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New Invasive Technologies and Devices in Pulmonary Hypertension

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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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 Hypertensio*n 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.

It is a great pleasure to introduce the newest issue of *Advances in Pulmonary Hypertension* (PH). During these challenging times when clinicians are combatting the COVID-19 pandemic while keeping their own patients safe, we are grateful to the Guest Editor and authors for taking the time to submit this eloquent update on techniques we are using in the catheterization lab to diagnose and manage patients with PH.

I would like to congratulate Dr Richard A. Krasuski, our guest editor of this issue. Rich is a Professor of Medicine and Director of Adult Congenital Disease and Pulmonary Hypertension at Duke University. Throughout his career, Rich has been at the forefront of advancing techniques in the cath lab for patients with PH. He proposed the idea for this issue of updating our community on where we are now and we are going with "New Invasive Technologies" in the cath lab for PH and right heart dysfunction.

Dr Eric Bonno and colleagues have written an excellent and thorough discussion on right heart catheterization (RHC). In this first article, they educate us not only on invasive hemodynamics and waveform interpretation, but also on what is needed technically to perform the procedure. They also go into detail on specific studies performed during the RHC (ie, fluid challenge, cardiac output reading, vasodilator testing, exercise), pointing out important features that are required for accuracy.

Drs Julie Wacker and Maurice Beghetti do an excellent job discussing the complex topic of pulmonary arterial hypertension (PAH) and shunts. They first go through the pathophysiology and the etiologies of shunt physiology and then discuss multiple areas of management. This comprehensive article covers medical management as well as how to manage a shunt in the cath lab or the operating room and when each is recommended. They also discuss when a shunt may be created in the management of severe PAH (atrial septostomy or reversed Potts shunt).

Dr Takeshi Ogo scripted a complete review and update on balloon pulmonary angioplasty for chronic thromboembolic PH. He goes through the evolution, history, criteria, and the procedure itself. He also discusses some of the complicated issues of outcomes and its future.

We also have a thought-provoking roundtable with a group of experts deliberating the benefits and outcomes of new invasive techniques in PH. Dr Krasuski moderates this group that includes Drs Jamil Aboulhosn, Raymond Benza, and J. Eduardo Rame.

To round out the issue, in our Ask the Expert section, Drs Allison L. Tsao and Alexander Opotowsky review the role of devices (percutaneous or surgically implanted right ventricular assist devices) in patients with PAH. And in our PH Grand Rounds section, Dr Amy Goodrich-Harris and colleagues analyze a case of a giant pulmonary artery aneurysm and severe multi-factorial PH. This case brings up several issues that are elucidated with a literature review and teaching points.

We hope you enjoy and learn from this excellent reference on current and future tools for both the diagnosis as well as the management of PH and right heart failure.

And to everyone during this time—be safe and stay well.

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In 1956, the Nobel Prize in Physiology or Medicine was shared by three individuals who helped shape the field of invasive hemodynamics.[1] Werner Forssmann was a rebellious first-year medical student who in 1929 inserted a urinary catheter into his own antecubital vein and utilized radiography to document the event,[2] while Dickinson Richards and Andre Cournard started the first hemodynamics laboratory at Columbia University, where they perfected techniques of right heart pressure assessment, first in animals and then in humans in the 1930s and 40s.[3] These pioneers set the scene for David Dresdale, who in 1950 found elevated pulmonary pressures in the absence of left heart pathology in three patients with "primary pulmonary hypertension"[4] and later (in 1954) performed the first successful vasodilator challenge in this patient population.[5] Many advances in the fields of coronary, structural, and congenital heart intervention have since followed; and the modern-day catheterization laboratory is a potpourri of hemodynamics, advanced and integrated imaging, as well as novel interventional procedures. In the spirit of these tremendous innovations, we have devoted this issue of *Advances in Pulmonary Hypertension* to "New Invasive Technologies."

In the first article Dr Ryan Tedford and his colleagues walk us through the features of a standard hemodynamic assessment in a patient with pulmonary hypertension (PH). As noted, preparation is the key to successful data collection and appropriate interpretation. Diagnostic and prognostic information can be gleaned from simple measures, but provocations such as exercise, volume loading, and vasodilator administration can further ensure appropriate diagnosis and subsequent therapy. Drs Maurice Beghetti and Julie Wacker then

discuss shunt physiology and how it is altered by changes in the pulmonary vascular resistance. It is important to recognize that a procedure as simple as closure of a secundum atrial septal defect, now standardly performed under minimal conscious sedation and echo and fluoroscopic guidance, may have potential detrimental effects depending on the clinical scenario. In fact, for some patients with advanced degrees of PH, the opposite procedure (creation of such a shunt), either at the atrial level or further downstream, may have beneficial effects on maintaining cardiac output, albeit at the expense of systemic cyanosis. Dr Takeshi Ogo follows with a review of the current status of balloon pulmonary angioplasty (BPA) for inoperable chronic thromboembolic pulmonary hypertension. Adapting techniques first developed in congenital heart patients, BPA has demonstrated significant hemodynamic and clinical improvements with an acceptable clinical risk.[6]

A significant remaining challenge in the management of advanced PH is how to support the failing right ventricle. Drs Alexander Opotowsky and Allison Tsao review for us currently available devices and their inherent limitations.

Finally, our Roundtable discussion covers the newest technologies we now have available and how some of these advances are taking the hemodynamic laboratory outside of the confines of the catheterization suite. It is exciting to think of how far we have come over the last century, but also daunting to think of how much further we still need to go. I hope you all enjoy this issue as much as I have enjoyed putting it together.

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Modern Right Heart Catheterization: Beyond Simple Hemodynamics

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INTRODUCTION

In the latter part of the 20th century, Drs Jeremy Swan and William Ganz introduced the use of balloon-tipped, flow-directed catheters, and the modern era of right heart catheterization (RHC) began. It remains the "gold standard" for diagnosis and management of a wide spectrum of cardiopulmonary diseases, and accordingly, the techniques of the procedure have continued to evolve into the 21st century. This review will discuss the modern practice of RHC, including best practices in procedure technique, updated hemodynamic definitions of disease states, and recent developments in the interpretation of provocative maneuvers.

INDICATIONS FOR RHC

RHC may be performed to confirm a diagnosis of pulmonary hypertension (PH) when its presence has been suggested by noninvasive imaging or clinical suspicion. Hemodynamic evaluation is critical to properly phenotype PH patients, and this information is crucial before initiation of pulmonary vasodilator therapy. RHC is also standard in those being considered for advanced heart failure (HF) therapies. In the most recent mechanical support and cardiac transplant guidelines, RHC has a class 1 indication to include measurement of the pulmonary vascular resistance (PVR). Pre–heart transplant candidates should undergo RHC every 3 to 6 months, especially if reversible PH is present or HF symptoms are worsening.[1,2] This screening may be omitted in stable patients with a left ventricular assist device who had no evidence of PH before implant.[3]

The routine use of pulmonary artery (PA) catheter-guided therapy in patients admitted with HF and symptomatic congestion has failed to reduce hospital length of stay or mortality and may increase adverse events.[4] Therefore, RHC should only be performed in those whose hemodynamics are unclear. A commonly encountered clinical situation is that of worsening renal function while attempting diuresis, a situation in which knowing filling pressures and cardiac output (CO) can guide medical therapy or the need to initiate inotropic or mechanical support.

BEFORE YOU BEGIN

Preparation is the key to success. Even before entering the catheterization lab, the operator should have a suspicion of what will be found on the hemodynamic evaluation. Do the findings fit the clinical scenario? For example, if a 26-year-old woman without risk factors for left heart disease, normal left atrial (LA) size, a severely dilated right ventricle (RV) with D-shaped septum, and an estimated RV systolic pressure of 100 mm Hg is found to have a significantly elevated PA wedge pressure (PAWP), the measurement accuracy should be questioned (and confirmed). Issues with patient positioning, calibration, leveling, zeroing, and measurement technique can all contribute to these errors.

Whenever possible, RHC should be performed in stable, noncritical patients who are able to lay supine with their legs flat. Operators should have an unobstructed view of hemodynamic monitors, real-time electrocardiogram, and waveforms. Pressure measurements should be recorded during spontaneous breathing without breath-hold maneuvers, which can lead to inadvertent Valsalva and preload alteration. To avoid altered breathing patterns associated with sedation, use of topical and subcutaneous local anesthetics is favored over intravenous sedation. If premedication is required for particularly anxious patients, oral conscious sedation should be considered.

The pressure transducer should be zeroed to atmospheric pressure at the level of the LA. To help ascertain LA position using external landmarks, Kovacs et al. retrospectively compared commonly cited anatomic landmarks to computed tomography–derived biatrial

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levels. They found that the right atrium (RA) was one-third of the thoracic diameter posterior to the anterior thorax surface in 98.5% of patients. The LA was located in the midthorax level (halfway between the anterior sternum and the table surface, ie, midchest) in 97.4% of patients. Deviations from these points can significantly alter the number of patients classified as having PH and elevated LV pressure.[5] Therefore, it is advisable to use a measuring stick to accurately place the transducer at the midthoracic level as an estimation of the LA location.

In addition to inspecting the waveform to determine the current location of the catheter, operators should examine the pressure tracing quality, looking for signs of overdampening or underdampening (see Figures 1A and 1B). Overdampening can occur when air is introduced into the catheter or tubing and may result in the loss of a dicrotic notch in the PA tracing, a blunted RV end-diastolic inflection point, or reduction in the overall amplitude of the pressure tracing (Figure 1A) with concurrent decrease in measured systolic pressure and increase in diastolic pressure (therefore, the mean pressure is usually not affected).[6] This can be addressed by fastidiously flushing the catheter or tubing. Catheter ringing (underdampening; Figure 1B) may occur when the frequency of the transmitted waveform (heart rate) approximates the natural resonance frequency of the transducer system and falsely increases the amplitude of the resultant waveform. Similar to overdampening, mean pressure is usually not affected.[6] Ringing may be exacerbated by microbubbles in the system; therefore, flushing the system or the introduction of a denser fluid, such as blood or contrast, into the catheter to alter the resonant frequency of the system may reduce this artifact.[7] Reducing the length of tubing between the transducer and the fluid-filled catheter may also ameliorate catheter ringing. Pressure lines and transducers should always be inspected for bubbles, which should be removed via adequate flushing before beginning.

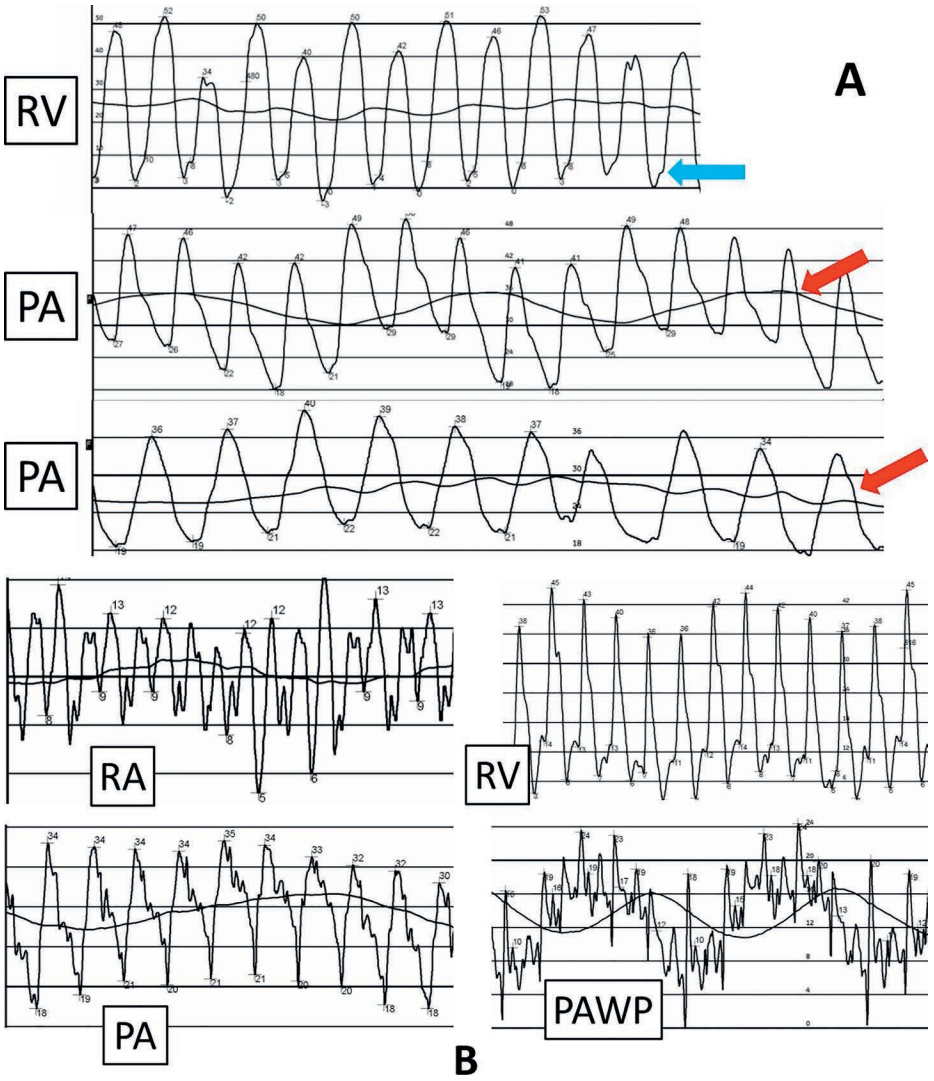

Figure 1: (**A**) Overdampening. Three separate examples are shown. Overdampening is usually caused by air in the catheter or tubing and may result in loss of the right ventricle (RV) inflection point at end diastole (blue arrow) and loss of the dicrotic notch in the downslope of the pulmonary artery (PA) tracing (red arrow). Overall waveform amplitude is reduced, with falsely low systolic and high diastolic measurements; however, mean pressure is usually not affected. (**B**) Underdampening. Contiguous tracings in a posttransplant patient with "catheter ringing," which occurs when the heart rate approaches natural resonance frequency of the transducer system. Sharp, jutting peaks and troughs are seen. The peaks are falsely elevated and troughs falsely lowered. Ringing can be addressed by flushing the system or introducing more dense fluid into the catheter to lower compliance. RA = right atrial; PAWP = pulmonary artery wedge pressure.

