Pathophysiology of right ventricular heart disease: the role of structure, apoptosis and inflammation
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“Life can be pulled by goals just as surely as it can be pushed by drives”.
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Heart failure, a major and still growing public health problem, appears to result not only from cardiac overload or injury but also from a complex interplay among genetic, neurohormonal, inflammatory, and biochemical changes acting on cardiomyocytes, the cardiac interstitium, or both. Multitudes of recent studies suggest that loss of terminally differentiated cardiac myocytes contributes to the development of heart failure. Studies have reported that apoptosis occurs in myocardial tissue samples from patients suffering from myocardial infarction, dilated cardiomyopathy and end-stage heart failure [1-4] as well as in animal model of ischemia-reperfusion injury [5-7]. Apoptosis is activated in cardiomyocytes by multiple stressors that are commonly seen in cardiovascular disease such as cytokine production [8,9], increased oxidative stress [10], and DNA damage [11].

It is generally accepted that apoptosis plays an important role in left ventricular (LV) disease [12]. While initial studies of LV failure reported unrealistically high levels of apoptotic cell death [13], later work has consistently shown that approximately 80-250 cardiomyocytes per $10^5$ cardiac nuclei undergo apoptosis at any given time in patients with late-stage dilated cardiomyopathy [14-16]. In contrast, the base-line rate of apoptosis in healthy human hearts is only 1-10 cardiomyocytes per $10^5$ nuclei. Whether the chronically elevated but extremely low level of cardiomyocytes observed in LV failing hearts play a causal role remains a controversial issue with major therapeutic implications. In contrast, the association of apoptosis with RV disease progression (17,18) is unclear.

In the MCT rat model we demonstrated that apoptosis exhibits a particular time course, peaking at early disease stages (RV hypertrophy) and declining thereafter (RV failure), but remaining significantly increased over
baseline values at all RV disease stages. Furthermore, we showed that serial $^{99m}$Tc-ANX V scintigraphy can be used to monitor apoptosis throughout RV disease progression in a noninvasive manner [19]. $^{99m}$Tc-ANX V binds to exposed phosphatidylserine on the outer surface of apoptotic cells [20], thus allowing the visualization and localization of cells undergoing apoptosis. Also, we found that a delay in RV disease progression by Valsartan (angiotensin II receptor antagonist) was attended by a reduction in RV apoptosis [19]. 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 is causally related to RV disease. Still, 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. The reported percentage of apoptosis in end-stage LV failure is similar to our findings in the RV failure stage [21]. The occurrence of apoptosis during early RV disease stages suggests a potentially beneficial effect of apoptosis inhibition. Studies from a transgenic mouse model of cardiac-restricted expression of ligand-activated pro-caspase 8 have demonstrated that even low levels of cardiomyocyte apoptosis are sufficient to cause lethal dilated cardiomyopathy. Most significantly, the treatment with caspase inhibitors prevents cardiac dilatation and attenuates cardiac decomposition [22].

Since the regenerative capacity of the myocardium is limited, there is intense interest in the prevention of cardiomyocytes loss in cardiovascular diseases to prevent development of heart failure.

Apart from apoptosis, the past decade has provided increasing evidence that inflammation is involved in the clinical deterioration of patients with LV failure, with increased production and enhanced release of
pro-inflammatory cytokines. Patients with heart failure have high plasma levels of tumor necrosis factor-alpha (TNF-α), and soluble TNF-α receptors 1 and 2 serve as prognostic markers in this population [23].

The association between immune-inflammatory activation and RV disease progression is an essential observation in our study. The inflammatory activation exhibited a particular time course, becoming elevated at an early disease stage (RV hypertrophy), peaking at the stage of RV dilation, and remaining elevated compared to baseline throughout disease progression to RV failure. Furthermore, the immune-inflammatory response was non-invasively assessed with 67Ga-scintigraphy and reflected local inflammation in RV, as confirmed by 67Ga autoradiography, immunohistochemistry, and gene expression profiles [24].

Over the last years, two large clinical studies were conducted with TNF-α blockers in patients with LV failure. The RENAISSANCE study used Etanercept and the ATTACH study used Infliximab [25]. Both agents directly antagonized TNF-α but did not prove to have any clinical benefit [26]. One possible explanation for the lack of response to Etanercept is that it is a highly selective TNFα inhibitor, and this compound has no cross-reaction with any known cytokine, and the highly selective nature of this compound could be a disadvantage [23,26]. One other argument is that the immune system is redundant and other pro-inflammatory cytokines (interleukin 1-beta, interleukin 6, and transforming growth factor-beta) can participate in the process of heart failure. Following this concept, there are now at least two forms of non-specific immunomodulatory strategies under investigation: the intravenous gamma globulin [27,28] and immunoadsorption [29].
A better understanding of the mechanism of RV failure may enable us to find a better cure and improve the prognosis. Will it be a better insight into the apoptotic cascade or the inflammatory system? Will it be the ability to manipulate the immunological system or maybe stem cell transplantation? Which one of these approaches will open the door to long-term success in the fight against RV failure? This enigma has yet to be solved.

The remodeling of the RV myocardium in rare diseases such as arrhythmogenic right ventricular cardiomyopathy/dysplasia ARVC/D and BrS was further focus of our investigation. Regardless of the mode of inheritance, it appears that the majority of ARVC/D-related genes encode for proteins that make up desmosomes, which are intracellular adhesion complexes that provide mechanical connections between cardiac myocytes. When placed under mechanical stress, the impaired desmosomes cause myocytes to detach from each other leading to cell death [30, 31]. This cell death causes inflammation with scar formation and fat deposition.

Since ARVC/D involves focal areas of the RV and spares the interventricular septum, myocardial biopsy tends to have a low sensitivity and specificity. Myocardial biopsy of the RV free wall may increase the diagnostic yield, at the risk of increased perforation rate. Moreover, some degree of fat is interspersed between myocytes in healthy individuals, affecting the specificity of the biopsy sample. Conversely, in early stages of ARVC/D changes to the myocardium may not be well developed and not detected.

In ARVC/D, we conducted studies using $^{99m}$Tc-ANX V and $^{67}$Ga-scintigraphy. Our results demonstrate increased $^{99m}$Tc-ANX V uptake in the RV free wall of ARVC/D patients, suggestive of RV-specific apoptotic
activity in these patients. [32]. Also, with a combined analysis of plasma level of inflammatory cytokines and cardiac $^{67}$Ga-scintigraphy, we demonstrate that myocardial inflammation can be noninvasively detected in ARVC/D patients [33]. \textit{In vivo} imaging approaches play an important role in understanding the complex pathophisiological mechanisms underlying ARVC/D disease progression, thus aiding in the development of tailored and efficient therapeutic tools.

It has long been assumed that cardiac structural abnormalities are undetectable by standard clinical imaging methods in individuals with loss-of-function \textit{SCN5A} channelopathies. We found evidence that patients with a loss-of-function \textit{SCN5A} mutation had enlargement of both RV and LV, as measured by CMR analysis [34]. These result support the idea that Nav1.5 is involved in maintaining structural integrity of the heart.

The increasing recognition of the importance of RV dysfunction in the pathogenesis and outcomes of many cardiovascular diseases has led to resurgence in interest in assessing its pathological remodeling and function. While remaining a challenge, the last decades have been yielded improved understanding the pathophysiological mechanism underlying RV progression.
References


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