clinically useful it should fulfill several criteria: 1) biomarker levels should be able to be accurately assessed using widely available and cost-efficient methods, 2) biomarkers should provide additional information from the tests already conducted such as MRI, and 3) biomarker information should aid in medical decision making (Braunwald, 2008; Morrow & de Lemos, 2007). A growing list of enzymes, hormones, markers of cardiac stress or necrosis, cytokines and other biological agents have been examined as possible biomarkers for HF (Table 2). Although biomarkers are discussed in this review by category (e.g. those associated with cardiac damage or inflammation), in reality many of these biomarkers interact or are associated with one another suggesting that combinations of biomarkers are likely to provide the best assessment of HF risk. This review will focus on HF biomarkers from Table 2 that have been studied in myocarditis/ DCM patients or experimental models.

3.1 Biomarkers of cardiovascular injury or stress

Myocyte injury can occur from many causes including infections, oxidative stress, inflammation or severe ischemia (Brauanwald, 2008). Cardiac myosin is typically not used as a biomarker for HF because it is rapidly cleared from the circulation. Cardiac troponin I and T are current standard biomarkers used to diagnose acute myocardial infarction and to stratify patient risk in acute coronary syndromes (ACS) because of their long half-life in the circulation (Hochholzer et al., 2010). B-type natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) are important indicators of cardiovascular stress having the advantage of being able to distinguish acute from chronic HF. Recently ST2 has emerged as another biomarker of cardiac damage that has prognostic ability in patients suspected of HF.

3.1.1 Troponins I and T

The cardiac troponins are proteins located in myocytes that are responsible for regulating cardiac muscle contraction. Cardiac troponin is composed of three subunits that are products of different genes- troponin C, troponin I and troponin T. Compared to myosin and actin, troponins are present at low levels in the heart. However, both troponin I and T are ideally suited to detect myocardial damage because they are expressed as cardiac-specific isoforms (Agewall et al., 2011). Elevated sera troponins are associated with

Biomarker
Myocyte inury
Cardiac-specific troponins I and T
Myosin light-chain kinase I
Creatine kinase MB fraction
Myocyte stress
Brain natiuretic peptide
N-terminal pro-brain natriuretic peptide
ST2/ interleukin-33
Inflammation
C-reactive protein
Tumor necrosis factor
Fas (APO-1)
Interleukins 1, 6, 18
Galectin-3
Oxidative stress
Oxidized low-density lipoproteins
Myeloperoxidase
Urinary and plasma isoprostanes
Neurohormones
Norepinephrine
Renin
Angiotensin II
Aldosterone
Endothelin
Extracellular-matrix remodeling
Matrix metalloproteinases
Tissue inhibitors of metalloproteinases
Collagen propeptides

Table 2. Biomarkers in heart failure. (Adapted from Braunwald, 2008)

myocardial ischemia and necrosis and have been found to be excellent diagnostic and prognostic biomarkers for thrombotic ACS. But many cardiac conditions can lead to elevated troponins in addition to ACS including myocarditis, DCM and HF (Table 3). With new high-sensitivity detection methods for troponins, very minor changes in cardiac damage can be detected. Although troponins released to the circulation do not identify the type of heart damage, their levels may indicate the severity of damage (Figure 2) (Miller et al., 2007). A number of studies have been conducted examining troponin release during myocarditis, DCM or heart failure in patients (Smith et al., 1997; Brandt et al., 2001; Imazio et al., 2008; Miller et al., 2007; Peacock et al., 2008). Troponin I and T have also been found to predict the severity of myocarditis and the short-term prognosis in children with acute and fulminant myocarditis and DCM (Soongswang et al., 2002; Al-Biltagi et al., 2010). Overall, troponin levels were found to increase in relation to the severity of myocardial inflammation or ventricular wall stress caused by remodeling (Agewall et al., 2011; Miller et al., 2007). DCM patients with elevated serum troponin I levels were more dilated and had a worse outcome that troponin I-negative patients (Miettinen et al., 2008). Additionally, acute decompensated heart failure patients who were positive for troponin had a lower EF and

higher in-hospital mortality, independent from other predictive values, than those who were negative for troponin (Peacock et al., 2008). Troponin T was found to be an important independent variable that predicted increased risk of death in patients with chronic HF (Latini et al., 2007). These findings demonstrate that troponin measurement is an important tool in early risk assessment of myocarditis/ DCM patients.

Condition
Acute coronary syndrome
Myocarditis
Pericarditis
Endocarditis
Dilated cardiomyopathy
Acute heart failure
Pulmonary embolism
Stroke
Sepsis
Acute aortic dissection
Tachyarrhythmias
Cardiac contusion
Tako-tsubo cardiomyopathy
Strenuous exercise e.g. marathon runners
Sympathomimetic drugs
Chemotherapy

Table 3. Cardiac conditions that can result in acutely elevated troponins. (Adapted from Agewall et al., 2011)

Interestingly, autoantibodies against circulating troponin I have been found in patients with ACS and acute myocardial infarction (Eriksson et al., 2005; Leuschner et al., 2008; Shmilovich et al., 2007). These autoantibodies were discovered because they interfered with troponin detection assays (Eriksson et al., 2005). This discovery led to the realization that autoantibodies against troponin I were also present in the sera of patients with DCM and heart failure (Miettinen et al., 2008; Shmilovich et al., 2007). One study of DCM patients found that troponin I, but not troponin I autoantibodies, were associated with dilation and poor outcome (Miettinen et al., 2008). In another study a significant number of DCM patients had autoantibodies against troponin I, but the autoantibodies were not found to bind to cardiac myocytes or activate Ca^{2+} currents (Shmilovich et al., 2007). Myocardial infarction patients with elevated troponin I autoantibodies had poor recovery of LV EF suggesting that troponin autoantibodies affect heart function (Leuschner et al., 2008). Further evidence that troponin autoantibodies may directly affect heart function comes from animal studies. PD-1 receptor deficient mice were found to develop severe DCM with high levels of autoantibodies against troponin I (Kaya et al., 2010; Nishimura et al., 2001). These troponin I autoantibodies were found to bind to heart tissue and to induce Ca^{2+} influx in cardiac myocytes. Inoculation of mice with recombinant troponin I with complete Freund's adjuvant was found to induce severe myocarditis and increased proinflammatory cytokines that progressed to fibrosis, DCM and heart failure (Goser et al., 2006; Kaya et al., 2008; 2010). However, this inflammatory response was only observed for troponin I but not troponin T inoculation. More research is needed to better understand the relationship of circulating

troponin I and its autoantibodies in the progression of myocarditis to DCM and heart failure.
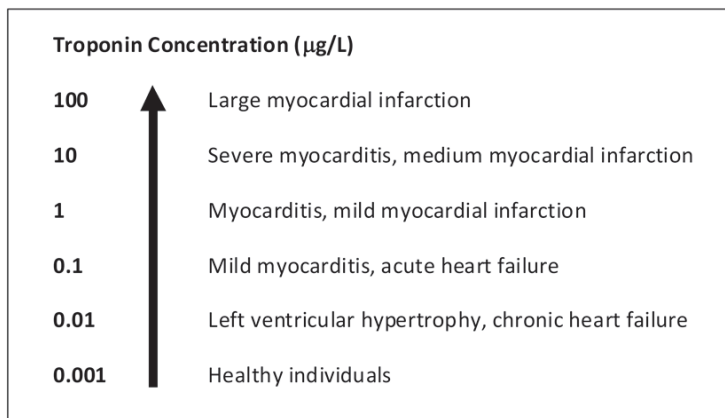
Troponin Concentration (µg/L)

100	Large myocardial infarction
10	Severe myocarditis, medium myocardial infarction
1	Myocarditis, mild myocardial infarction
0.1	Mild myocarditis, acute heart failure
0.01	Left ventricular hypertrophy, chronic heart failure
0.001	Healthy individuals

Fig. 2. Relationship between serum troponin levels and the severity of cardiac damage caused by myocarditis, heart failure or myocardial infarction. Adapted from Agewall et al., 2011.

3.1.2 BNP and NT-pro-BNP

In contrast to cardiac myosin or troponins that are released due to cell wall compromise, BNP is synthesized in healthy cardiac myocytes from its precursor NT-pro-BNP (Braunwald, 2008; Chen et al., 2010). The prohormone BNP is only released to the circulation when the ventricles become dilated, hypertrophic or during other conditions that induce wall distension and stretching, and by neurohormonal activation (Table 4). Prohormone BNP is cleaved by an endoprotease, corin, in the circulation into two polypeptides: the inactive NT-pro-BNP and the bioactive BNP. BNP causes arterial vasodilation, natriuresis and diureses while reducing the renin angiotensin system and adrenergic response (Braunwald, 2008; Palazzuoli et al., 2011). Elevated plasma BNP levels occur during hypertrophic cardiomyopathy, diastolic dysfunction and LV hypertrophy, and have been shown to be directly proportional to NYHA class and inversely related to cardiac output (Silver et al., 2004). Although few studies specifically address the topic, BNP has been found to be elevated in the serum of patients with myocarditis or DCM and in animal models of myocarditis (Grabowski et al., 2004; Miller et al., 2007; Ogawa et al., 2008; Talvani et al., 2004; Tanaka et al., 2011). Plasma BNP levels are also elevated in patients with acute myocardial infarction and this relationship persists into the late phases of cardiac remodeling (Hirayama et al., 2005). Many studies have linked higher levels of circulating BNP with heart failure diagnosis and worse outcome (Miller et al., 2007; Palazzuoli et al., 2011). BNP levels are a better predictor of death than norepinephrine or endothelin-1 (Braunwald, 2008). Several studies have found that NT-pro-BNP was better than BNP for predicting death or re-hospitalization for heart failure, probably due to the longer half-life of NT-pro-BNP in sera (Masson et al., 2006; Omland et al., 2007). However, BNP is a better

predictor than NT-pro-BNP of worse outcome in ACS (Palazzuoli et al., 2011). Natriuretic peptides were also found to be useful in screening asymptomatic subjects at risk of developing HF such as those with hypertension, diabetes and coronary artery disease (Braunwald, 2008). Noncardiac conditions that increase plasma BNP levels such as age, race, obesity and renal dysfunction should be taken into consideration when using this biomarker (Table 4). Overall, BNP and NT-pro-BNP are biomarkers with a high sensitivity and specificity in predicting HF in a number of conditions including myocarditis and DCM.