WHAT AND HOW TO MEASURE

Antecubital or internal jugular venous access under ultrasound guidance is generally preferred and associated with a better safety profile. Once the venous sheath has been placed, we recommend documenting an oxygen saturation from the high superior vena cava. This allows for an immediate assessment of perfusion status and, importantly, will be compared to the PA saturation to rule out left-to-right intracardiac shunting. A significant step up in oxygenation should prompt further investigation. With the balloon inflated, the PA catheter is then advanced into the RA. A typical RA pressure (RAP) tracing is shown in Figure 2A, consisting of a and v waves with x and y descents.

During RAP assessment, the presence or absence of the Kussmaul sign should be documented (Figure 2B). This paradoxical increase in pressure (or failure to fall) during inspiration is indicative of a noncompliant RV and can be seen in constrictive pericarditis and advanced

HF, including dilated, ischemic, or restrictive cardiomyopathies. In a single-center study, the Kussmaul sign was found in 43% of patients referred for transplantation and was associated with worse hemodynamics, echocardiographic parameters, higher natriuretic peptide levels, higher diuretic doses, lower sodium levels, and worse clinical outcomes.[8] The RAP tracing may show prominent y descents, in which the downward slope is more prominent than that of the x wave and the nadir usually deeper (Figure 2B). This suggests a less distensible RV from a variety of causes. Recent work by Harada et al. suggests that this finding, in combination with elevated RV systolic pressure, may predict worse outcomes in HF patients with preserved ejection fraction (HFpEF).[9]

A step up in systolic pressure occurs with advancement of the catheter into the RV (Figure 2C). Occasionally, a square root (or dip-and-plateau) sign may be present, which can be seen with severe tricuspid regurgitation, pericardial constriction, and restrictive physiology.[10] As the catheter passes the pulmonic valve and enters the PA, a step up in diastolic pressure and a characteristic dicrotic notch in the downslope of the PA tracing are seen (Figure 2D). Finally, when the catheter is advanced into the distal PA, pressure will fall as the catheter achieves a wedge position (Figures 2E and 2F). The PAWP tracing is achieved when a static column of blood is created between the occlusive balloon, the distal pulmonary arterial and venous vasculature, and the LA. The PAWP serves as a surrogate for LA pressure and—in the absence of mitral stenosis—LV end diastolic pressure (LVEDP).

Because of the diagnostic and therapeutic implications of the PAWP, it is of paramount importance to measure it in a standardized fashion with regard to the respiratory and cardiac cycle. In most situations, pressure measurements should be recorded at end expiration, when intrathoracic pressure closely approximates 0 and has the least impact on intracardiac pressures.[11] In some situations, particularly severe lung disease or morbid obesity, large respiratory pressure variation may be present, and intrathoracic pressure at end expiration may be higher than 0. Esophageal pressure–transducing balloon catheters can be used to estimate intrathoracic pressure, thus allowing for more exact determination of intracardiac pressures by subtracting the esophageal pressure.[12] As these instruments are not routinely available, reporting an average pressure over the respiratory cycle may be preferred.[13] We typically report both end expiratory and averaged values when significant respiratory variation is present. Additionally, Cheyne-Stokes breathing may be present in patients referred for RHC. Operators should be careful to measure all pressures during the same phase of the breath cycle (hyperpnea versus apnea).

Recent work has also highlighted the importance of standardization of PAWP measurement with regard to the cardiac cycle. At end diastole, the mitral valve is open, and thus LA pressure (and PAWP) should be equal to LVEDP. On the PAWP tracing, end diastole occurs just before the c-wave (mitral valve closure). Because the c-wave may be difficult to identify on a fluid-filled catheter tracing, the peak and trough of the a-wave is averaged and correlates with the pre–c-wave value (Figure 2E). This value is the best estimate of LVEDP. Because no a-wave exists when atrial fibrillation is present, end-diastolic PAWP is measured 130 to160 milliseconds after the onset of QRS and before the v-wave.[11,14,15] Mean PAWP, or PAWP averaged over the cardiac cycle, encompasses the pressure waveform during both systole and diastole. This may best represent the pressure "felt" by the pulmonary circulation from the left heart. Although in many instances mean PAWP approximates end-expiratory PAWP, the presence of large v-waves and atrial fibrillation lead to a mean PAWP greater than end-diastolic PAWP (Figure 2F). The use of mean PAWP rather than end-diastolic PAWP contributes to the phenomenon of "negative" diastolic pulmonary gradients.[16–18] The presence of large v-waves suggests a contribution of left heart disease (significant mitral regurgitation or stiff LA syndrome) regardless of the measured PAWP and should always be noted as part of the hemodynamic report. Frequently, large v-waves resolve during systemic vasodilator challenge.

Whenever a PAWP tracing is atypical or if a diagnosis of PH is being considered and measured PAWP is greater than 15 mm Hg, a PAWP saturation should be obtained to confirm complete occlusion and an accurate measurement.[11] An inadequately wedged balloon allows the transduction of higher pressure from the more proximal PA into the wedge tracing, falsely elevating it. It also allows leakage of deoxygenated blood into the static column distal to the balloon. To obtain a wedge saturation, slowly withdraw and waste a sample of blood from the distal port of the PA catheter with the balloon inflated in wedge position until the blood appears bright red, then withdraw another 1- to 2-mL sample for oxygen saturation measurement. A truly wedged catheter should yield an oxygen saturation reflective of the postcapillary pulmonary bed, typically >90% or within 5% of systemic oxygen saturation. Lower values should prompt repeat attempts to wedge or consideration of a direct LVEDP measurement.

CO MEASUREMENTS

The direct Fick method remains the "gold standard" for estimating CO. However, the technique requires specialized equipment to properly measure oxygen consumption, which is generally not feasible in most catheterization laboratories. Therefore, thermodilution (TD) and the indirect Fick method are more commonly used. The indirect Fick method uses estimated values for oxygen uptake originally derived from the TD method in patient populations that were highly selected, lean, and homogeneous with regards to age and race. Therefore, extrapolating oxygen consumption to a population of patients with HF, PH, or obesity is likely to induce error.[19]

When measuring TD CO, injection of saline should occur at the same point of the respiratory cycle.[20] Although TD is commonly cited to be less accurate in the setting of tricuspid regurgitation and extremes of CO, studies have shown good correlation with TD and Fick in these situations.[21,22] TD is the preferred method of measuring CO,[23] with one

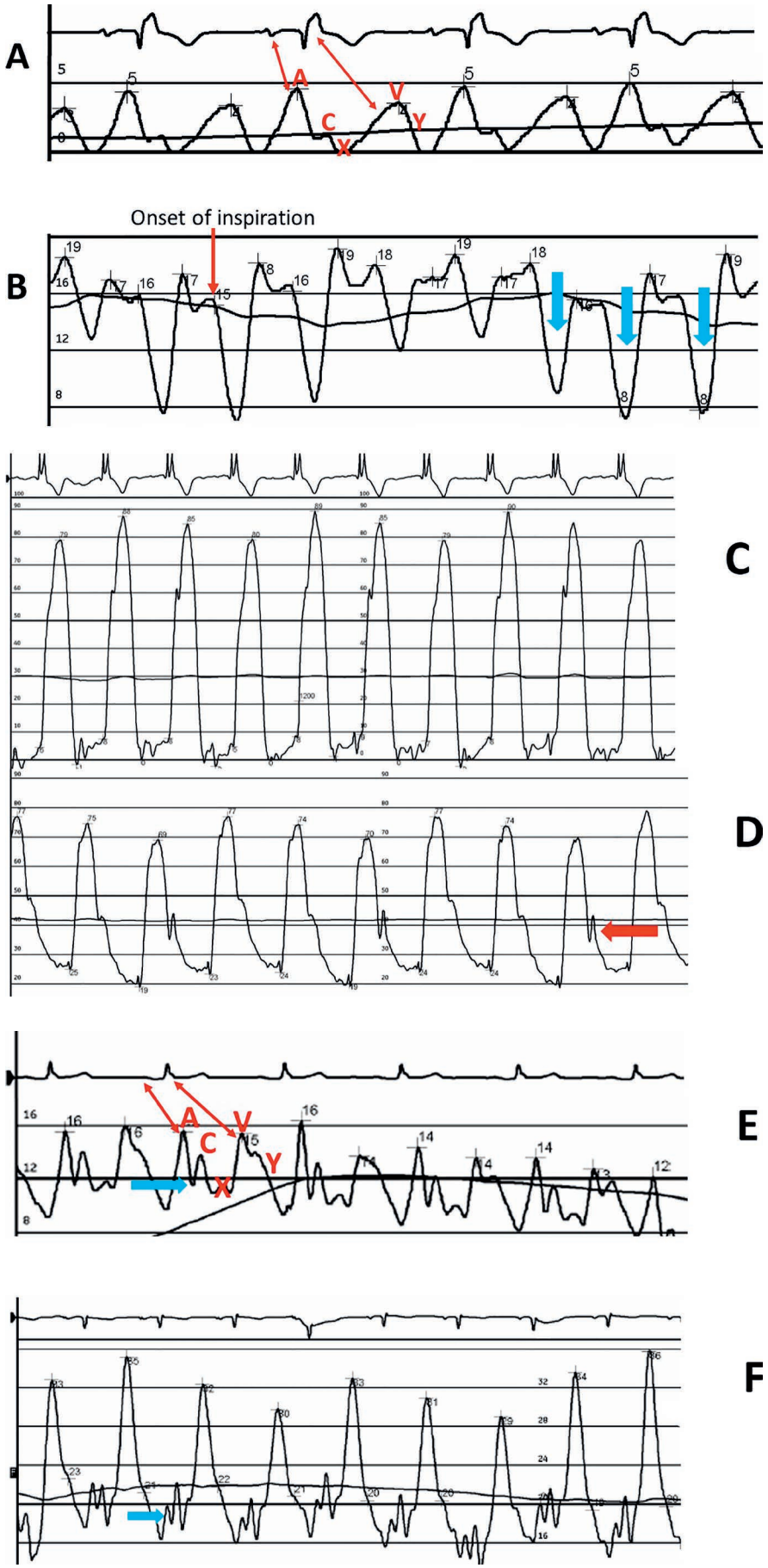

Figure 2: (**A**) Typical right atrial pressure (RAP) tracing. The a-wave represents a rise in atrial pressure due to atrial contraction and temporarily occurs after the P-wave on electrocardiogram. The c-wave represents closure of the tricuspid valve (akin to a dicrotic notch) and occurs in the downslope of the x-descent, which represents atrial relaxation. Therefore, the pre–c-point represents the end of ventricular diastolic filling, just before tricuspid valve closure. The v-wave is a rise in atrial pressure due to ventricular contraction and temporally occurs after the QRS complex on electrocardiogram. The y-descent represents ventricular relaxation. (**B**) RAP tracing with positive Kussmaul sign and steep y-descents. Kussmaul sign is a paradoxical increase (or a lack of decline) in overall RAP with inspiration (onset starting at red arrow). Steep y-descents are also seen (blue arrows) in which the downslope may be sharper and the nadir lower than the x-descent. (**C**) Typical right ventricle (RV) tracing. A ventricular waveform is now clearly seen, with step up in peak systolic pressure as compared to RAP. (**D**) Typical pulmonary artery (PA) tracing. Advancement of the PA catheter past the pulmonic valve is indicated by a step up in diastolic pressure as compared to the RV diastolic pressure and the appearance of a dicrotic notch in the downslope (red arrow). (**E**) End-diastolic PA wedge pressure (PAWP). Further advancement of the PA catheter into the wedge position will cause overall pressure to decline, and reappearance of a-x-v-y waves. The end-diastolic PAWP is the best surrogate for left ventricular end-diastolic pressure and occurs just before the c-wave (blue arrow). If the c-wave is absent or difficult to identify, an average of the peak and trough of the a-wave is a surrogate. In atrial fibrillation, no a-wave is present, so end-diastole is 130 to 160 milliseconds after the QRS complex and before the v-wave. (**F**) Mean PAWP. The mean PAWP is often computer generated (black line), represents an average pressure over the entire cardiac cycle, and can be thought of as the totality of pressure the pulmonary circulation "feels" from the left heart. Although end-diastolic and mean PAWP are often similar, in the presence of large v-waves or in atrial fibrillation, the mean PAWP may be higher than the end-diastolic PAWP (blue arrow). This has contributed to "negative diastolic pressure gradients."

caveat being the presence of an intracardiac shunt, in which TD should not be used. An analysis of over 15000 patients undergoing RHC showed a poor correlation between TD and indirect Fick methods, with one-third of the cohort differing by greater than 20%. Low cardiac index as measured by the TD method was superior in predicting 90-day mortality to the Fick method;

therefore, TD should be favored in clinical practice.[24] This was recently corroborated in a cohort of pulmonary arterial hypertension (PAH) patients in which the TD and indirect Fick indices (with oxygen consumption estimated by 3 different formulas) were compared against direct Fick indices. The TD method and indirect Fick using the Dehmer formula had high accuracy (but poor precision) as compared to direct Fick, whereas indirect Fick using the Bergstra or La-Farge-Miettinen methods overestimated and underestimated oxygen consumption, respectively. Also notable in this study was the lack of effect of tricuspid regurgitation, even when severe, on TD accuracy.[25]

APPLICATION OF HEMODYNAMICS TO CLINICAL DIAGNOSES

The current hemodynamic definition of PH is a mean PA pressure (mPAP) >20 mm Hg.[26] Additional hemodynamic classification is based on the PAWP, with >15 mm Hg considered consistent with Group 2 PH, or PH due to left heart disease (PH-LHD). PH-LHD encompasses a spectrum of widely varying pathologies and clinical diagnoses, including HF with reduced (HFrEF) or preserved ejection fraction (HFpEF), valvular disease, restrictive cardiomyopathy or constrictive pericarditis, and congenital or acquired cardiovascular conditions associated with left-to-right shunting.

