A diverse remodeling of the right ventricle (RV) that affects RV systolic or diastolic function directly or indirectly by modulating changes to cavitary geometry is a principal determinant of poor outcome across the global spectrum of cardiopulmonary diseases.1,2 Indeed, even subclinical increases in RV mass are associated with substantially elevated risk for future heart failure and decreased lifespan.3 Unique embryological and anatomic features of the RV provide a pathophysiological basis by which to account for this observation. For example, precursor cells of the RV and left ventricle (LV) derive from the primary and anterior heart fields,4 respectively, indicating a different cellular lineage for each ventricle despite their close proximity and placement in series. In contrast to the LV, the RV is a triangular structure that is thin walled and noncompacted, and, thus, tolerates pressure-loading conditions poorly.3 Moreover, poor coronary blood flow reserve with increased RV strain due to elevations in wall tension is associated with decreased RV microvascular perfusion.6

Article see p 2859

Although these properties establish the RV-specific pressure–volume relationship profile, factors that precipitate impaired RV performance are less well characterized. Take, for example, the wide swath of classical reports that describe LV hemodynamic (patho)physiological responses to acute and chronic myocardial ischemia, systemic hypertension, valvular dysfunction, and pericardial disease.7 By contrast, a paucity of data exists to characterize the mechanistic and clinical contributions of similar processes (including LV dysfunction) to the natural history of adverse RV remodeling in non–congenital heart disease patients, despite the attendant clinical relevance of RV failure. Furthermore, the basic mechanism(s) that underpin RV dysfunction when contemporaneous with pulmonary hypertension, the most common end-pathophenotype associated with changes to RV loading,8 are largely unknown. In fact, only recently has consideration been given to RV function within the context of the larger lung-pulmonary circulatory-RV apparatus.5,9 This is a critical distinction, however, because defining the right heart axis in this way reidentifies the RV as a specific participant in the pathobiology of pulmonary hypertension and potential therapeutic target per se, thereby parting from traditional dogma in which RV dysfunction is a consequence of pulmonary vascular disease, an indicator of irreversible cardiac injury, and a dismal prognostic marker.

Current work in the field has advanced our understanding of RV myocyte pathobiology significantly in the context of pulmonary vascular disease, particularly with respect to maladaptive molecular mechanisms that modulate RV failure through changes in cellular metabolism,10 nitric oxide bioavailability,11,12 and ion channel dysfunction.13 These basic and translational scientific models, which emphasize novel RV-specific targets to improve RV performance, have illuminated a number of cell-signaling pathways with future therapeutic promise for patients afflicted with pulmonary hypertension–induced RV dysfunction. Notwithstanding these cutting-edge discoveries, however, a substantial knowledge gap persists with respect to the fundamental mechanism by which classical cardiovascular effectors associated with states of low cardiac output may promote circulatory failure vis-à-vis RV dysfunction, such as upregulation of neurohumoral signaling that is linked to unfavorable clinical outcome in patients with congestive heart failure due to LV dysfunction.14 For example, only recently has overactivation of the renin-angiotensin axis been described systematically in patients with pulmonary arterial hypertension and RV remodeling.15 Hyperaldosteronism, long recognized as a mediator of poor outcome in congestive heart failure due to LV dysfunction, now appears to be present in the pulmonary arterial circulation of patients with pulmonary arterial hypertension in the absence of abnormal LV remodeling or impaired function, and correlates positively with adverse pulmonary vascular remodeling.16 Others have reported recently on changes to the RV pressure–volume relationship following the administration of catecholamines in acute RV failure.17 However, overall, there remains a limited understanding of the biological framework with which these and other similar, systemically circulating vaso-active effectors differentially influence RV function. This has at least 2 important implications. First, neurohumoral hormones may be underrecognized therapeutic targets to modulate RV function. Second, few mechanistic (or clinical) data are available to inform clinicians on the consequences of repurposing pharmacotherapies commonly used to manage
LV heart failure, such as α- or β-adrenergic receptor (ant)agonists, to patients with pulmonary hypertension and RV dysfunction, despite the frequency with which this occurs in clinical practice. Thus, investigating the functional consequences of neurohumoral hormones on RV and LV performance in the context of RV failure is a timely and attractive avenue of investigation.