Cardiac condition	Noncardiac condition
Systolic dysfunction	Acute pulmonary embolism
Diastolic dysfunction	Pulmonary hypertension
Myocarditis	Anemia
Pericarditis	Septic shock
Myocardial fibrosis	Hyperthyroidism
Dilated cardiomyopathy	*Cor pulmonale*
Heart failure	Renal failure
Valvular heart disease	
Coronary artery disease	
Hypertension	
Atrial fibrillation	

Table 4. Conditions that increase plasma natriuretic peptide levels. (Adapted from Braunwald, 2008 and Palazzuoli et al., 2011)

3.1.3 Soluble ST2

Soluble ST2 (sST2), an interleukin (IL)-1 receptor (R) (IL-1R) family member, is basally expressed by cardiomyocytes and upregulated in the heart by mechanical strain and IL-1β (Weinberg et al., 2002). The ST2 gene is known to encode at least 3 isoforms of ST2 by alternative splicing: ST2L, a transmembrane receptor; sST2, a secreted soluble form of ST2 that can serve as a decoy receptor for the ST2 ligand, IL-33; and ST2V, a variant of ST2 found in the gut of humans (Miller & Liew, 2011). ST2L is a member of the Toll-like receptor (TLR)/IL-1R superfamily that share a common structure with an extracellular domain of three linked immunglobulin-like motifs, a transmembrane segment and a cytoplasmic Toll-interleukin-1 receptor (TIR) domain. ST2L forms a complex with IL-1R accessory protein (IL-1RAcP) that is required for IL-33 signaling (Ali et al., 2007). IL-33 signaling recruits the adaptor protein MyD88 to the TIR domain leading to activation of the transcription factors NF-κB and AP-1 and production of inflammatory mediators including proinflammatory tumor necrosis factor (TNF), IL-1β, IL-6, and the T helper (Th)2-associated cytokines IL-5, IL-13 and IL-10 (Liew et al., 2010; Miller & Liew, 2011). Both ST2L and sST2 are induced in cardiomyocytes by biomechanical strain (Weinberg et al., 2002). Elevated levels of sST2 in the sera are associated with poor prognosis in patients with acute myocardial infarction or chronic heart failure where sST2 levels correlate positively with creatine kinase and negatively with EF (Weinberg et al., 2002; 2003). In patients with severe chronic NYHA class III or IV heart failure, the change in sST2 levels was an independent predictor of subsequent mortality or transplantation (Weinberg et al., 2003). IL-33 is expressed largely within fibroblasts in the heart and is thought to be released from necrotic cells due to tissue damage caused by direct damage or infection (Liew et al., 2010). IL-33 has been shown to be

cardioprotective using animal models where recombinant (r)IL-33 treatment reduced hypertrophy and fibrosis following pressure overload induced by transverse aortic constriction (TAC) (Sanada et al., 2007). This effect was reversed by treating mice with sST2 prior to TAC, providing evidence that sST2 functions as a decoy receptor for IL-33. Additionally, rIL-33 treatment was found to decrease atherosclerosis in ApoE deficient mice fed a high fat diet by skewing the immune response from a Th1 to a Th2 response (Miller et al., 2008).

Currently there are no reports on the role of sST2 or IL-33 in the development of myocarditis or DCM even though sST2 is known to be a good biomarker predicting heart failure. Our laboratory is investigating the role of sST2/IL-33 signaling in an autoimmune model of coxsackievirus B3 (CVB3) myocarditis and DCM in mice. We found that IL-33 mRNA was upregulated in the heart during acute CVB3 myocarditis and chronic DCM (Figure 3A,B). Additionally, sST2 levels were elevated in the sera during acute CVB3 myocarditis in mice (Figure 3C) and correlated with poor heart function as assessed by echocardiography (not shown) or pressure-volume relationships (Figure 4). Serum sST2 is a good marker of disease because it could not be detected in the sera of undiseased mice (Figure 3C). Our findings of elevated sST2 levels in the sera of mice with CVB3 myocarditis and its relation to poor heart function suggest that sST2 may serve as a useful biomarker to predict progression to HF in myocarditis and DCM patients.
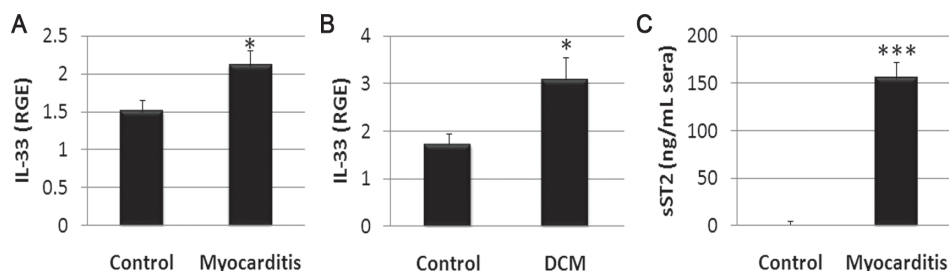

Fig. 3. IL-33 and sST2 are increased during autoimmune CVB3 myocarditis in mice. Male BALB/c mice were infected intraperitoneally with heart-passaged coxsackievirus B3 (CVB3) containing infectious CVB3 (10^3 plaque forming units) and heart proteins on day 0 and myocarditis examined at day 10 post infection (pi) and dilated cardiomyopathy (DCM) at day 90 pi. Saline inoculated age-matched mice were used as controls. Interleukin (IL)-33 mRNA was assessed by quantitative RT-PCR in the heart at day 10 (**A**) and 90 (**B**) pi and normalized to hypoxanthine phosphoribosyltransferase (HPRT) levels. sST2 levels were assessed in the sera of mice during acute myocarditis at day 10 pi by ELISA (**C**). Data are expressed as mean relative gene expression (RGE) ±standard error of the mean (SEM) in 7 to 10 mice per group. *$P < 0.05$; ***$P < 0.001$.

3.2 Biomarkers of inflammation

Inflammation is important in the pathogenesis of many of the conditions that lead to HF. Traditionally, inflammatory biomarkers have been considered to be risk markers rather than risk factors because their role in disease pathogenesis is not always clear (Rao et al., 2006). Many inflammatory biomarkers found in the circulation, such as C-reactive protein (CRP),
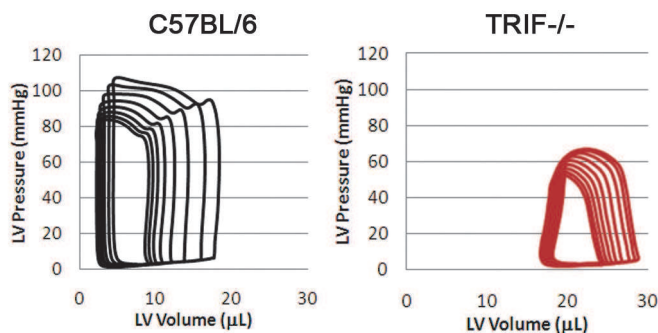
Fig. 4. Poor heart function in TRIF deficient mice is associated with elevated sST2 during acute CVB3 myocarditis. Male C57BL/6 (BL/6) or TRIF deficient (TRIF-/-) mice were infected intraperitoneally with heart-passaged coxsackievirus B3 (CVB3) containing infectious CVB3 (10^3 plaque forming units) and heart proteins on day 0 and myocarditis examined at day 10 post infection (pi) using end systolic pressure-volume relationships (ESPVR). Ees, a measure of LV end systolic stiffness/elastance, was 7.1 in BL/6 and 5.1 in TRIF-/- mice ($P = 0.04$) while V_0, the X-intercept of the ESPVR, was -5.4 in BL/6 and 26.8 in TRIF-/- mice ($P = 0.0001$). End diastolic volume (EDV) was 24±1.2 in BL/6 and 33±3.3 in TRIF-/- mice ($P < 0.01$). Thus, elevated sST2 in the sera of TRIF-/- mice (not shown) was associated with dilation and heart failure in TRIF deficient mice in an autoimmune model of CVB3 myocarditis.

IL-6 and serum amyloid A protein (SAA), are part of the acute phase response arising in the liver and although they are strongly associated with disease they may simply infer the presence of an inflammatory state. In clinical studies inflammatory mediators have been found to predict progression to HF similar to injury biomarkers and/or neurohormones (Table 2) (Mann, 2005). Inflammatory biomarkers have been shown in animal studies and the clinical setting to increase LV dysfunction, increase edema, and induce endothelial dysfunction and cardiomyocyte apoptosis, as well as other deleterious effects (Table 5).

A recent long-term study of myocarditis patients revealed that inflammation was the best predictor for the progression to HF following acute myocarditis (Kindermann et al., 2008). Viruses like CVB3, adenovirus, parvovirus B19 and hepatitis C virus are often detected in patient myocardial biopsies (Cooper, 2009; Gupta et al., 2008). Antiviral treatments such as interferon-β reduce inflammation and HF in animal models and patients, implying that viral infections are an important cause of myocarditis cases that lead to HF (Kuhl et al., 2003; Wang et al., 2007). Inflammation appears to be etiologically linked with the development of HF, not only because heart failure is a consequence of inflammatory CVDs but because patients with chronic HF that have elevated levels of inflammatory mediators have a worse prognosis (Robinson et al., 2011). Evidence exists that both cellular and auto/antibody-mediated damage contribute to the progression to DCM and HF following myocarditis (Cooper, 2009; Fairweather et al., 2008; Kallwellis-Opara et al., 2007). Similar to atherosclerosis, acute myocardial inflammation is associated with an elevated Th1 response in males (Daniels et al., 2008; Frisancho-Kiss et al., 2007; Huber and Pfaeffle, 1994; Nishikubo et al., 2007). A Th17 response has been shown to increase fibrosis leading to DCM in the experimental autoimmune myocarditis (EAM) model in mice (Baldeviano et al., 2010).

