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Group 2 PH

Program Description

The mission of *Advances in Pulmonary Hypertension* is to serve as the premiere forum for state-of-the-art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension (PH). The 2018 Nice revision of the World Symposium on Pulmonary Hypertension (Simmonneu G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1). DOI:10.1183/13993003.01913-2018) serves as a guide to categories of PH addressed in *Advances in Pulmonary Hypertension*. While focusing on Group 1 PH (PAH: pulmonary arterial hypertension), the other categories (Group 2, PH due to left heart disease; Group 3, PH due to lung diseases and/or hypoxia; Group 4, PH due to pulmonary artery obstructions; Group 5, PH with unclear and/or multifactorial mechanisms) are also addressed. This mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions.

Objectives

- Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of PH.
- Serve as a forum for presentation and discussion of important issues in the field, including new paradigms of disease understanding and investigational trial design.

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PUBLISHER
Pulmonary Hypertension Association
Matt Granato, LL.M., MBA, President and CEO

PHA OFFICE
Pulmonary Hypertension Association
8401 Colesville Road, Suite 200
Silver Spring, MD 20910
301-565-3004; 301-565-3994 (fax)
Advances@PHAssociation.org

PUBLISHING OPERATIONS
Tori Cortez,
Managing Editor

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Advances in Pulmonary Hypertension is directed to cardiologists, pulmonologists, rheumatologists, pediatricians, internists, and other health care professionals involved in the treatment of patients with PH.

Advances in Pulmonary Hypertension: Official Journal of the Pulmonary Hypertension Association is a quarterly publication directed by an editorial board of renowned pulmonary hypertension (PH) experts with oversight by PHA's Scientific Leadership Council. The mission of *Advances in PH* is to assist physicians in their clinical decision-making by informing them of important trends affecting their practice and providing an analysis of the impact of new findings and current information in peer-reviewed publications. Each article is reviewed and approved by members of the Editorial Board.

While most articles are invited by the Editorial Board, the following submissions will be considered for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics
- Letters to the Editor
- Clinical case studies

Submitted manuscripts are reviewed by the Editorial Board and other experts in the field. Acceptance of manuscripts is determined by factors such as quality, relevance, and perceived value to clinical decision-making.

Advances in Pulmonary Hypertension's Web Platform

Advances in Pulmonary Hypertension is available at www.AdvancesinPH.org. This site offers enhanced capabilities including a dedicated DOI and cross-referencing potential, as well as other features valuable to practitioners, researchers, and educators. Registration is recommended to access all site features and benefits.

This issue of *Advances in Pulmonary Hypertension* focuses on Group 2 pulmonary hypertension, a common cause of pulmonary hypertension with many diagnostic and therapeutic challenges. We read with great interest these wonderful articles put together by a spectacular group of authors, which provide excellent insights to the multiple nuances of this condition. This is clearly not a "one size fits all" disease, despite how commonly it presents to our clinics. In reading through this issue, a common theme reflected is how useful these articles will be to both experienced providers and all learners alike.

Jonathan Kusner and Richard Krasuski first provide an updated review of the echocardiographic evaluation of the right heart in pulmonary hypertension. The right ventricle (RV) is a complex structure, and we now have multiple markers to assist in its assessment. These can be highly useful in distinguishing primary right from left heart disease. The 2022 European guidelines incorporated an updated approach to echocardiographic assessment of possible pulmonary hypertension and this is nicely illustrated in the article. Their review is a helpful, focused update for experienced providers as well as guide for further study for all learners.

No discussion of Group 2 PH is complete without a review of heart failure with preserved ejection fraction (HFpEF), and this issue has a spectacular review on this topic from Yogesh Reddy. He addresses critical points in invasive assessment, including the use of exercise hemodynamics to uncover Group 2 PH. HFpEF can frequently masquerade as precapillary PH via resting hemodynamics and a careful assessment of pretest probability for left heart disease can help identify when exercise is most likely to be diagnostic. This is an up-to-the-minute updated approach to diagnosis and management that is geared to learners at all levels.

While not as common a cause of PH in pediatric patients, Group 2 PH is increasing in prevalence, as wonderfully detailed by William Patten and Usha Krishnan. Critical points of diagnosis with echocardiography and invasive hemodynamics are reviewed, as are the most common causes of pediatric Group 2 PH and therapeutic approaches.

The PHPN Corner of this issue is an excellent article on nonpharmacologic management of heart failure by Traci Stewart. While an array of medications is now available to alter the natural history for heart failure patients, including those with Group 2 PH, simple prescriptions do not always ensure clinical success. Detailed patient education on day-to-day assessments and early identification of when to seek medical attention is crucial to management. This review highlights the importance of a multidisciplinary, team-based approach to patient care throughout the patient's journey. Teaching our patients appropriately termed, "self-care," can improve clinical outcomes and empower patients and providers alike.

We are so very grateful to our outstanding contributing authors. Thank-you for continuing to share your knowledge and experience to improve the care of our patients. To our readers, we hope you enjoy and learn as much from this issue as we did in putting it together.

Marc A. Simon, MD, MS
Professor of Medicine
Division of Cardiology, Department of Medicine
University of California, San Francisco
San Francisco, California

Richard A. Krasuski, MD
Professor of Medicine
Division of Cardiovascular Medicine
Duke University Health System
Durham, North Carolina

REGULAR ARTICLE

Echocardiographic Evaluation of the Right Heart in Pulmonary Hypertension

Jonathan Kusner, MD
Department of Medicine, Duke University Medical Center, Durham, NC

Richard A. Krasuski, MD
Division of Cardiovascular Medicine, Duke University Medical Center, Durham, NC

Pulmonary hypertension (PH) is characterized by increased right ventricular (RV) afterload, which is accommodated early by dramatic increases in RV contractility to maintain right ventriculoarterial coupling. Related to its tissue biology, characteristics of RV contractility differ from those of the left ventricle (LV). As the RV undergoes adaptation in PH, echocardiographic signs emerge which can help identify PH and can be reassessed to noninvasively prognosticate outcomes in PH. Many of these indices can be calculated from standard echocardiographic views without significant modification to scanning procedures. This review will discuss contemporary diagnosis of PH, highlighting the role of echocardiography in this process. We will describe the differences between the LV and RV, including adaptations of the RV in PH, and how these factors impact echocardiographic assessment. We will conclude with a discussion of specific echocardiographic parameters and describe their role in diagnosis and reassessment. Routine assessment of the right heart improves noninvasive risk stratification in PH, may reduce delays in diagnosis, and ultimately may impact the significant and potentially modifiable disease burden in this patient population.

INTRODUCTION

Pulmonary hypertension (PH) refers to a diverse set of conditions that may act locally, at the level of the heart and lungs, or systemically to increase mean pulmonary arterial pressure (mPAP). In this way, PH represents a shared pathophysiology, with heterogenous upstream causes that ultimately impact the load experienced by the right ventricle (RV). The RV is able to accommodate dramatic increases in afterload to maintain cardiac output. These adaptive mechanisms have echocardiographic correlations, making echocardiography critical in both the screening for PH and for routine monitoring of PH patients.

This review will discuss contemporary diagnosis of PH, highlighting the role of echocardiography in this process. We will describe the differences between the left ventricle (LV) and RV, including adaptations of the RV in PH, and how these factors impact echocardiographic assessment. We will conclude with a discussion of specific echocardiographic parameters and describe their role in diagnosis and reassessment.

DIAGNOSIS AND THE ROLE OF ECHOCARDIOGRAPHY

In 1973, the first World Health Organization Symposium on PH was convened in Geneva, Switzerland. With minor revisions since that time, expert consensus defined PH as mPAP ≥ 25 mmHg. Subsequent studies have demonstrated a significant increase in mortality and hospitalization at mPAP below that value prompting societal guidelines to adjust the diagnostic threshold to mPAP > 20 mmHg.[1-5] This change has increased the population prevalence of PH, though the implications for patient management remain uncertain and it remains critically important for clinicians to recognize when referral to specialist care is necessary. Presently, the diagnosis of PH is estimated to be delayed by nearly 2 years, contributing to a significant and potentially modifiable disease burden.[6] Improved understanding of the role of echocardiography for PH screening provides an opportunity to identify patients who may be candidates for earlier, more invasive diagnostics and therapeutic interventions.

Role of Echocardiography

Right heart catheterization remains the "gold standard" of PH diagnosis and classification.[7] In spite of this, echocardiography serves an important role in PH screening, differentiation of PH etiologies, and disease monitoring following formal diagnosis. The 2022 European Society of Cardiology (ESC) and the European Respiratory Society (ERS) Guidelines for the Diagnosis and Treatment of PH recommend using peak tricuspid regurgitation velocity (TRV) as the first step for assigning echocardiographic probability of PH

Key Words—diagnosis, eccentricity index, echocardiography, pulmonary hypertension, right ventricular-pulmonary artery coupling, tissue annular plane systolic excursion
Correspondence: Richard.krasuski@duke.edu
Disclosure: Dr. Krasuski serves as a consultant for Actelion/Janssen, Bayer, Gore Medical, Medtronic and Neptune Medical. He has received research grants from Actelion/Janssen and the Adult Congenital Heart Association. He serves as an investigator in studies for Artivion, Corvia, Medtronic and Edwards Life Sciences. Dr. Kusner has nothing to disclose.

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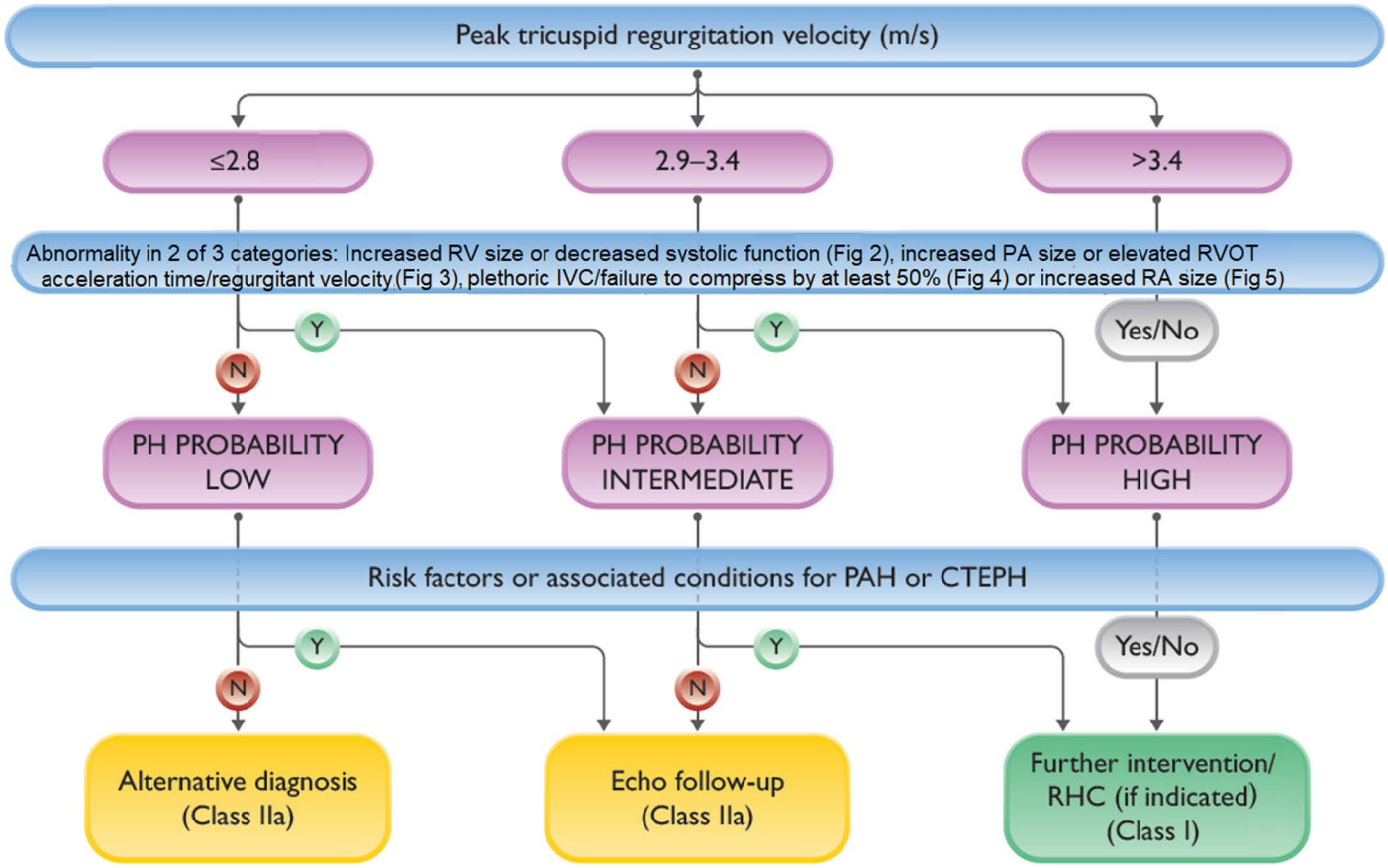

Figure 1: Echocardiography is an important screening tool for the diagnosis of pulmonary hypertension. This figure has been adapted from the 2022 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension. The first step is the assessment of peak tricuspid regurgitation velocity, followed by a careful review of right ventricular size and function, pulmonary arterial size and flow velocity tracings and inferior vena cava/right atrial sizes. If 2 or more of these categories are abnormal, the probability of pulmonary hypertension increases. High probability necessitates invasive assessment, while intermediate/low probability is further differentiated by associated risk factors and clinical conditions. Patients ultimately defined as intermediate probability should receive follow-up echocardiography, as they remain at risk for developing pulmonary hypertension. CTEPH indicates chronic thromboembolic pulmonary hypertension; IVC, inferior vena cava; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RA, right atrial; RHC, right heart catheterization; RV, right ventricle; RVOT, right ventricular outflow tract.

