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Conflict of Interest Statement

Dr. Aggarwal has nothing to disclose.

Dr. Aldred reports grants from NHLBI during the conduct of the study.

Dr. Archer has nothing to disclose.

Dr. Benza reports grants from Abbott during the conduct of the study; grants from Actelion, grants from United Therapeutics, grants from Bayer, grants from NIH/NHLBI outside the submitted work.

Dr. Bristow has nothing to disclose.

Dr. Brittain has nothing to disclose.

Dr. Chesler reports personal fees from Endotronix, Inc. and personal fees from Aria CV outside the submitted work.

Dr. de Man has nothing to disclose.

Dr. Erzurum has nothing to disclose.

Dr. Gladwin is a co-inventor of patents and patent applications directed to the use of recombinant neuroglobin and heme-based molecules as antidotes for CO poisoning, which have been licensed by Globin Solutions, Inc. Dr. Gladwin is a shareholder, advisor, and director in Globin Solutions, Inc. Dr. Gladwin is also co-inventor on patents directed to the use of nitrite salts in cardiovascular diseases, which were previously licensed to United Therapeutics, and is now licensed to Globin Solutions and Hope Pharmaceuticals. Dr. Gladwin is a principal investigator in a research collaboration with Bayer Pharmaceuticals to evaluate riociguat as a treatment for patients with SCD. Dr. Gladwin has served as a consultant for Epizyme, Inc., Actelion Clinical Research, Inc., Acceleron Pharma, Inc., Catalyst Biosciences, Inc., Modus Therapeutics, Sujana Biotech, LLC, Complexa Inc., Pfizer Inc., and United Therapeutics Corporation. Dr. Gladwin is also on Bayer HealthCare LLC's Heart and Vascular Disease Research Advisory Board.

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Dr. Leopold has nothing to disclose.

Dr. Lima has nothing to disclose.

Dr. Loscalzo is a scientific co-founder of Scipher, a startup company that uses network concepts to explore human disease treatment strategies.

Dr. Maron reports other from Actelion Pharmaceuticals Inc., outside the submitted work. In addition, Dr. Maron has a patent U.S. Patent #9,605,047 issued, a patent U.S. Provisional Application ID: 62475955 pending, a patent U.S. Provisional Application Cover Sheet ID: 24624 pending, and a patent U.S. Patent application PCT/US2019/059890 pending.

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Dr. Lei Xiao has no conflict of interest to disclose.

Dr. Zhao has nothing to disclose.

Diagnosis and Treatment of Right Heart Failure in Pulmonary Vascular Diseases: A National Heart, Lung, and Blood Institute Workshop

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Abstract

Right ventricular dysfunction is a hallmark of advanced pulmonary vascular, lung parenchymal, and left heart disease, yet the underlying mechanisms that govern (mal)adaptation remain incompletely characterized. Owing to the knowledge gaps in our understanding of the right ventricle (RV) in health and disease, the National Heart, Lung, and Blood Institute (NHLBI) commissioned a working group to identify current challenges in the field. These included a need to define and standardize normal RV structure and function in populations; access to RV tissue for research purposes and the development of complex experimental platforms that recapitulate the *in vivo* environment; and the advancement of imaging and invasive methodologies to study the RV within basic, translational, and clinical research programs. Specific recommendations were provided, including a call to incorporate precision medicine and innovations in prognosis, diagnosis, and novel RV therapeutics for patients with pulmonary vascular disease.

In 1929, Werner Forssmann performed the first right heart catheterization on himself and ushered in the era of using hemodynamics to characterize cardiopulmonary function. Early investigators who utilized this technique in patients with chronic heart and lung diseases recognized the critical contribution of the right ventricle (RV) to clinical outcomes. Over the past 20 years, studies have established RV dysfunction as a key determinant of morbidity and mortality in patients with pulmonary vascular disease (PVD), parenchymal lung disease, and left heart disorders. Despite recognition of this pathophysiology, there is limited mechanistic insight into the timing of, and contributors to, the transition from normal RV structure and function to the (mal)adapted RV and RV failure.