Interestingly, Th2 responses have also been implicated in the pathogenesis of myocarditis leading to HF (Afanasyeva et al., 2001; Fairweather et al., 2004a; 2004b). IFN-γ deficient mice, which have elevated IL-4 levels and a Th2 response, progress to severe DCM and HF following CVB3 myocarditis (Fairweather et al., 2004a).

Deleterious effects
Known
Left ventricular dysfunction
Pulmonary edema
Cardiomyopathy
Inflammation
Left ventricular remodeling
Endothelial dysfunction
Inducible nitric oxide synthase activation
Decreased skeletal-muscle blood flow
Anorexia and cachexia
Potential
Receptor uncoupling from adenylate cyclase
Activation of the fetal-gene program
Apoptosis of cardiac myocytes

Table 5. Deleterious effects of inflammatory biomarkers on acute and chronic heart failure. (Adapted from Anker & von Haehling, 2004; Braunwald, 2008; Mann, 2005)

3.2.1 C-reactive protein

Interest in the study of inflammatory mediators in patients with HF began in 1954 when an assay for CRP was first developed (Braunwald, 2008). CRP is an acute phase protein synthesized in the liver in response to IL-6 and released to the circulation during inflammation (Pepys & Hirschfield, 2003). Its levels are synergistically increased by IL-1β. In phagocytes CRP has been shown to bind Fcγ receptor I and II and to function in the clearance of apoptotic and necrotic cells (Devaraj et al., 2009; Rhodes et al., 2011). In 1956 a study was published showing that CRP was detectible in the sera of 30 out of 40 patients with chronic HF, and that elevated CRP levels were associated with more severe disease (Braunwald, 2008; Elster et al., 1956). Since then many studies have shown that CRP independently predicts adverse outcomes in patients with acute or chronic HF (Braunwald, 2008; Osman et al., 2006). Higher levels of CRP are associated with more severe HF and independently associated with morbidity and mortality (Anand et al., 2005). Additionally, elevated CRP levels identified asymptomatic elderly individuals who were at a high risk of developing HF in the future (Vasan et al., 2003). The main problem with CRP as a biomarker is that it lacks specificity for CVD. That is, CRP levels are elevated in the sera during most conditions that increase inflammation such as acute or chronic infection, cigarette smoking, ACS and some autoimmune diseases (Pepys & Hirschfield, 2003; Perez-De-Lis et al., 2010; Rhodes et al., 2011). There is increasing evidence that CRP may be able to exert direct proinflammatory effects on the heart by increasing matrix metalloproteinase-1 (MMP)-1 and IL-8 in endothelial cells and by increasing CD11b and CC-chemokine receptor 2 (CRR2) in monocytes, for example (Table 6) (Devaraj et al., 2009; Osman et al., 2006; Venugopal et al., 2005).

Endothelial cells	Monocyte-macrophages	Smooth muscle cells
Increased VCAM, ICAM-1, E-selectin, MCP-1 and monocyte adhesion	Increased tissue factor	Increased AT-1 and VSMC migration and proliferation
Increased PAI-1, IL-8, CD40/CD40L, MMP-1, ET-1 and M-CSF	Increased superoxide and myeloperoxidase	Increased neointimal formation *in vivo*
Decreased tPA	Increased proinflammatory cytokines (e.g. TNF) and decreased IL-10	Increased iNOS
Decreased prostacyclin	Increased CD11b and CCR2	Increased ROS
Increased superoxide and iNOS	Promoted oxLDL uptake and decreases cholesterol efflux	Increased tissue factor
Promoted endothelial dysfunction *in vivo*	Increased MMPs and HMGB1	
Impaired EPC number and function *in vitro*	Increased M-CSF and proliferation	

Table 6. Inflammatory effects of C-reactive protein. (Adapted from Devaraj et al., 2009) Abbreviations: AT, angiotensin receptor; CCR2, CC-chemokine receptor-2; CD40L, CD40 ligand; EPC, endothelial progenitor cell; ET, endothelin; HMGB1, high-mobility group protein B1; ICAM, intercellular adhesion molecule; IL, interleukin; iNOS, inducible nitric oxide synthase; MCP, monocyte chemotactic protein; M-CSF, macrophage colony-stimulating factor; MMP, matrix metalloproteinase; oxLDL, oxidative low-density lipoprotein; PAI, plasminogen activator inhibitor; ROS, reactive oxygen species; TNF, tumor necrosis factor; tPA, tissue plasminogen activator; VCAM, vascular cell adhesion molecule; VSMC, vascular smooth muscle cell.

Although many studies have examined the relationship between serum CRP levels and HF, few studies have examined CRP levels in myocarditis patients. In one study, 31 patients with clinical and histological evidence of lymphocytic myocarditis were found to have elevated plasma CRP levels that correlated positively with the NYHA functional class (Kaneko et al., 2000; Osman et al., 2006). Five of these patients who died of HF during the study had significantly higher levels of CRP, suggesting that CRP measurement may be a useful tool for determining prognosis in myocarditis patients. A separate study found that 80% of patients with clozapine-induced myocarditis (an antipsychotic drug used to treat schizophrenic symptoms) had elevated levels of CRP compared to a control group (Ronaldson et al., 2010). Several studies have examined CRP levels in idiopathic/ non-ischemic DCM patients where CRP levels have been found to independently predict disease outcome (Ishikawa et al., 2006; Kaneko et al., 1999; Senes et al., 2008). CRP levels increased with the severity of symptoms and the level of systolic impairment in DCM patients, while ongoing statin treatment was found to decrease CRP levels (De Gennaro et al., 2008). Interestingly, CRP has been found to co-express with TNF, macrophages and complement in the myocardium of DCM patients suggesting that CRP may play a role in the pathogenesis of disease (Satoh et al., 2005; Zimmermann et al., 2009). One of the obstacles to understanding the role of CRP in myocarditis and DCM is that mouse CRP appears only in trace amounts during the acute phase response (Pepys & Hirschfield, 2003). Instead of CRP mice upregulate serum amyloid P component (SAP), which is a non-acute phase protein in

humans. Thus, CRP deficient or transgenic mice may provide only limited information on the role of CRP in HF promotion.

3.2.2 Cytokines: TNF, IL-1β and IL-18

The inability of hemodynamic factors to fully explain HF cases led to the hypothesis that cytokines released from cardiac tissue and/or inflammatory cells also contribute to disease progression. According to the "cytokine hypothesis", HF develops because cytokine cascades that are activated following myocardial injury or stress exert deleterious effects on heart function (Table 5) (Anker & von Haehling, 2004; Braunwald, 2008; Seta et al., 1996). Cytokines can induce hemodynamic abnormalities and/or direct toxic effects on the heart. Since the original report in 1990 by Levine et al. there have been many studies showing that an increase in circulating TNF levels directly relates to a patient's NYHA classification and predicts patient mortality (Anker & von Haehling, 2004; Mann, 2005; Seta et al., 1996; Vasan et al., 2003). Similar relationships between IL-1β, IL-6 or IL-18 and HF have been found (Anker & von Haehling, 2004; Hedayat et al., 2010; Jefferis et al., 2011; Vasan et al., 2003). Cardiac myocyte hypertrophy, contractile dysfunction, cardiac myocyte apoptosis and extracellular matrix (ECM) remodeling contribute critically to the progression from cardiac injury to HF (Hedayat et al., 2010).

More than any other category of biomarker (Table 2), the role of cytokines in the pathogenesis of myocarditis and DCM has been studied by researchers (Fairweather & Rose, 2005; Hedayat et al., 2010). TNF, IL-1β and IL-18 have all been shown to play a role in myocarditis by inducing myocyte hypertrophy, contractile dysfunction, myocyte apoptosis and contributing to ECM remodeling, a step critical in the progression from myocarditis to DCM (Cain et al., 1999; Fairweather et al., 2004a; 2004b; Hedayat et al., 2010). In one study, TNF mRNA expression was found to be elevated more often in myocarditis patients when viral genomes were also detected, and greater mRNA levels of TNF and its receptor TNFRI correlated with impaired cardiac function (Calabrese et al., 2004). In a mouse model of CVB3 myocarditis, TNF was found to increase CD1d expression on lymphocytes resulting in increased inflammation in males (Huber, 2010). However, viral replication and acute CVB3 myocarditis was not altered in TNFRI deficient mice (Fairweather et al., 2005). Out of the 13 or so TLRs that have been described so far in humans and mice, TLR4 is unique in its ability to work with the inflammasome to produce bioactive IL-1β and IL-18 in the heart (Fairweather et al., 2003; Vallejo, 2011). TLR2 and TLR4 signaling increase TNF levels, and TLR2 can act with TLR4 to increase IL-1β levels (Vallejo, 2011). TLR4 mRNA expression has been found to be higher in patients with myocarditis than controls, and to correlate with viral RNA levels in the heart (Satoh et al., 2003). Myocarditis patients with active viral replication had higher levels of TLR4 that was associated with lower systolic function. In a mouse model of CVB3 myocarditis, our laboratory found that TLR4 deficient mice develop reduced acute inflammation and lower IL-1β and IL-18 levels in the heart (Fairweather et al., 2003). The importance of TLR4 signaling in a strictly autoimmune model of myocarditis was demonstrated by Nishikubo et al. where TLR4 signaling was found to be necessary to mount a Th1-type immune response (Nishikubo et al., 2007). We have shown that TLR4 is upregulated on macrophages and mast cells during the innate immune response to CVB3 and during acute CVB3 myocarditis and this response results in increased inflammation and progression to DCM and HF in males compared to females (Frisancho-Kiss et al., 2007; 2009; Onyimba et al., 2011). A Th1 response in male mice was found to be due to TLR4-derived IL-

18, which was originally named IFN-γ-inducing factor, rather than to a classical IL-12/STAT4-induced Th1 response (Frisancho-Kiss et al., 2006). We were surprised to find that TLR4 was expressed on alternatively activated M2 macrophages (induced by Th2 cytokines) rather than classically activated M1 macrophages (induced by Th1 cytokines) within the heart during acute CVB3 myocarditis (Fairweather & Cihakova 2009; Frisancho-Kiss et al., 2009). These CD11b+GR1+F4/80+ M2 macrophages expressed TLR4 and IL-1β (Frisancho-Kiss et al., 2009). We, and others, have shown that IL-1β is particularly important in the cardiac remodeling that leads to fibrosis, DCM and HF following acute myocarditis (Blyszczuk et al., 2009; Cihakova et al., 2008 Fairweather et al., 2004a; 2006). Further work is needed to better understand the role of innate TLRs and cytokine production/regulation in the heart in order to determine whether anti-cytokine therapies will be effective once disease has progressed to the point of being clinically apparent (Mann, 2005). Another area that needs to be addressed in animal models is the relationship between sera levels of proinflammatory cytokines and the stage of disease (i.e. acute myocarditis vs. DCM) and whether increases in sera levels of cytokines predict HF.