(Figure 1).[7] A peak TRV > 2.8 m/s should prompt further consideration of PH. The presence of additional echocardiographic findings help to further refine this assessment and justify subsequent invasive hemodynamic assessment via right heart catheterization.[7] These include assessments of RV size and systolic function (Figure 2), pulmonary size and outflow/regurgitant velocities (Figure 3), and inferior vena cava (IVC; Figure 4) and right atrial (RA) size (Figure 5). Echocardiography is therefore a critically important screening tool in the evaluation of patients with suspected PH.

Echocardiography may also help to distinguish between PH etiologies. It is particularly well suited to evaluate whether PH is related to LV dysfunction (group 2 disease); for this reason every echocardiographic assessment for PH should also include metrics of LV diastolic function, left atrial size, and measurement of LV wall thickness.[7] Echocardiography can also identify comorbid congenital heart disease, although additional studies including transesophageal echocardiography, computed tomography (CT), or cardiac magnetic resonance imaging (MRI) may be required to provide anatomic clarity. A bubble study should be performed during the initial echocardiographic study to evaluate for the presence of intracardiac or intrapulmonary right to left shunting. The former could be due to patent foramen ovale, a lesion present in over a quarter of the population. Whether patent foramen ovale was present from birth in the pulmonary arterial hypertension (PAH) patient or stretched open due to pressure and volume loading of the right atrium cannot be determined unless prior echo bubble injection was performed. A positive bubble study can also suggest the presence of an atrial septal defect, which can occasionally be the cause of PH. Often a secundum defect (in the middle of the atrial septum) can be identified by color Doppler. It's important to note that sinus venosus defect (present in the roof or the floor of the right atrium) also results in a positive bubble study, but can require a transesophageal echocardiograph, a cardiac CT scan, or a cardiac MRI for its detection. Finally, if the bubbles appear in the left atrium after more than 3 heartbeats of reaching the

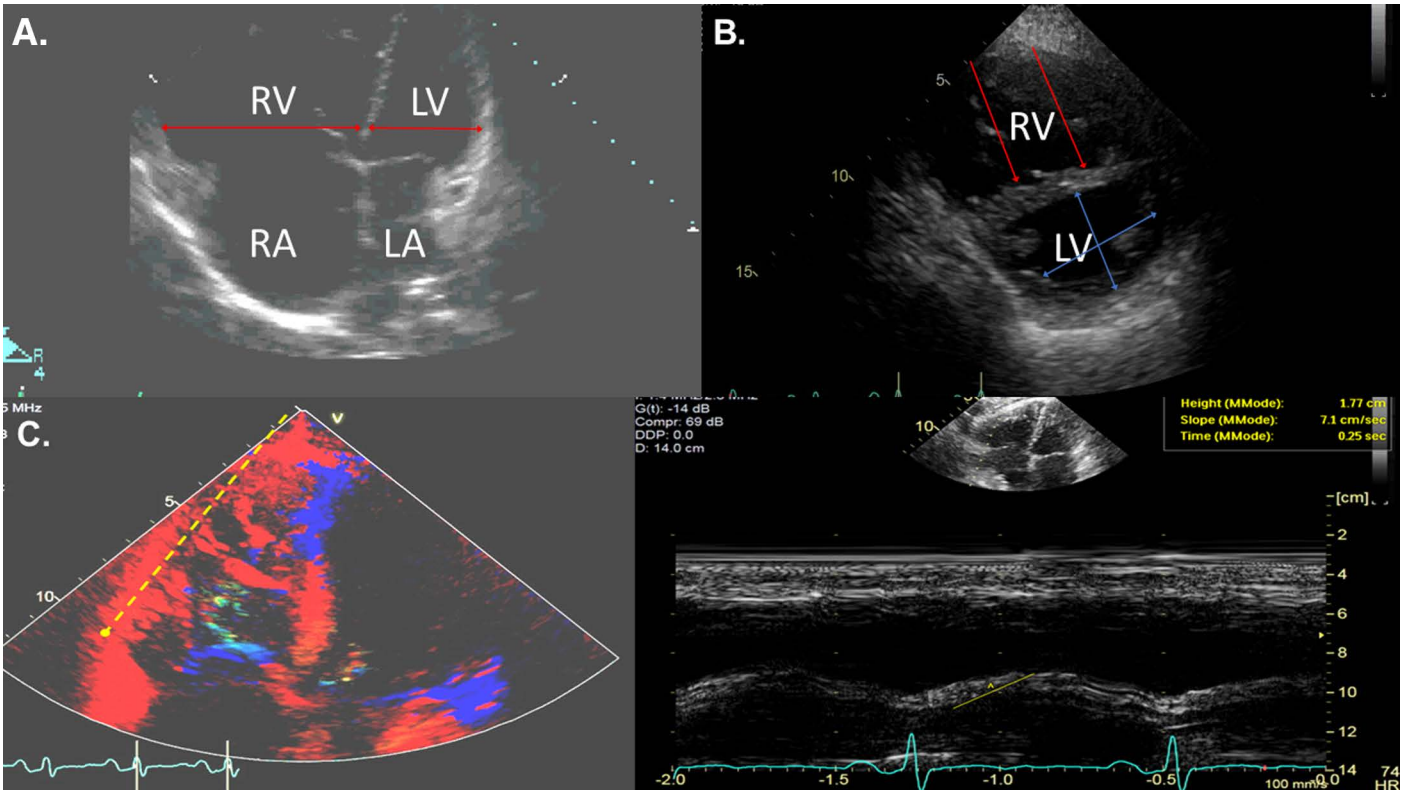

Figure 2: Assessment of the right ventricle for signs suggestive of pulmonary hypertension. The simplest assessment of right ventricular (RV) size is to compare it to the left ventricle (LV). Normally the RV should be smaller than the LV (ratio < 1). In (**A)** the RV:LV ratio is significantly > 1.0. Flattening of the interventricular septum (**B**) is also a common feature of pulmonary hypertension. The LV is essentially squashed by the RV, as assessed by the LV eccentricity index (the ratio of the LV axis parallel to the septum divided by the axis perpendicular to the septum > 1.1 as measured in the parasternal short-axis view at the level of the LV papillary muscles). (**C**) Because of the contractile pattern of the RV, tissue annular plane systolic excursion can be used to measure systolic function, with further refinement by comparing it to the systolic pulmonary artery pressure to assess RV-pulmonary arterial coupling. LA indicates left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

right atrium, it suggests the presence of pulmonary arteriovenous malformations. These are generally rare, but can develop in patients with advanced liver disease and result in profound hypoxia (hepatopulmonary syndrome).

Following diagnosis of PH and characterization of likely etiology, echocardiography is an important element for routine follow-up. For those with PAH (group 1 disease), noninvasive assessment with echocardiography is recommended every 3 to 6 months, following any change in therapy, and immediately upon suggestion of clinical worsening.[7] For PH related to LV dysfunction (group 2 disease), there is no current recommendation for echo cadence beyond what is recommended for reassessment of LV dysfunction. In PH related to underlying pulmonary disease (group 3 disease), the sensitivity of many echocardiographic indices of PH, including TRV, are reduced leading to lower utility of echocardiography for disease monitoring.[8] Given this, PH diagnosis in group 3 disease is often best aided by stepwise, composite echocardiographic assessment or pairing with contrast-enhanced CT imaging.[9,10] Echocardiography plays a clear role in the monitoring of chronic thromboembolic PH (group 4 disease) for which yearly posttreatment echocardiography is recommended in light of known recurrent or persistent PH in some patients.[7,11] For those with PH related to unknown or multifactorial mechanisms (group 5 disease), evidence to support routine echocardiographic monitoring has not yet been established.

RV ADAPTATIONS IN PH

Echocardiographic assessment of the right heart in PH necessarily seeks to identify, trend, and quantitate RV adaptive mechanisms that seek to preserve RV function in PH. During disease progression, echocardiography is also critical for identifying the point at which these mechanisms fail and RV dysfunction manifests. Recognizing anatomic and functional differences between the LV and RV, as well as the RV's response to stress, provides a foundation for understanding the specifics that echocardiographic assessment of the right heart intends to capture.

The functional and anatomic differences between the LV and RV draw both from their separate embryologic and hemodynamic environments. The LV originates from the primary heart field, which develops into 3 muscular layers that together form a truncated ellipsoid structure.[12] The fiber orientation of these 3 layers confers specific mechanical properties that impact ventricular contractility and function; specifically, the LV derives the majority of its contractility from circumferentially oriented fibers that serve to nearly ablate the ventricular cavity in systole

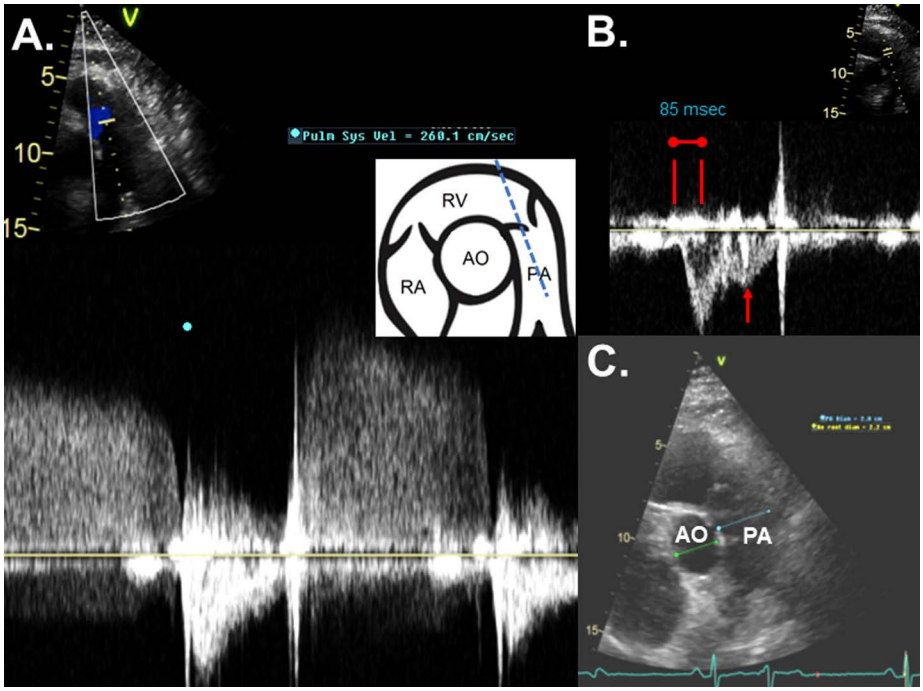

Figure 3: Assessment of the right ventricular outflow tract and pulmonary artery for signs suggestive of pulmonary hypertension. The peak regurgitant velocity in the patient in (**A**) is higher than the established threshold of 2.2 m/sec. In (**B**), the forward velocity is assessed. The acceleration time is measured from onset of flow to peak and in this patient was < 105 ms (the threshold for being abnormal). Also seen (arrow) is midsystolic notching (a very suggestive finding for significantly elevated pulmonary resistance). In (**C**), the pulmonary and aortic diameters are compared. A pulmonary artery diameter greater than the aortic diameter (as seen here) or > 2.5 cm is considered abnormal. AO indicates aorta; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

and forcefully eject blood, making it particularly well suited as a high-pressure pump.[13,14] In contrast, the RV is formed from the secondary (anterior) heart field, a structure contiguous with the conotruncus, which will ultimately give rise to the RV outflow track and the great arteries.[12,15] This proximity to structures that ultimately give rise to blood vessels belies the separate character of the RV myocardium in comparison to the LV. This thin-walled structure exists as a crescent attached to the anterior surface of the LV and is composed of 2 muscular layers with fibers oriented primarily longitudinally, from apex to base.[13,16] Such fiber orientation confers greatest contractility in the longitudinal direction, allowing the RV to serve as a pump that is particularly well suited to accommodate changes in volume.[16]

Typically, blood flow through the pulmonary vascular beds is maintained by an efficient pairing between RV systolic function and pulmonary vascular resistance (PVR), a process known as right ventriculoarterial (VA) coupling. This pairing maintains stroke volume (SV) over a wide range of PVR, including increases imposed by exertion. In PH, as PVR increases, many humoral and cellular responses are initiated that seek to maintain right VA coupling and preserve RV SV.[17,18] Structurally, these responses manifest first as progressive RV hypertrophy, whereby increasing wall thickness attempts to maintain the needed increase in contractility.[19] In contrast to systemic vascular resistance, which may increase by ~50% in states of systemic hypertension, PVR in PH often undergoes an ~400% increase from baseline values.[20] Remarkably, through cellular changes, including hypertrophy, the RV is able to achieve 4- to 5-fold increases in contractility to maintain VA coupling, albeit at a higher metabolic demand.[19] If elevated ventricular load continues or increases, additional humoral responses halt the hypertrophic process and the SV begins to drop.[18] As the next phase in adaptation, the RV dilates in order to maintain absolute SV; ultimately, as this mechanism fails, the heart rate will increase in order to preserve right-sided cardiac output. These factors dramatically impact RV myocardial oxygen supply and demand, resulting in mismatch, which is closely followed by VA uncoupling and reduced cardiac output.[19,21-23] Echocardiographic assessment of the RV in PH intends to trend ventricular health, determine the state of VA coupling, and ultimately guide the escalation of therapies.