To address limitations in our understanding of the RV in health and disease, the National Heart, Lung, and Blood Institute (NHLBI) Division of Lung Diseases sponsored a workshop to identify knowledge gaps and research priorities to improve the prevention, prediction, diagnosis, and treatment of RV failure, with a focus on patients with PVD. Various stakeholders attended the workshop, including basic and translational scientists; biomedical engineers; clinical epidemiologists and trialists; and clinician-scientists with interests in hemodynamics, imaging, sleep, directed therapeutics, and network medicine (see Appendix for other contributors). The goal was a research agenda that would lead to improvements in the health and outcomes of patients with PVD with, or at high-risk for, RV failure (Figure).

SPECIFIC AREAS OF INVESTIGATION AND RECOMMENDATIONS

1. Understanding RV function across the spectrum of PVD clinical phenotypes

Even in adults without clinical cardiovascular disease, RV structure and function vary by age, sex, race/ethnicity, timing of birth, and prenatal, childhood, and adult exposures (1-4). Considering this variability even amongst apparently healthy individuals, differences

in RV morphology and function between and within the traditional WHO PH groups are not surprising. These distinctions might be attributable to the effects of the disease states themselves directly on the RV or manifestations of pulmonary vascular endotypes of afterload. The hydraulic load on the RV in a pulsatile system may be influenced by the location of PVD (proximal versus distal or both), heterogeneity of vascular and pulmonary structural disease, temporospatial variability, and other disease-specific features.

For example, patients with pulmonary arterial hypertension (PAH) attributable to systemic sclerosis (SSc) have reduced intrinsic myocardial contractility (both decreased end-systolic elastance and cardiomyocyte contractility) and increased RV fibrosis compared to patients with idiopathic PAH (IPAH), despite having lower pulmonary vascular resistance and higher cardiac index (5, 6). When challenged with submaximal exercise, SSc-PAH patients did not augment RV contractility and ventricular-vascular coupling declined, phenomena that were not seen in IPAH patients (7). In contrast to patients with SSc-PAH, patients with PAH secondary to congenital heart disease commonly have the benefit of RV adaptation to increased load beginning *in utero*. This results in a different natural history of RV failure owing to sustained exposure to volume/preload (e.g., from tetralogy of Fallot repair with resultant pulmonary valve insufficiency) or pressure/afterload (e.g., Eisenmenger's syndrome) with outcomes related to the type of repair and ventricular function (8). RV remodeling in chronic thromboembolic PH is affected by variability in acute pulmonary embolism and the site of pulmonary vascular remodeling which extends from the proximal large vessels to the small distal vasculature (9). Following pulmonary thromboendarterectomy (which may be clinically curative), RV systolic function, volume, strain, and asynchrony may improve over time, but the RV does not completely normalize (10).

Notwithstanding the focus on rare diseases, most RV dysfunction occurs in the setting of common conditions which themselves have several phenotypes. For example, chronic obstructive pulmonary disease (COPD) has been linked both to smaller RV size, which may increase with bronchodilation, as well as to RV hypertrophy and dilation with concomitant abnormalities in RV function (11, 12). In patients with severe COPD, the greatest loss of pulmonary vasculature led to larger RV volumes, associated with impaired functional capacity and an increased risk of death (13).

RV dysfunction occurs frequently in patients with heart failure with reduced ejection fraction (HFrEF) and almost one-third of patients with heart failure with preserved ejection fraction (HFpEF) (14, 15). RV dysfunction causes increased venous impedance and renal congestion and impaired diuresis and natriuresis and leads to worse survival in patients with left ventricular disease (15-18). RV dysfunction in combined pre- and post-capillary PH is a strong prognostic marker of adverse outcomes (16, 19).

Finally, sleep disordered breathing (SDB) affects more than 25% of adults in the US (20). Approximately 17 to 53% of obstructive sleep apnea (OSA) patients and 83% of patients with central sleep apnea/Cheyne Stokes respiration and heart failure are estimated to have PH and are at risk of RV failure (21). OSA causes recurrent upper airway obstruction and swings in intrathoracic pressure, thereby cyclically and repetitively increasing cardiac

preload and post-capillary pressure. Despite the frequency of these diagnoses, there is a paucity of data on the impact of SDB screening and treatment in PH and effects on RV dysfunction.