3.3 Biomarkers of extracellular matrix remodeling

Remodeling of the ventricles plays an important role in the progression to HF (Braunwald, 2008). The extracellular matrix provides a framework for cardiac myocytes, mediates cell adhesion and cell-to-cell communication, mediates diastolic stiffness, promotes cell survival or apoptosis, and is a reservoir for growth factors and cytokines (Liu et al., 2006). Release of cytokines and growth factors at the site of tissue injury and by inflammatory cells induces fibroblast proliferation and deposition of collagen, which is the primary component of the ECM resulting in scar tissue (Figure 5). Profibrotic cytokines, such as TNF and IL-1β, and growth factors, like transforming growth factor (TGF)β1 and fibroblast growth factor (FGF), induce collagen production from fibroblasts. Normally a balance exists between matrix metalloproteinases (MMPs) that proteolytically degrade fibrillar collagen and tissue inhibitors of MMPs (TIMPs). However, during inflammatory CVDs an imbalance in MMPs and TIMPs contributes to collagen deposition, ventricular dilatation and remodeling resulting in DCM and HF. The activity of MMPs has been shown to be increased in the progression to HF (Bradham et al., 2002; Tyagi et al., 1996). Serum MMP9, for example, has been found to predict CVD mortality better than other traditional prognostic markers such as cholesterol, CRP or IL-6 (Blankenberg et al., 2003; Liu et al., 2006).

The progression from myocarditis to fibrosis, DCM and HF has been well documented in clinical studies and animal models (Fairweather et al., 2004a; Kania et al., 2009; Looi et al., 2010). Studies in our laboratory have revealed a two-stage process where increases in profibrotic mediators during acute CVB3 myocarditis, which occurs from day 8 to 12 post infection, result in a gradual remodeling that progresses to fibrosis and DCM by day 35 post infection (Figure 5) (Fairweather et al., 2004a; 2006; Fairweather & Rose, 2007). In both animal and human studies of DCM, genes associated with extracellular matrix remodeling and fibrosis are upregulated with disease (Piro et al., 2010; Yung et al., 2004). TNF, IL-1β, IL-4, IL-6, IL-17 and TGF-β have all been found to initiate remodeling (Baldeviano et al., 2010; Blyszczuk et al., 2009; Fairweather et al., 2004a; Heymans, 2006; Kania et al., 2009). There are many MMPs, but only 4 known TIMPS. MMPs are upregulated in the heart during EAM and during viral myocarditis (Marchant & McManus, 2009; Tang et al., 2007; Westermann et al., 2010). Individual MMPs and TIMPs have been found to differ in their effects on

myocarditis in rodents (Liu et al., 2006; Marchant & McManus, 2009; Westermann et al., 2010). For example, MMP9 deficient mice had increased CVB3 replication and inflammation, and worse heart function than wild type controls, indicating that MMP9 protects the heart from CVB3 myocarditis (Cheung et al., 2008). In contrast, TIMP-1 deficient mice were protected from CVB3 myocarditis indicating that TIMP-1 increases disease (Crocker et al., 2007). Although a number of studies have examined the role of MMPs and TIMPs in myocarditis, the relationship between serum levels of these factors and the progression to DCM and HF is not yet clear from animal models.
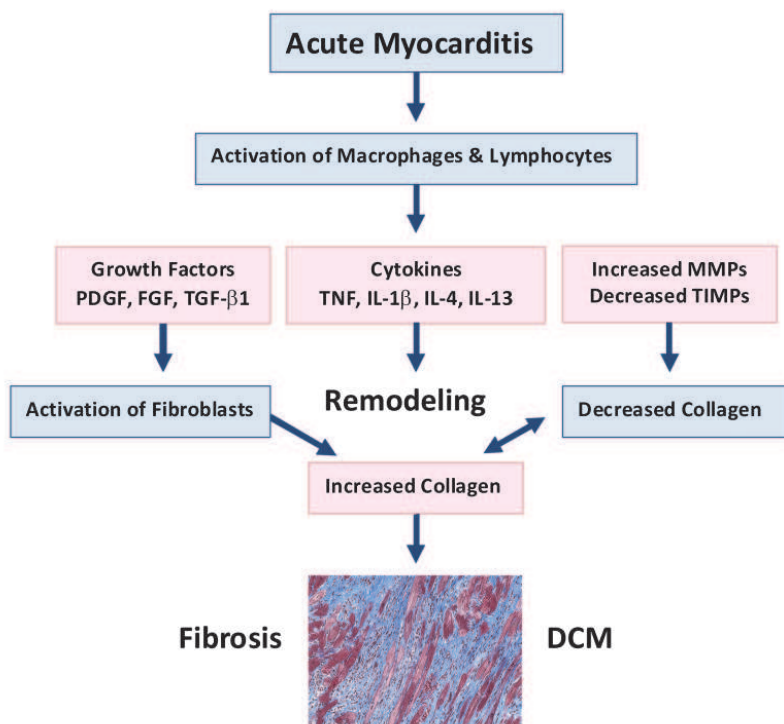
Fig. 5. Development of fibrosis and DCM following acute myocarditis. Macrophages and lymphocytes present within the myocardium during acute myocarditis release profibrotic cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1β, IL-4 and IL-13 that activate fibroblasts to release collagen. Inflammation additionally stimulates the release of growth factors like platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and transforming growth factor (TGF)-β1, which act with cytokines to increase collagen production. Cytokines and growth factors released from inflammatory cells and cardiac tissues contribute to pathology. Normally a balance exists between matrix metalloproteinases (MMPs) that proteolytically degrade fibrillar collagen and tissue inhibitors of MMPs (TIMPs). However, during acute myocarditis an imbalance in MMPs and TIMPs contributes to collagen deposition, ventricular dilatation and remodeling resulting in dilated cardiomyopathy (DCM) and heart failure.

3.4 Thrombosis biomarkers

Atherosclerosis is a major initiator of thrombi formation that can restrict blood flow and lead to a heart attack (Carter, 2005). Cardiac mural thrombi can arise from a myocardial infarction, infection, inflammation (e.g. myocarditis) or rheumatic heart disease, for example. Although research has led to a clear understanding of conditions that induce thrombosis, the precise pathology leading to disease remains unclear. Thrombi can develop anywhere in the cardiovascular system like in the ventricular or atrial chambers, arteries, veins or capillaries. The size and shape of individual thrombi vary depending on the circumstances leading to their development. They often are found at sites of endothelial injury. Once thrombi have formed (acute) they may accumulate more platelets and fibrin and grow larger, or dislodge and travel to other sites, or be removed by fibrinolytic activity, and finally they can attract inflammation, undergo remodeling with deposition of collagen and be reincorporated into the vessel or myocardium (Kumar et al., 2005) (Figure 6).
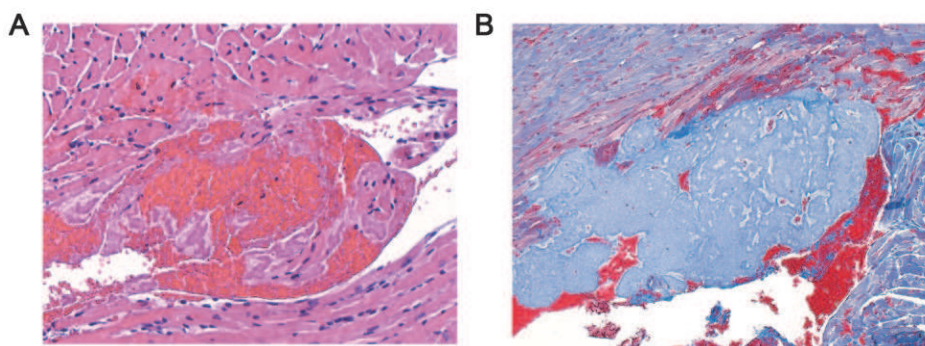

Fig. 6. Mural thrombi develop during acute CVB3 autoimmune myocarditis in mice and reincorporate into the myocardium. Male BALB/c mice were infected intraperitoneally with heart-passaged coxsackievirus B3 (CVB3) containing infectious CVB3 (10^3 plaque forming units) and heart proteins on day 0 and thrombus formation examined at day 10 post infection (pi) during acute myocarditis (**A**) or during chronic myocarditis/DCM at day 35 pi (**B**). H&E staining shows ventricular mural thrombus at day 10 pi (magnification, x100) (**A**). Masson's trichrome stains bright blue revealing collagen composition of mural integrated ventricular thrombus at day 35 pi (magnification, x100) (**B**).

