Pathophysiology of right ventricular heart disease: the role of structure, apoptosis and inflammation
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"When a scientist is ahead of his times, it is often through misunderstanding of current, rather than intuition of future truth. In science there is never any error so gross that it won't one day, from some perspective, appear prophetic."

Jean Rostand
The pathophysiology of RV remodeling is a complex process and includes changes in geometry, wall thickness, and ventricular pressure-volume relationships. Additionally, myocyte dimensions, myocyte number and myocardial extracellular matrix are modified and infiltration of inflammatory cells might occur. Next to structural remodeling, alterations in gap junction and ion channel expression and function (electrical remodeling) might occur. Remodeling has been associated with pulmonary hypertension, RV failure, lung transplantation, LV pathology, Chagas' disease, ARVC/D, and recently Brugada syndrome.

In Chapter I the development, structure and the function of the RV is reviewed with an emphasis on the differences with the LV. Furthermore, the purpose of this thesis was formulated. The cellular and molecular mechanisms underlying the progression to RV failure were reviewed. Although there is a clear distinction between both ventricles, there is a lack of data to understand these differences, similarities, and interplay between the right and left ventricle. These issues must be addressed in chamber-specific studies in both animal models and in specific human RV diseases. These studies should focus on changes in gene expression, protein expression, histology, and geometry during the development of RV failure, using different RV “injury” and stress modalities. The importance of choosing a relevant animal model to study the pathophysiological mechanism underlying RV failure was emphasized in Chapter II.

Chapter III describes the sequence of echocardiographic changes during development of RV failure in a monocrotaline-injected rat model of chronic pulmonary hypertension (PAH). In this model PAH and RV-free wall thickness preceded RV dilation and RV contractile dysfunction. In
addition, echocardiography allowed for accurate determination of clinical disease stage.

In **Chapter IV**, $^{99m}$Tc-ANX V scintigraphy showed that apoptosis starts in the early stages of RV disease progression and declined when clinically manifest RV failure occurred. TUNEL labeling confirmed that the $^{99m}$Tc-annexin scintigraphic results were a reflection of apoptosis. The study demonstrated that serial $^{99m}$Tc-ANX V scintigraphy can be used to monitor RV apoptosis throughout disease progression in a noninvasive manner. In addition the occurrence of apoptosis during early stages of RV disease suggests a potentially beneficial outcome of a novel therapy targeting at apoptosis inhibition. The delay in RV disease progression after Valsartan treatment caused a reduction in RV apoptosis, as detected with serial *in vivo* $^{99m}$Tc-ANX V scintigraphy. This observation not only illustrates that serial *in vivo* $^{99m}$Tc-ANX V scintigraphy may be used to monitor the effects of therapy aimed at counteracting apoptosis, but supports the notion that apoptosis might be related to RV disease progression in this model. However, it must be noted that it does not prove a causal relation, because RV disease progression was not completely arrested, and apoptosis was not completely abolished. Although these findings are in line with previous studies focusing on LV failure the role of apoptosis in the progression of RV disease into heart failure, is still controversial.

Thus far, the role of immune-inflammatory processes has been studied only in patients with left ventricular disease. In these patients increased levels of circulating inflammatory cytokines have been shown, e.g., tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), IL-1β, and various chemokines, e.g., monocyte chemoattractant peptide (MCP)-1 and macrophage inflammatory protein (MIP)-1α. Furthermore, levels of
activated circulatory cytokines correlated directly with the severity of left ventricular disease. Little is known about the role of immune-inflammatory activation in RV disease. Chapter V presents data of immune-inflammatory activation during the development of RV failure in a monocrotaline induced PAH rat model. Early in the development of RV failure there was an activation of neutrophiles in the RV. In addition noninvasive serial in vivo $^{67}$Ga-scintigraphy for the monitoring of myocardial inflammation during RV disease progression was shown to be feasible. These data suggest a possible role of immune-inflammatory processes in the development of RV failure. It is anticipated that the ability to detect inflammation serially in vivo using $^{67}$Ga-scintigraphy will not only facilitate mechanistic studies related to inflammation, but will also allow for monitoring the time course of the disease or the response to various treatments aimed at counteracting RV heart failure. Translational research, with an emphasis on human myocardial tissue, is required to determine the specific markers of RV function and dysfunction. Studies to identify markers in plasma as well as those in tissue might facilitate early diagnosis of ventricular dysfunction and may prevent failure. In Chapter VI, with a combined analysis of plasma level of inflammatory cytokines and cardiac $^{67}$Ga-scintigraphy, we demonstrated that myocardial inflammation can be noninvasively detected in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D). The ability to detect inflammation noninvasively provides us with an important tool that may be used to obtain a better understanding of the role of inflammation in the pathophysiology of ARVC/D. In addition to inflammation, apoptosis has been proposed as an important mechanism in ARVC/D mediating the slow, ongoing loss of heart muscle cells followed by ventricular dysfunction. The relation between fibro-fatty replacement and
apoptosis remains a matter of speculation. The possibility to detect apoptosis in ARVC/D patients may add to a better understanding of the pathophysiological mechanisms underlying disease progression. In Chapter VII, 99mTc-annexin V scintigraphy was performed for in vivo assessment of apoptosis in patients with ARVC/D. Our results demonstrated an increased 99mTc-annexin V uptake in the RV free wall in 3 of the 6 studied ARVC/D patients. The variation in myocardial uptake of 99mTc-annexin V between patients is not surprising and might be explained by the random distribution and the episodic nature of apoptosis. Our results are suggestive of a chamber specific apoptotic process. Although the role of apoptosis in ARVC/D is unresolved, the ability to assess apoptosis non-invasively may aid in the diagnostic course. In addition, the ability to detect apoptosis in vivo with 99mTc-annexin V scintigraphy might allow for individual monitoring of disease progression and response to treatments aimed at counteracting ARVC/D progression.

With the aim of obtaining clinical evidence on the involvement of SCN5A in maintaining cardiac structural integrity, we systematically studied 144 BrS patients (Chapter VIII). Using complementary findings from imaging assays (CMR dimensions) and functional assays (CMR contractile function), we provide clinical evidence that support the idea that Na\textsubscript{v}1.5 is involved in maintaining structural integrity of the heart.