ECHOCARDIOGRAPHIC ASSESSMENT OF THE RIGHT HEART

Echocardiographic assessment of the right heart is challenging due to the anterior position of the RV in the chest directly behind the sternum, its thin walls, and its complex contractile pattern. Considering these challenges, a complete assessment of RV structure and function requires the composition of multiple echo windows and metrics.

As previously noted, the 2022 ESC/ERS Guidelines for the Diagnosis and Treatment of PH propose a stepwise approach starting with TRV and followed by assessment of the ventricles, the pulmonary artery (PA), and the IVC and RA in order to improve diagnostic yield of invasive diagnostics. Below we will discuss the constituent metrics for this algorithm alongside additional echocardiographic metrics of RV function in PH.

Peak TRV

Traditionally, measurement of the systolic pulmonary arterial pressure (sPAP) has been a central focus of echocardiography in screening for PH. This is achieved, in the absence of pulmonary stenosis, through application of the modified Bernoulli equation ($4V^2$) using TRV. This provides the pressure gradient across the tricuspid valve during systole, which when added to noninvasive estimates of RA pressure, provides an estimate of the sPAP. This is no longer recommended as the sole screening tool given documented inaccuracies including fallacious estimates of RA pressure and amplification of measurement error

with the modified Bernoulli. Instead, new guidelines recommend use of peak TRV directly.[7]

Peak TRV is measured by continuous-wave Doppler across the tricuspid valve. Multiple views may be needed in order to obtain the optimal window; the best windows for assessment include the RV inflow, parasternal short axis (PSAX), and the apical 4-chamber (A4C) views.[24] The highest velocity with the cleanest signal most parallel to the regurgitant jet should be recorded. Accurate quantification of peak TRV requires colinearity between the continuous-wave Doppler ray and the axis of the regurgitant jet. Eccentricity will necessarily underestimate peak TRV through dot product of these 2 vectors. Peak TRV can additionally be underestimated in severe or "free" tricuspid regurgitation given the dispersion of focal flow acceleration and a broad local peak velocity. A peak TRV ≤ 2.8 m/s is considered within normal range.[7]

Tricuspid Annular Plane Systolic Excursion

Given that the principal axis of contractility in the RV is oriented apex to base, related to the fiber orientation described above, tricuspid annular plane systolic excursion (TAPSE) has evolved as a metric of RV contractility. This describes the apical movement of the tricuspid annulus during systole and is obtained using motion mode, typically from the A4C view (Figure 2). Grounded in the tissue biology of the heart, TAPSE appears to have close correlation with RV systolic function.[25-27] In PH specifically, investigation has identified a cutoff value of < 1.8 cm to have an unadjusted hazard ratio of 5.7 for risk of death over a 2-year interval.[28] TAPSE has been further combined with sPAP to form the TAPSE:sPAP ratio, which demonstrates good correlation when trended with both invasive hemodynamics and functional class in PAH.[29] More generally, TAPSE < 1.6 cm has been shown to be highly predictive of RV systolic dysfunction.[26,27,30]

Fractional Area Change

Given the prognostic significance of RV systolic function in PH, several metrics have been developed to assess it.[31,32] One such method is fractional area change (FAC), a 2-dimensional metric calculated by comparing manual tracings of the RV endocardial border in end-diastole and end-systole. In comparison to other methods like TAPSE, FAC has demonstrated similar or better correlation with high-resolution 3-dimensional RV ejection fraction measurement by cardiac MRI, with the added advantage of faster assessment and lower cost.[33,34] FAC is generally obtained from the A4C view, with normal values of ≥ 30% in men and ≥ 35% in women.[35]

Eccentricity Index

The eccentricity index (EI) assesses for RV pressure or volume overload by evaluating LV dimensions. The EI is a quantitative metric of the classic "D" sign and is calculated from the parasternal short-axis view midway along the LV (Figure 2), at the level between the papillary muscle and tip of the mitral valve leaflets. Two internal cavity dimensions are obtained from this view, one parallel to the septum (D2) and one perpendicular to the septum (D1). EI = D2/D1 and is typically ≤ 1 in both systole and diastole. RV volume overload causes eccentricity in diastole; while RV pressure overload causes eccentricity in both systole and diastole. A systolic EI > 1.1 increases the likelihood of PH, while values > 1.7 have been associated with a very poor prognosis.[7,31]

RV Index of Myocardial Performance

The index of myocardial performance, also known as the Tei index, describes the ratio between the sum of isovolumetric contraction and isovolumetric relaxation times divided by ejection time. This is a metric that can be evaluated for both RV and LV and includes elements of both systole and diastole in an attempt to assess global ventricular function.[36,37] The RV index of myocardial performance (RIMP) has been studied in PH specifically to evaluate RV function, and has been shown to be an independent predictor of mortality and correlate with invasive hemodynamics.[38,39]

RIMP was developed using pulsed-wave (PW) Doppler; this method is technically challenging and requires comparison of PW signals at both the lateral tricuspid annulus and the RV outflow tract obtained during cardiac cycles with near-identical R-R intervals. Given this difficulty, a tissue Doppler RIMP methodology has been developed which requires a single tissue Doppler sample along the lateral tricuspid annulus. This tissue Doppler RIMP has demonstrated excellent correlation with RIMP and slightly improved correlation with RV ejection fraction and RV FAC as compared with RIMP.[40] RIMP > 0.43 by PW Doppler, or > 0.54 by tissue Doppler indicates RV dysfunction.[41] In PH specifically, RIMP > 0.64 is associated with lower overall survival at 4 years.[38]

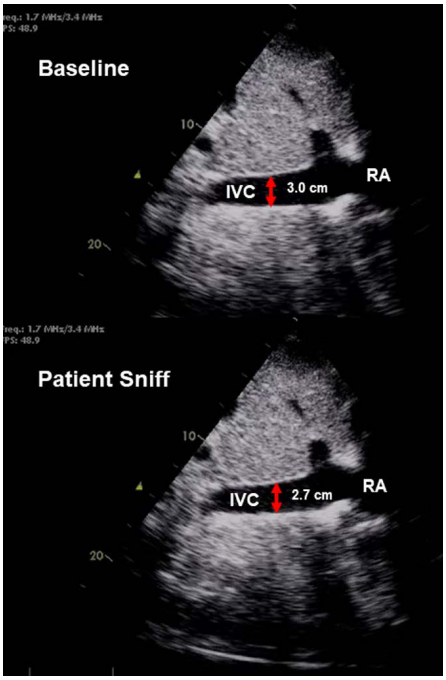

Figure 4: Assessment of the inferior vena cava (IVC) artery for signs suggestive of pulmonary hypertension. Normally the IVC diameter should be ≤ 2.1 cm in diameter on this subcostal view and should collapse > 50% with a sniff. This usually correlates to an estimated right atrial pressure of < 5 mmHg. If the IVC is either > 2.1 cm or collapses ≤ 50%, the RA pressure is ~5 to 10 mm Hg. If the IVC is both > 2.1 cm and collapses < 50% (as in this patient), the RA pressure is ~10 to 20 mm Hg. IVC indicates inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

RV Strain

RV strain has been studied as a modality to assess RV contractility and prognosticate outcomes. Typically,

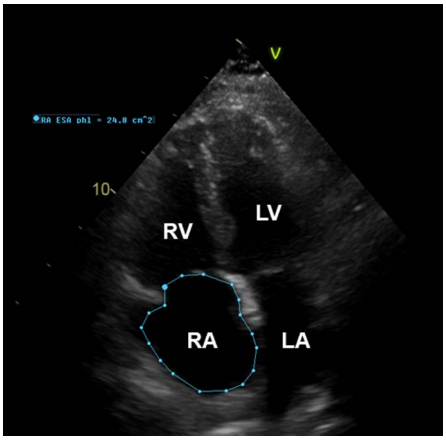

Figure 5: Assessment of the right atrium for signs suggestive of pulmonary hypertension. This patient has a right atrial area which is greater than the normal threshold of 18 cm^2. LA indicates left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

global RV strain is assessed in 6 segments obtained in the A4C view; this assessment can be technically challenging given that imaging must remain within 10° to 15° of the axis of contraction for full reliability. RV free wall longitudinal strain (RV-FWLS) analyzes the lateral 3 segments and excludes the 3 septal segments, which has the advantage of being far more angle-independent while still demonstrating good performance;[42-46] in PAH, RV-FWLS correlates with worsened function class, shorter 6-minute walk distances, higher N-terminal pro-B-type natriuretic peptide levels, and the presence of clinical RV failure.[44] RV-FWLS can identify subclinical RV dysfunction when other parameters like TAPSE are still within normal ranges.[42,43] Additionally, after adjustment for PVR, pulmonary pressures, and RA pressure, RV-FWLS has been shown to predict survival in PH.[44] Normal ranges for RV-FWLS are disputed, although meta-analysis has demonstrated patients with PH and RV-FWLS > –19% are at significantly greater risk of experiencing a combined endpoint of mortality and PH-related event. Furthermore, patients with RV-FWLS > –22% had significantly higher risk for all-cause mortality.[47]

PA Diameter

Mean PA diameter has been studied as a marker of elevated PA pressure and is measured in end diastole halfway between the pulmonary valve and bifurcation of the main PA (Figure 3). The PA dilates in the presence of either pressure or volume overload. CT measurements of PA diameter correlate with catheter-derived measurements of elevated pulmonary pressures, which have subsequently been correlated with echocardiographic measurements.[48,49] Guidelines support PA diameter > 2.5 cm as increasing the likelihood of PH.[7]

RA Area

Elevated mean RA pressure measured by right heart catheterization is an independent risk factor for mortality in PH.[50] Right atrial area (RAA) measured by echocardiography corrrelates to invasive assessments of mean right atrial pressure and has by itself been demonstrated to predict poorer survival.[51] RAA in PH is measured in the A4C view at end systole on the frame just prior to tricuspid valve opening (Figure 5). A RAA > 18 cm^2 is associated with a poor prognosis, with a relative risk of 2.6 for death or transplantation at 3 years compared to those with RAA ≤ 18 cm^2.[51]

RA Strain

As discussed earlier, emerging techniques are extending beyond structural metrics to assess functional parameters. In line with this trend, RA strain has emerged as a hopeful metric to prognosticate precapillary PH. Hasselberg et al.[52] performed 6-segment speckle tracking of the RA in 151 patients with precapillary PH. Over a follow-up interval of 5 years, 48% of patients died; those in the lowest quartile of RA strain experienced a significant risk of death ($P = .006$), while intact RA strain was independently associated with survival following multivariable analysis ($P = .039$).[52] When combined with RV strain, RA strain provided added prognostic value; individuals with preserved RA and RV strain demonstrated improved survival over those with intact RV strain and impaired RA strain, who in turn had improved survival over those with impaired RV and RA strain. Further development of these techniques may allow for quantification of strain value cutoffs that prognosticate disease progression or suggest a need for specific therapies.

Additional Parameters

Several right heart echocardiographic indices have not been correlated to outcomes or disease progression in PH specifically but have been shown to indicate elevated right-sided pressures. These parameters remain important elements of a complete echocardiographic assessment of the right heart.

IVC Size and Collapsibility: From the subcostal view, with the IVC and cavo-atrial junction into the RA in view, the IVC diameter is measured across the width of the IVC, 1 to 2 cm from the cavo-atrial junction. This is most reliably obtained at end expiration, with normal values being ≤ 2.1 cm. The collapsibility should also be assessed. This is best done by assessing the IVC in motion mode and asking the patient to sniff; under normal circumstances the IVC should collapse by > 50% with a sniff (Figure 4). If the IVC is > 2.1 cm or collapses ≤ 50%, the RA pressure is ~5 to 10 mm Hg. If the IVC is both > 2.1 cm and collapses < 50%, the RA pressure is ~10 to 20 mm Hg.

RV to LV Diameter Ratio: Similar to EI, the basal diameters of the RV and LV may be compared. This measurement is obtained in the A4C view, mindful to exclude any foreshortening. Measured at end diastole, the basal cavity dimensions of the RV and LV are compared. A ratio of RV:LV > 1 suggests RV dilation.