Damage of cardiac tissue by viruses and inflammation is known to release tissue factor (TF), the main initiator of the coagulation cascade that results in the formation of fibrin and thrombotic clots (Mackman, 2009). Mural thrombi are known to occur in viral models of myocarditis in mice as well as in myocarditis patients (Antoniak et al., 2008; Kojima et al., 1988; Kuh & Seo, 2005). Furthermore, DCM patients demonstrate a high frequency of LV thrombi and prothrombotic characteristics like high levels of circulating fibrinogen and antithrombin III (Abdo et al., 2010). Many studies have shown that TF can increase inflammation by stimulating release of IL-6, a cytokine that along with TNF and IL-1β has been strongly associated with poor CVD outcome (Braunwald, 2008; Carter, 2005; Mackman, 2009; Rao et al., 2006). Complement components also contribute to thrombosis by depositing at sites of tissue damage and by activating platelets (Fairweather et al., 2006; Peerschke et al.,

2010). Eosinophils are potent inducers of ECM remodeling, releasing many profibrotic factors including IL-1β, IL-6, TGF-β, MMPs, and TIMPs (Shamri et al., 2011). Additionally, eosinophils release potent prothrombotic agents such as major basic protein, eosinophilic cationic protein, and eosinophil peroxidase, as well as directly and/or indirectly activating TF (Ames et al., 2010). Eosinophilia, fibrosis and thrombosis are characteristics of eosinophilic cardiovascular diseases like Churg Strauss syndrome, a form of vasculitis, hypereosinophilic syndrome, eosinophilic myocarditis and giant cell myocarditis (Ames et al., 2010; Cooper, 2000; 2009; Kleinfeldt et al., 2010; Rezaizadeh et al., 2010). Circulating biomarkers that may indicate a hypercoagulable state include complement C3, C4, IL-6, fibrinogen or antithrombin III (Abdo et al., 2010). Complement components were recently found to be elevated in the sera of mycarditis and DCM patients (Cooper et al., 2010). We have found that complement receptor 1 deficient mice, a receptor that regulates C3 levels, develop severe CVB3 myocarditis, dilation and HF with elevated levels of IL-1β in the heart and fibrosis (Fairweather et al., 2006). Overactivation of the terminal complement complex (C5b-9) has been shown to contribute to the progression of myocarditis to DCM in mice, indicating the importance of complement in regulating disease (Zwaka et al., 2002). Overall, these findings suggest that biomarkers of coagulation and/or thrombosis are likely to be important indicators of progression to DCM and HF following myocarditis.

4. Conclusions

Biomarkers are an important clinical tool for assessing progression to heart failure. DCM often leads to HF, and myocarditis is an important cause of acute (sudden death) and chronic (arising from DCM) forms of HF. Even though myocarditis is known to be an important cause of HF, few clinical studies have been conducted to determine the presence or usefulness of HF biomarkers in predicting adverse outcomes in myocarditis patients. Studies that have been conducted in myocarditis/DCM patients or animal models suggest that many of the biomarkers used to assess the likelihood of progression to heart failure in other CVDs will also provide useful information in myocarditis/DCM patients. More studies examining the ability of circulating HF biomarkers to predict poor outcome and HF in animal models of myocarditis/DCM are needed. Animal models will also provide valuable information on the potential role of HF biomarkers in the pathogenesis of disease. This knowledge is critical in determining the ability of therapies targeted to these biomarkers to prevent disease progression.

5. Acknowledgements

6. References

Abdo, A.S., Kemp, R., Barham, J. & Geraci, S.A. (2010) Dilated cardiomyopathy and role of antithrombotic therapy. *American Journal of Medical Science* 339: 557-560.

Afanasyeva, M., Wang, Y., Kaya, Z., Park, S., Zilliox, M.J., Schofield, B.H., Hill, S.L. & Rose, N.R. (2001) Experimental autoimmune myocarditis in A/J mice is an interleukin-4-dependent disease with a Th2 phenotype. *American Journal of Pathology* 159: 193-203.

Afanasyeva, M., Georgakopoulos, D., Fairweather, D., Caturegli, P., Kass, D.A. & Rose, N.R. (2004) A novel model of constrictive pericarditis associated with autoimmune heart disease in interferon-γ knockout mice. *Circulation* 110: 2910-2917.

Agewall, S., Giannitsis, E., Jernbert, T. & Katus, H. (2011) Troponin elevation in coronary vs. non-coronary disease. *European Heart Journal* 32: 404-411.

Al-Biltagi, M., Issa, M., Hagar, H.A., Abdel-Hafez, M. & Aziz, N.A. (2010) Circulationg cardiac troponin levels and cardiac dysfunction in children with acute and fulminant viral myocarditis. *Acta Paediatrica* 99: 1510-1516.

Ali, S., Huber, M., Kollewe, C., Bischoff, S.C., Falk, W. & Martin, M.U. (2007) IL-1 receptor accessory protein is essential for IL-33-induced activation of T lymphocytes and mast cells. *Proceedings from the National Academy of Sciences USA* 104: 18660-18665.

Ames, P.R.J., Margaglione, M., Mackie, S. & Alves, J.D. (2010) Eosinophilia and thrombophilia in Churg Strauss syndrome: a clinical and pathogenetic overview. *Clinical Applied Thrombosis/ Hemostasisis* 16: 628-636.

Anand, I.S., Latini, R., Florea, V.G., Kuskowski, M.A., Rector, T., Masson, S., Signorini, S., Mocarelli, P., Hester, A., Glazer, R., Cohn, J.N. & Val-HeFT Investigators. (2005) C-reactive protein in heart failure: prognostic value and the effect of valsartan. *Circulation* 112: 1428-1434.

Anker, S.D. & von Haehling, S. (2004) Inflammatory mediators in chronic heart failure: an overview. *Heart* 90: 464-470.

Antoniak, S., Boltzen, U., Riad, A., Kallwellis-Opara, A., Rohde, M., Dorner, A., Tschope, C., Noutsias, M., Pauschinger, M., Schultheiss, H.-P. & Rauch, U. (2008) Viral myocarditis and coagulopathy: increased tissue factor expression and plasma thrombogenicity. *Journal of Molecular and Cellular Cardiology* 45: 118-126.

Baldeviano, G.C., Barin, J.G., Talor, M.V., Srinivasan, S., Bedja, D., Zheng, D., Gabrielson, K., Iwakura, Y., Rose, N.R. & Cihakova, D. (2010) Interleukin-17A is dispensable for myocarditis but essential for the progression to dilated cardiomyopathy. *Circulation Research* 106: 1646-1655.

Blankenberg, S. (2003) Plasma concentrations and genetic variation of matrix metalloproteinase 9 and prognosis of patients with cardiovascular disease. *Circulation* 107: 1579-1585.

Blauwet, L.A. & Cooper, L.T. (2010) Myocarditis. *Progress in Cardiovascular Diseases* 52: 274-288.

Blyszczuk, P., Kania, G., Dieterle, T., Marty, R.R., Valaperti, A., Berthonneche, C., Pedrazzini, T., Berger, C.T., Dirnhofer, S., Matter, C.M., Penninger, J.M., Luscher, T.F. & Eriksson, U. (2009) Myeloid differentiation factor-88/interleukin-1 signaling controls cardiac fibrosis and heart failure progression in inflammatory dilated cardiomyopathy. *Circulation Research* 105: 912-920.

Bradham, W.S., Moe, G., Wendt, K.A., Scott, A.A., Konig, A., Romanova, M., Naik, G. & Spinale, F.G. (2002) TNF-alpha and myocardial matrix metalloproteinases in heart failure: relationship to LV remodeling. *American Journal of Physiology and Heart Circulation Physiology* 282: H1288-H1295.

Brandt, R.R., Filzmaier, K. & Hanrath, P. (2001) Circulation cardiac troponin I in acute pericarditis. *American Journal of Cardiology* 87: 1326-1328.

Braunwald, E. (2008) Biomarkers in heart failure. *New England Journal of Medicine* 358: 2148-2159.

Bui, A.L., Horwich, T.B. & Fonarow G.C. (2011) Epidemiology and risk profile of heart failure. *Nature Reviews Cardiology* 8: 30-41.

Cain, B.S., Meldrum, D.R., Dinarello, C.A., Meng, X., Joo, K.S., Banjeree, A. & Harken, A.H. (1999) Tumor necrosis factor-alpha and interleukin-1beta synergistically depress human myocardial function. *Critical Care Medicine* 27: 1309-1318.

Calabrese, F., Carturan, E., Chimenti, C., Pieroni, M., Agostini, C., Angelini, A., Crosato, M., Valente, M., Boffa, G.M., Furstaci, A. & Thiene, G. (2004) Overexpression of tumor necrosis factor (TNF)alpha and TNFalpha receptor I in human viral myocarditis: clinicopathologic correlations. *Molecular Pathology* 17: 1108-1118.

Carter, A.M. (2005) Inflammation, thrombosis and acute coronary syndromes. *Diabetes Vascular Disease* Research 2: 113-121.

Chen, W.-C., Tran, K.D. & Maisel, A.S. (2010) Biomarkers in heart failure. *Heart* 96: 314-320.

Cheung, C., Marchant, D., Walker, E.K., Luo, Z., Zhang, J., Yanagawa, B., Rahmani, M., Cox, J., Overall, C., Senior, R.M., Luo, H. & McManus, B.M. (2008) Ablation of matrix metalloproteinase-9 increases severity of viral myocarditis in mice. *Circulation* 117: 1574-1582.

Cihakova, D., Barin, J. G., Afanasyeva, M., Kimura, M., Fairweather, D., Berg, M., Talor, M.V., Baldeviano, G.C., Frisancho-Kiss, S., Gabrielson, K., Bedja, D. & Rose, N.R. (2008) Interleukin-13 protects against experimental autoimmune myocarditis by regulating macrophage differentiation. *American Journal of Pathology* 172: 1195-1208.

Cooper, L.T. Jr. (2000) Giant cell myocarditis: diagnosis and treatment. *Herz* 3: 291-298.

Cooper, L.T. Jr. (2009) Myocarditis. *New England Journal of Medicine* 360: 1526-1538.

Cooper, L.T. Jr., Onuma, O.K., Sagar, S., Oberg, A.L., Mahoney, D.W., Asmann, Y.W. & Liu, P. (2010) Genomic and proteomic analysis of myocarditis and dilated cardiomyopathy. *Heart Failure Clinics* 6: 75-85.

Crocker, S.J., Frausto, R.F., Whitmire, J.K., Benning, N., Milner, R. & Whitton, J.L. (2007) Amelioration of coxsackievirus B3-mediated myocarditis by inhibition of tissue inhibitors of matrix metalloproteinase-1. *American Journal of Pathology* 171: 1762-1773.

Daniels, M.D., Hyland, K.V., Wang, K. & Engman, D.M. (2008) Recombinant cardiac myosin fragment induces experimental autoimmune myocarditis via activation of Th1 and Th17 immunity. *Autoimmunity* 41: 490-499.

De Gennaro, L., Brunetti, N.D., Cuculo, A., Pellegrino, P.L. & Di Biase, M. (2008) Systemic inflammation in nonischemic dilated cardiomyopathy. *Heart Vessels* 23: 445-450.