Recommendations for future research:

- Understand how aging, sex, race, and ethnicity affect RV function across the lifespan. Study how these factors modulate the development of RV dysfunction.
- Prenatal and early life events and lifetime exposures should be examined to determine how these affect RV development and maturation as well as determine long-term risk for RV failure.
- Investigate the role of systemic comorbidities and modifiable risk factors, such as SDB, in mediating the transition from RV health to dysfunction.
- Study differences between diseases (and types of RV afterload) to understand RV responses. Utilize these profiles to construct RV endophenotypes associated with RV adaptation or maladaptation to PVD and transition to failure.

2. Assessment of RV structure and function

While the pressure-volume relationship has been considered the gold standard for assessing ventricular function, these hemodynamic measurements are invasive and currently impractical for routine clinical practice or research in large numbers of patients (22). Derivative methodologies, such as single-beat pressure-volume loops, have limitations but may be useful (23, 24). Although the prevailing conventional thinking is that RV elastance and coupling predict clinical outcomes, data supporting this assumption are sparse (24). Measures of RV contractile reserve provide additional prognostic information in various types of RV dysfunction (7, 25-28).

Speckle tracking echocardiography to evaluate longitudinal and segmental strain in the RV can demonstrate early RV dysfunction and has prognostic implications (29). Magnetic resonance imaging (MRI) is still considered the gold standard for the measurement of RV ejection fraction, volumes, and mass and can also determine extracellular volume as well as RV metabolism (30, 31). 4D MRI can assess flow and biomechanical consequences of RV and pulmonary vascular remodeling (32).

Functional imaging modalities can give insight into metabolic reprogramming in the RV. Noninvasive 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) imaging has demonstrated increased RV glucose uptake in PVD as well as mechanical dyssynchrony (33, 34). Other novel methods, such as magnetic resonance spectroscopy, are being utilized to detect metabolic abnormalities and lipid accumulation in cardiomyocytes (35).

Traditional findings on electrocardiography are not useful for screening for RV hypertrophy in adults without known cardiovascular disease (36); enhanced electrophysiologic mapping or machine learning approaches could identify novel signatures of RV dysfunction.

Continuous monitoring using implantable devices or wearable activity trackers may provide a more comprehensive profile of RV performance over time while patients are engaged in their activities of daily living (37-39). These methods capture variation in physiological markers over rest, stress, circadian rhythms, and sleep-wake cycles, which may be more informative than simple resting or one-time exercise assessments. Technical advances and standards in image quality and data fidelity, transmission, storage, and security are required to incorporate these devices into large multicenter human studies. The Table summarizes some of the methods of assessment and measurements which provide insight into RV structure and function.

Recommendations for future research:

- Define normative values of RV structure and function for imaging modalities.
- Studies of RV reserve and coupling should be pursued to determine the importance of these parameters in functional outcomes and survival in PVD.
- Develop and advance hemodynamic challenges and exercise to assess RV response under stress.
- Identify biomarkers for RV structure and function.
- Determine the optimal analytics for implantable monitors and wearable devices that provide detail about RV phenotypes.

3. Understanding the pathobiology of the RV

The biomechanical milieu of the RV—Although classical pathologic examination of the RV has demonstrated gross structural changes at end-stage PVD, reliance on this approach alone to phenotype the RV has not been highly informative to date. Striking differences in cardiomyocyte contractile force have been demonstrated in patients with IPAH as compared to those with SSc-PAH. Using isolated RV cardiomyocytes, maximal Ca^{2+}-activated force was 28% higher in patients with IPAH compared to controls but 37% lower in patients with SSc-PAH. Passive stiffness, however, was increased in both PAH populations (5-7). This difference has been attributed, in part, to reduced titin phosphorylation and increased collagen-mediated stiffness (40). Multiscale (cardiomyocyte, myofibril, and RV) computational modeling has provided additional insight into the contributions of RV cardiomyocyte dysfunction to overall hemodynamics. Simulations revealed that pressure overload and cardiomyocyte dysfunction predicted a decrease in RV ejection fraction and cardiac output (41).