Peak Regurgitant Velocity of the Pulmonary Valve: Imaging in the PSAX near the cardiac base with the RV outflow tract (RVOT) in view, the pulmonary regurgitant jet of the pulmonary valve can be registered on continuous-wave Doppler (Figure 3). This pulmonary regurgitant jet is measured in early diastole with values > 2.2 associated with elevated mPAP.[7]

PA Midsystolic Notching: Midsystolic notching is observed in the PSAX through placement of PW Doppler sample volume just below the pulmonic cusp in the RVOT. Increased PVR, and PA stiffness, change pulmonary vascular impedance in a manner that promotes earlier wave reflection and impedes RV ejection. Waves here refer to the transmission of energy, largely through compressive forces, separate from the flow

of blood that emanates from ventricular contraction and can be reflected back towards the ventricle. This early reflection is appreciated by a "notch" in the midportion of the RV systolic Doppler signal as the RV's ejection is momentarily reduced by early wave reflection seen with elevated PVR (Figure 3). Given this phenomenon's relationship to the material properties of the pulmonary arteries, it is more commonly observed in precapillary PH as compared to group 2 PH.[53]

RVOT Acceleration Time: In the same PSAX view and PW Doppler sample volume as above, the RVOT acceleration time can be assessed. Measured at end expiration, the Doppler profile of flow through the RVOT in systole is assessed. As PA pressures increase, the time from the onset of RV ejection until the profile's peak, referred to as the RVOT acceleration time, shortens (Figure 3). Heart rates between 60 and 100 beats/min provide the most reliable measurement.[54] In those with atrial fibrillation, values should be averaged over at least 5 beats. RVOT acceleration times ≤105 milliseconds have been correlated with elevated mPAP.[55]

CONCLUSION

PH is characterized by increased RV afterload, generally accommodated early by dramatic increases in RV contractility to maintain right VA coupling. As the RV undergoes early adaptation, characteristic echocardiographic signs emerge which can be followed in order to noninvasively prognosticate outcome in PH. As this process continues, the RV exceeds its ability to compensate for increased pulmonary pressures, which ultimately manifests as right VA uncoupling. The progression to this late finding can be observed on echocardiography through the evaluation of right heart structures. Many of these indices can be calculated from standard echocardiographic views without significant modification to scanning procedures. Routine assessment of the right heart for severity of PH holds promise to improve the noninvasive risk stratification for PH, reduce delays in diagnosis, and ultimately impact the significant and potentially modifiable disease burden.

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REGULAR ARTICLE

Heart Failure With Preserved Ejection Fraction and the Diagnosis of Pulmonary Hypertension

Yogesh N. V. Reddy, MBBS, MSc
Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN

Heart failure with preserved ejection fraction (HFpEF) is now the most common cause of pulmonary hypertension (PH), and the diagnosis of HFpEF should be considered in any patient with a preserved left ventricular systolic function being evaluated for PH. Accurately diagnosing HFpEF as compared with pulmonary arterial hypertension has critical treatment implications, given the vastly different treatment options available, and can be accurately guided using exercise right heart catheterization. In this review, the diagnostic approach and treatment implications of PH in patients at risk for HFpEF will be discussed.

INTRODUCTION

Elevated pulmonary artery (PA) pressure can arise from multiple different disease states. One of the most common causes of pulmonary hypertension (PH) worldwide is left-sided heart failure.[1,2] Coupled with the obesity epidemic,[3] the epidemiology of heart failure has gradually shifted over the last few decades to where heart failure with preserved ejection fraction (HFpEF) is now the most common cause of heart failure and thereby the most common cause of PH.

CURRENT DIAGNOSIS OF HFpEF AND PH

The diagnosis of PH relies on measurement of an elevated mean PA pressure. Based on normative values from population studies and thresholds of risk, the diagnostic threshold for PH has been progressively lowered from a mean PA pressure of ≥25 mm Hg to now ≥20 mm Hg.[4] Importantly, the threshold for diagnosing left heart disease at rest has not changed, where a mean pulmonary capillary wedge pressure (PCWP) ≥15 mm Hg is considered diagnostic of left heart disease. The margin of error for diagnosis of HFpEF compared with precapillary pulmonary arterial hypertension (PAH) is therefore now smaller and requires meticulous performance of right heart catheterization to accurately classify patients with mild PH at rest.

MEASURING PRESSURES AT END EXPIRATION DURING RIGHT HEART CATHETERIZATION

Pressures are measured during right heart catheterization by means of a fluid filled catheter connected to a pressure transducer system. This allows measurement of relative pressure changes over time, but pressure changes must be referenced to an external zero reference point, which is set by convention to atmospheric pressure with the pressure transducer leveled at the midchest. Since pressures are measured relative to atmospheric pressure, it is important to measure pressures manually at end expiration, when the lung is at its functional residual capacity and intrathoracic pressure is closest to atmospheric pressure (the chosen zero reference point). During inspiration, a drop in intrathoracic and pleural pressure normally occurs, which results in a decrease in all pressures in the chest (including the pressure recorded by the catheter in the heart), but no true change in intracardiac pressures as assessed by the transmural pressure (intracardiac pressure – pleural pressure).[5] Therefore, relying on computer-generated mean pressures throughout the respiratory cycle will include false declines in intracardiac pressure during inspiration and thereby underestimate the true PCWP. Due to the competing effects of increased venous return and right-sided stroke volume during inspiration (which tends to increase PA pressure) and decreased intrathoracic pressure (which tends to decrease PA pressure), the error-inducing effect of inspiration on PA pressure is smaller than its effect on the PCWP since the PCWP generally demonstrates greater respiratory variation. Therefore, failing to measure pressures at end expiration will generally underestimate the contribution of left heart disease to the PH and may result in misdiagnosis as precapillary PAH as opposed to the true diagnosis of HFpEF (Figure 1).

WEDGE PRESSURE OR LEFT VENTRICULAR END DIASTOLIC PRESSURE?

It is also important to use the PCWP and not the left ventricular (LV) end diastolic pressure (LVEDP) when trying to diagnose HFpEF and determine the precapillary contribution to PH.[6] The PCWP allows measurement of left atrial (LA) pressure throughout systole and diastole and therefore allows understanding of whether large V waves are present in the LA from atrial noncompliance during atrial filling. Large V waves impart a late systolic load to the right ventricle and contribute to PH and pulmonary arterial stiffness from

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Correspondence: reddy.yogesh@mayo.edu
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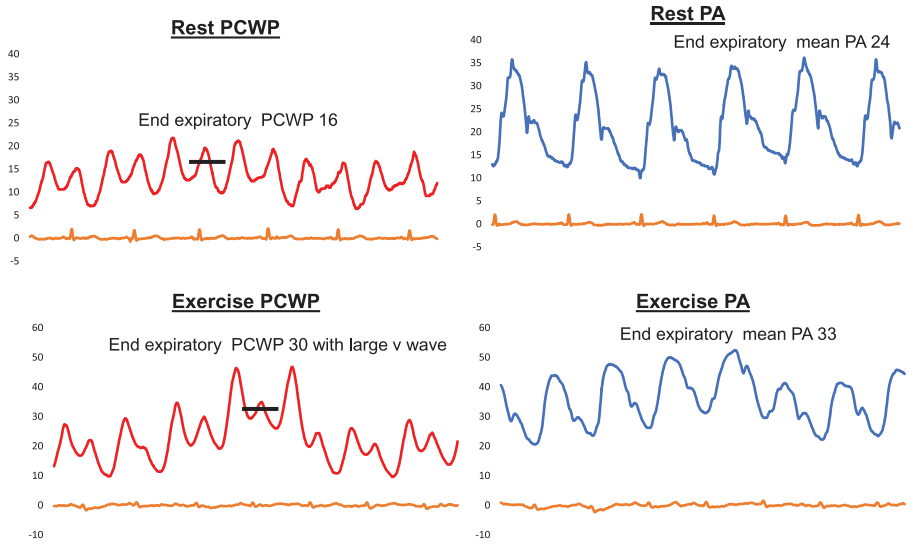

Figure 1: Value of end expiratory exercise hemodynamics to differentiate HFpEF from pulmonary arterial hypertension.

postcapillary mechanisms in HFpEF.[7,8] In contrast, the LVEDP reflects only a static measurement at end diastole, and although helpful in identifying LV pathology in HFpEF, the LVEDP does not allow assessment of LA myopathy and compliance, which is ultimately the critical determinant of pulmonary venous pressures and the degree to which the left heart is contributing to PH. Increasing atrial fibrillation burden with symptoms is generally associated with worse underlying LA myopathy with HFpEF[7], and even the mere presence of atrial fibrillation in a symptomatic patient with a preserved LV ejection fraction (EF) serves as a highly specific biomarker for underlying HFpEF.[9] The presence of atrial fibrillation in particular is uncommon in true Group 1 PAH and raises the pretest probability that HFpEF is the correct diagnosis and cause of PH. Therefore, when trying to understand if HFpEF is the cause of PH and to allow quantification of the burden of pulmonary vascular disease by calculation of pulmonary vascular resistance (PVR), it is important to use the PCWP and not the LVEDP.

PH IN HFpEF—NOT UNIVERSAL AT REST

Further complicating the evaluation for HFpEF in a patient with suspected PH is the dynamic nature of hemodynamic abnormalities in patients with HFpEF. Many patients with HFpEF and PH may have relatively normal left-sided filling pressures at rest that may increase with provocation or mild changes in volume status.[10] Exercise right heart catheterization is therefore the gold standard diagnostic test to either exclude or diagnose HFpEF based on the exercise PCWP measured during occurrence of exertional symptoms. Given the inaccuracies of resting right heart catheterization to diagnose HFpEF (a sensitivity of only 56%),[10] consideration of clinical characteristics is important to quantify the pretest probability of HFpEF and guide use of exercise catheterization so that the correct diagnosis is established in the presence of resting PH. We developed and validated the H_2FPEF score, to estimate this pretest probability more quantitatively. HFpEF is increasingly likely when patients have obesity, atrial fibrillation, hypertension, and are older.[10,11] When borderline resting hemodynamics with PH occurs with an intermediate to high H_2FPEF score, exercise right heart catheterization can therefore be helpful in clarifying the diagnosis and guide treatment (Table 1).

The presence of hypoxia during exercise is generally associated with PH and abnormal PVR in patients with HFpEF.[12] Patients with combined precapillary and postcapillary PH HFpEF have the greatest hypoxemia and ventilatory abnormalities coupled with greater hemodynamic derangements.[13] Isolated postcapillary PH in HFpEF is rarely associated with severe hypoxemia[14] despite dynamic occurrence of pulmonary edema during exercise.[15] Therefore, the presence of clinical hypoxemia should raise consideration for pulmonary vascular disease that can be seen either in precapillary PAH or combined precapillary and postcapillary PH due to HFpEF.

SPECTRUM OF PH PHENOTYPES IN HFpEF

Based on resting and exercise hemodynamics in a patient with PH at rest (mean PA ≥ 20 mm Hg), 3 hemodynamic profiles in a patient at risk for HFpEF are generally possible:

(1) isolated postcapillary PH HFpEF with mean PA ≥ 20, exercise PCWP ≥ 25 mm Hg, and normal PVR at rest (<2 Wood units);
(2) combined precapillary and postcapillary PH HFpEF with mean PA ≥ 20, PVR > 2 Wood units, and exercise PCWP ≥ 25 mm Hg; or
(3) precapillary PAH without HFpEF with mean PA ≥ 20, PVR > 2 Wood units, and exercise PCWP < 25 mm Hg.

In clinical practice, patients whose hemodynamics may be borderline or lie outside the boundaries of these categorical definitions may require consideration of pretest probability based on clinical profile and risk factors to help guide therapeutic decision making. Although some have advocated for use of PA pressure or PCWP indexed to change in cardiac output to define precapillary versus postcapillary PH, the use of flow-adjusted pressure measurements may not add incremental diagnostic value for most patients, at least during supine exercise. In a multicenter study, use of PCWP indexed to cardiac output appeared to misclassify patients without incremental diagnostic value.[11] Given the added complexity of using flow-adjusted PA and PCWP measurements with uncertain diagnostic value, use of absolute pressures is preferred for diagnostic purposes, with the cardiac output response providing independent physiological information with prognostic value.[16]

Table 1. Steps in Performance of Exercise Right Heart Catheterization for Evaluation of Borderline Hemodynamics at Rest

1	Jugular venous access with 9 French venous sheath to allow continuous monitoring of right atrial pressure throughout exercise from the side arm of the venous sheath
2	Right heart catheterization with end hole single lumen catheter with high fidelity micromanometer to avoid whip and ringing artifact which improves fidelity for accurate measurement of end expiratory hemodynamics
3	Arterial line placement to obtain accurate arterial saturations which may be unreliable with exercise using noninvasive oximetry
4	Measurement of PA saturation and SVC saturation with simultaneous VO_2 measurement using a metabolic cart to calculate cardiac output and rule out a left to right shunt
5	Measurement of PCWP saturation to confirm an appropriate PCWP position before exercise with a wedge saturation >90%. Without this confirmation, we risk that the PCWP tracing is a damped or partial PA tracing from incomplete occlusion of the PA segment with the inflated balloon volume
6	Exercise in 2 min ramped stages with measurement of PA and PCWP and cardiac output at each stage
7	Absolute PCWP during early and peak exercise at end expiration helps rule in (≥25 mm Hg) or rule out HFpEF (<25 mm Hg)
8	Relative changes in PA to PCWP during rest and exercise help determine the relative precapillary versus postcapillary component along with pretest probability
9	Relative changes in RA to PCWP ratio help determine the contribution of relative pericardial restraint to intracardiac hemodynamics

Abbreviations: HFpEF, heart failure with preserved ejection fraction; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RA, right atrium; SVC, superior vena cava.