Devaraj, S., Singh, U. & Jialal, I. (2009) The evolving role of C-reactive protein in atherothrombosis. *Clinical Chemistry* 55: 229-238.

Elster, S.K., Braunwald, E. & Wood, H.F. (1956) A study of C-reactive protein in the serum of patients with congestive heart failure. *American Heart Journal* 51: 533-541.

Eriksson, S., Hellman, J. & Pettersson, K. (2005) Autoantibodies against cardiac troponins. *New England Journal of Medicine* 352: 98-100.

Fairweather, D. & Cihakova, D. (2009) Alternatively activated macrophages in infection and autoimmunity. *Journal of Autoimmunity* 33: 222-230.

Fairweather, D. & Rose, N.R. (2005) Inflammatory heart disease: a role for cytokines. *Lupus* 14: 646-651.

Fairweather, D. & Rose, N.R. (2007) Coxsackievirus-induced myocarditis in mice: a model of autoimmune disease for studying immunotoxicity. *Methods* 41: 118-122.

Fairweather, D., Yusung, S., Frisancho(-Kiss), S., Barrett, M., Gatewood, S., Steele, R. & Rose, N.R. (2003) IL-12Rβ1 and TLR4 increase IL-1β and IL-18-associated myocarditis and coxsackievirus replication. *Journal of Immunology* 170: 4731-4737.

Fairweather, D., Frisancho-Kiss, S., Yusung, S.A., Barrett, M.A., Gatewood, S.J.L., Davis, S.E., Njoku, D.B. & Rose, N.R. (2004a) IFN-γ protects against chronic viral myocarditis by reducing mast cell degranulation, fibrosis, and the profibrotic cytokines TGF-β_1, IL-1β, and IL-4 in the heart. *American Journal of Pathology* 165: 1883-1894.

Fairweather, D., Frisancho-Kiss, S., Gatewood, S., Njoku, D., Steele, R., Barrett, M. & Rose, N.R. (2004b) Mast cells and innate cytokines are associated with susceptibility to autoimmune heart disease following coxsackievirus B3 infection. *Autoimmunity* 37: 131-145.

Fairweather, D., Frisancho-Kiss, S., Yusung, S.A., Barrett, M.A., Davis, S.E., Steele, R.A., Gatewood, S.J.L. & Rose, N.R. (2005) IL-12 protects against coxsackievirus B3-induced myocarditis by increasing IFN-γ and macrophage and neutrophil populations in the heart. *Journal of Immunology* 174: 261-269.

Fairweather, D., Frisancho-Kiss, S., Njoku, D.B., Nyland, J.F., Kaya, Z., Yusung, S.A., Davis, S.E., Frisancho, J.A., Barrett, M.A. & Rose, N.R. (2006) Complement receptor 1 and 2 deficiency increases coxsackievirus B3-induced myocarditis and heart failure by increasing macrophages, IL-1β and immune complex deposition in the heart. *Journal of Immunology* 176: 3516-3524.

Fairweather, D., Frisancho-Kiss, S. & Rose, N.R. (2008) Sex differences in autoimmune disease from a pathologic perspective. *American Journal of Pathology* 173: 600-609.

Frisancho-Kiss, S., Nyland, J.F., Davis, S.E., Frisancho, J.A., Barrett, M.A., Rose, N.R. & Fairweather, D. (2006) Sex differences in coxsackievirus B3-induced myocarditis: IL-12Rβ1 signaling and IFN-γ increase inflammation in males independent from STAT4. *Brain Research* 1126: 139-147.

Frisancho-Kiss, S., Davis, S.E., Nyland, J.F., Frisancho, J.A., Cihakova, D., Rose, N.R. & Fairweather, D. (2007) Cutting Edge: Cross-regulation by TLR4 and T cell Ig mucin-3 determines sex differences in inflammatory heart disease. *Journal of Immunology* 178: 6710-6714.

Frisancho-Kiss, S., Coronado, M.J., Frisancho, J.A., Lau, V.M., Rose, N.R., Klein, S.L. & Fairweather, D. (2009) Gonadectomy of male BALB/c mice increases Tim-3^{+} alternatively activated M2 macrophages, Tim-3^{+} T cells, Th2 cells and Treg in the heart during acute coxsackievirus-induced myocarditis. *Brain Behavior and Immunity* 23: 649-657.

Gaddam, K.K., Ventura H.O. & Lavie C.J. (2011) Metabolic syndrome and heart failure- the risk, paradox and treatment. *Current Hypertension Research* 13: 142-148.

Goser, S., Andrassy, M., Buss, S.J., Leuschner, F., Volz, C.H., Ottl, R., Zittrich, S., Blaudeck, N., Hardt, S.E., Pfitzer, G., Rose, N.R., Katus, H.A. & Kaya, Z. (2006) Cardiac troponin I but not cardiac troponin T induces severe autoimmune inflammation in the myocardium. *Circulation* 114: 1693-1702.

Grabowski, M., Karpinski, G.J., Filipiak, K., Rdzanek, A., Pietrasik, A., Wretwoski, D., Rudowski, R. & Opolski, G. (2004) Diagnostic value of BNP in suspected perimyocarditis- a preliminary report. *Kardiology Pol.* 61: 451-458.

Grzybowski, J., Bilinska, Z.T., Ruzyllo, W., Kupsc, W., Michalak, E., Szczesniewska, D., Poplawska, W. & Rydlewska-Sadowska, W. (1996) Determinants of prognosis of nonischemic dilated cardiomopathy. *Journal of Cardiac Failure* 2: 77-85.

Gupta, S., Markham, D.W., Drazner, M.H. & Mammen, P.P.A. (2008) Fulminant myocarditis. *Nature Clinical Practice* 5: 693-706.

Hebert, K., Macedo, F.Y., Trahan, P., Tamariz, L., Dias, A., Palacio, A. & Arcement, L.M. (2011) Routine serial echocardiography in systolic heart failure: is it time for the heart failure guidelines to change? *Congestive Heart Failure* 17: 85-89.

Hedayat, M., Mahmoudi, M.J., Rose, N.R. & Rezaei, N. (2010) Proinflammatory cytokines in heart failure: double-edged swords. *Heart Failure Reviews* 15: 543-562.

Heymans, S. (2006) Inflammation and cardiac remodeling during viral myocarditis. *Ernst Schering Research Foundation Workshop* 55: 197-218.

Hirayama, A., Kusuoka, H., Yamamoto, H., Sakata, Y., Asakura, M., Higuchi, Y., Mizuno, H., Kashiwase, K., Ueda, Y., Okuyama, Y., Hori, M. & Kodama, K. (2005) Serial changes in plasma brain natriuretic peptide concentration at the infarct and non-infarct sites in patients with left ventricular remodeling after myocardial infarction. *Heart* 91: 1573-1577.

Hochholzer, W., Morrow, D.A. & Giugliano, R.P. (2010) Novel biomarkers in cardiovascular disease: update 2010. *American Heart Journal* 160: 583-594.

Huber, S.A. (2010) Tumor necrosis factor-alpha promotes myocarditis in female mice infected with coxsackievirus B3 through upregulation of CD1d on hematopoeitic cells. *Viral Immunology* 23: 79-86.

Huber, S.A. & Pfaeffle, B. (1994) Differential Th1 and Th2 cell responses in male and female BALB/c mice infected with coxsackievirus group B type 3. *Journal of Virology* 68: 5126-5132.

Imazio, M., Cecchi, E., Demichelis, B., Chinaglia, A., Lerna, S., Demarie, D., Ghisio, A., Pomari, F., Belli, R. & Trinchero, R. (2008) Myopericarditis versus viral or idiopathic acute pericarditis. *Heart* 94: 498-501.

Ishikawa, C., Tsutamoto, T., Fujii, M., Sakai, H., Tanaka, T. & Horie, M. (2006) Prediction of mortality by high-sensitivity C-reactive protein and brain natriuretic peptide in patients with dilated cardiomyopathy. *Circulation Journal* 70: 857-863.

Jameson, J.N., Kasper, D., Harrison, T.R., Braunwald, E., Fauci, A.S., Hauser, S.L. & Longo, D.L. (2005) Harrison's Principles of Internal Medicine. McGraw-Hill Medical Publishing Division, New York.

Jefferis, B.J., Papacosta, O., Owen, C.G., Wannamethee, S.G., Humphries, S.E., Woodward, M., Lennon, L.T., Thomson, A., Welsh, P., Rumley, A., Lowe, G.D. & Whincup, P.H. (2011) Interleukin 18 and coronary heart disease: prospective study and systematic review. *Atherosclerosis* April 8 [Epub ahead of print].

Kallwellis-Opara, A., Dorner, A., Poller, W.-C., Noutsias, M., Kuhl, U., Schultheiss, H.-P. & Pauschinger, M. (2007) Autoimmunological features in inflammatory cardiomyopathy. *Clinical Research Cardioliology* 96: 469-480.

Kaneko, K., Kanda, T., Yamauchi, Y., Hasegawa, A., Iwasaki, T., Arai, M., Suzuki, T., Kobayashi, I. & Nagai, R. (1999) C-reactive protein in dilated cardiomyopathy. *Cardiology* 91: 215-219.

Kaneko, K., Kanda, T., Hasegawa, A., Suzuki, T., Kobayashi, I. & Nagai, R. (2000) C-reactive protein as a prognostic marker in lymphocytic myocarditis. *Japan Heart Journal* 41: 41-47.

Kania, G., Blyszczuk, P. & Eriksson, U. (2009) Mechanisms of cardiac fibrosis in inflammatory heart disease. *Trends in Cardiovascular Medicine* 19: 247-252.

Karamitsos, T.D. & Neubauer, S. (2011) Cardiovascular magnetic resonance in heart failure. *Current Cardiology Report* doi: 10.1007/s11886-011-0177-2.

Kaya, Z., Goser, S., Buss, B.J., Leuschner, F., Ottl, R., Li, J., Volkers, M., Zittrich, S., Pfitzer, G., Rose, N.R. & Katus, H.A. (2008) Identification of cardiac troponin I sequence

motifs leading to heart failure by induction of myocardial inflammation and fibrosis. *Circulation* 118: 2063-2072.