PH-LHD can be further dichotomized into isolated postcapillary PH (IpcPH)—in which elevated PA pressure is a result of (and proportional to) the degree of chronic passive elevation of LV filling pressure—and combined postcapillary and precapillary PH (CpcPH), in which PA pressure is often higher than expected ("out of proportion") to the degree of LV filling pressure.

How to define the precapillary component remains debated. The Fifth World Symposium on Pulmonary Hypertension (WSPH) proposed that the diastolic pressure gradient (DPG) alone should differentiate these 2 entities (with DPG < 7 mm Hg in IpcPH and ≥7 mm Hg in CpcPH), but subsequent controversy over its prognostic ability and concerns related to measurement fidelity led to its abandonment in favor of PVR in the Sixth WSPH position statement. Thus, IpcPH is currently defined as PAWP > 15, mPAP > 20 mm Hg, and PVR < 3 Wood units (WU), and CpcPH is defined as PAWP > 15, mPAP > 20 mm Hg, and PVR ≥ 3 WU.[11] Because the use of PAH-specific therapies is not recommended in the CpcPH population, this differentiation is more relevant for risk stratification, assessment of candidacy for advanced HF therapies, and clinical trial enrollment rather than to specifically guide treatment.

Other hemodynamic parameters useful in risk stratification are shown in Table 1.

Table 1. Derived Hemodynamic Parameters[a]

Parameter	Equation
RV stroke work index (RVSWI) A measure of effective work done by the RV with each cardiac cycle	$\frac{(\text{mPAP} - \text{RAP})*\text{cardiac index}*0.0136}{\text{heart rate}}$
RAP/PAWP ratio A ratio of the filling pressures in the right heart compared to the left heart	$\frac{\text{RAP}}{\text{PAWP}}$
PA compliance	$\frac{\text{stroke volume}}{\text{PA systolic pressure} - \text{PA diastolic pressure}}$
PA elastance A measure of total RV afterload	$\frac{\text{PA or RV systolic pressure}}{\text{stroke volume}}$
PA pulsatility index (PAPi) A surrogate for RV's ability to generate stroke volume indexed to its filling pressure	$\frac{\text{PA systolic pressure} - \text{PA diastolic pressure}}{\text{RAP}}$
Total pulmonary resistance (TPR)	$\frac{\text{mPAP}}{\text{CO}}$
Pulmonary vascular resistance (PVR)	$\frac{\text{mPAP} - \text{PAWP}}{\text{CO}}$

[a]RV = right ventricle; mPAP = mean pulmonary artery pressure; RAP = right atrial pressure; PAWP = pulmonary artery wedge pressure; PA = pulmonary artery; CO = cardiac output.

PROVOCATIVE TESTING

In the early stages of cardiopulmonary disease, resting pressures may be normal, with abnormalities in hemodynamics only becoming apparent with provocation.[27] Diuretics may also lower LV filling pressures into the normal range despite the presence of LHD. This practice can make PH-LHD in the setting of HFpEF particularly difficult to differentiate from PAH. Therefore, saline loading or dynamic exercise can be important additional tools in the evaluation of undifferentiated dyspnea. These provocative maneuvers may unmask occult PH-LHD, differentiate PAH from HFpEF, or diagnose exercise PH (EPH). Vasodilator challenges can be performed to assess reactivity of the pulmonary vasculature in select patients with Group 1 PAH or Group 2 PH as part of cardiac transplant candidacy evaluation.

SALINE LOADING: WHAT CONSTITUTES AN ABNORMAL RESPONSE?

Patients undergoing RHC are in a fasting state, and many have undergone diuresis prior to the procedure. Therefore, resting PAWP can be normal even in the setting of LHD and perhaps lead to an erroneous diagnosis. In a cohort of 207 patients labeled as PAH, 22% were reclassified to occult PH-LHD when normal resting PAWP increased to >15 mm Hg after an infusion of 0.5 L of saline over 5 to 10 minutes.[28] However, one criticism of this study is that a rise in PAWP to >15 mm Hg with saline infusion can be seen even in healthy controls, as suggested by Fujimoto et al.[29] and Borlaug.[30] In their study of healthy young and older subjects, several increased PAWP to >15 mm Hg, but

none reached a PAWP >18 mm Hg after 500 cc of normal saline.

Data further confirming a cutpoint of 18 mm Hg as an abnormal response to saline loading come from D'Alto et al., who infused 7 mL/kg of saline (mean volume infused 478 mL, and 40% of the cohort received >500 mL) into a cohort of 212 patients referred for RHC. The authors found that 6% of those with baseline precapillary PH and 8% of those with no PH at baseline were relabeled as postcapillary (hidden) PH. Prediction bands derived from quadratic fits of the individual responses in no-PH and precapillary PH patients confirmed 18 mm Hg as an abnormal response to saline loading (see Figure 3).[31]

Finally, Andersen et al. recently explored the effects of both saline loading (150 mL/min to total 10 mL/kg) and exercise during the same procedure in a cohort of healthy and HFpEF patients. With saline loading, healthy controls had a baseline mean PAWP of 7 mm Hg and rose to a mean of 13 ± 6 mm Hg (ie, less than 19 mm Hg), while patients with known HFpEF had a baseline mean PAWP of 14 mm Hg which rose to 21 ± 4 mm Hg with saline.[27]

In summary, a PAWP > 18 mm Hg immediately after a 500-mL saline bolus over 5 minutes is likely abnormal and may be consistent with LHD.[11] Data are lacking about optimal treatment for these individuals, whom we are likely including in PAH clinical trials.

EXERCISE: HEMODYNAMIC INTERPRETATION

Exercise RHC is more challenging to perform and interpret than resting hemodynamic assessment. Large swings in intrathoracic pressure are common and end-expiratory pressure may be an overestimate.[13] Because of this, it is recommended to take the average pressure over several respiratory cycles (respiratory mean) during exercise maneuvers.[32] Exercise increases catheter ringing and motion artifacts, which are known to amplify the peaks and troughs of waveforms. Therefore, only the mean of the individual waveforms for RAP, mPAP, and PAWP are typically reported.

Exercise positioning is another important consideration. It may be performed supine, semi-upright, or upright. Many operators feel upright exercise reproduces symptoms more consistently. Exercise duration is longer and chronotropic response is more significant in the upright position compared with supine.[33] However, upright positioning may also be more difficult to perform, requires additional equipment and personnel, and may not always be feasible. Thus, it is important to understand the impact of positioning on hemodynamic data. At rest, an upright patient will have a lower mPAP, PAWP, stroke volume, and CO, and a higher heart rate, PVR, and arteriovenous oxygen difference as compared with a supine patient. With exercise, these positional differences diminish, and at maximal exercise, there are likely no major differences.[32] The PAWP increases linearly with CO in either supine or upright exercise,[34,35] although typically supine PAWP is ~5 mm Hg higher than upright.[11] During exercise a supine patient will have a slight reduction in PVR, thought to be due to the increased distensibility of pulmonary resistive vessels in zone 3 when fully recruited in supine position. PVR also declines in

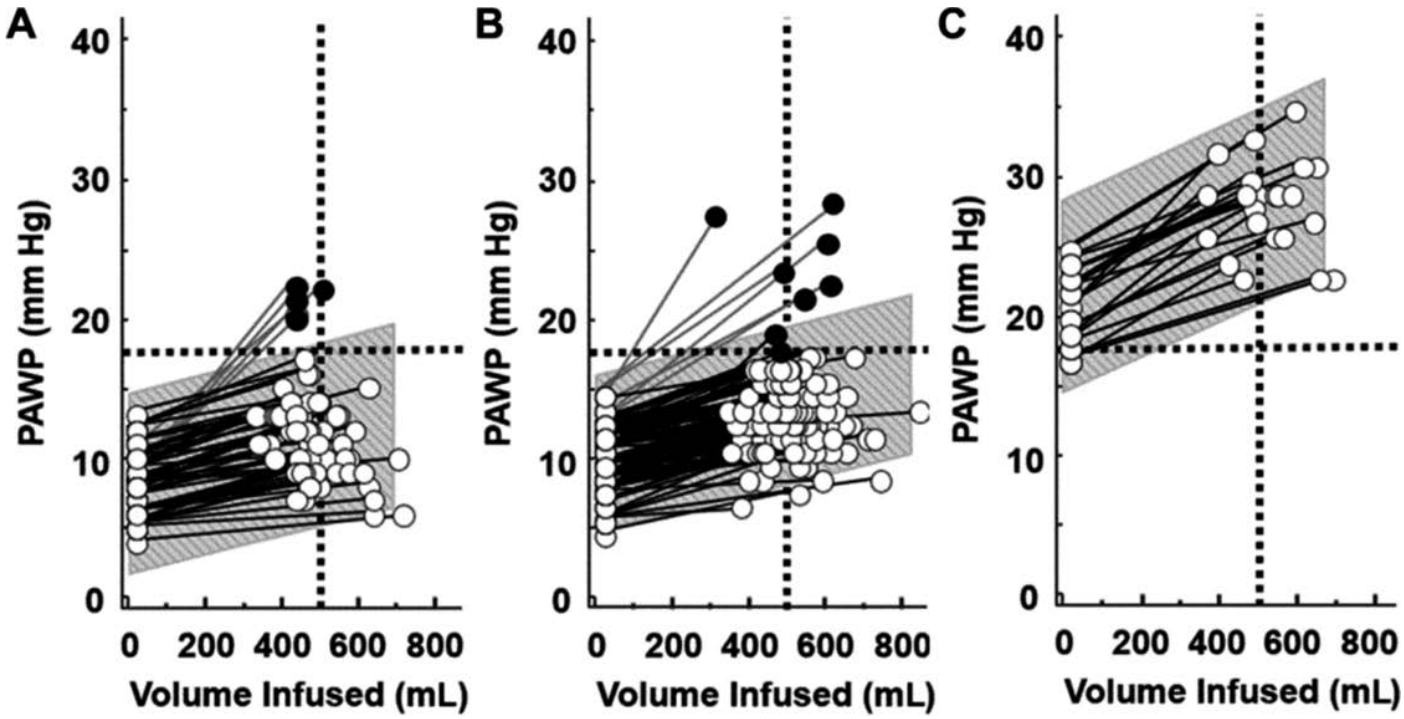

Figure 3: Pulmonary artery wedge pressure (PAWP) relative to saline infusion. Data from D'Alto et al.[31] showing increases in PAWP with 500 mL saline bolus in those with no baseline pulmonary hypertension (PH; left), baseline precapillary PH (middle), and baseline postcapillary PH (right). The shaded areas represent quadratic fits of the pooled responses and indicate that 18 mm Hg is a reasonable cut point for abnormal PAWP response to saline infusion. Black dots represent patients with hidden left heart disease, defined by PAWP > 18 mm Hg after fluid challenge. Used with permission.

upright exercise, but as the resting PVR is generally higher than supine, the decline in exercise PVR is more marked.[34]

The duration of exercise is also relevant. Older but otherwise healthy individuals may have delayed pulmonary vascular accommodation to exercise-induced increases in CO, as manifested by marked early increase in PA pressure and PAWP that may decline within several minutes of sustained exercise. In a cohort of healthy volunteers, Wright et al. saw that with light semi-upright exercise, the mean baseline PAWP of 11 mm Hg significantly increased to 22 mm Hg at 2 minutes but declined to 17 mm Hg by 7 minutes (still significantly higher than baseline). With continued exercise to a higher workload, the PAWP increased again to 20 mm Hg at 2 minutes and again declined to 15 mm Hg by 7 minutes. Therefore, even healthy patients may routinely exceed 20 mm Hg early in exercise, but decline within several minutes.[36] The most recent position statement from the European Respiratory Society (ERS) recognizes that, while 3 to 5 minutes per stage is ideal to achieve steady-state oxygen uptake, for practical purposes, a shorter interval of 2 minutes is reasonable, with an exercise duration goal of 10 minutes total.[32]