THE CLINICAL CHALLENGE OF ATYPICAL PAH WITH RISK FACTORS FOR HFpEF BUT RESTING HEMODYNAMICS SUGGESTIVE OF PAH

Since patients with both PAH and HFpEF present with a preserved LV EF and symptoms, this can lead to diagnostic challenges in hemodynamic evaluation in patients with risk factors for HFpEF, as described above. When patients with risk factors for HFpEF (obesity, atrial fibrillation, hypertension) appear to have hemodynamics at rest consistent with PAH, they do not respond as well to pulmonary vasodilator therapy.[17,18] More aggressive pulmonary vasodilator therapy, in particular, did not appear to be associated with improved outcomes or symptoms in such patients with atypical PAH whose hemodynamics support PAH, but the risk factor profile and pretest probability suggest the possibility of undiagnosed HFpEF.[18] Since HFpEF cannot be ruled out with resting right heart catheterization and clinical profile alone, the diagnosis of HFpEF remains a probabilistic diagnosis based on standard resting clinical measures. This suggests that our current hemodynamic measures at rest may not provide sufficient diagnostic clarity in patients with atypical PAH. These patients likely represent a heterogenous cohort with (i) true precapillary PAH, (ii) combined precapillary and postcapillary PH HFpEF that has been missed by resting right heart catheterization, or (iii) passive isolated postcapillary PH with measurement error due to inaccurate PCWP or cardiac output measurements. The use of exercise hemodynamics may therefore enhance diagnosis and selection of patients with atypical PAH for appropriate therapies.[19] With the emergence of effective therapies for HFpEF, particularly with the sodium glucose cotransporter (SGLT)-2 inhibitors,[20] making an accurate diagnosis of HFpEF as compared with PAH has very important therapeutic implications, for which HFpEF requires treatment with SGLT2 inhibitors and PAH would require pulmonary vasodilator therapy.

SUMMARY

HFpEF is now the most common cause of PH, and the diagnosis of HFpEF should be considered in any patient with a preserved EF being evaluated for PH. Accurately diagnosing HFpEF as compared with PAH has critical treatment implications, given the vastly different treatment options available, and can be accurately guided using exercise right heart catheterization.

Hemodynamics obtained from a 70-year-old female with hypertension and unexplained dyspnea, using pressures averaged through the respiratory cycle, showed the mean PA pressure was 23, mean PCWP was 12, with a PVR of 2 Wood units, which would be consistent with precapillary PH. Using end-expiratory measures would measure the true PCWP, which is higher and consistent with HFpEF. End-expiratory mean PA pressures can be calculated using the Chemla regression equation using end-expiratory PA systolic pressure as (0.6 × PA systolic pressure) + 2. With exercise, end-expiratory wedge pressure increased to 30 with large V waves to 44 with associated PH and normal pulmonary vascular response with a decline in PVR during exercise. The patient symptoms are therefore consistent with HFpEF and not atypical PAH

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REGULAR ARTICLE

Pediatric Pulmonary Hypertension in Left-Sided Heart Disease

William F. Patten, MD
Department of Pediatrics, Division of Pediatric Cardiology, New York-Presbyterian—Morgan Stanley Children's Hospital, Columbia University Irving Medical Center, New York, NY

Usha S. Krishnan, MD
Department of Pediatrics, Division of Pediatric Cardiology, New York-Presbyterian—Morgan Stanley Children's Hospital, Columbia University Irving Medical Center, New York, NY

Pulmonary hypertension (PH) from left-sided heart disease (group-II PH) is an increasingly recognized cause of PH in pediatrics. Group-II PH can result from obstruction at any level of the left heart, and can progress over time. Management can be particularly difficult, as targeted PH therapy in the setting of a fixed obstruction carries a risk of pulmonary vascular congestion and pulmonary edema. Based on existing evidence, the use of pulmonary vasodilators in group II PH is not recommended, and management centers around early identification and correction of the underlying left-sided lesion. In this review, we highlight the pathophysiology of group-II PH, the diagnostic evaluation of left heart pathology, and a general approach to both medical and surgical management, with particular attention to relevant left-sided lesions. Group-II PH is a multifaceted and progressive disease process that poses a difficult challenge to clinicians, and requires a thoughtful and individualized approach to management.

INTRODUCTION

Pulmonary hypertension (PH) is a rare disease in children and is associated with significant morbidity and mortality.[1] Data from various registries have shown that 6th World Symposium of Pulmonary Hypertension (WSPH) group I and group III are the commonest forms; however, group II PH in pediatric patients has achieved increasing recognition in the two more recent WSPH classifications of PH.[2,3] PH from left-sided heart disease (group II PH) results when left heart pathology transmits passive hydrostatic pressure to the pulmonary vascular tree, first to the post–alveolar-capillary pulmonary venous system and then to the pre–alveolar-capillary pulmonary arterial system.[4,5]

Although epidemiologic data in pediatric patients are limited, group II PH is becoming increasingly common, accounting for 5% to 14% of cases of pediatric PH.[2,5,6] While left ventricular (LV) systolic dysfunction is the primary cause of PH in adults, pediatric group II PH can be secondary to obstruction at any level of the left heart, including pathology of the pulmonary veins or the mitral or left atrioventricular valve (LAVV), LV systolic or diastolic dysfunction, or LV outflow tract obstruction.[7,8] These lesions can occur in isolation or in combination with each other, such as in Shone complex, and can progress and worsen over time.[9]

Group II PH can be further subdivided into two categories: postcapillary PH and combined precapillary and postcapillary PH (Cpc-PH).[8] Elevations in left-sided pressures lead to distension and endothelial disruption of the post–alveolar-capillary vasculature, resulting in remodeling, including smooth muscle proliferation and intimal and medial thickening.[8] The pulmonary veins, which normally lack a significant muscular medial layer, develop histologic features resembling pulmonary arterioles. This vascular remodeling helps mitigate the backward transmission of elevated left-sided pressures, at the expense of increased resistance to the left atrium (LA) leading to increased mean pulmonary artery (mPA) pressure and so-called postcapillary PH. Cpc-PH occurs with chronic elevations in left-sided pressures, which, if not adequately addressed, results in the remodeling of the pulmonary arterial system, including hypertrophy, fibrosis, thrombosis, and an increase in resistance in the pulmonary vasculature.[10]

Both isolated group II PH and Cpc-PH share common hemodynamic definitions reflective of the underlying pathophysiology, including mPA pressure of ≥20 mm Hg and pulmonary capillary wedge pressure (PCWP) of ≥15 mm Hg. Cpc-PH is further differentiated from isolated postcapillary PH by hemodynamic measurements reflective of increased pulmonary vascular resistance, either a transpulmonary gradient (TPG) of ≥7 mm Hg or an indexed pulmonary vascular resistance (PVRi) of ≥3 Wood units · m^2 (WU m^2).[2] Given the high prevalence of group II PH in adult populations, the most recent European Society of Cardiology/Respiratory Society adult guidelines have lowered the threshold for the diagnosis of Cpc-PH to a PVR of >2 WU; however, these criteria have not yet been adopted for pediatric populations.[11]

GENERAL APPROACH

Evaluation and management of group II PH are largely dependent on the underlying etiology of left heart disease, and much of the current understanding of this physiology comes from experience in adult populations with left heart failure and either a preserved or reduced ejection fraction. The use of pulmonary vasodilators in adult as well as pediatric

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Correspondence: wfp9002@nyp.org.

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Table 1. Echocardiographic Parameters and Measurements Included as Part of the Evaluation of Pediatric Group II Pulmonary Hypertension

Echocardiographic Evaluation of Pediatric Group II Pulmonary Hypertension	
Right-Sided Chamber Dimensions	**Mitral Valve or LAVV**
Right atrial size	2D and color Doppler assessment of LAVV
Right ventricular end-diastolic volume	Pulsed-wave Doppler assessment
Right ventricular hypertrophy	Continuous-wave Doppler assessment
	Mean gradient measurement of LAVV inflow
Right Ventricular and Pulmonary Artery Pressure	**Left Ventricular Diastolic Function**
Tricuspid regurgitation jet	Lateral LAVV annulus tissue Doppler assessment
Interventricular septum position	LV inflow Doppler measurements
Pulmonary regurgitation gradient (peak and end diastolic)	
Right Ventricular Function	**Left Ventricular Systolic Function**
Qualitative systolic function assessment	Qualitative systolic function assessment
TAPSE	Quantitative systolic function assessment
Right ventricular FAC	Left ventricular strain measurement
Right ventricular MPI	Left ventricular dp/dt measurement
Right ventricular strain measurement	
Pulmonary Veins	**Aortic Valve and Aorta**
2D and color Doppler assessment of all 4 pulmonary veins	2D and color Doppler assessment of aortic valve
Mean gradient measurements	2D and color Doppler assessment of ascending and transverse aorta and aortic isthmus
	Pulsed-wave Doppler assessment of descending aorta

Abbreviations: FAC indicates fractional area change; LAVV, left atrioventricular valve; LV, left ventricular; MPI, myocardial performance index; TAPSE, tricuspid annular plane systolic excursion.

group II PH varies by center without a single unifying strategy, and treatment is considered off-label due to the lack of supporting data. Central to the management of pediatric group II PH is the timely identification and surveillance of the underlying lesion and the reduction of the hydrostatic pressure in the alveolar capillary bed while monitoring for signs of worsening pulmonary edema.

Diagnostic Evaluation

The diagnostic evaluation of a patient with group II PH has to account for the many underlying etiologies.[12] A thorough history should include evidence of effort intolerance, fatigue, respiratory distress, and failure to thrive as well as prior diagnoses of congenital heart disease or myocarditis/cardiomyopathy. Physical examination findings can be useful to localize left-sided lesions, such as an opening snap and diastolic murmur in mitral or LAVV stenosis, a gallop in LV systolic or diastolic dysfunction, or diminished femoral pulses with brachiofemoral delay in coarctation of the aorta.

Laboratory testing, including B-type natriuretic peptide (BNP) or N-terminal ProBNP (NTProBNP), has been used in the surveillance of PH in both adults and children.[13] Serial NTProBNP measurements may reflect left atrial distension and the progression of group II PH.[14] Chest radiography may demonstrate cardiomegaly consistent with the disease or reveal evidence of pulmonary vascular congestion. Chest radiographs in this population are less likely to show significant oligemia as can be seen in other types of PH as the PH is secondary to vascular congestion.

An electrocardiogram (ECG) is a noninvasive tool to assess for structural heart disease of the left heart. ECG may demonstrate evidence of left heart dilation or hypertrophy, left-axis deviation, or left atrial enlargement. ECG can also help identify atrial arrhythmias, which can occur in LA dilation secondary to left-sided obstructive disease.

Echocardiography

Echocardiography can be pivotal in the diagnosis of group II PH. A complete and thorough anatomic assessment is essential to evaluate all lesions contributing to group II PH.[2,3,12] Echocardiographic assessment, including color Doppler, can be used to evaluate for LAVV stenosis or regurgitation, aortic stenosis (AS), aortic hypoplasia, or coarctation of aorta (CoA). Each echocardiogram for a patient with concern for PH should include a thorough evaluation of all four pulmonary veins as pulmonary vein stenosis (PVS) has a variable onset and can be progressive. Qualitative and quantitative function assessments, including LV strain measurements, are necessary to evaluate for LV systolic dysfunction. Diastolic function may be difficult to fully assess using echocardiography but can be supported by abnormalities of left atrial size, tissue Doppler velocity of the LAVV lateral annulus, and/or pulsed-wave Doppler profile of the LAVV inflow.[15]

Echocardiography can provide an estimate of right ventricular (RV) and pulmonary artery pressure with a combination of the interventricular septal position, tricuspid regurgitation jet, and pulmonary regurgitation jet, as well as evaluating for RV systolic dysfunction.[3] A comprehensive list of echocardiographic parameters as part of group II PH assessment is included in Table 1.