Kaya, Z., Katus, H.A. & Rose, N.R. (2010) Cardiac troponins and autoimmunity: their role in the pathogenesis of myocarditis and of heart failure. *Clinical Immunology* 134: 80-88.

Kindermann, I., Kindermann, M., Kandolf, R., Klingel, K., Bultmann, B., Muller, T., Lindinger, A. & Bohm, M. (2008) Predictors of outcome in patients with suspected myocarditis. *Circulation* 118: 639-648.

Kleinfeldt, T., Nienaber, C.A., Kische, S., Akin, I., Turan, R.G., Korber, T., Schneider, H. & Ince, H. (2010) Cardiac manifestation of the hypereosinophilic syndrome: new insights. *Clinical Research Cardioliology* 99: 419-427.

Kojima, J., Miyazaki, S., Fujiwara, H., Kumada, T. & Kawai, C. (1988) Recurrent left ventricular mural thrombi in a patient with acute myocarditis. *Heart Vessels* 4: 120-122.

Krumholz, H.M., Want, Y., Parent, E.M., Mockalis, J., Petrillo, M. & Radford, M.J. (1997) Quality of care for elderly patients hospitalized with heart failure. *Archives of Internal Medicine* 157: 2242-2247.

Kuh, J.H. & Seo, Y. (2005) Transatrial resection of a left ventricular thrombus after acute myocarditis. *Heart Vessels* 20: 230-232.

Kuhl, U., Pauschinger, M., Schwimmbeck, P.L., Seeberg, B., Lober, C., Noutsias, M., Poller, W. & Schultheiss, H.P. (2003) 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: 2793-2798.

Kumar, V., Abbas, A.K. & Fausto, N. (2005) *Robbins and Cotran Pathologic Basis of Disease*, 7th edn. Elsevier Saunders, Philadelphia.

Latini, R., Masson, S., Anand, I.S., Missov, E., Carlson, M., Vago, T., Angelici, L., Barlera, S., Parrinello, G., Maggioni, A.P., Tognoni, G., Cohn, J.N. & Val-HeFT Investigators. (2007) Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. *Circulation* 116: 1242-1249.

Leuschner, F., Li, J., Goser, S., Reinhardt, L., Ottl, R., Bride, P., Zehelein, J., Pfitzer, G., Remppis, A., Giannitsis, E., Katus, H.A. & Kaya, Z. (2008) Absence of autoantibodies against cardiac troponin I predicts improvement of left ventricular function after acute myocardial infarction. *European Heart Journal* 29: 1949-1955.

Levine, B., Kalman, J., Mayer, L., Fillit, H.M. & Packer, M. (1990) Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *New England Journal of Medicine* 323: 236-241.

Liew, F.Y., Pitman, N.I. & McInnes, I.B. (2010) Disease-associated funcitons of IL-33: the new kid in the IL-1 family. *Nature Reviews Immunology* 10: 103-110.

Liu, P., Sun, M. & Sader, S. (2006) Matrix metalloproteinases in cardiovascular diseae. *Canadian Journal of Cardiology* 22(Suppl. B): 25B-30B.

Looi, J.L., Edwards, C., Armstrong, G.P., Scott, A., Patel, H., Hart, H. & Christiansen, J.P. (2010) Characteristics and prognostic importance of myocardial fibrosis in patients with dilated cardiomyopathy assessed by contrast-enhanced cardiac magnetic resonance imaging. *Clinical Medicine Insights in Cardiology* 4: 129-134.

Mackman, N. (2009) The many faces of tissue factor. *Journal of Thombosis and* Haemostasis 7: 136-139.

Maisch, B. (1994) Pericardial diseases, with a focus on etiology, pathogenesis, pathophysiology, new diagnostic imaging methods, and treatment. *Current Opinion in Cardiology* 9: 379-388.

Mann, D.L. (2005) Targeted anticytokine therapy and the failing heart. *American Journal of Cardiology* 95(Suppl): 9C-16C.

Marchant, D. & McManus, B.M. (2009) Matrix metalloproteinases in the pathogenesis of viral heart disease. *Trends in Cardiovascular Medicine* 19: 21-26.

Masson, S., Latini, R., Anand, I.S., Vago, T., Angelici, L., Barlera, S., Missov, E.D., Clerico, A., Tognoni, G., Cohn, J.N. & Val-HeFT Investigators. (2006) Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Fialure (Val-HeFT) data. *Clinical Chemistry* 52: 1528-1538.

Miettinen, K.H., Eriksson, S., Magga, J., Tuomainen, P., Kuusisto, J., Vanninen, E.J., Turpeinen, A., Punnonen, K.R., Pettersson, K. & Peuhkurinen, K.J. (2008) Clinical significance of troponin I efflux and troponin autoantibodies in patients with dilated cardiomyopathy. *Journal of Cardiac Failure* 14: 481-488.

Miller, A.M. & Liew, F.Y. (2011) The IL-33/ST2 pathway- a new therapeutic target for cardiovascular disease. *Pharmacology and Therapeutics* Feb 26 [Epub ahead of print].

Miller, W.L., Hartman, K.A., Burritt, M.F., Burnett, J.C. & Jaffe, A.S. (2007) Troponin, B-type natriuretic peptides and outcomes in severe heart failure: differences between ischemic and dilated cardiomyopathies. *Clinical Cardiology* 30: 245-250.

Miller, A.M., Xu, D., Asquith, D.L., Denby, L., Li, Y., Sattar, N., Baker, A.H., McInnes, I.B. & Liew, F.Y. (2008) IL-33 reduces the development of atherosclerosis. *Journal of Experimental Medicine* 205: 339-346.

Morgera, T., Di Lenarda, A., Dreas, L., Pinamonti, B., Humar, F., Bussani, R., Silvestri, F., Chersevani, D. & Camerini, F. (1992) Electrocardiography of myocardtiis revisited: clinical and prognostic significance of electrocardiographic changes. *American Heart Journal* 124: 455-467.

Morrow, D.A. & de Lemos, J.A. (2007) Benchmarks for the assessment of novel cardiovascular biomarkers. *Circulation* 115: 949-952.

Nishikubo, K., Imanaka-Yoshida, K., Tamaki, S., Hiroe, M., Yoshida, T., Adachi, Y. & Yasutomi, Y. (2007) Th1-type immune responses by Toll-like receptor 4 signaling are required for the development of myocarditis in mice with BCG-induced myocarditis. *Journal of Autoimmunity* 29: 146-153.

Nishimura, H., Okazaki, T., Tanaka, Y., Nakatani, K., Hara, M., Matsumori, A., Sasayama, S., Mizoguchi, A., Hiai, H., Minato, N. & Honjo, T. (2001) Autoimmune dilated cardiomyopathy in PD-1 receptor deficient mice. *Science* 291: 319-322.

Ogawa, T., Veinot, J.P., Kuroski de Bold, M.L., Georgalis, T. & de Bold, A.J. (2008) Angiotensin II receptor antagonism reverts the selective cardiac BNP upregulation and secretion observed in myocarditis. *American Journal of Physiology and Heart Circulation Physiology* 294: H2596-H2603.

Olimulder, M.A., van Es, J. & Galjee, M.A. (2009) The importance of cardiac MRI as a diagnostic took in viral myocarditis-induced cardiomyopathy. *Netherlands Heart Journal* 17: 481-486.

Omland, T., Sabatine, M.S., Jablonski, K.A., Rice, M.M., Hsia, J., Wergeland, R., Landaas, S., Rouleau, J.L., Domanski, M.J., Hall, C., Pfeffer, M.A., Braunwald, E. & PEACE Investigators. (2007) Prognostic value of B-type natriuretic peptides in patients with

stable coronary artery disease: the PEACE Trial. *Journal of American College of Cardiology* 50: 205-214.

Onyimba, J.A., Coronado, M.J., Garton, A.E., Kim, J.B., Bucek, A., Bedja, D., Gabrielson, K.L., Guilarte, T.R. & Fairweather, D. (2011) The innate immune response to coxsackievirus B3 predicts progression to cardiovascular disease and heart failure in male mice. *Biology of Sex Differences* 2: 2.

Osman, R., L'Allier, P.L., Elgharib, N. & Tardif, J.-C. (2006) Critical appraisal of C-reactive protein throughout the spectrum of cardiovascular disease. *Vascular Health and Risk Management* 2: 221-237.

Palazzuoli, A., Antonelli, G., Quantrini, I. & Nuti, R. (2011) Natriuretic peptides in heart failure: where we are, where we are going. *Internal Emergency Medicine* 6: 63-68.

Peacock, W.F. 4th, DeMarco, T., Fonarow, G.C., Diercks, D., Wynne, J., Apple, F.S., Wu, A.H. & ADHERE Investigators. (2008) Cardiac troponin and outcome in acute heart failure. *New England Journal of Medicine* 15: 2117-2126.

Peerschke, E.I., Yin, W. & Ghebrehiwet, B. (2010) Complement activation on platelets: implications for vascular inflammation and thrombosis. *Molecular Immunolunology* 47: 2170-2175.

Pepys, M.B. & Hirschfield, G.M. (2003) C-reactive protein: a critical update. *The Journal of Clinical Investigation* 111: 1805-1812.

Perez-De-Lis, M., Akasbi, M., Siso, A., Diez-Cascon, P., Brito-Zeron, P., Diaz-Lagares, C., Ortiz, J., Perez-Alvarez, R., Ramos-Casals, M. & Coca, A. (2010) Cardiovascular risk factors in primary Sjogren's syndrome: a case-control study in 624 patients. *Lupus* 19: 941-948.

Piro, M., Bona, R.D., Abbate, A., Biasucci, L.M. & Crea, F. (2010) Sex-related differences in myocardial remodeling. *Journal of the American College of Cardiology* 55: 1057-1065.

Rao, M., Jaber, B.L. & Balakrishnan, V.S. (2006) Inflammatory biomarkers and cardiovascular risk: association or cause and effect? *Seminars in Dialysis* 19: 129-135.

Rezaizadeh, H., Sanchez-Ross, M., Kaluski, E., Klapholz, M., Haider, B. & Gerula, C. (2010) Acute eosinophilic myocarditis: diagnosis and treatment. *Acute Cardiac Care* 12: 31-36.