Metabolic reprogramming of the RV—The RV typically reverts to the “fetal phenotype” under stress. This phenotypic switch is characterized by inhibition of pyruvate dehydrogenase and shunting to aerobic glycolysis, which generates less ATP and leads to RV hibernation. Pyruvate dehydrogenase can be targeted therapeutically either directly (pyruvate dehydrogenase kinase inhibitors) or indirectly (glutaminolysis) to improve RV contractility (42). Mitochondria themselves remodel in RV cardiomyocytes with changes in their transcriptome that affect metabolism (43, 44). Mitochondrial fission increases reactive oxygen species generation impairing RV diastolic function (45).

Fatty acid oxidation is also downregulated in RV cardiomyocytes in PVD (46). RV lipotoxicity has been demonstrated in PAH patients using proton magnetic resonance spectroscopy, which revealed an increase in RV triglyceride content compared to controls (35). The RV may be affected by obesity and the Western diet, suggesting a susceptibility to micro- and macro-nutrients (47, 48). Metabolic or nutritional interventions for the RV in PVD are just starting to be tested (49).

Sex, sex steroid hormones, and RV function—Women have better RV function compared to men both in health and disease (2, 50, 51). Plausible mechanisms for these observations include direct effects of sex steroid hormones and their metabolites on RV adaptation as well as interactions between sex and the sex steroid hormone milieu with treatment (52-54). Experimental models and human studies have shown mixed results for the role of female sex and estrogen (resulting in the term “estrogen paradox”) (55).

Evidence suggests that sex hormones affect the RV in patients with PAH. The cytochrome superfamily, which includes CYP1B1 and aromatase (CYP19A1), is preferentially expressed in the RV as compared to the left ventricle (56). Higher estradiol and lower dehydroepiandrosterone-sulfate levels in PAH are associated with worse heart function (57, 58). Response to PAH treatment also varies by sex (52, 53). One study showed that RV ejection fraction improved over time with PAH treatment in women but not in men, explaining the better survival for women (54). In a pilot study, the aromatase inhibitor anastrozole lowered estradiol levels and improved six-minute walk distance, but had no effect on RV function (59). A larger, longer Phase II trial of anastrozole in post-menopausal women and men with PAH is underway (NCT03229499), as are trials of tamoxifen (NCT03528902) and dehydroepiandrosterone supplementation (NCT 03648385).

Experimental models in preclinical studies—Animal models of precapillary PH are well-established. Models which aim to recapitulate WHO Group 2 disease incorporate aortic banding or limitation of coronary flow or infarction. Recently, the normoxic ZSF1 rat model treated with a single high dose of Sugen was shown to develop pulmonary vascular remodeling, characteristics of HFpEF, and increased RV mass (60). The mouse myocardial infarction model of HFrEF also has RV contractile dysfunction, increased RV stiffness, and evidence of RV-pulmonary artery uncoupling (61). Models with systemic co-morbidities, including mild renal insufficiency, hypertension, insulin resistance and obesity, mimic human disease. Sub-type specific induced pluripotent stem cell-derived cardiomyocytes have been generated and characterized, but, to date, this has not been done for the RV in PH (62).

Recommendations for future research:

- Define the normal molecular (genomic, metabolomic, and proteomic) and cellular RV profile as well as the effect of perturbations of these factors.
- Develop tissue repositories of RV myocardial samples. Further develop RV induced pluripotent stem cells as a relevant model for mechanistic studies and preclinical testing of therapies. Utilize advanced cell culture methodologies, such as 3D matrix and organ-on-a-chip.

- Determine if decreased contractility, increased diastolic stiffness, and fibrosis are reversible and correctable at a cellular level.
- Determine if targeting metabolic and mitochondrial dysfunction improves RV function.
- Understand the effects of specific sex hormones, age, and sex-based lifecycle changes (menarche and menopause) on the RV response to stress.
- Develop animal models of RV dysfunction that incorporate the full range of ages, sexes, human health, resilience, and PVD. Novel ways to interrogate such models of RV dysfunction and isolate therapeutic effects on PVD from those on RV dysfunction are needed.