In the current issue of Circulation, Piao and colleagues investigate the contribution of β/α-adrenergic and dopaminergic (D) receptor signal transduction to changes in RV functional (ie, inotropic) reserve under conditions of acute and chronically increased RV afterload. To accomplish this, the investigators thoughtfully selected 3 different rodent models of pulmonary hypertension (pulmonary artery banding [mechanical ligation of the pulmonary artery, acute RV dysfunction], monocrotaline-induced pulmonary hypertension [inflammatory pulmonary vascular injury, chronic RV dysfunction], and chronic hypoxia/Sugen-5416 [angioproliferative pulmonary vascular injury, chronic RV dysfunction]) to test their hypothesis that, akin to LV heart failure, dysregulation of β-adrenergic receptor signaling impairs inotropic reserve in the hypertrophied RV. An additional objective of this work was to further characterize the pathobiological mechanisms that modulate RV dysfunction-dependent changes to LV performance to identify optimal vasopressor pharmacotherapy for improving cardiopulmonary circulation in RV failure in vivo.

The central findings of the work are 3-fold. First, RV myocyte β1-, α1-, and D1-receptor expression levels and receptor-dependent signal transduction are downregulated in the hypertrophied RV in patients with pulmonary arterial hypertension, and, in the tested animals models, this limits RV contractile reserve, particularly in chronic RV failure. Second, G-protein–coupled receptor kinase 2, which is an established intermediary involved in the reversible inhibition of β1- and D1-receptor expression/activation in LV myocytes, is identified as a legitimate potential therapeutic target by which to restore RV contractile reserve, cardiac output, and functional capacity in RV failure. Third, the investigators demonstrate the superiority of dobutamine over dopamine for enhancing RV systolic function in the tested models, an observation that is internally consistent with their findings of dysfunctional D1 receptors in RV myocytes, which interact with dopamine and not dobutamine. To make this determination, a clever experimental design was used in which the effects of inotropes was assessed in separate RV and LV Langendorff models, thereby allowing for the assessment of contractile reserve in each ventricular chamber independent of pre- and afterload.

Collectively, these observations provide a comprehensive evaluation of catecholamine-dependent changes to RV function in pulmonary hypertension and identify provocative differences in the molecular profile of RV myocytes based on acute versus chronic temporal patterns of RV injury. Although the mechanism(s) by which to account for these differences were not addressed fully in this work, obvious future endeavors are likely to include characterizing these differences further, and to account for the observation that inhibition of G-protein–coupled receptor kinase 2 improved RV contractile reserve without attendant changes to β1-receptor expression levels, as well. This finding raises the possibility that inhibition of G-protein–coupled receptor kinase 2 may modulate beneficial effects on RV performance, at least in part, indirectly via off-target suppression of G-protein–coupled receptor kinase 2–dependent catecholamine hyperactivity in adrenal tissue. Moreover, the observation that, in 1 model of chronic (but not acute) RV heart failure, downregulation of β1-adrenergic receptor signaling was noted in both RV and LV myocardium is intriguing and may ultimately prove to be an important clue in identifying (mal)adaptive cross-talk between RV and LV cardiomyocyte cell-signaling pathways involved in regulating inotropic reserve.

Taken together, Piao and colleagues have synthesized a series of observations that leverages classical catecholamine physiology to redefine RV myocyte biology in the context of pulmonary hypertension. The broader implications of this work are that RV β1-, α1-, and D1-receptor signaling is actively involved in the pathobiology of pulmonary hypertension. Pursuing answers to questions derived from the authors’ observations is evident: defining neurohumoral effects on RV function is likely to provide a novel window into understanding LV function and add clarity to the unresolved controversy over appropriate strategies by which to target β1-, α1-, and D1-receptor–signaling pathways in patients with heart failure from RV and/or LV dysfunction. In this way, the current work is well within the ideals outlined at the recently concluded international Right Heart Failure Summit (Boston, MA), which provided strong evidence for placing the RV into better focus within the framework of cardiovascular disease, far beyond its traditionally held position as simply an orphan structure adversely affected as a bystander in cardiovascular pathophysiology.

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References


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