Cardiac Catheterization

Cardiac catheterization allows for direct measurements of mPA pressure as well as PCWP. Additionally, actual measurements of the TPG and the PVR can be useful in differentiating isolated postcapillary PH (TPG, <7 mm Hg; PVRi, <3 WU m^2) from Cpc-PH (TPG, ≥7 mm Hg; PVRi, ≥3 WU m^2).[3,16]

If there is concern for group II PH, additional measurements in the left heart can be taken to diagnose the underlying pathology, stratify severity, inform surgical decision-making, and, in some cases, even provide interventions to relieve left-sided obstruction. This can be particularly useful in group II PH secondary to more than one form of left-sided obstruction. A complete hemodynamic assessment must include measurements of pressure gradients along the left heart, including the pulmonary veins and the LAVV, or across the LV outflow tract. Measurement of the LV end-diastolic pressure can be useful in determining diastolic dysfunction that may be either contributory to or the underlying cause of PH.[8,9]

Acute vasodilator testing with inhaled nitric oxide should be done very carefully (with watch for the development of pulmonary edema) and may provide anticipatory guidance prior to the use of pulmonary vasodilators by documenting any change in right heart hemodynamics, including a reduction in the mPA pressure or PVR, but, more importantly, monitoring for a corresponding increase in the PCWP.[3,16] Great care is needed if vasoresponsiveness testing is done as increasing pulmonary blood flow could lead to pulmonary edema in patients with group II PH.

Pulmonary Vasodilator Therapy

While pulmonary vasodilator therapy is a mainstay of precapillary PH, its use in pediatric group II PH is risky.[17] Vasodilation of the pulmonary vasculature in the setting of left-sided obstructive disease can worsen pulmonary vascular congestion and lead to pulmonary edema. Even after medical or surgical correction of left-sided disease, the remodeling of the postalveolar capillary vessels takes time to normalize, and the initiation of pulmonary vasodilators can still have deleterious effects.

Most of the current data regarding medications in group II PH come from adult trials investigating medical therapies, and there is a significant need for similar research in pediatric populations. The phosphodiesterase-5 inhibitor sildenafil is the most-studied drug in group II PH. An early randomized, placebo-controlled study of sildenafil in adult patients with heart failure showed improvements in functional status in those taking sildenafil as well as improvements in echocardiographic indices of LV diastolic function.[18] However, subsequent trials in adults with heart failure and valvular heart disease have failed to show a benefit, even suggesting potential harm.[19,20] Similar trials in adults with heart failure investigating the use of endothelin receptor antagonists have shown no significant benefit, with increased fluid retention and worsening symptomatology in treatment groups.[21] A randomized, placebo-controlled trial of epoprostenol in adults with heart failure was stopped prematurely due to increased mortality observed in the treatment arm.[22] Based on existing evidence, the use of pulmonary vasodilators in group II PH is not currently recommended for adult or pediatric patients.[11] Patients with Cpc-PH and a PVRi elevated out of proportion to their left-sided obstructive disease present a challenge to pediatric practitioners, and currently, no consensus practice exists regarding the use of pulmonary vasodilators in these patients. Most pediatric pulmonary hypertension specialists may choose to use small doses of pulmonary vasodilators very carefully, along with diuretics, in patients with evidence of Cpc-PH on cardiac catheterization and clinical evidence of response to some pulmonary vasodilation.[6] When utilized, vasodilator therapy is initiated cautiously, often with a phosphodiesterase-5 inhibitor and less commonly with an endothelin receptor antagonist. Due to the risk of pulmonary edema and evidence of harm from adult trials, prostaglandin-based therapies are not used in group II PH.

Other Medical Therapies

Medical therapy in children with group II PH should focus on minimizing pulmonary vascular congestion and promoting flow into and out of the left heart to minimize the hydrostatic pressure on the post–alveolar-capillary venous system. Diuretic therapy can help relieve pulmonary vascular congestion in group II PH, improving symptoms and slowing progression to precapillary PH. Rate control with either a beta blocker or digoxin can encourage diastolic filling time, decompressing the LA in the setting of LAVV stenosis or LV diastolic dysfunction with LV afterload reduction. LV dysfunction can also be medically treated with digoxin, angiotensin-converting enzyme (ACE) inhibitors, and diuretics, including spironolactone, and in cases of severe dysfunction, intravenous inotropes may be needed.[22]

PULMONARY VEIN STENOSIS

PVS is an emerging cause of both left-sided obstructive disease and PH with increased survival of infants born extremely preterm.[23] PVS can be either primary, affecting normally draining pulmonary veins, or secondary to anomalous pulmonary venous return that has been surgically repaired, with stenosis at the anastomosis site or in the distal veins. The underlying pathobiology of primary PVS is poorly understood and is likely multifactorial with known associations with prematurity and comorbid conditions, including bronchopulmonary dysplasia and necrotizing enterocolitis.[23,24]

Primary PVS is a heterogeneous disease characterized by neointimal proliferation at the area of stenosis. Disease can range from discrete stenosis at the venoatrial junction to diffuse hypoplasia of the extrapulmonary pulmonary

veins. PVS can involve one or more pulmonary veins and is often progressive, needing recurrent interventions, with high morbidity and mortality rates.[23–25] Due to its progressive nature, early identification using echocardiography is key. Computed tomography (CT) can be used to further evaluate the extent and location of vein stenosis or evidence of obliteration or atresia. Noninvasive imaging can underestimate pressure gradients, and cardiac catheterization is the gold standard for diagnosis. Catheterization can identify stenoses with angiography, directly measure pressure gradients, and allow for balloon angioplasty with or without stent placement.

Medications, including the mTOR inhibitor sirolimus, have been shown to slow the progression of the disease as well as improve rates of in-stent stenosis and neointimal proliferation.[26] Current surgical approaches for repair, including the so-called "sutureless repair," have led to improvements in rates of restenosis and mortality.[25] Current management strategies with frequent surveillance catheterizations and interventions every 6 to 8 weeks have improved long-term outcomes; however, mortality rates 5 years from diagnosis remain as high as 40%.[27]

COR TRIATRIATUM SINISTER

Cor triatriatum sinister is a rare congenital anomaly whereby an accessory membrane separates the LA into two chambers: a posterior chamber that receives blood flow from the pulmonary veins and an anterior chamber that drains across the LAVV into the LV. Restriction across this membrane prevents effective inflow into the LA and, if not addressed, can progress to group II PH. In severe cases, presentation can be early; however, in some cases, symptomatology can be vague, and diagnosis can be delayed well into adulthood.[28] Echocardiography is used to accurately make the diagnosis, and definitive treatment involves surgical resection of the intra-atrial membrane and is associated with favorable long-term outcomes with low rates of restenosis.

LEFT ATRIOVENTRICULAR VALVE OR MITRAL STENOSIS

Stenosis of the LAVV can occur in isolation or in combination with additional left-sided obstructive lesions, such as in Shone complex. LAVV stenosis can either be congenital or occur following repair of the LAVV.[29] These patients can develop group II PH with symptoms of pulmonary vascular congestion, hypoxia, or even syncope. Postrepair, there can be persistent PH, and overzealous vasodilator therapy may result in pulmonary vascular congestion and pulmonary edema.[30] Echocardiography can estimate mean pressure gradients across the LAVV, which can be further delineated by cardiac catheterization. Surgical repair by either valvuloplasty or valve replacement can have an effective result in lowering mPA pressure, with favorable outcomes.[31]

SHONE COMPLEX

Shone complex is a constellation of left-sided obstructive lesions, including LAVV stenosis with a supramitral ring, parachute LAVV, subaortic or aortic valve stenosis, and CoA. The extent and location of obstruction can be variable, and the degree of LAVV stenosis is one of the primary predictors of disease prognosis.[9] Compared to isolated congenital LAVV stenosis, the concomitant LV outflow tract obstruction seen in Shone complex, combined with a potentially hypoplastic or noncompliant LV, further exacerbates left-sided disease and increases the risk of group II PH. Additional reoperations and reinterventions also carry a risk of worsening diastolic dysfunction on what can often already be a dysfunctional LV. PH in Shone complex is a risk factor for reintervention and worsened outcomes.[32]

Repair is typically staged, with repairs of the aortic arch occurring earlier in infancy and delaying intervention on the LAVV until the patient reaches a favorable size for LAVV intervention. Close surveillance is needed to identify recurrent or worsening obstructive lesions and the development of atrial arrhythmias.

LEFT VENTRICULAR SYSTOLIC AND DIASTOLIC DYSFUNCTION

LV dysfunction is the most common form of PH in adults and is becoming an increasingly recognized cause in pediatric patients.[3] LV dysfunction can be either systolic, diastolic, or a combination of the two. It can be secondary to dilated or restrictive cardiomyopathy or myocarditis, or it can occur following surgical repair of congenital heart disease.[2,3]

Echocardiography should be used for both qualitative and quantitative assessments of LV function. Careful assessment for reversible causes of LV dysfunction, such as coronary anomalies, should be performed. LV diastolic dysfunction leading to PH should be further evaluated using cardiac catheterization prior to therapy.[12,16] Catheterization allows for measurements of the PCWP and LV end-diastolic pressure and direct measurements of the cardiac index and PVRi. In patients with severe dysfunction requiring heart transplantation, a lowered PVRi following acute vasodilator testing can inform transplant candidacy and prognosis.[33]

Treatment of group II PH and LV dysfunction with pulmonary vasodilators has been studied in both animal models and adult clinical trials, but data are limited for pediatric patients. Sildenafil can promote LV remodeling in heart failure as well as improvements in LV systolic and diastolic performance.[34] Sildenafil has been associated with improvements in echocardiographic indices of PH in adults with LV dysfunction and is largely tolerated in pediatric patients when administered with careful, in-hospital titration.[35] Despite these findings, clinical trials show conflicting results for sildenafil with respect to its impact on clinical status, quality of life, or symptomatology.[18–20] The guanylate cyclase stimulator riociguat has also demonstrated improved hemodynamics in heart failure, without any difference in clinical symptoms.[36] Given the conflicting evidence and potential for harm, current guidelines recommend against the use of pulmonary vasodilator therapy in group II PH from LV dysfunction, and any use in pediatric populations is

considered off-label.[11] In patients with severe LV dysfunction, ventricular assist devices have been utilized to decompress the left heart, either as a bridge to heart transplantation or as destination therapy.[37]

AORTIC STENOSIS

AS is an uncommon cause of group II PH in children and is typically a late finding from decompensated heart failure. AS can be congenital, secondary to a bicuspid or even unicuspid aortic valve, or acquired secondary to rheumatic heart disease.[38] While clinically significant PH is uncommon, congenital AS is associated with remodeling and arterialization of the pulmonary venous vasculature, both in utero and in the early neonatal period.[3] This is likely due to changes in LV compliance in the setting of increased afterload, which can significantly improve following successful aortic valve intervention.[39] Balloon aortic valvuloplasty is often an initial transcatheter option for the treatment of congenital AS; however, in patients with more severe or long-standing disease, surgery with aortic valve repair or replacement is indicated.[38]

CONCLUSION

The management of group II PH can be extremely challenging due to the wide array of contributing left-sided lesions that lead to it. Management is directed toward correcting the left-sided lesions, treating volume overload with diuretics, and, in very select cases, targeted PH therapy. While the importance of reducing left-sided pressures and the underlying left-sided lesion is well known, an individualized approach is vital to appropriately manage each patient with group II PH.

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Nonpharmacological Management of Heart Failure

Traci Stewart, RN, MSN, CHFN
University of Iowa Hospitals and Clinics
Iowa City, IA

Self-care abilities in patients with heart failure (HF) are directly related to quality of life and outcomes such as hospitalizations and mortality. Patient education is essential in helping patients gain knowledge and skills to become successful in self-care. As the trajectory of the patient's course changes, the HF team members identify barriers, help the patient adapt, and work toward desired goals. Communication and shared decisions about prognosis, symptom management, and treatment options require the HF team to connect with patients and have difficult conversations that can be facilitated with palliative care consultations.

INTRODUCTION

Pulmonary hypertension (PH) associated with left heart disease is the most common cause of PH.[1] PH is a parameter of increased risk and disease progression in patients with heart failure (HF) with reduced and preserved ejection fraction, left-sided valvular, and congenital heart diseases leading to postcapillary PH.[2] HF guideline-directed medical therapy (GDMT) is often the topic of focus; however, nonpharmacological management of HF including attention to self-care, adherence, diet, exercise, and supportive care are complementary components to pharmacological management. The HF multidisciplinary team educates patients on disease process, medication purpose and side effects, and self-care through the continuum of care. Self-care skills in patients with HF are commonly thought of as acts of monitoring of symptoms, weight, diet, and activity. Poor adherence to self-care can lead to hospitalizations and worsened outcomes despite optimal medical management. Knowledge alone is not sufficient for patients to create long-term self-care strategies. Patients with HF require time and ongoing support to develop skills to overcome barriers to effective self-care.[3] Time constraints can make it difficult for health care providers (HCPs) to create conversations around effective ways to improve self-care. This is a review focused on helping nurse coordinators develop a collaboration with patients to develop self-care management strategies and will also explore tips for patient education and use palliative care to help with support of the patient and caregiver.

HF SPECIALIZED CARE

Patients should be referred to HF specialists for assistance with disease management and for consideration of advanced cardiac therapies. Triggers for referral include need for inotropes, advancing function classification, end organ dysfunction, persistent reduced ejection fraction, defibrillation shock, hospitalizations, refractory edema, low blood pressure, and down titration of GDMT (acronym I-NEED-HELP).[4] It is essential for the HF team to deliver accurate diagnosis and, through shared decision making, determine the best treatment options as the patient's course progresses. The multidisciplinary HF team supports patients to obtain and titrate medications and devices and monitor response to therapy. The HF team provides social and psychological support and resources, coordination of care for comorbidities, and offers supportive and palliative care. Education for the patient and caregiver is necessary throughout the entire continuum of care, including prognosis, disease state, treatment options, lifestyle changes, and self-care.