4. A path towards development of novel therapeutics and utilization of devices

Challenges associated with RV drug discovery and implementation—Currently approved pharmacotherapeutics are not known to target the RV directly. The pursuit of therapeutics which have shown efficacy in left ventricular disease has not yet borne fruit in treating RV dysfunction (49, 63-66). The development of an effective therapy for RV remodeling and dysfunction will face distinct challenges, including: 1) inability to use short-term exercise capacity as a primary endpoint in trials of beta-blockers and possibly other drug classes (67); 2) lack of endpoints focused on remodeling in left-sided heart disease (including improved ventricular function) that are accepted by the Food and Drug Administration and other regulatory agencies; 3) potential proarrhythmic properties of therapies that either a) initially depress ventricular function prior to improving it, or b) are inotropes; and 4) the requirement that investigators have equipoise.

Many decisions need to be made before designing a development program of RV therapy, including whether to target patients with advanced heart failure or with no or subclinical disease (primary or secondary prevention), the optimal duration of Phase II and III trials, and the role of intermediate or ultimate end points in the absence of validated surrogates.

The success of drug and device development for left heart failure has been predicated on targeting adverse remodeling (i.e., contractile dysfunction), which has translated into improvement in hard clinical endpoints, like survival, in a much more common syndrome than RV failure. This traditional pathway may hold promise for treatment of RV failure.

Novel therapeutics require equally innovative approaches to study and regulatory approval. Gene transfer for PH and RV dysfunction has been trialed in preclinical models showing safety and efficacy, but questions remain with respect to the method of gene transfer, target selection, target cell type, and delivery technique as this therapeutic is translated to the clinic (68-70). The optimism for cell-based therapy as a therapeutic for the RV has been tempered by the track record to date in other cardiovascular diseases despite beneficial results in preclinical studies (71).

Network medicine to identify RV clinical endpoints, treatment targets, and therapeutics—Network medicine could identify treatment targets from RV disease

modules from the (incomplete) human interactome or by using systems pharmacology for drug repurposing (72, 73). Unbiased strategies for drug discovery involve screening millions of small-molecule compounds against all of the human proteins with known tertiary structures and identifying relevant RV targets from a network analysis (73). Networks of clinical variables may also have utility for RV endophenotyping. A module of ten variables from a network of all variables measured during invasive cardiopulmonary exercise testing identified distinct exercise phenotypes in PVD and predicted outcomes (74). This unbiased approach identified clinical variables relevant to RV pathophysiology that could be used to identify specific intermediate phenotypes and mechanism(s) of RV dysfunction.

Advancing mechanical support and interventions for RV dysfunction—The use of mechanical devices and surgical or percutaneous interventions for RV support and rescue in PVD is not well studied. RV assist devices, intra-pulmonary artery balloon pumps, RV volume adjustments, and extracorporeal life support are all under evaluation for the management of RV failure. The benefits of mechanical strategies to support the failing RV are suggested by atrial septostomy, where decreasing right atrial pressure and RV filling improves cardiac output, functional capacity, and potentially survival, all without targeting PVD directly (75). The role of surgical approaches to correct functional tricuspid regurgitation is undefined. Percutaneous RV assist devices, which pump blood from the right atrium to the pulmonary artery to unload the RV, have shown promise in acute RV failure (76). Isolated implantable RV assist devices for longer duration support of chronic RV failure in PVD are not currently available; however, in some instances, left ventricular assist devices can support the RV in the setting of biventricular failure (77, 78). There is an unmet need for durable mechanical support of the failing RV in patients with PH who are not candidates for (or are awaiting) lung- or heart-lung transplantation. The potential of RV assist devices as destination therapy or bridge-to-recovery requires further study.

Recommendations for future research:

- New therapeutics that selectively target the RV should continue to be developed and tested.
- New analytical methodologies, such as systems biology and network medicine, should be used to endophenotype RV dysfunction in PVD and identify new RV treatment targets, new drugs, or drugs that can be repurposed for patients with RV dysfunction.
- Design trials to assess existing techniques while fostering innovation in mechanical support for RV dysfunction.