Oxygen consumption for Fick estimation of exercise CO must be directly measured and cannot be derived from standard formulas as is done with indirect Fick at rest. Given the rapidity of obtainment during an exercise protocol, the TD method is a reasonable alternative and should be collected. However, data from Hsu et al. suggest that, as CO increases, TD may significantly underestimate the CO obtained via the direct Fick method (9.0 L/min versus 11.3 L/min at peak exercise). The lower TD CO estimates subsequently led to significant overdiagnoses of EPH when applied to 2 newer criteria (described below).[37]

EXERCISE: WHAT CONSTITUTES AN ABNORMAL RESPONSE

The most recent ERS position statement does not identify a widely accepted hemodynamic definition of EPH.[32] A prior guideline threshold of mPAP > 30 mm Hg was abandoned at the Fourth WSPH, as it was realized that the pulmonary response to exercise depends on multiple variables, and no single value threshold would suffice to define pathology. This decision was influenced by a large meta-analysis of almost 1200 healthy patients showing the age dependency of mPAP during exercise: the upper limit of normal for those <50 years old was 29 mm Hg, but was 46 mm Hg for those >50 years old; almost 50% of healthy patients >50 years old achieved an mPAP > 30 mm Hg with exercise.[38]

Furthermore, pressure is a flow-dependent variable that may be elevated due to high CO in the absence of pathology. Therefore, more recently proposed criteria for EPH have focused on the pressure-output slope relationship. Naeije et al. suggested that the normal limits of total pulmonary resistance (TPR, mPAP/CO) are between 0.5 and 3.0 mm Hg·min·L^{-1} and that a multipoint slope of this relationship at progressive time points of >3 corresponds to a diagnosis of EPH.[35] Ho et al. recently showed reduced cardiovascular event-free survival among individuals with normal resting pressures, but who met this criteria during exercise.[39]

Herve et al. investigated a simpler approach in a cohort of 169 patients comprised of normal controls, those with known pulmonary vascular disease, and those with known LHD—but all with a resting mPAP ≤ 20 mm Hg. In the normal controls, the upper limits of exercise PAWP and mPAP were 19 and 37 mm Hg, respectively, and a quarter (26%) had mPAP > 30 mm Hg. The diagnostic accuracy of resting and exercise mPAP, PVR, and TPR was assessed. All resting hemodynamic parameters had low diagnostic specificity, but exercise TPR and mPAP had high diagnostic accuracy at optimal values of 2.97 WU and 31 mm Hg, respectively. As seen in Figure 4, using cutoff lines at these approximate values, the controls were clearly able to be discriminated from the 2 pathological groups. Finally, the authors noted that the combined criteria were met at low workloads (CO) in most patients, implying that,

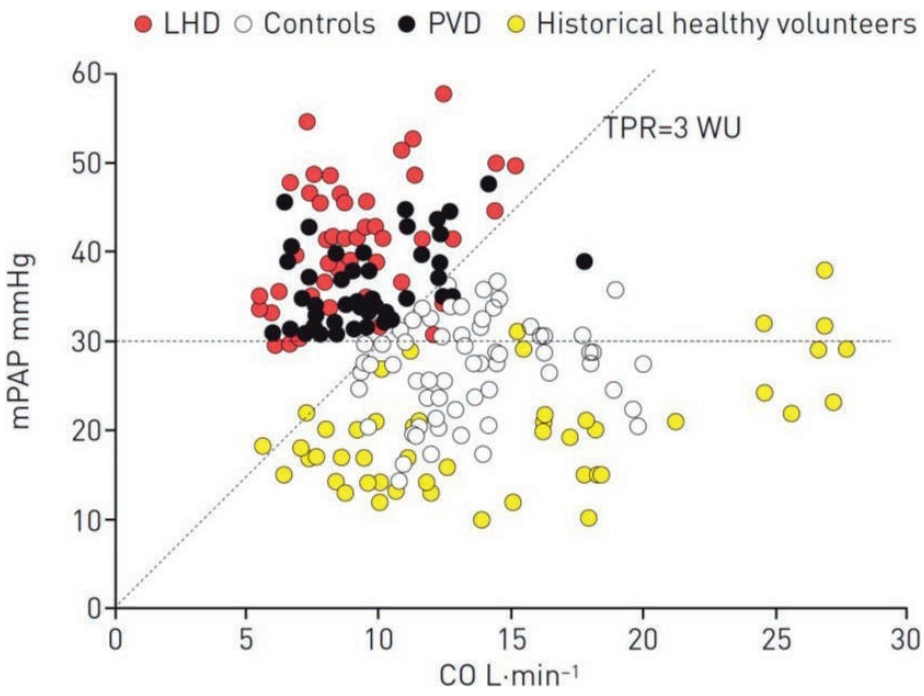

Figure 4: Relationship between exercise mean pulmonary artery pressure (mPAP) and cardiac output (CO). Data from Herve et al.[40] showing that the exercise response in known left heart disease (LHD) or pulmonary vascular disease (PVD) was accurately discriminated from controls and healthy volunteers using cutoff values of 30 mm Hg for mPAP (horizontal dashed line), 3 Woods units (WU) for total pulmonary resistance (TPR; mPAP/CO, sloped dashed line). This relationship implies that reaching an mPAP > 30 mm Hg at CO < 10 L/min is pathologically abnormal. Used with permission.

if an mPAP > 30 mm Hg is reached before 10 L/min is reached, the test can be terminated even at low workload, having already met the aforementioned criteria.[40] Most recently, 2 retrospective studies have suggested the Herve method (combination of mPAP > 30 mm Hg and TPR > 3 WU) is more sensitive than the mPAP-CO slope method.[41,42]

The criteria defining an abnormal PAWP response to exercise have been similarly debated. The ERS position statement suggests that a PAWP of 20 (upright) or 25 mm Hg (supine) may be considered the upper limit of normal, but also points out that evidence supporting these thresholds is scarce. Wolsk et al. showed that, in a cohort of healthy patients, no subject aged 20 to 39 years had PAWP > 25 mm Hg at peak exertion, but 30% of those aged 60 to 79 years exceeded this value.[43]

Similar to the above discussion with mPAP, the inadequacy of a single timepoint PAWP and the flow-dependency of the wedge pressure have also been recognized. In a cohort of 175 patients comprised of controls, HFpEF patients, and those with exertional dyspnea but normal PAWP and LVEF, Eisman et al. found that PAWP rose linearly with CO, with the lowest PAWP/CO slope in the control group and the highest in the HFpEF group (1.2 versus 3.6 mm $Hg \cdot min \cdot L^{-1}$). When a PAWP/CO slope of 2 mm $Hg \cdot min \cdot L^{-1}$ was defined as abnormal (2 standard deviations above the control mean), approximately 40% of the dyspneic patients with normal PAWP and normal LVEF were found to have abnormal PAWP/CO slope. More importantly, these patients were found to have a 3.4-fold higher risk for cardiovascular death, incident HF hospitalization, or subsequent RHC with PAWP ≥ 15 mm Hg.[44] In the aforementioned Wright et al. cohort of healthy patients, PAWP/CO slopes were <2 mm $Hg \cdot min \cdot L^{-1}$ with both sustained light and moderate exercise.[36]

OTHER EXERCISE CONSIDERATIONS

Oldham et al. described a cohort of 49 patients consisting primarily of young women with exertional intolerance, normal biventricular ejection fractions, no PH, and impaired oxygen consumption due to decreased CO in the face of low biventricular filling pressures during upright exercise testing. After infusion with normal saline, this cohort still had lower peak exercise RAP and PAWP compared with normal subjects, resulting in lower stroke volume augmentation and suggesting preload insufficiency as a cause of impaired exercise output. Almost 20% of the cohort had evidence of abnormal neuroendocrine testing (postural orthostatic tachycardia syndrome, adrenal insufficiency, autonomic neuropathy). The group termed this syndrome "preload insufficiency" and suggested that the diagnosis should be considered when maximal exercise RAP is <6.5 mm Hg, maximal PAWP is <12.5 mm Hg, or when the increase in RAP is <5.5 mm Hg or PAWP increase is <6.75 mm Hg, particularly when other causes of impaired output have not been identified.[45]

Operators should be aware that development of an RV outflow tract (OT) gradient may occur during exercise. In a cohort of almost 300 patients without congenital heart disease, Van Riel et al. described a mean RVOT gradient of 8.8 mm Hg at rest and 18.7 mm Hg with exercise. High gradients were more commonly found in younger males with higher peak oxygen consumptions. Subsequent work showed that a high RVOT gradient was not associated with HF but in fact the opposite: lower biventricular filling pressures, higher CO, and higher peak oxygen consumption. Given that these patients were referred for exertional symptoms, it is unclear at present whether development of an RVOT gradient with exercise can be a normal finding or is pathological.[46,47] This may also have important implications for using stress echocardiography as a diagnostic tool.

COMPARISON OF EXERCISE AND SALINE LOADING

Both saline loading and exercise increase venous return to the heart; however, saline loading has minimal effects on blood pressure and heart rate as compared with exercise testing[29] and thus theoretically isolates ventricular compliance as the sole variable being tested. Alternatively, exercise testing is more physiologic and induces other stresses on the heart, such as increased heart rate with shorter diastolic filling time and increased contractility with resultant increased myocardial wall stress and oxygen demand.[27] Exercise testing may be more sensitive than saline loading for the detection of occult LHD.[27]

While exercise testing may provide a more accurate reflection of exertional physiology, it requires more specialized equipment and expertise. Saline infusion is less technically difficult to perform, requires less preparation and specialized equipment, and is more widely available. As mentioned, exercise causes more dramatic respiratory variation and thus a higher likelihood of error in waveform interpretation. For these reasons, the Sixth WSPH has recommended that patients with intermediate to high pretest probability of PH-LHD and PAWP 13 to 15 mm Hg undergo a fluid challenge over exercise testing.[11]

VASODILATOR CHALLENGES

A vasoreactive challenge should be performed in individuals with idiopathic or anorexigen-associated PAH. This maneuver is typically performed with inhaled nitric oxide at 10 to 80 ppm. Other vasodilators may also be used, including intravenous epoprostenol or adenosine, or inhaled iloprost. A positive vasoreactive response is defined as a decrease in mPAP ≥ 10 mm Hg to an absolute value ≤40 mm Hg with unchanged or increased CO. It is not recommended in other forms of PAH, as a positive test is not associated with a long-term response to calcium channel monotherapy.[48] Conversely, the presence of vasoreactivity has been associated with improved survival in a cohort of PH patients regardless of etiology, and therefore, a vasoreactive challenge may be considered for prognostic purposes.[49]

Vasoreactivity testing is typically not indicated in PH-LHD, unless it is being performed in the context of heart transplantation evaluation. Heart transplant candidates with a PVR > 5 WU and transpulmonary gradient >15 mm Hg are at higher risk of early mortality.[50] However, if PVR can be reduced to <2.5 WU while maintaining a systol-

ic aortic pressure of 85 mm Hg, risk appears mitigated.[51] Nitroprusside is the most commonly used and has the added safety benefit of a short half-life. Inhaled nitric oxide may increase LA pressure and cause pulmonary edema.[52] Other agents like intravenous nitroglycerin, milrinone, intravenous prostacyclin, and prostaglandin E1 have also been used to test for reversibility. Although prior guidelines suggest testing only when PA systolic pressure is >50 mm Hg, a recent study by Crawford et al. found that elevated PVR in those with mPAP < 25 mm Hg had similar postoperative risk.[53] Therefore, we recommend testing in any candidate with PVR > 3 WU regardless of PA pressure.

CONCLUSIONS

Invasive hemodynamics are critical for diagnosis and treatment of cardiopulmonary disease. The modern era has seen substantial progress in the standardization of procedural techniques and waveform interpretation. Provocative maneuvers are increasingly being used to refine diagnosis and assess for early pathology.

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Shunts: When to Close Them and When to Create Them for Palliation

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Pulmonary hypertension, despite specific therapies, remains an incurable disease with a dreadful prognosis. A systemic-to-pulmonary shunt, if left unrepaired, can cause pulmonary arterial hypertension. With time, pulmonary vascular disease develops, and closure of the shunt becomes contraindicated. Operability criteria are not well defined and rely mainly on hemodynamic values that fail to predict long-term survival. Shunts can also be created in selected cases of advanced pulmonary hypertension, in view of off-loading the right ventricle and improving cardiac output at the cost of cyanosis. Shunt creation is not without risks and remains indicated only in selected severe cases.

INTRODUCTION

A shunt is an abnormal communication between the systemic and the pulmonary circulation, which are normally in series. Discussing shunts in pulmonary hypertension (PH) is both interesting and complicated, as the presence of a shunt can be a cause of PH, but the creation of a shunt represents a palliative procedure performed in a subset of idiopathic PH patients with severe disease. This antagonism makes more sense, however, when you consider timing.