Educating HF Patients

The nurse coordinator's primary role includes educating patients about HF self-care. An effective teacher is engaged and keeps learners interested. When teaching, it is important to be optimistic, nonjudgmental, and apply the material to the patient's specific circumstances while managing time and resources. Assess the patient's readiness to learn and how the patient best receives information. To improve efficiency, consider what the patient already knows and what the patient needs to know without making any assumptions. Establish and set goals and identify what is immediately applicable for the initial information exchange.

It is important not to overteach and remember that most people can store 7 items in short-term memory (±2 items).[5] Storytelling can aid in remembering for the learner because it uses memories and experiences from long-term memory. Using medical terminology instead of plain language is a common mistake made by HCPs when teaching, so be selective with words.[6] Use vocabulary and examples that the learner will relate to from life experiences. Educational materials from Internet sources are often written at much higher readability than the recommended fifth- to sixth-grade reading levels and can be a barrier to adherence; therefore, checking readability levels is necessary for handouts and tools provided to patients.[7]

Upon diagnosis, introduce topics of self-care during clinic visits or during inpatient admissions but not at time of discharge. Focus on topics that are most essential to prevent patients from

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Correspondence: traci-stewart@uiowa.edu
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becoming overwhelmed. Plan time for education when it is convenient for the patient, caregiver, and nurse.

Present topics with visual and written materials while verbally reviewing basic skills to allow visual and auditory learners to process knowledge. Ask patients to repeat back certain parts of the instructions to reinforce concepts for those who learn by doing tasks. Handouts with areas for notes and questions can be beneficial for those who remember by taking notes. Materials should be culturally appropriate and reviewed with family and caregivers when possible.[8] It is important to keep the initial information extremely basic while focusing on information necessary for the patient to start immediately after instruction.

Next steps of the education process should include adding more chunks of information and reinforcing information from earlier discussions. Explore how the patient is tracking or applying information to a daily routine during follow-up telemonitoring, medication titration, or blood work reminder phone checks. Quiz patients about daily habits during follow-up appointments and phone calls to identify barriers and identity misunderstandings or forgotten information. It is important to keep information simple and reinforce often.

Create handouts, resource lists, and tip sheets for patients to use and refer to later. It will improve efficiency for the HF team to have checklists and resources to ensure that essential messages are completed and documented for each patient. Guidelines and disease-specific organizations have tip sheets that can be modified for telemonitoring and patient education materials to include nonpharmacological management and self-care skills. (Table 1).[9]

SELF-CARE CONCEPTS IN HF

Self-care is the foundation of maintaining health and preventing and managing chronic illness.[11] In patients with HF, patients with better self-care have higher quality-of-life scores and lower mortality and readmissions than patients with poor self-care practices.[12] Three concepts of self-care described by Riegel and Dickson[13] include self-care maintenance, symptom perception (monitoring), and self-care management. Self-care maintenance is achieved when patients can consistently log daily weights and keep intake of fluid and sodium levels at recommended levels. Patients recognize the importance of taking medications as prescribed and avoid gaps in treatments. Patients have an exercise regimen and advance activity safely. It can be summarized as treatment adherence and involves the patient, caregivers, and HCPs. Symptom monitoring or symptom perception is the next skill in self-care, where patients recognize changes, then label change, and make note of the change in condition. Finally, self-care management involves action or a response to the identified concern. This could include contacting HCPs for guidance or adjusting diuretics if authorized to take diuretics as needed.

HF readmissions are common and often preventable; therefore, initiatives to prevent readmission include education on medication management as part of self-management skills, focusing on purpose, changes in doses/frequency, and which to start and stop as part of self-care education topics. Medication nonadherence should be assessed during phone calls and during clinic visits to identify potential deviations from prescribed regimens. Deviations may include not refilling, doubling up doses, skipping doses, incorrect intervals, interrupting therapy, or borrowing someone else's medications and may give clues into deterioration in symptoms or unusual side effects.[14]

BARRIERS TO SELF-CARE

Nurse coordinators have opportunities to impact self-care as a patient's course changes to continually help learn new skills and adapt.[15] Understanding barriers to self-care is an important way to identify if resources are needed or skill review is necessary. Barriers can be complex medical or social issues and may require additional resources such as home health nursing, social services, community agencies, and consultations to other services to manage underlying comorbidities.[16] Adherence to self-care can be limited by a patient's perceived lack of effect, poor health literacy, physical impairments, depression, and cognition. Behavior change is necessary to perform self-care and may be limited by an attachment to the unhealthy behavior, lack of motivation to change, difficulty deciding when to start the healthy behavior, and difficulty in maintaining the healthy behavior over time.[17] Illness-related barriers to self-care include difficulty integrating self-care across other comorbid conditions, not responding promptly to symptoms, and life events that interfere with healthy behaviors. These barriers make it difficult to start and maintain momentum of behaviors that lead to lifestyle changes.

As a patient's condition progresses and medical regimen increases in complexity, it can be more difficult to expend energy to maintain self-care behaviors. Increasing frequency of telemonitoring and implantable monitors can assist HCPs monitor patients more closely by remote capabilities.[18] Desai and Stevenson[19] describe an intense integrated home management regimen involving a multidisciplinary HF team approach to monitor and direct education, social resources, and supportive care to prevent hospitalizations. Breakdowns in communication with patients and caregivers can be barriers to care such as being unable to leave messages, blocked calls, and unreturned missed calls and letters from the HF team. In addition, changes associated with caregiver support, expenses associated with medications, diet, and transportation can impact adherence.

PALLIATIVE CARE

Finally, palliative care is another essential component of nonpharmacological care for patients with chronic illness and a HF or PH care center. Risk assessment tools such as Seattle Heart Failure Model or PARADIGM Risk of Events and Death in the Contemporary Treatment of HF (PREDICT-HF) help support clinician judgment to estimate prognosis and help HCPs and patients engage in shared decision making.[20] Decisions for timing and types of advanced therapies should be reassessed often and with condition changes or HF hospitalizations.[21] Patients with HF have a high burden of symptoms, are frequently hospitalized, and often have poor prognostic awareness.[22] Palliative care has been shown to improve quality of life, anxiety, depression, and spiritual wellbeing over usual care.[23]

Table 1. HF Self-Care Educational Resources[a]

HF self-care topic	Resources for patients	Resources for nurse coordinators
Concerning HF symptoms	• Symptom tracker (green, yellow, red), HF team contact numbers, follow-up appointments • Weight, vital signs log	• Telemanagement form • Developing skills of gathering history and physical by phone • Remote monitoring devices
Daily weights	• Scale • Step by step instructions • Log sheet or weight tracking app	• Telemanagement form • Remote monitoring devices
Diet goals: Weight management Cardiac cachexia Sodium/fluid intake	• Weight loss tips • Tips for calorie dense foods, eating small meals more often, supplements • Sodium handout • Fluid and thirst tip tool • Dining-out guide • Dietitian consultation	• Lists of diet resources • Sodium handout • Fluid and thirst tip tool • Potassium food lists
Exercise and activity	• Activity tracker, wearables pedometer • Intimacy guide • Cardiac or pulmonary rehabilitation consultation	• Safe exercise handout • Intimacy guide • Wearables/device monitoring
Medications	• Current medication list • Recognizing and calling with side effects • Pill box, pill packs • Alarms, app reminders • Copay cards, coupons, grants	• Treatments for anticipated side effects • Safe over-the-counter medication list • Med titration tip sheet: slower titration or spacing out 2 vasodilating meds to help get to GDMT • Pair follow-up labs with teaching topics
Mental health: Coping Anxiety Depression	• Conserving energy tips • Anxiety app, exercise, yoga • Counseling • Support group meetings • Medication treatments	• Depression screening tool (PHQ-9) • Support group information
Sleep	• Reporting symptoms related to HF (orthopnea, paroxysmal nocturnal dyspnea) • Sleep tracker/relaxation app • Sleep hygiene tip sheet	• Screening tool for sleep apnea (Epworth sleepiness scale, STOP-Bang)
Substance avoidance	• Smoking/vaping cessation aids • Limiting alcohol • Counseling/substance abuse rehabilitation • Caution/avoidance list for herbal and over the counter medications	• Potassium food list • Referral sources for substance abuse counseling/rehabilitation • Suicide hotline info accessible • Safe over-the-counter medication list
Travel	• Travel tip sheet • Sodium handout • Dining-out guide • Airline oxygen form	• Travel letters templates for security • Find a HF treating center at destination
Vaccinations and wellness	• Instruction to get respiratory vaccines as indicated • Handwashing tips to avoid illness • Dental consultation	• Vaccine documentation • Safe over-the-counter medication list
Supportive care	• Advanced directives handouts/forms • Medical durable power of attorney document • Living will document • Physician orders for scope of treatment document • Palliative care consultation • Hospice referral	• Kansas City Cardiomyopathy Questionnaire • Risk assessment tools • REMAP stepwise approach to goals of care discussion[10] • Goals of care documentation form • NURSE acronym for dealing with strong emotions[10] • Serious illness conversation guide • Physician orders for scope of treatment form

Abbreviations: GDMT, guideline-directed medical therapy; HF, heart failure; STOP-Bang, Snore, Tired, Observed, Pressure, Body mass index, Age, Neck size, Gender; REMAP, REframe, Map, Align, Plan; NURSE, Naming, Understanding, Respecting, Supporting, Exploring.

[a]Create materials for patients or use existing materials from HF guidelines, organizations, or colleagues. Explore more at: American Association of Heart Failure Nurses-Patient Education, Heart Failure Society of America-Patient Education, American Heart Association-Get with the Guidelines, Pulmonary Hypertension Association-Patients, Living with PH.

Since the trajectory of each patient is different, timing of a formal referral to palliative care should be early and increase in frequency of interactions as disease progresses. Common triggers for referral include worsening symptoms, functional decline, hospitalization, increase in diuretic, hypotension, or decline in renal function. Areas of management include physical and psychological symptom management, goals of care in complex medical decisions, advanced care planning, and caregiving support.[24] HF team members become skilled at discussing symptom burden and disease progression; however, goals of care and advanced care planning are less likely to be discussed.[25] Often, patients want HCPs to initiate discussions about disease progression, but HCP are reluctant to initiate discussions due to concerns of causing patient anxiety.[26] A discrepancy in approaching sensitive topics can make a palliative care consultation appreciated by patients and HCPs. Primary palliative care may be best initiated by providers with established relationships with patients to identify values, goals, and preferred treatments. Palliative care specialists have expertise in more difficult conversations can collaborate with the HF team, patient, and family for more challenging needs and discussions. Palliative care tools such as the serious illness conversation guide and practice by role play sessions have been shown to improve effective communication.[27] The benefits of palliative care early in the patient's course can improve quality of life and prevent suffering.[16]

CONCLUSION

The nonpharmacological aspects of HF management are the focus of HF nurse coordinators. Working with patients to educate, set goals, change behaviors, identify barriers, and achieve self-management is a continual process. Along with the HF team and palliative care clinicians, nurses serve as a direct link between the patient's treatment plan and outcome.

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REGULAR ARTICLE

Effects of Face-to-Face Nursing Support on Optimal Adherence to Oral Titratable PAH Therapies

Evangelia Sourounis, PharmD
CVS Health, Northbrook, IL

Pavlo Kyrychenko, MD, PhD
CVS Health, Northbrook, IL

Elisea Avalos-Reyes, PhD
CVS Health, Northbrook, IL

Denise Bagford, BSN, RN, CRNI
CVS Health, Northbrook, IL

Rashmi Grover, PharmD
CVS Health, Northbrook, IL

Lucia Feczko, RPh
CVS Health, Northbrook, IL

Kjel Johnson, PharmD
CVS Health, Northbrook, IL

Background: Therapies currently available to pulmonary arterial hypertension (PAH) patients do not reverse the disease; however, they improve pulmonary hemodynamics, offer symptomatic relief, and lengthen the time to clinical worsening. These therapies do not come without their challenges, which include side effects and compliance with challenging titration regimens. Health care providers, particularly nurses, play a significant role in improving patient medication adherence. In-home nurse visits offer disease state education, set medication expectations, and provide support tools for patients when experiencing adverse events that may lead to therapy discontinuation. The purpose of this study is to determine the impact that in-home, face-to-face nursing visits have on optimal adherence to oral PAH therapies.

Methods: We identified patients who received an oral PAH drug (riociguat, selexipag, or treprostinil) supported by a nursing program (study group) and patients who received an oral PAH drug (bosentan, ambrisentan, or macitentan) not supported by a nursing program (control group) using CVS Health pharmacy data from January 1, 2018, to June 30, 2019. A logistic regression model examined demographic and medication factors associated with adherence.