Conclusion

RV dysfunction contributes to adverse clinical outcomes in patients with PVD. Despite the recognition of the clinical importance of RV dysfunction, the parameters that define normal RV structural and functional adaptation under (patho)physiological conditions have not been defined. To improve health in patients with (or destined for) RV failure, the workshop has identified basic, translational, and clinical areas for study. Advances in these

areas will provide novel mechanistic understanding into RV dysfunction as well as improve, preventative, diagnostic, therapeutic, and prognostic RV-specific modalities.

Appendix.: Other Workshop Participants

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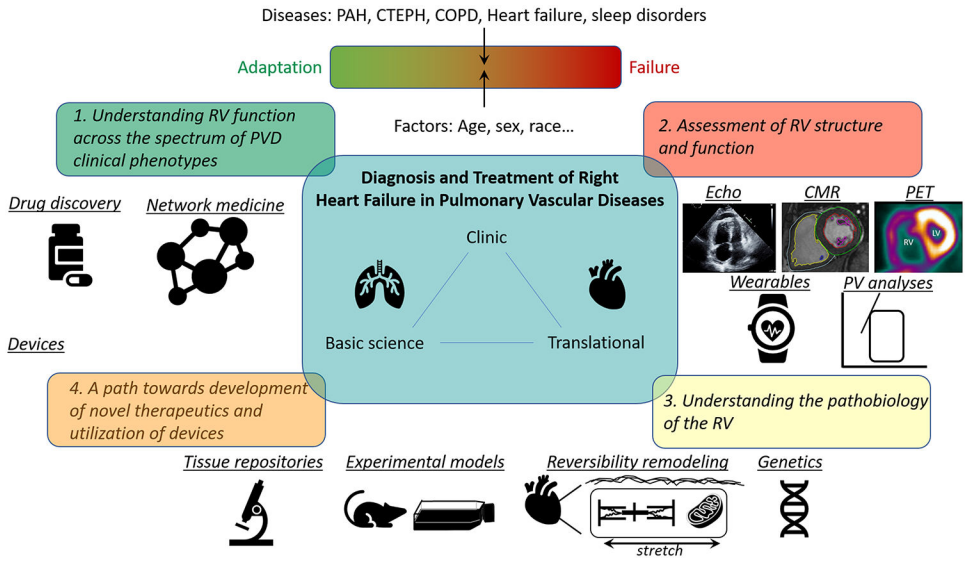

Figure.
Right Ventricular Investigation: From Phenotype to Therapy

Table.

Methods and measures of right ventricular shape and function

Method	Measures
Hemodynamic	Right atrial pressure, RV systolic and diastolic pressures, cardiac output, stroke volume, RV power, pulmonary vascular resistance
Pressure-volume loops	Elastance, coupling
Echocardiographic (2-dimensional and 3-dimensional)	Right atrial volume, right atrial emptying fraction, RV basal, mid-cavity, and outflow tract dimensions, end-diastolic and systolic ventricular areas, RV/left ventricular ratio, RV wall thickness, RV end-diastolic and end-systolic volumes, RV ejection fraction, RV fractional area change, RV myocardial performance index, RV free wall strain, RV global longitudinal strain, tricuspid annular plane systolic excursion, transtricuspid E/A, early component (e')/atrial component (a') of tricuspid annular tissue Doppler velocity, e', E/e', tricuspid annular lateral systolic velocity (s')
Magnetic resonance imaging	Right atrial and ventricular end-diastolic and -systolic volumes, RV ejection fraction, main pulmonary artery forward and reverse flows, RV cardiac output, RV stroke volume, main pulmonary artery peak velocity, RV strain, RV extracellular volume fraction, late gadolinium enhancement
Computed tomographic imaging	Right atrial and ventricular end-diastolic and -systolic volumes, RV ejection fraction, RV stroke volume,
Positron emission tomography	Metabolism, fatty acid uptake
Wearable/mobile health/ implantable devices	Heart rate, heart rate variability, electrocardiogram, accelerometry, step count, minutes of physical activity, pulmonary artery pressure, stroke volume
Exercise testing	Six minute walk distance, oxygen consumption at peak exercise, pulmonary arterial and systemic blood pressure response to exercise
Biomarkers	Brain natriuretic peptide, N-terminal probrain natriuretic peptide, galectin-3, ST2, troponin