The stressed right ventricle and its impact on the left ventricle

From the work presented in this thesis as well as from other investigators, it is evident that various stressors can adversely affect the RV. These include increased pressure and volume loading and dyssynchronous activation, most typically from right bundle branch block. It is also evident from the results presented in this thesis that RV pressure loading triggers transforming growth factor beta and integrin molecular signaling leading to not only RV, but also LV myocardial fibrosis, in a regionally distinct pattern. These mechanical to molecular effects negatively impact ventricular function. Indeed, my thesis demonstrates that the stressed RV, particularly the pressure-loaded, and in particular the pulmonary hypertensive RV, affects not only RV function, but also the function of the neighboring LV. These adverse ventricular-ventricular interactions have important clinical implications in that we, and others, have shown that RV dysfunction is linked to clinically important outcomes and that the presence of biventricular dysfunction portrays worse outcomes.

The results of the studies presented in my thesis show that it is not only pressure loading per se that triggers RV dysfunction and adverse RV-LV interactions, but that the temporal aspects of these interactions and synchronous RV contraction and relaxation are central to effective RV function and physiological RV-LV interactions.

These results further our understanding of the mechanisms of RV and LV dysfunction in RV stress and also suggest potentially new therapeutic directions. My work suggests that the aspects of ventricular function detailed above are under-appreciated in clinical practice and under-utilized as therapeutic targets. For example, modestly increasing LV afterload is not a current therapeutic strategy in pulmonary hypertension and pharmacologically targeting RV fibrosis pathways is not a prevalent or current therapeutic strategy in RV pressure or volume loading; but based on my results, is expected to be beneficial to patients. Moreover, my work suggests that pulmonary valve replacement may be overutilized in repaired tetralogy of Fallot, and that regardless of pulmonary valve replacement, resynchronizing the dyssynchronous RV in these patients may be vastly underutilized. Likewise, the results agree with previous work by my supervisors that pacing the RV in pulmonary hypertension may be beneficial in addressing not only the regional distribution of RV wall stress, but also improve RV-LV interactions.

The pathophysiological mechanisms interrogated in this thesis also have bearings on how we diagnose RV dysfunction and hence ultimately how we manage patients. My work shows that adverse RV remodeling occurs at the RV apex and not only at the base. As current clinical assessment of the RV by echocardiography overwhelmingly focuses on the RV base (e.g. tricuspid annular plane systolic excursion (TAPSE) and tissue Doppler velocities (TDI)), my work suggests that changes in clinical assessment may be important to

detect adverse remodeling in the dysfunctional and failing RV. Moreover, as the myocardial fibers spiral at the cardiac apex to form a common apex to the RV and LV, apical dysfunction likely signifies biventricular dysfunction and adverse RV-LV interactions.

Currently, many of the aspects investigated in this thesis are considered separately in clinical practice, but the results presented in this thesis suggest that the parameters that affect RV function and RV-LV interactions are highly linked. My work suggests that pressure loading triggers RV dysfunction and also LV dysfunction that affects hemodynamic interactions and LV filling. Moreover, these adverse interactions extend beyond hemodynamics to induce tissue injury, in the form of biventricular fibrosis, predominantly at the high-stress septal hinge-point regions where the RV and LV anatomically join and interact. Integral to these adverse mechanical-molecular interactions in the RV and LV are the timing of events and the generation of asymmetrical RV work in both pressure-loading, particularly pulmonary hypertension, and RBBB induced electro-mechanical dyssynchrony in rTOF. These asymmetrical mechanics and injury cause stretching of the septum and leftward septal shift, producing inefficient RV function on the one hand and adverse RV-LV interactions on the other. Prolonged RV systole into LV diastole impairs LV filling and there is a temporal disconnect between RV and LV events that worsens biventricular systolic and diastolic function, in both pulmonary hypertension and in RBBB induced mechanical dyssynchrony. These abnormalities are greatly exaggerated by tachycardia and the dysfunctional or failing ventricle cannot summon sufficient reserve and cannot relax rapidly enough when heart rate increases. The asymmetrical RV mechanics leads to uneven wall stress within the RV, which imposes additional work on the already burdened RV free-wall and worsens myocardial fibrosis. Hence the chapters of this thesis indicate readily applied and simple measures to image this pathophysiology and its consequences for myocardial injury using echocardiography, that are not currently part of routine clinical practice.

At the same time, many questions remain unanswered. One of these is the precise relation between increased interstitial fibrosis and RV function. My data suggest a negative relationship between increased interstitial fibrosis and function: i.e. the more fibrosis, the greater the dysfunction. These data correlate with other experimental and clinical findings, but recent papers present different findings-showing increased fibrosis, that is not directly related to dysfunction. Likewise, the ability of the RV to recover after its load is removed, such as occurs following lung transplant in pulmonary hypertension, even though fibrosis is thought to be irreversible, raises questions regarding the clinical significance of fibrosis and whether it is a truly irreversible process.

Our findings suggest that in RV pressure loading and in pulmonary hypertension, LV fibrosis occurs predominantly at the septal hinge points, in conjunction with an upregulation of elastin that may act as a protective buffer, protecting the LV from more extensive damage, despite increased LV end-diastolic pressures. However, the significance of these experimental findings and whether pharmacologically increasing elastin production is a viable and effective therapeutic option remains unknown.

Our studies show that the pathophysiology of RV dysfunction in pulmonary hypertension is different from pulmonary stenosis and indeed the clinical course and outcomes of these 2 pressure-loading conditions is very different. The different pulmonary vascular dynamics and the possible presence of reflective waves in pulmonary hypertension which act to increase the load on the RV may explain some of these differences but was not investigated in this thesis. While pulmonary stenosis is thought to produce adaptive hypertrophy and pulmonary hypertension maladaptive failure, our results, especially our experimental results in our animal models, show many similarities between the 2 conditions that questions why this differential response occurs. In both conditions we observed RV remodeling with increased RV end-systolic and end-diastolic dimensions, markedly increased fibrosis, increased end-diastolic pressures and decreased function by echocardiography. However, myocardial strain was lower in pulmonary hypertension versus pulmonary stenosis, across a range of similar RV pressures. This suggests that RV myocardial function is worse in PAH, even if other features of RV 'failure' are present in both. Still, it may be that pulmonary stenosis being a congenital condition allows adaptive function of the RV-from fetal life, whereas in pulmonary hypertension, the load, in most cases, is acquired, rapidly increases and cannot be adequately alleviated. These may explain the differences between the 2 conditions.