Results: From January 2018 to June 2019, we identified 107 patients in the study group and 213 patients in the control group. After 6 months, patients in the study group reported 0.6 more fill counts (5.1 vs 4.5; $P = .002$) and an 11% higher medication possession ratio (MPR) than those in the control group (86.4% vs 75.0%; $P = .001$). After adjusting for patient characteristics, control patients tended to be more likely to drop therapy in the first 6 months after the index fill (hazard ratio = 1.52; $P = .064$). After 6 months, the study group reported higher rates of therapy persistence than the control group (72.0% vs 60.6%; $P < .05$).

Conclusions: Patients receiving oral PAH therapies (riociguat, selexipag, or treprostinil) supported through a visiting nurse program had significantly higher rates of optimal adherence as demonstrated by a statistically significant improvement in the MPR and a higher prescription fill count than a control group. Ultimately, a multidisciplinary approach supporting the patient and providing patient education, proper motivation, and face-to-face nursing may support improved patient outcomes.

BACKGROUND

Pulmonary hypertension (PH) is a progressive disease characterized by elevated pulmonary vascular resistance. Pulmonary arterial hypertension (PAH), defined as a mean pulmonary arterial pressure of ≥20 mm Hg at rest, is a subset of PH that results from increased vascular resistance in the pulmonary arteries and may ultimately result in right heart failure.[1–7] Over the past 25 years, the number and routes of PAH therapies have increased. Current PAH therapies are available via intravenous, subcutaneous, inhaled, and oral routes.[6] Five classes of drugs (phosphodiesterase type 5 inhibitors, guanylate cyclase stimulators, endothelin receptor antagonists [ERAs], prostacyclin analogs, and selective prostacyclin receptor agonists) are Food and Drug Administration (FDA) approved for the treatment of PAH. These drugs target three main pathways: the nitric oxide, endothelin-1, and prostacyclin pathways.[1,6] While these PAH therapies do not reverse the disease, they do improve pulmonary

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Correspondence: Evangelia.Sourounis@cvshealth.com.

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hemodynamics, offer symptomatic relief, and lengthen the time to clinical worsening.[8] These therapies do not come without their challenges, which include side effects and adherence to challenging titration regimens.

Treatment failure for a patient may result from nonadherence to therapy.[9] The reasons for nonadherence are complex and may include several factors (age, gender, drug cost, disease severity, comorbidities, medication dosing frequency, side effects, lack of social support, and confusion between the patient and provider when communicating administration instructions).[10,11] For some patients, a lack of understanding of the disease contributes to nonadherence; thus, patient health literacy is essential to maintaining adherence.[11] For other patients, a lack of education, expectations around potential side effects, as well as the time to symptomatic improvement may also contribute to nonadherence. In a prospective study of systemic hypertensive patients, adding patient education to provider education was associated with improved blood pressure control compared to provider education alone.[12]

Health care providers, particularly pharmacists and nurses, play a significant role in improving patient medication adherence; they promote patient care by interacting with both the patient and the provider. Additionally, they are available to assist with patient counseling, disease state education, side effect management, and coordination of care.[13]

While evidence supports the use of an integrated nurse model for the management of specialty diseases,[14,15] few studies have assessed medication adherence rates among patients with PAH.[16] We hypothesize that in-home, face-to-face nursing visits provide additional patient support around education and side effect management, which leads to improved optimal adherence. The purpose of this study is to determine the impact that nursing visits have on optimal adherence to oral PAH therapies.

METHODS

We conducted a retrospective cohort study of patients with PAH throughout the United States who received one of six oral PAH drugs (treprostinil [Orenitram], selexipag [Uptravi], riociguat [Adempas], bosentan [Tracleer], ambrisentan [Letairis], and macitentan [Opsumit]) from January 1, 2018, to June 30, 2019. Specific inclusion criteria were (1) male and female patients greater than 18 years of age; (2) new to an oral PAH drug with at least 1 fill between January 1, 2018, and June 30, 2019, and no oral PAH fills 180 days before the index fill; (3) receiving one of the following drugs: treprostinil, selexipag, riociguat, bosentan, ambrisentan, or macitentan; and (4) continuously eligible for pharmacy benefits for the entire study period. We extracted claims from a large national specialty pharmacy for patients who met the inclusion criteria for 180 days after the index fill. The study was reviewed and approved by the Advarra Institutional Review Board as an exempt study under 45 CFR 46.104(d)(4).

Patients were divided into two groups: the study group consisted of those patients on drugs supported by an in-home, face-to-face nursing program (treprostinil, selexipag, and riociguat), and the control group consisted of patients on drugs not supported by such a nursing program (bosentan, ambrisentan, and macitentan). The nursing program may vary by therapy. At the start of care, the nurse meets the patient in their home for disease state education and therapy overview. The nurse walks through therapy-specific patient education materials, reviewing the titration schedules and how frequently the prescriber has ordered to increase their dose along with educating the patient on how to utilize their pharmacy-provided titration guide. While the nurse is in the patient's home, they are assessing the home environment. The field nurses provide updates back to the prescriber on the current dose and/or blood pressure, patient tolerance of the medication, and side effects experienced, if any. Patients are also trained on having an emergency plan and are provided an emergency contact binder and resources to help with any emergency room visits. Riociguat has an average of around 6 in-home visits, which align with the dose increase frequency (every 2 to 4 weeks) and run through the end of the titration schedule and one additional follow-up visit at month 12 of therapy. For selexipag and oral treprostinil, there is again an initial visit at the start of therapy. The number of selexipag nursing visits is tied to the dose increase schedule. Patients on oral treprostinil had an average of 5 to 6 nurse visits.

Patient feedback from the individual nursing visits is then shared with the specialty pharmacy PAH team and the PAH provider. The specialty pharmacy team communicates closely with the nurses who support PAH patients, making the experience seamless for the patient as relevant health information is shared among the specialty pharmacy nurses, the PAH provider, and the patient.

The following measures were compared by group:

- Standardized 30-day fill count—defined as the total number of days covered by medication divided by 30
- Medication possession ratio (MPR)—defined as the sum of the days' supply of medication divided by 180 (the number of days in the study period)
- First-fill drop-off rate—the percentage of patients with only 1 fill during the study period
- Therapy persistence—the length of time when the patient has medication on hand. If the patient had a 60-day or longer gap without medication after the previous fill was exhausted in each month, they would be considered dropped, and future fills were not taken into account

Descriptive statistics for continuous variables were expressed in the form of means and standard deviations (SDs). Categorical variables were expressed as percentages and numbers of cases. A logistic regression model was utilized to examine demographic and medication factors associated with adherence. A *P* value of .0445 was considered statistically significant. We performed all statistical analyses using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

Table 1. Demographic Characteristics by Group

Parameter	Study group N = 107	Control group N = 213	*P* value
Age, years, mean (SD)[a]	65.1 (15.1)	55.1 (21.1)	**.0001**
Male gender, N (%)[a]	49 (45.8)	57 (26.8)	**.0006**
Median income in the patient household area, mean (SD)	$52,061 ($24,577)	$52669 ($20,285)	.8141
College degrees in the patient household area, mean rate (SD)	15.8% (8.0%)	15.4% (7.4%)	.6120
African American, mean rate (SD)	18.7% (25.6%)	18.5% (24.9%)	.2749
Asian, mean rate (SD)	2.3% (3.4%)	4.3% (9.4%)	**.0331**

Abbreviation: SD indicates standard deviation.

[a]The final statistical model accounted for all differences between patient characteristics.

Table 2. Medication Characteristics by Group

Parameter at 6 months[a]	Study group N = 107	Control group N = 213	*P* value
Fill count	5.1	4.5	**.0016**
MPR	86.4%	75.0%	**.0013**
First-fill drop-off rate	2.7%	5.7%	.1438

Abbreviation: MPR indicates medication possession ratio.

[a]Controlled for patient characteristics through the regression model.

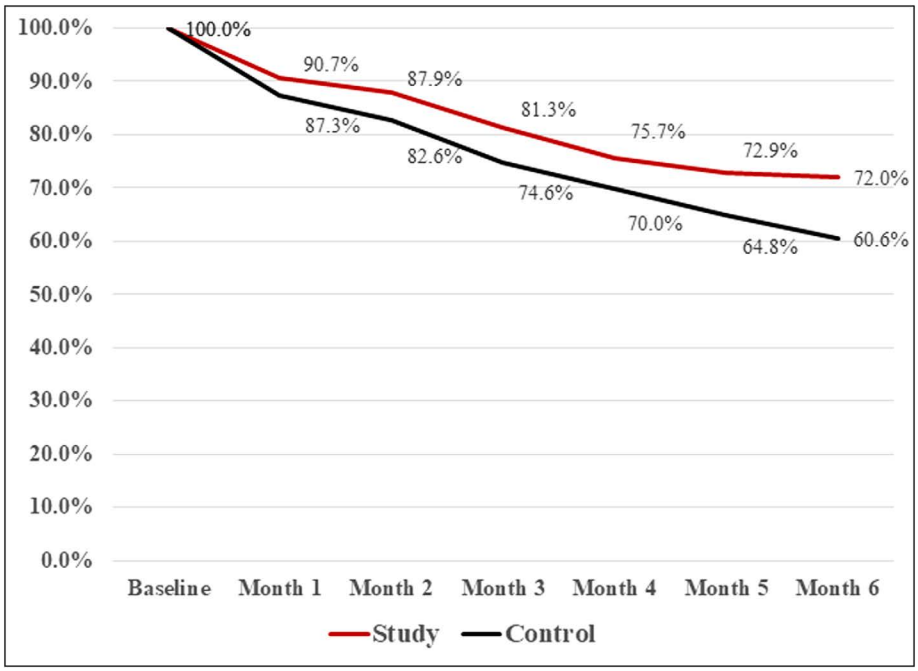

Figure 1: Six-month therapy persistence table by group.

RESULTS

From January 2018 to June 2019, we identified 107 patients in the study group and 213 patients in the control group. The average age of the study group was 65.1 years (SD = 15.1); the majority of patients were female (54.2%) and white (71%). The average age of the control group was 55.1 years (SD = 21.1); the majority of the patients were female (73.2%) and white (65.7%) (Table 1).

After 6 months, patients in the study group reported 0.6 more fill counts (5.1 vs 4.5; $P = .002$) and an 11.4% higher MPR than those in the control group (86.4% vs 75.0%; $P = .001$) (Table 2).

After adjusting for patient characteristics, control patients tended to be more likely to drop therapy in the first 6 months after the index fill (hazard ratio = 1.52; $P = 0.064$). After 6 months, the study group reported higher rates of therapy persistence than the control group (72.0% vs 60.6%; $P < .05$) (Figure).

DISCUSSION

This study evaluated the impact that in-home, face-to-face nursing visits have on optimal adherence to oral PAH therapies. Overall, patients in the study group achieved higher medication adherence and persistence over 6 months than the control group. Our adherence results are similar to those of Shah et al, who reported high adherence rates among patients receiving care in a specialty pharmacy with an integrated care model.[16] However, our study utilized the MPR to measure adherence, whereas Shah et al utilized the proportion of days covered.

The first contact that a patient has with a health care provider offers the patient an opportunity to talk and ask questions and allows the provider to understand the patient's individual needs in terms of disease state and therapy-specific information. Too much information may be overwhelming,[17] and patients may vary in the degree to which they benefit from participation in patient education.[18] Providers must gauge what level of information is appropriate and how much information the patient can process and retain at different stages of their disease. Our nursing program was designed with these considerations and includes follow-up visits during the titration phase of therapy to reinforce side effect management and adherence. Additionally, we provide a patient assessment to gather insight into how the patient progresses with their current therapy. Each patient assessment is completed by a PAH-trained CVS Health nurse and is a comprehensive assessment that includes, but is not limited to, evaluating medication side effects, tolerability, and changes in activities of daily living. This assessment is used to help nurses better understand the needs of individual patients and stimulate discussions specific to each patient; this assessment is also shared with the patient's PAH provider.

This study is not without its limitations. First, we compared three different therapy classes, prostacyclin and soluble guanylate cyclase stimulators versus ERAs, which have different side effects and tolerability profiles and patients in different functional classes. The ideal study design would have compared patients on prostacyclin or riociguat therapies receiving and not receiving the nursing intervention; however, the patient sample was insufficient to power this study design. Second, this study used pharmacy claims without access to the medical claims; thus, we could not confirm the diagnosis of PAH via medical claims or chart records. Third, pharmacy refill records might not reflect actual consumption. In our study, the fill count was higher in the study group than in the control group. This finding may relate to adherence or may have been skewed given the more complicated titrated dosing of the therapies within study group, as compared the the ERA class. Fourth, we evaluated patients for only 6 months; the results from our study might not be generalizable to longer periods. Future studies should attempt to confirm the findings using a longer evaluation period. Additionally, other unknown confounders may exist, which could result in biased estimates. Due to the single-site, nonrandomized, retrospective design of this study, we can interpret the results only as associative rather than causative. The results of this study may not be generalizable to the general PAH population.

CONCLUSIONS

Patients receiving oral PAH therapies (riociguat, selexipag, or treprostinil) supported through a visiting nurse program had significantly higher rates of optimal adherence as demonstrated by a statistically significant improvement in the MPR and a higher prescription fill count than a control group. A multidisciplinary approach supporting the patient and providing patient education, proper motivation, and face-to-face nursing may support improved patient outcomes.

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