Patients with a systemic-to-pulmonary shunt have increased pulmonary blood flow (PBF) and can develop pulmonary arterial hypertension (PAH) and increased pulmonary vascular resistance (PVR) over time. The definition of PH was updated in 2018 at the 6th World Symposium on Pulmonary Hypertension in Nice, and is a mean pulmonary artery pressure > 20 mm Hg assessed by a right heart catheterization.[1] PH secondary to systemic-to-pulmonary shunt is classified as PAH, Group 1 of the PH classification. In PAH, pulmonary wedge pressure is lower than 15 mm Hg and indexed pulmonary vascular resistance (PVRi) is elevated (> 3 Wood Units [WU] · m^2).[1]

Remembering the equation pulmonary pressure = PBF × PVR is very helpful to understand PAH. In patients with systemic-to-pulmonary shunts, the shear stress provoked by increased PBF damages the pulmonary vascular bed, resulting in endothelial dysfunction and remodeling of the pulmonary arteries. At the early stage of the disease, the increased pulmonary pressure usually reflects the increase in PBF previously described as "hyperkinetic PH." But progressively, pulmonary vascular disease also develops, and PVR increases. In Eisenmenger syndrome (ES), the most advanced form of PAH secondary to congenital heart disease, PVR exceeds systemic vascular resistance, leading to shunt reversal and cyanosis.[2]

Targeted therapies (phosphodiesterase-5 inhibitors, endothelin-receptor antagonists, and prostacyclin analogues) have improved the dreadful prognosis of most forms of PAH, including ES, but curative therapy remains elusive.

The guidelines are well established for the treatment of both ends of the spectrum of PAH secondary to a systemic-to-pulmonary shunt. When the PVR is low and increased pulmonary pressure is mainly due to increase in flow, there is no PAH by definition, and the shunt can safely be closed. When ES has developed, surgery is contraindicated and the patient should benefit from specific medical PAH therapies. The challenge remains in selecting candidates for shunt closure from among the patients with mild or moderate PVR elevation. Persisting PAH after shunt closure has a very poor prognosis, hence the importance of selecting candidates for surgery very carefully.[3,4] We will discuss management strategies for PAH secondary to systemic-to-pulmonary shunt, espe-

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cially operability criteria, in the section "When to Close a Shunt."

Observing that patients with ES have reported better survival than patients with idiopathic PAH, physicians have started to create shunts in severe idiopathic PAH to allow for right-to-left shunting.[5,6] The aim is to prolong survival, postpone lung transplant, or improve quality of life at the expense of systemic arterial desaturation. It is, however, important to note that most of the studies evaluating survival in ES do not take into account immortal time bias. Indeed, only patients surviving long enough to enter clinical follow-up at research institutions have been enrolled into these studies. Diller et al[7] nicely demonstrated that not dealing with this effect overestimates the survival prospects of ES patients. We will address the different types of palliative shunts, and the literature reporting outcomes of this strategy, in the section "When to Create a Shunt."

WHEN TO CLOSE A SHUNT

As overviewed in the introduction, outcomes of patients with congenital heart diseases and a systemic-to-pulmonary shunt, also called a left-to-right shunt, are of special interest in PH. The consequence of the shunt is increased PBF, creating shear stress in the endothelium of the pulmonary vascular bed, leading to thickened and stiff pulmonary arterioles through a cascade of events involving inflammation and remodeling. The PVR progressively increases and leads to PAH.

The velocity of those changes depends on many variables, most of which are not well understood. There is an interindividual variation, implying a role of genetics in the propensity to develop PAH. The location of the shunt also seems to be of importance. Posttricuspid shunts tend to develop PAH much faster than pretricuspid shunts, mainly because the pulmonary vascular bed faces an overload in pressure and increase in pulsatility on top of the volume overload.[8]

The consensus is to close a left-to-right shunt early in life, before the consequences to the pulmonary vascular bed become too severe or irreversible (generally less than 6 months for truncus arteriosus, atrioventricular septal defect, and transposition of the great arteries; less than 12 months for ventricular septal defect and patent ductus arteriosus; and less than 30-40 years for atrial septal defect). However, in some cases, a left-to-right shunt diagnosis is made once some degree of PAH already exists. So, when is it too late to close the shunt? This is a subject of great controversy. The Pediatric Task Force of the 6th World Symposium on Pulmonary Hypertension issued a table with very conservative hemodynamic criteria to be used as a "guidance for assessing operability in PAH associated with congenital heart disease."[1] As the authors outline, these recommendations are based on expert opinion rather than on robust data. The shunt is deemed operable when PVRi is < 4 WU $\cdot$ m^2, with favorable long-term outcome. It is also admitted that a shunt is inoperable when PVRi is > 8 WU $\cdot$ m^2. In between, there is a gray zone with suggested case-by-case decision making in tertiary centers, taking into account many variables such as the age of the patient, the type of shunt, the comorbidities, the resting and exercise saturation, and the clinical history.[1]

The American Heart Association and the European Pediatric Pulmonary Vascular Disease Network issued some slightly different guidelines, with shunt repair to be considered if PVRi is < 6 WU $\cdot$ m^2, or if the ratio of PVR:systemic vascular resistance is < 0.3 at baseline.[9,10] For patients with elevated PVRi, acute vasoreactivity testing can be used to help determine operability. Again, this approach is not based on any study, but rather reflects expert opinion. One of the main limitations is that a universal definition of a positive response to acute vasoreactivity testing in pediatrics and its ability to predict long-term outcome after surgery is still lacking.[11,12]

The Pediatric Task Force of the 6th World Symposium on Pulmonary Hypertension also emphasizes that the long-term outcome of shunt closure in patients with PAH and increased PVR is unknown.[1] Indeed, surviving shunt closure (operability) and normalizing hemodynamics with regression of the lesions in the pulmonary vascular bed (reversibility) are two different concepts.[13] As discussed previously, hemodynamics, although used widely, are not a good predictor of reversibility, and hence not a surrogate for long-term prognosis. Identifying criteria able to better discriminate patients who will benefit from shunt closure with reversal of PAH is needed.[13]

The importance of identifying patients who will normalize their hemodynamics after shunt closure is reinforced by the poor prognosis of persisting PAH after shunt closure. In the categories of PAH associated with congenital heart disease, persisting PAH after shunt closure carries the worst prognosis of PAH secondary to congenital heart diseases.[3,4,14] The strategy to repair the shunt and treat with targeted therapies can therefore not be recommended based upon the currently available data.

Another approach is the "treat with intent to repair," when patients are treated with pulmonary vasodilators in an effort to improve their hemodynamic parameters and then shunt closure is performed. This strategy aroused some interest when first reported; however, the literature on the subject is still very sparse. A few case reports and more recently a multicenter retrospective study of 69 patients have been published, but they mainly concern atrial septal defect, a pretricuspid shunt that seldom causes severe PAH and irreversible lesions.[15,16] No larger-scale studies are published or underway to the best of our knowledge. Moreover, the plausibility of this approach is questionable. We know that idiopathic PAH is not a disease that can regress and be cured with targeted therapies; why should PAH secondary to systemic-to-pulmonary shunt behave any differently? This strategy is hence not proven, and is not supported in the treatment algorithm of the international guidelines.

Other strategies worth mentioning in selected cases where the hemodynamics are not favorable are partial closure of the shunt (patch fenestration)[17] or pulmonary artery banding.[18] These approaches warrant further studies, and are beyond the scope of this article.

WHEN TO CREATE A SHUNT

Shunt creation has been performed in congenital heart surgery for more than

half a century, most often as a palliative procedure to provide pulmonary blood flow (ie, Potts shunt for cyanotic congenital heart diseases), or to create mixing between oxygenated and deoxygenated blood (ie, atrial septostomy in transposition of the great arteries[19]). As PH is a disease with a dreadful prognosis that no specific therapy can cure, physicians have been looking at other treatment strategies.

Based on the observation that patients with ES have a better survival than patients with idiopathic PAH, mainly because of decreased right ventricle (RV) afterload from right-to-left shunting,[5] the idea to perform a surgical or percutaneous shunt to create an "Eisenmenger physiology" arose.

Atrial septostomy has been performed as a palliative procedure for patients with refractory PAH since 1983.[20] In patients with a failing RV and elevated right atrial pressure (RAp), pretricuspid right-to-left shunting unloads the RV and improves left ventricular preload and systemic cardiac output. It is worth mentioning that unlike adults, children with PAH seldom have elevated RAp. Atrial septostomy has the advantage of being a percutaneous procedure, either via blade septostomy or balloon dilation of the atrial septum. It has been reported that atrial septostomy improves symptoms (most notably syncope) and quality of life in adults and children with PAH.[21] A meta-analysis has recently been published demonstrating benefits with this intervention.[22] It may also serve as a bridge to lung transplantation.[23] The procedural morbidity of atrial septostomy is mainly related to uncontrolled right-to-left shunting, resulting in insufficient PBF and profound hypoxemia in patients with elevated RAp and large defects. The relative contraindications for atrial septostomy are a mean RAp > 20 mm Hg, a resting oxygen saturation < 90%, and severe RV failure. Another longer-term disadvantage is the risk of paradoxical cerebral thromboembolism. The international guidelines suggest considering atrial septostomy in patients in World Health Organization (WHO) functional Group III and Group IV with recurrent syncope on combined medical therapy.[1]

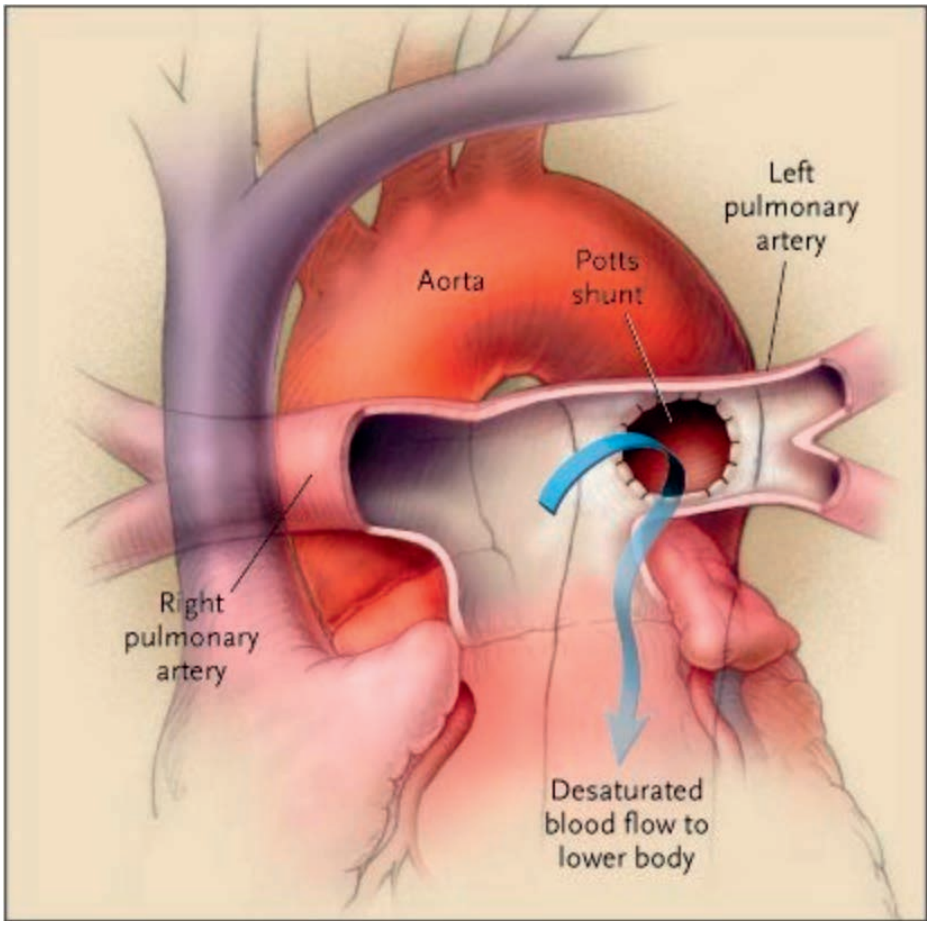

Figure 1: Reversed Potts shunt. The left pulmonary artery is anastomosed to the descending aorta, allowing the desaturated blood to go from the left pulmonary artery to the lower part of the body (arrow). Of note, the right pulmonary artery passes in front of the ascending aorta in the illustrated case, because a Lecompte maneuver has been performed. Reproduced with permission from Blanc et al.[24]

A reversed Potts shunt is the creation of a connection between the left pulmonary artery and the descending aorta, which allows right-to-left shunting (hence the term "reversed"; Figure 1).[24] It has the advantage over atrial septostomy of providing oxygenated blood to the brain and the coronary arteries and only causes desaturation of the lower body. The reversed Potts shunt relieves RV pressure overload in systole and in diastole, improves RV–pulmonary artery coupling, and improves left ventricular performance by reducing the interventricular septum left shift.[25] It has the potential to be effective before RV failure develops. The chief concern remains the risk of operating in PAH patients who have a nonnegligible anesthetic and surgical mortality. Transcatheter procedures have been performed in some highly experienced centers,[26,27] either by stenting an existing small patent ductus arteriosus, or by creating a transcatheter de novo stent–secured aortopulmonary connection, though this approach also appears to carry a high risk of severe complications. Regardless of the technique, reversed Potts shunt creation remains a high-risk procedure with a reported mortality of 12% to 30%.[26,28] One of the main complications is an early acute low-output state secondary to sudden reduction in the left ventricular preload. Despite the high periprocedural mortality, long-term results are very encouraging, with prolonged survival and improvement in functional status, allowing progressive weaning from prostanoids in children.[28] Further studies should help to understand if these favorable effects are long-lasting and further define the indications and contraindications of the procedure.