Rhodes, B., Furnrohr, B.G. & Vyse, T.J. (2011) C-reactive protein in rheumatology: biology and genetics. *Nature Reviews Rheumatology* April 5 [Epub ahead of print].

Robinson, T., Smith, A. & Channer, K.S. (2011) Reversible heart failure: the role of inflammatory activation. *Postgraduate Medical Journal* 87: 110-115.

Roger, V.L., Go, A.S., Lloyd-Jones, D.M., Adams, R.J., Berry, J.D., Brown, T.M., Carnethon, M.R., Dai, S., de Simone, G., Ford, E.S., Fox, C.S., Fullerton, H.J., Gillespie, C., Greenlund, K.J., Hailpern, S.M., Heit, J.A., Ho, P.M., Howard, V.J., Kissela, B.M., Kittner, S.J., Lackland, D.T., Lichtman, J.H., Lisabeth, L.D., Makuc, D.M., Marcus, G.M., Marelli, A., Matchar, D.B., McDermott, M.M., Meigs, J.B., Moy, C.S., Mozaffarian, D., Mussolino, M.E., Nichol, G., Paynter, N.P., Rosamond, W.D., Sorlie, P.D., Stafford, R.S., Turan, T.N., Turner, M.B., Wong, N.D., Wylie-Rosett, J., American Heart Association Statistics Committee and Stroke Statistics Subcommittee. (2011) Heart disease and stroke statistics- 2011 update. *Circulation* 123: e18-e209.

Ronaldson, K.J., Taylor, A.J., Fitzgerald, P.B., Topliss, D.J., Elsik, M. & McNeil, J.J. (2010) Diagnostic characteristics of clozapine-induced myocarditis identified by an analysis of 38 cases and 47 controls. *Journal of Clinical Psychiatry* 71: 976-981.

Sanada, S., Hakuno, D., Higgins, L.J., Schreiter, E.R., McKenzie, A.N.J. & Lee R.T. (2007) IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. *The Journal of Clinical Investigation* 117: 1538-1549.

Satoh, M., Nakamura, M., Akatsu, T., Iwasaka, J., Shimoda, Y., Segawa, I. & Hiramori, K. (2003) Expression of Toll-like receptor 4 is associated with enteroviral replication in human myocarditis. *Clinical Science (London)* 104: 577-584.

Satoh, M., Nakamura, M., Akatsu, T., Shimoda, Y., Segawa, I. & Hiramori, K. (2005) C-reactive protein co-expresses with tumor necrosis factor-alpha in the myocardium in human dilated cardiomyopathy. *European Journal Heart* 7: 748-754.

Schultz, J.C., Hilliard, A.A., Cooper, L.T. & Rihal, C.S. (2009) Diagnosis and treatment of viral myocarditis. *Mayo Clinical Proceedings* 84: 1001-1009.

Senes, M., Erbay, A.R., Yilmaz, F.M., Topkaya, B.C., Zengi, O., Dogan, M. & Yucel, D. (2008) Coenzyme Q10 and high-sensitivity C-reactive protein in ischemic and idiopathic dilated cardiomyopathy. *Clinical Chemistry Laboratory Medicine* 46: 382-386.

Seta, Y., Shan, K., Bozkurt, B., Oral, H. & Mann, D.L. (1996) Basic mechanisms in heart failure: the cytokine hypothesis. *Journal of Cardiac Failure* 2: 243-249.

Shamri, R., Xenakis. J.J. & Spencer, L.A. (2011) Eosinophils in innate immunity: an evolving story. *Cell Tissue Research* 343: 57-83.

Shmilovich, H., Danon, A., Binah, O., Roth, A., Chen, G., Wexler, D., Keren, G. & George, J. (2007) Autoantibodies to cardiac troponin I in patients with idiopathic dilated and ischemic cardiomyopathy. *International Journal of Cardiology* 117: 198-203.

Silver, M.A., Maisel, A., Yancy, C.W., McCullough, P.A., Burnett, J.C. Jr., Francis, G.S., Mehra, M.R., Peacock, W.F. 4th, Fonarow, G., Gibler, W.B., Morrow, D.A., Hollander, J. & BNP Consensus Panel. (2004) NBP Consensus Panel 2004: A clinical approach for the diagnostic, prognostic, screening, treatment monitoring, and therapeutic roles of natriuretic peptides in cardiovascular diseases. *Congestive Heart Failure* 10(Suppl. 3): 1-30.

Smith, S.C., Ladenson, J.H., Mason, J.W., & Jaffe, A.S. (1997) Elevations of cardiac troponin I associated with myocarditis. Experimental and clinical correlates. *Circulation* 95: 163-168.

Soongswang, J., Durongpisitkul, K., Ratanarapee, S., Leowattana, W., Nana, A., Laohaprasitiporn, D., Akaniroj, S., Limpimwong, N. & Kangkagate, C. (2002) Cardiac troponin T: its role in the diagnosis of clinically suspected acute myocarditis and chronic dilated cardiomyopathy in children. *Pediatric Cardiology* 23: 531-535.

Talvani, A., Rocha, M.O., Barcelos, L.S., Gomes, Y.M., Ribeiro, A.L. & Teixeira, M.M. (2004) Elevated concentrations of CCL2 and tumor necrosis factor-alpha in chagasic cardiomyopathy. *Clinical Infectious Disease* 38: 943-950.

Tanaka, K., Ito, M., Kodama, M., Tomita, M., Kimura, S., Hoyano, M., Mitsuma, W., Hirono, S., Hanawa, H. & Aizawa, Y. (2011) Sulfated polysaccharide fucoidan ameliorates experimental autoimmune myocarditis in rats. *Journal of Cardiovascular Pharmacology and Therapy* 16: 79-86.

Tang, Q., Huang, J., Qian, H., Xiong, R., Shen, D., Wu, H., Bian, Z. & Wei, X. (2007) Microarray analysis reveals the role of matrix metalloproteinases in mouse experimental autoimmune myocarditis induced by cardiac myosin peptides. *Cell Molecular Biology Letters* 12: 176-191.

Tyagi, S.C., Campbell, S.E., Reddy, H.K., Tjahja, E. & Voelker, D.J. (1996) Matrix metalloproteinase activity expression in infracted, noninfarcted and dilated cardiomyopathic human hearts. *Molecular Cell Biochemistry* 155: 13-21.

Vallejo, J.G. (2011) Roleof Toll-like receptors in cardiovascular diseases. *Clinical Science* 121: 1-10.

Vasan, R.S., Sullivan, L.M., Roubenoff, R., Dinarello, C.A., Harris, T., Benjamin, E.J., Sawyer, D.B., Levy, D., Wilson, P.W., D'Agostino, R.B. & Framingham Heart Study. (2003) Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. *Circulation* 107: 1486-1491.

Venugopal, S.K., Devaraj, S. & Jialal, I. (2005) Effect of C-reactive protein on vascular cells: evidence for a proinflammatory, proatherogenic role. *Current Opinion in Nephrology and Hypertension* 14: 33-37.

Wang, Y.-X., da Cunha, V., Vincelette, J., White, K., Velichko, S., Xu, Y., Gross, C., Fitch, R.M., Halks-Miller, M., Larsen, B.R., Yajima, T., Knowlton, K.U., Vergona, R., Sullivan, M.E. & Croze, E. (2007) Antiviral and myocyte protective effects of murine interferon-β and –α2 in coxsackievirus B3-induced myocarditis and epicarditis in BALB/c mice. *American Journal of Physiology and Heart Circulation Physiology* 293: H69-H76.

Weinberg, E.O., Shimpo, M., De Keulenaer, G.W., MacGillivray, C., Tominaga, S., Solomon, S.D., Rouleau, J.L. & Lee, R.T. (2002) Expression and regulation of ST2, an interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction. *Circulation* 106: 2961-2966.

Weinberg, E.O., Shimpo, M., Hurwitz, S., Tominaga, S., Rouleau, J.L. & Lee, R.T. (2003) Identification of serum soluble ST2 receptor as a novel heart failure biomarker. *Circulation* 107: 721-726.

Westermann, D., Savvatis, K., Schultheiss, H.P. & Tschope, C. (2010) Immunomodulation and matrix metalloproteinases in viral myocarditis. *Journal of Molecular and Cellular Cardiology* 48: 468-473.

Wexler, R.K., Elton, T., Pleister, A. & Feldman, D. (2009) Cardiomyopathy: an overview. *American Family Physician* 79: 778-784.

Yung, C.K., Helperin, V.L., Tomaselli, G.F. & Winslow, R.L. (2004) Gene expression profiles in end-stage human idiopathic dilated cardiomyopathy: altered expression of apoptotic and cytoskeletal genes. *Genomics* 83: 281-297.

Zimmermann, O., Bienek-Ziolkowski, M., Wolf, B., Vetter, M., Baur, R., Mailander, V., Hombach, V. & Torzewski, J. (2009) Myocardial inflammation and non-ischaemic heart failure: is there a role for C-reactive protein? *Basic Research in Cardiology* 104: 591-599.

Zwaka, T.P., Manolov, D., Ozdemir, C., Marx, N., Kaya, Z., Kochs, M., Hoher, M., Hombach, V & Torzewski, J. (2002) Complement and dilated cardiomyopathy: a role of sublytic terminal complement complex-induced tumor necrosis factor-alpha synthesis in cardiac myocytes. *American Journal of Pathology* 161: 449-457.
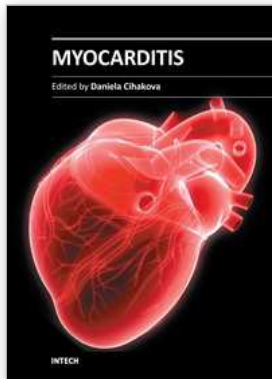
Myocarditis

Edited by Dr. Daniela Cihakova

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' 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:

DeLisa Fairweather, Eric D. Abston and Michael J. Coronado (2011). Biomarkers of Heart Failure in Myocarditis and Dilated Cardiomyopathy, Myocarditis, Dr. Daniela Cihakova (Ed.), ISBN: 978-953-307-289-0, InTech, Available from: http://www.intechopen.com/books/myocarditis/biomarkers-of-heart-failure-in-myocarditis-and-dilated-cardiomyopathy

INTECH
open science | open minds