Table 1. Comparison of Atrial Septostomy and Reversed Potts Shunt[a]

	Advantages	Drawbacks
Atrial septostomy	Percutaneous procedure RV diastolic decompression Increases LV preload	May require repeated procedures (for spontaneous closure) Whole body desaturated Requires elevated RAp Risk of cerebrovascular events
Reversed Potts shunt	Preserved saturation to brain and coronaries Independent of RAp Reduces RV afterload RV systolic decompression, leading to better RV to pulmonary artery coupling Some RV diastolic decompression Improves septal geometry Improves LV performance	Surgical or high-risk percutaneous procedure Requires supra-systemic PAH Risk of decreasing LV preload

[a] RV indicates right ventricle; LV, left ventricle; RAp, right atrial pressure; PAH, pulmonary arterial hypertension.

As per the international guidelines, reversed Potts shunt "may be considered in patients with suprasystemic PH refractory to any medical treatment, including combined therapy presenting with WHO FC IV symptoms."[1] The recent implant of unidirectional valved anastomosis in PAH patients with infrasystemic pulmonary pressures offers new potential to use this approach at earlier stages of disease.[27,28]

Table 1 summarizes the main features of atrial septostomy and the reversed Potts shunt. Shunt creation remains a therapy used only in severe PAH cases, mainly because of the significant periprocedural mortality. With the improvement of procedural techniques and better patient selection, and after collecting longer-term follow-up data, we may well be tempted to offer shunt creation earlier in the course of PH. The creation of a shunt does not seem to contraindicate a future lung transplant, but might rather represent a valuable bridge to transplantation.

Apart from the question of the timing of the shunt, the application of the technique to other groups of PAH (eg, heritable PAH, PAH secondary to connective tissue disease) and to adult populations warrants further studies.

Finally, before reproducing ES physiology by means of shunt creation, it should be kept in mind that patients with ES do not have such a benign prognosis.[7]

CONCLUSION

Shunts and PAH have a complex relationship that evolves with time. In the early stages of PH secondary to left-to-right shunt, the best therapeutic option remains closing the shunt. When PH has developed with concomitant significant pulmonary vascular disease, the shunt should not be closed and patients should be treated with specific therapies. In severe cases of idiopathic PH, shunt creation (atrial septostomy or reversed Potts shunt) may represent a therapeutic option that improves functional status and may delay the need for lung transplantation in those who survive the high-risk procedure. Further studies are needed to assess the indications for shunt creation, as well as the long-term effects of this approach.

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The Evolving Role of Balloon Pulmonary Angioplasty in the Management of Chronic Thromboembolic Pulmonary Hypertension

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Patients with chronic thromboembolic pulmonary hypertension (CTEPH), characterized by pulmonary artery obstruction with unresolved embolism, have poor prognosis. Although pulmonary endarterectomy is the treatment of choice in the management of CTEPH, some patients are not operable. Balloon pulmonary angioplasty (BPA) is a catheter-based interventional treatment for patients with CTEPH. BPA has been considered a high-risk procedure, although the beneficial effects were promising. BPA has been modified and refined over the last 10 years. Recent evidence about modern BPA has consistently demonstrated the beneficial clinical effects with acceptable risks. BPA is now recommended in nonoperable CTEPH patients in addition to targeted medical therapy, although several questions such as long-term prognosis remain unanswered. BPA is still evolving for its application in the CTEPH treatment strategy. Further investigations are still necessary to define the role of BPA.

HISTORY AND EVOLUTION OF BALLOON PULMONARY ANGIOPLASTY

Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease characterized by pulmonary artery occlusion or stenosis by embolism. CTEPH is a life-threatening disease associated with high pulmonary artery pressure that leads to right heart failure and death, if left untreated.[1] While the preferred, evidence-based treatment for CTEPH is pulmonary endarterectomy (PEA),[2] more than one-third of patients with CTEPH do not qualify for this procedure, according to the international CTEPH registry.[3] Instead, a targeted medical therapy can be employed and has been shown to be effective in treating nonoperable CTEPH,[4,5] although it is not curative.

Balloon pulmonary angioplasty (BPA) is a catheter-based interventional treatment that uses a balloon catheter (commonly 2 to 4 mm in diameter) to open an obstructed pulmonary artery (Figure 1). The first case in which

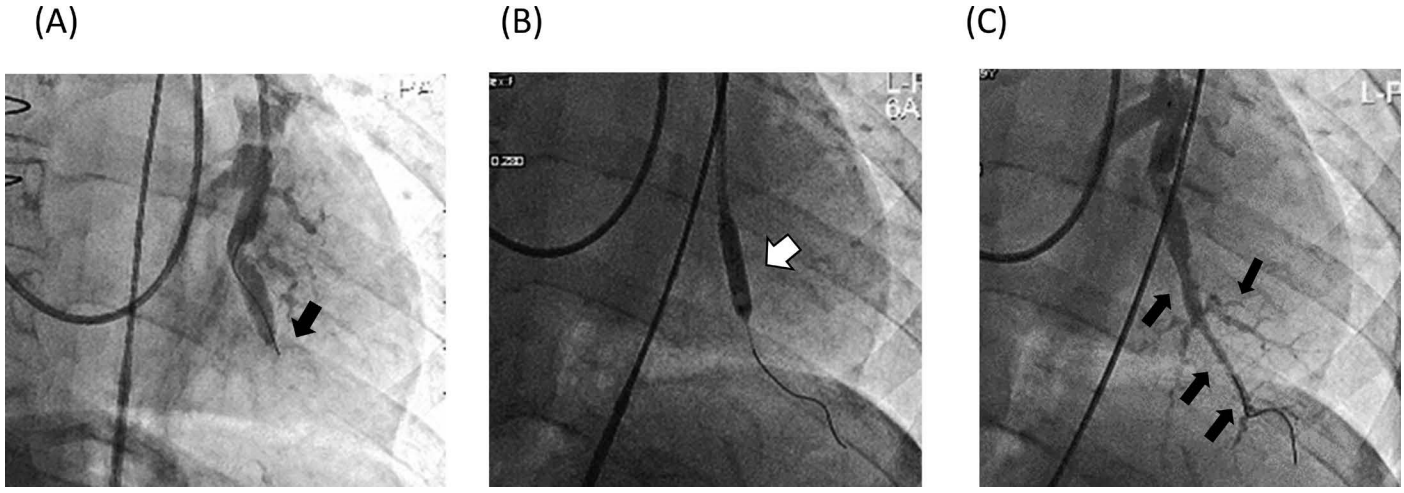

Figure 1: Angiography images of balloon pulmonary angioplasty. (**A**) Selective pulmonary angiography just before balloon angioplasty. Arrow: stenosis. (**B**) Ballooning for pulmonary artery stenosis. (**C**) Selective pulmonary angiography just after balloon angioplasty. Arrow: improved distal pulmonary artery flow.

Key Words—chronic thromboembolic pulmonary hypertension, balloon pulmonary angioplasty, catheter intervention
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Table 1. Hemodynamic Results of Balloon Pulmonary Angioplasty[11,a]

Study	n	PVR (dyn/s/cm^{-5}) before BPA	PVR (dyn/s/cm^{-5}) After BPA	BPA effects on PVR
Sugimura et al.[8]	12	627 ± 236	310 ± 73	–54%
Mizoguchi et al.[10]	68	942 ± 367	327 ± 151	–65%
Andreassen et al.[12]	20	704 ± 320	472 ± 288	–33%
Fukui et al.[13]	20	889 ± 365	490 ± 201	–45%
Taniguchi et al.[15]	29	763 ± 308	284 ± 128	–63%
Ogo et al.[17]	80	880 ± 424	376 ± 160	–57%
Ogawa et al.[18]	308	853.7 ± 450.7	288.1 ± 194.5	–66%
Olsson et al.[19]	56	591 ± 286	440 ± 279	–26%
Brenot et al.[20]	154	604 ± 226	329 ± 177	–43%

Abbreviations: BPA, balloon pulmonary angioplasty; PVR, pulmonary vascular resistance.

[a]Data are presented as mean ± standard deviation unless otherwise noted.

BPA was used in the management of CTEPH was reported in 1988.[6] In 2001, Feinstein et al. described a series of 18 cases of CTEPH that were treated with BPA with positive hemodynamic effects, but a high incidence of complications.[7] Since then, Japanese pulmonary hypertension physicians and interventionists have modified and refined BPA procedures.[8–11] This review summarizes the evolving role of BPA in the management of CTEPH.

CLINICAL BENEFITS OF BPA IN CTEPH

Reports on the use of BPA over the last 10 years have consistently demonstrated favorable hemodynamic effects (Table 1). Early reports from Japan showed beneficial effects in nonoperable CTEPH, such as lowering of pulmonary vascular resistance (PVR) by 33% to 65% and improvement in World Health Organization functional class and 6-minute walking distance (6MWD).[8,10,12–15] Furthermore, exercise capacity and ventilatory efficiency, as measured by cardiopulmonary exercise tests, were reported to have improved.[16] Right ventricular (RV) remodeling has been reported to be reversed with BPA, improving RV volume, RV systolic function, interventricular septal bowing, and RV dyssynchrony.[13] A number of recent BPA reports from Japan also support the beneficial effects in CTEPH (Table 1),[17,18] though the reproducibility of these results in non-Japanese populations has been questioned. Recent BPA data from Germany[19] and France[20] also showed the applicability and reproducibility of BPA in their patient populations (Table 1).

There still remains a lack of long-term follow-up in patients having undergone BPA, although mid-term survival appears excellent in BPA groups.[21] Moreover, the prognosis of the patients who undergo BPA without targeted medical therapy is not clear.[21]

COMPLICATIONS OF BPA

BPA still carries a risk of potentially fatal complications. Clinically apparent lung injuries in early reports were frequent, occurring in approximately 60% of cases, and 17% of patients required mechanical ventilation.[10] High pulmonary arterial pressure,[7] the first BPA session, and severe hemodynamic parameters such as low cardiac output and high serum brain natriuretic peptide levels[9] have been reported to be the risk factors for lung injury after BPA. However, recently, the understanding of the mechanism for lung injury has been clarified. Lung injury caused by reperfusion edema is now considered a relatively rare complication of BPA.[11] Current consensus is that lung injury after BPA is mainly mechanical vascular injury caused by the distal tip of the wire or balloon overinflation (Figure 2).[22] Pulmonary perforation is identified in 0% to 7% of cases.[9,10,12,13] The pulmonary vascular perforation or rupture can

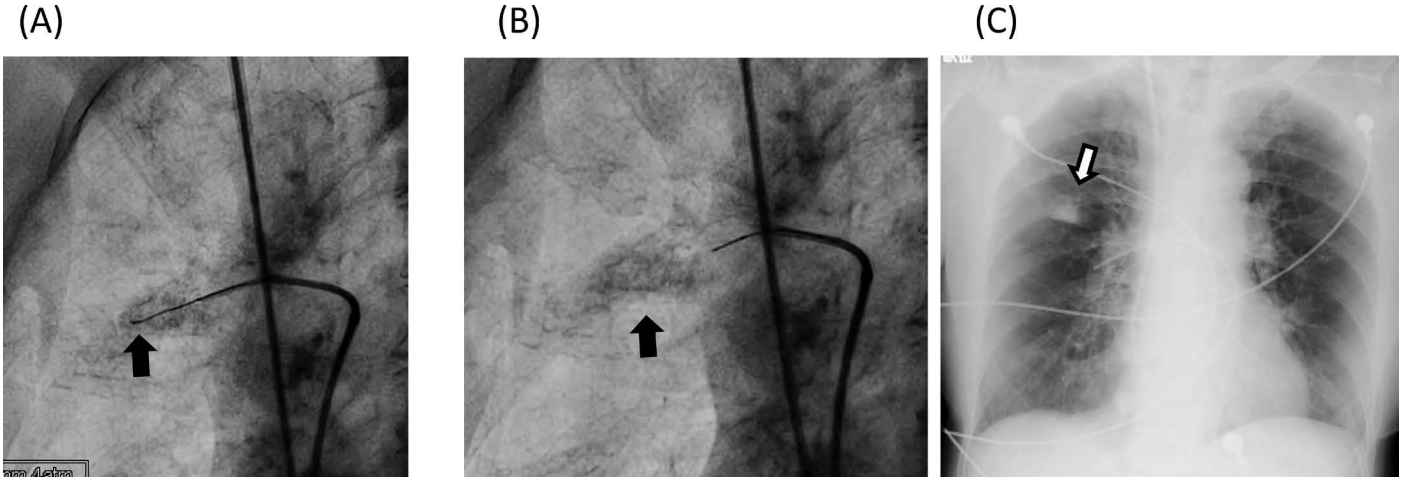

Figure 2: Lung injury caused by wire perforation during balloon pulmonary angioplasty. (**A**) Intervention wire. Arrow: wire and consolidation around the tip of wire. (**B**) After pullback of wire. Arrow: consolidation. (**C**) Chest x-ray image after balloon pulmonary angioplasty. Arrow: consolidation.

result in severe lung hemorrhage and even death. Periprocedural mortality has been reported to be up to 10%.[9,13,14] The incidence of BPA complications is decreasing, and the procedure is becoming safer due to a better understanding of the mechanisms, refined technical approach, and the improved management of complications.[22] Using a soft wire and a small-sized balloon is important to avoid serious lung injury. Employing a stepwise strategy to open some target vessels using balloons smaller than the size of the surrounding vessel during early sessions, particularly in cases with adverse hemodynamic parameters followed by the opening of larger vessels in subsequent sessions, has become standard.

CURRENT ISSUES AND LIMITATIONS OF BPA

Current BPA complication rates are obtained from large BPA expert centers. BPA is highly reliant on operator techniques and experiences. French data demonstrated better hemodynamic improvement and fewer complications with more recent procedures, suggesting that a learning curve exists for BPA.[20] Whether BPA procedures carried out in nonexpert centers increase the complication rates remains unclear. The restenosis or recurrence rates and long-term prognosis more than 5 years after BPA also remain undetermined. Comparison of the clinical effects between PEA and BPA for more distal forms of CTEPH also remains to be determined. One retrospective study suggested that the prognoses of patients who underwent BPA were comparable to those who underwent PEA.[14] However, these results should be carefully interpreted because BPA was only performed in nonoperable CTEPH patients. Analyses of long-term patency and impact on subsequent prognosis are awaited for BPA. One of the limitations of current BPA studies is the inclusion of patients treated with targeted medical treatment. Therefore, the efficacy of BPA and impact on survival may be confounded by medical treatment. Furthermore, BPA treatment goals, the role of preexistent targeted medical therapy, residual pulmonary hypertension after BPA, radiation exposure, and cost effectiveness[23] are issues that require further clarification.

FUTURE PERSPECTIVES

Patients with chronic vascular occlusions but normal pulmonary hemodynamics at rest, otherwise described as chronic thromboembolic disease (CTED), also require attention. BPA may be beneficial for CTED, as PEA has previously showed beneficial effects in CTED patients.[24] Comparisons between BPA and targeted medical therapy raise important clinical questions and the results of the RACE trial (NCT02634203) may be helpful in this regard.

BPA can also be applied in combination with PEA. A case series of hybrid treatment with BPA and PEA has been reported from Germany.[25] PEA for proximal lesions in one lung and BPA for distal lesions in the other lung is certainly a unique approach. BPA for residual pulmonary hypertension after PEA has been shown to be beneficial in terms of hemodynamics, but clinical benefits remain uncertain.[26] The role of pretreatment with BPA followed by PEA may also be an interesting approach to reduce PEA risk. Further investigation is needed to respond to each of these important yet unanswered questions.

CONCLUSIONS

CTEPH is a life-threatening disease with pulmonary hypertension that is characterized by obstruction in the pulmonary arteries. BPA, a catheter-based interventional treatment for CTEPH, was previously a less effective treatment with significantly higher rates of complications. Improvements in the BPA procedure continue to result in higher efficacy and lower complication rates. BPA is currently not a substitute for PEA but is one of the treatment choices for nonoperable CTEPH. Therefore, application of BPA should be thoroughly discussed by multidisciplinary CTEPH teams which include PEA surgeons. Further investigations into the unanswered questions regarding BPA, such as long-term prognosis, are required to further define its clinical role.

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New Invasive Technologies in Pulmonary Hypertension

This spring, Guest Editor Richard A. Krasuski, MD, Professor of Medicine at Duke University School of Medicine in Durham, North Carolina, convened a group of experts to discuss the present and future of invasive technologies in the diagnosis and treatment of pulmonary hypertension. The guests included Jamil A. Aboulhosn, MD, Professor of Medicine at the University of California Los Angeles David Geffen School of Medicine in Los Angeles, California; Raymond Benza, MD, Director of the Division of Cardiovascular Medicine and Professor of Medicine at The Ohio State University College of Medicine in Columbus, Ohio; and J. Eduardo Rame, MD, FACC, Louis R. Dinon MD Professor of Cardiovascular Medicine and Physiology and Chief for Advanced Cardiac and Pulmonary Vascular Disease at Thomas Jefferson University Hospital in Philadelphia, Pennsylvania.

Dr Krasuski: I'd like to welcome everyone to today's roundtable discussion. This is a real honor and pleasure for me; I've had the chance to invite what I consider to be some of the best people around to discuss this particular topic, new invasive technologies that are in use in the pulmonary arterial hypertension (PAH) catheterization lab.

Obviously, we've seen a lot of changes over the last decade. The field has moved forward tremendously, and we're doing a lot more therapeutically, certainly with medications. Some of the things that we now have available to us in the catheterization lab have also advanced in a pretty rapid fashion, and that's the topic of this particular issue of *Advances in Pulmonary Hypertension*.

The group I've put together probably needs no introduction, though I will do so anyway. We have one of the real gurus in the field of pulmonary hypertension (PH), Dr Ray Benza. We have a leader in the field of adult congenital heart disease and innovative interventionalist, Dr Jamil Aboulhosn. And last, but certainly not least, one of the great minds in heart failure and PH, Dr Eddie Rame. I'd like to start our discussion with this question: With all the technological advances that have occurred over the last few decades, how has your approach to catheterization of patients with PH changed?

Dr Benza: That's a really good question, because the advancement in imaging modalities has really called into question the necessity of continuing invasive monitoring in patients with PH. As a cardiologist, I feel very comfortable with hemodynamics, and I still believe that hemodynamics help paint the entire picture of risk profiles in this disease. I am still a very big proponent of routinely monitoring patients using hemodynamics and taking them to the cath lab to see if we have their disease adequately controlled, that it's not progressing silently, which we know this disease can do. We are still taking people to the cath lab to do their initial risk stratification diagnosis, and usually again the first 4 to 6 months after new therapy introduction to make sure that hemodynamic profiles are moving in the right direction. Finally, we continue to bring stable patients back to the cath lab to assess hemodynamics on a yearly basis as part of their annual risk stratification process.

Dr Krasuski: I follow a very similar strategy. In terms of follow-up catheterization, we probably perform it a little bit less. I do think that it's very important, especially when considering adding therapies or changing therapies, that you have accurate hemodynamic data. I think we all know that echocardiography is a nice, noninvasive way to assess pulmonary pressure and get a sense of how the right ventricle (RV) is doing over time, but there are times that it is just not good enough or can even be misleading. I think there is no substitute for accurate hemodynamics.

Jamil, I know your practice has expanded mostly into transcatheter valves and other interventions in congenital heart disease. Do you still find yourself doing catheterizations for patients with PH? What are you doing differently now than you did in the past?

Dr Aboulhosn: The main focus of my practice at this point, frankly, is the congenital heart population, many of whom have PH. As far as the yearly diagnostic catheterizations on pure PAH patients, those are done by many of my other colleagues, pulmonologists and cardiologists. In the work that I do, to answer your question as to how things have changed in the last decade with the use of new technology, I have incorporated a number of things over the last 10 or 15 years that we weren't using in the past as much. For example, the use of intracardiac echocardiography in helping to figure out sites of shunting and helping to guide any interventions that we're doing.

Take as an example a patient with PH who is desaturated and may have a pulmonary-level shunt versus an atrial-level shunt versus a combination of both. That's where I find intracardiac echocardiography during a cardiac catheterization to be extremely useful, and that's become quite standard for me to use.

I also incorporate stress catheterization much more than I did in the past, as a means of helping me figure out what happens to people's hemodynamics at rest and with exercise. Often I'm doing these studies not just with the right heart catheterization and checking pulmonary artery (PA) and wedge pressure and such, but using 4 or 5 transducers, checking central venous pressure (CVP), PA pressure, wedge pressure, systemic arterial pressure through a radial arterial line, and even occasionally going as far as putting in a dual lumen pigtail into the left ventricle (LV) and checking simultaneous LV and ascending aorta pressure in those whom I suspect are going to develop gradients with exercise.

It's much more sophisticated hemodynamic assessment and imaging guidance.

You brought up the transcatheter valve work, and that's really taken off as far as pulmonary valve replacements initially in purely congenital patients, but increasingly now in those with acquired pulmonary valve regurgitation, many of whom have PH. The latest is tricuspid valve interventions with the use of the MitraClip in the tricuspid location to try to decrease the degree of tricuspid regurgitation as well as the placement of valves into the cavae, both the inferior and superior vena cava.

I'd say those are probably the main changes that I have seen in my personal practice in the way I approach patients with complex PH. Many of them are structural or congenital.

Dr Benza: I think in the world of noncongenital PH, the advances in the catheterization lab really fall into 3 areas. One was already mentioned, and that is exercise hemodynamics. The second is the rechallenging of patients with selective pulmonary vasodilators, like nitric oxide, to determine if reactivity has reemerged. Lastly, the incorporation of high-fidelity catheters to our workflow to generate pressure-volume (PV) loops in order to give us a better understanding of ventricular-vascular coupling is being applied in several centers.

I think there are emerging data that bringing people to the cath lab and exercising them does add an element of additional information with which you can project a patient's risk and outcome. As all of us know, we typically measure hemodynamics at rest and in the supine position. We do this even with the recognition that people are not flat on their backs all day and thus resting parameters are not reflective of the hemodynamic load our hearts see most of the day. Adding exercise information really tells us more about the hemodynamic burden of the disease during a patient's normal experiences in the ambulatory environment. Presently, there's a lot of work going on with exercise hemodynamics prognostically and diagnostically, and I think we're moving into an area of more comfort with those. Although, again, performing exercise hemodynamics in a busy cath lab is not always logistically possible and they are not always simple to perform. Exercise protocols in the cath lab require some special equipment and they are not standardized from lab to lab. Some labs use upright bicycles, some supine bicycles, and others arm ergometry. In addition, some labs incorporate gas exchange studies. This variability makes results difficult to interpret and incorporate into our prognostication schemes. I think that it's something we definitely need to watch, because more consistent data are coming out suggesting that this is the right thing to do prognostically for patients.

Dr Krasuski: I find that the information I get from exercise catheterization can be very helpful for patient management. One of the biggest challenges in exercise right-heart catheterization is which technique to utilize and as you mentioned, Ray, the room setup. We often are adopting equipment that may not have been designed for that particular purpose. Other challenges include how to measure cardiac output accurately during exercise. While we might do a thermodilution initially at rest, use of the same equipment and technique during exercise often gives automated error messages. Fick technique, on the other hand, is only accurate if oxygen consumption is carefully measured using a metabolic cart. Also, the hemodynamic tracings can get rather noisy and challenging to interpret. Speaking of tracings and ways to clean up their appearances and get more accurate data, Eddie, you've done some seminal work with high-fidelity catheters, PV loop collection and RV-PA coupling. Could give us some background on that?

Dr Rame: Before I comment on that, let me just say that I think the role of exercise catheterization is an important matter to consider. Just 15 to 20 years ago, colleagues would perform exercise catheterization in the low-risk patients to see if they actually had PH by provoking a higher PA pressure and a higher pulmonary vascular disease metric like a pulmonary vascular resistance or diastolic pulmonary gradient. Actually, many of us discovered that the patients with exercise-induced PH would not often progress to more severe disease states and so a "positive" test would not capture prognostic value other than that the patient would have to be followed over time to determine if disease progression occurred.

In the current era, we see the role of exercise catheterization or invasive cardiopulmonary exercise test (CPET) studies in PH quite differently. These tests are often performed to answer the question: Do you have right heart failure or do you not, upon the demand of exercise? We know that everybody with PH has a risk for right heart failure because of the potential for RV-PA uncoupling, but not everybody has bona fide right heart failure, elevated central venous pressure, congestive right-sided indices, and diuretic requirements, which is clearly a significant marker of disease state—both in terms of how these patients are neurohormonally activated and how they respond to pulmonary vascular disease–targeted therapy. We know these patients with right heart failure and diuretic resistance or significant volume retention and variability in weight are often on a very different trajectory in terms of disease progression.

If you have someone with right heart failure and PH, just to your point, Rich, I think that's where it's helpful to consider an exercise catheterization as opposed to using the usual right atrial pressure and cardiac output. I think an exercise catheterization, especially over a time period of years in which you see these patients, could instruct to the fact that they're declining. And maybe if you don't do exercise catheterization, if you're able to start using PV loop measurements, our experience with it has been mostly in patients with PH in the setting of left heart disease and with, let's say for example, a left ventricular assist device (LVAD). We're able to see how the RV responds to both changes in the pulsatile load from the LV, from left-sided heart failure as we change the LVAD speed, and we're also able to measure how the RV may actually respond to volume changes acutely with left-sided unloading or even with a vasodilator challenge; all of that, which

as you know is basically more clinical research.

I think we are seeing now an era where several centers, some with a protocol and some that are just trying to get their hands around the technology, are using the PV loop catheter technology that's out there, and the FDA approved of this PV loop system which is being used to secure an assessment of RV function. In terms of clinical application in PAH and PAH associated with congenital heart disease, I think it's early, but the enthusiasm is definitely there to investigate how it might provide more insight than the current tools we have to understand the transitions of the RV which correlate with disease progression. As far as PAH, I have not used PV loops yet to assist in the guidance of risk stratifying our patients.

In our program here at Jefferson we're already starting the CPET program with invasive hemodynamics in order to estimate RV function and reserve in patients across the spectrum of pulmonary vascular disease. The invasive CPET program has just been launched with our colleague Mahek Shah leading this effort in various clinical states where RV function needs to be better phenotyped. With the PV loop systems, we're still trying to sort out how that's going to differentiate what you do next, but I think it's going to be hugely instructive to know that your patient has an RV that may be more compliant, more responsive, versus an RV that's much more stiff, chronically ill from years of pressure overload hypertrophy, and maybe even more dysfunctional than what the echocardiogram shows.

Dr Krasuski: A specific challenge with collecting PV loops is that you need to have ventricular volumes collected in relatively close proximity to the time that you do the catheterization. Coordinating an MRI, the "gold standard" for volume measurement, and a heart catheterization on the same day can be very difficult.

Jamil, we both have patients who are sent to us with large atrial septal defects (ASDs) and PH. The task we face is determining which ones are potentially and safely closeable. When you have someone lying flat on their back and at rest, as Ray pointed out, it doesn't really truly reflect what happens when they're active. Occasionally I have exercised these patients in the cath lab and been surprised that moderate PH becomes severe. Some of them even developed right-to-left shunting across the ASD, in which case I started worrying about whether it was wise to take away a pop-off valve with device closure. Whereas we traditionally balloon-occlude their defects and say, "Now I know what is going to happen after I close the defect." In fact, you still don't know what will happen with exercise after closure. I'm curious to hear how you personally handle this situation.

Dr Aboulhosn: That is a bit of a challenge. Ideally, if I could have my dream cardiac cath–CPET lab–stress echo lab, what I would love to be able to do is have multiple transducers so I could measure all of these pressures simultaneously, to be able to do stress echo simultaneously, to be able to get cardiopulmonary exercise measures, and be able to occlude a shunt, say a patent foramen ovale or an ASD, while having someone actually do bicycle or ergometry. This would mean that you're going to have to occlude the atrial-level communication with a balloon coming from the neck, not from the leg; therein lies the challenge. In the absence of that ideal, what I will often do is bring someone to the cath lab and do the following.

Let's just take an example of somebody with an ASD and some degree of PH, and you're not sure whether it's appropriate to close or not. In that setting, what I'll do is put in multiple venous sheaths as well as an arterial sheath—I use the femoral approach here—and I'll go ahead and get a baseline arterial blood gas on the patient, and I'll go in and get baseline pressures and baseline saturations on room air. Then I will go ahead and do upper extremity exercises, where we give the patient weights, usually 5- or 10-pound weights in each arm and basically have them do fly presses. It does not mimic the exercise that someone is doing when walking or running, but at least it is increasing the heart rate and causing some increase in blood pressure and giving us some information about the changes that may occur with that level of exertion. We do that and repeat a lot of those same measurements. Then I'll go in and balloon-occlude the defect and get baseline measurements with the defect balloon occluded. I've even gone so far, and this is where the cath lab staff and everybody is like, "Oh my God, please stop," to do another phase with inhaled nitric oxide, with the shunt open and the shunt balloon occluded. You can do so many variations on this. In the end, I find that if somebody desaturates with exercise, that is concerning. If somebody has an elevated PA resistance that is beyond 50% systemic, that is generally a hard stop for me as far as closing an interarterial-level shunt unless there's a really good reason to do it.

You can do all sorts of variations on the scene, but I do believe it is important to balloon-occlude these defects before closing them if there is a question as to whether or not to close them. If I balloon-occlude an atrial-level shunt and I find that the systemic arterial pressure drops, the RV pressure jumps up, the CVP jumps up, those are very concerning findings for me. I will generally then either not close the defect, or if I'm considering closing it, I'll fenestrate an atrial septal device, or use a fenestrated device to basically downsize the defect. That's the way I go along and do it. It's relatively time-intensive.

Dr Krasuski: Great point. You probably won't make the technicians and nurses in charge of a busy lab too happy when you go through so many steps. But I often find that when you explain why you are going through all of these steps, they all appreciate the fact that you are being so thorough. The other point worth mentioning is the use of complementary medical therapy. When I put in a fenestrated device or I completely close a shunt that may be pushing the limits, the fallback is that I can start or add on the many different and new advanced medical therapies for PAH. The other thing that I do is if the pulmonary vascular resistance is borderline prohibitive, I'll first treat them medically with a plan to bring them back and reassess

hemodynamics at a later time with the hope that we've reversed the disease to the point that the shunt can be safely repaired.

Dr Aboulhosn: There's one quote from an old mentor of mine, Dr John Michael Criley, who taught me how to catheterize back in the good old days at Harbor UCLA, one of the county hospitals that UCLA faculty and trainees staff. He used to say, and now I borrow his saying all the time, that it's called the cardiac cath *lab* for a reason. It's actually a laboratory. It's not just a place that we bring patients to in order to do an intervention and then get them out. In my mind, it's actually a place where we can figure things out and can alter the baseline state in such a way as to help us make the right decision. I think this is really the art of medicine. It can still be practiced in the cardiac cath lab, and we should treat it more like a laboratory than just a technical location with some equipment that allows us to do an intervention.

Dr Krasuski: I couldn't agree more. Ray, tell us a little bit about your experience with implantable hemodynamic monitoring. I think you already alluded to this. We get a chance to assess what happens hemodynamically when people are in the community doing what they normally do.

Dr Benza: I think that it's a really appropriate time to bring that up in the conversation, because as I listened to this, some of the things that are emerging in my mind are, again, why are hemodynamics so important? They're important because really they're the earliest things that change in this disease, and assessing hemodynamics on an ongoing basis really gives you a very complete picture of how the patient is responding to the disease. Remember, we're not at a point now where we have molecular markers that tell us when the disease is progressing at a very early level, and beyond that, hemodynamics are the first things that change as the disease progresses. All the other things that we measure—neurohormones, the 6-minute walk test, imaging—are all later down the line. At present, hemodynamics really give us the earliest warning signals about when this disease is changing.

The beautiful thing about the implantable hemodynamic monitors is that they add to that knowledge. They add to that knowledge by giving us multiple different touchpoints to assess hemodynamics over a period of time. It's not an isolated point when a person is lying supine on a cath table. It's multiple pieces of prognostic information that can be obtained every single day, which you can then plot and mark the course of a patient's disease state. Changes in these cumulative plots can then warn a clinician if a patient is straying off course. The importance of this is that many of these hemodynamic changes can occur weeks before a change in symptoms, such that it serves as an early warning signal of decompensation. You can also get the benefit of both resting hemodynamics and some ambulatory hemodynamics with these devices. They are relatively easy to implant in patients. The congenital patients that we've been talking about, though, are probably the one situation where it might be a little more difficult to implant. In the normal PH patients, it's easier.

Dr Aboulhosn: Can I ask you a question about that? When it comes to, say, the CardioMEMS device and the utility of getting PA pressures, we all think it's very useful, but do you think that is sufficient when it comes to the treatment of patients and figuring out what's going on with them? I'm always worried that a drop in PA pressures is not necessarily a good sign in somebody with decompensated heart failure. I always wonder whether I should take a CardioMEMS and put it into somebody's vena cava so that I can end up getting regular CVPs, which seem in my mind to be probably more useful than PA pressures alone. Can you talk a little bit about site of pressure measurement and the importance of maybe adding flow measurement to just pressure measurement?

Dr Benza: Yes, in fact, you took the words right out of my mouth. I was about to say that the current clinically available pressure readings that you get from the CardioMEMS device aren't going to be as useful in PH without the additional stroke volume information, which is presently only available for research. Stroke volume determination with these devices is a hot new area of research.

In the studies that we've conducted, we have looked at the stroke volumes that we calculate with the CardioMEMS device and compared them with those we derive from cardiac MRI, which as you know is really the "gold standard" for stroke volume, and they're pretty accurate. In the NIH-funded studies we conducted in PH using the CardioMEMS device, we had a plethora of hemodynamics that we were able to derive using the stroke volume information and heart rate, including cardiac output, cardiac index. In addition, because you have the pressure measurements, you can also calculate cardiac power, cardiac efficiency, total pulmonary resistance, and elastance.

Thus, the addition of stroke volume information from the device is a very powerful tool that can then be applied in the area of prognostication in pulmonary vascular diseases. We've gone even so far as to look at these combined hemodynamics before and after 6-minute walk tests, and we have found very, very clearly that patients with PH are stroke volume–limited with activities of daily living and that they only maintain cardiac output by increasing their heart rate. That's a very novel finding found using this device.

The addition of stroke volume and the ability to do these types of hemodynamic challenges in patients in the ambulatory situation and not on a bicycle or in the cath lab have really added to our knowledge about these patients. Using the sum total of these events, you really see trends in hemodynamics very clearly over time. When a patient's cardiac output is dropping because their stroke volume's dropping and that's coupled with a drop in pressure, as you mentioned before, it's a bad sign. It's quite different from when the stroke volume stays flat with rising pressures. That means the heart's still able to maintain

stroke volume to some degree during this patient's disease state.

I think with the advancement in technology that we just reviewed, the CardioMEMS device may serve as a very useful tool in the management of people with this disease.

Dr Krasuski: That's really taking the cath lab hemodynamic data collection outside of the cath lab, so that's a great diagnostic advance.

Dr Benza: Yes, and there are people that we haven't had to repeat a right heart catheterization for in years. There's very little hemodynamic drift with the devices, and as I mentioned, the stroke volume calculations are pretty good, particularly when you do them at rest.

Dr Aboulhosn: Ray, could you touch upon the potential for the use of the CardioMEMS device or any other devices that you're aware of for also measuring CVP? Requiring 2 devices, obviously, but if you're going to have one in the PA and one somewhere in the systemic venous circuit, do you think that is something that would be useful to you, that would add additional information over and above what we're getting from a PA pressure and stroke volume and all of the important measurements that you mentioned already?

Dr Benza: Yes, I think that's the one piece of information that we do not get from the device, and in right heart failure it's so critical to know what that CVP is. I think the addition of the stroke volume information really has advanced our knowledge in how this device is good for predicting outcome. Knowing the right atrial pressure would obviously be very, very helpful. This sensor was originally developed for deployment in the aorta. They have sensors of different sizes and they certainly can be applied to the venous system. They haven't done that now, but I know that these have been conducted in animal studies. The only issue with the device in the venous system could be early migration when the device is deployed. Once the devices are endothelialized, however, they will not move, but prior to that, I think that early migration would be the only issue to worry about from a venous deployment of the device.

Dr Krasuski: Let's shift gears just a little bit and talk about the patient who is failing advanced medical management and potentially heading toward a need for lung transplantation. But maybe that patient is either not a great candidate for transplant due to social reasons or has an unusual blood type or antibodies that are not going to get them transplanted quickly. Or maybe they need some assistance to stabilize them until we can get them safely transplanted. Eddie, could you talk a little bit about some of the newer techniques for right ventricular support? What is new and in in what direction do you think the field is heading?

Dr Rame: Let me talk a little bit about what I think is a very early phase right now of having several centers beginning to look at a paradigm for 2 different types of patients. You talk about the patient refractory to medical therapy, who is basically failing, and as we know, right heart failure has a lot of overlap with left heart failure as far as neurohormonal activation, with high levels of circulating neurohormones, including adrenaline and noradrenaline, which induce a metabolic adaptation in these more advanced patients that leads to mobilizing lipids to a state of cachexia due to fat and muscle wasting. That's what we see with these patients. The question is, of course, changing the natural history of that end-stage disease into some survivable endpoint with better quality of life. There's a group right now that's basically putting together a protocol that we are sharing in terms of patient selection for these refractory-to-medical-therapy PAH patients. We're talking about PAH predominantly, solely Group 1 PH, and predominantly idiopathic familial along the spectrum right now, only because right now it's more of a proof of concept. But just to be clear, one paradigm is the idea of long-term support devices that can be built for the right side.

Right now, what do we have? We have LVADs that are very much designed by engineers for generating continuous flow against a left-sided systemic afterload. They are geared for that purpose. When you put them on the right side, you can get away with it in a limited number of patients, but it's not ideal, especially in patients with elevated pulmonary vascular resistance. There are several interested industry partners that are engaging in a long-term project to build a long-term right ventricular assist device (RVAD). This bridge to transplant, or even more of a short-term bridge to getting on PH therapies, is a really interesting question, because how many times are we actually seeing refractory patients? Unlike left heart failure, blood pressure could be an absolute limiting factor for getting people titrated aggressively on PH meds. Often our patients just run out of time. They're getting too sick or having just too much RV failure.

I think that a second paradigm of patients who could be more completely treated with PAH therapies in congenital heart disease is one where they could benefit from temporary to midterm support devices, and there are several companies looking to see if they can use what they have developed. There's one paradigm of a surgical RVAD. The right-direct VAD, which was actually put on the shelf by AbioMed, worked very well, but was not developed since the percutaneously implanted Impella RP was more preferentially used with increasing demand by shock interventionalists. This surgical intermediate RVAD paradigm could allow some patients to be effectively supported, unloading the RV while patients can be more aggressively treated if they are more naïve to PH meds. Maybe that's the paradigm of the bridge to recovery for these patients who are really, really sick. Like you said, these patients are low output, with marginal systemic blood pressure and progressing in terms of end-organ ischemic injury from a deficient cardiac output. In terms of the exercise capacity and the physiology of how flow-adaptive these pumps can be designed, this paradigm is so new that we have no idea how these patients will do in terms of ambulatory or exercise-induced demand.

Dr Krasuski: There are so many challenges to developing RV support, not

the least of which is that you're trying to pump blood through a very-high-resistance circuit, which requires very high flows. As an institution, Duke is very experienced in using veno-arterial extracorporeal membrane oxygenation (VA ECMO), and we utilize it a lot for support, not only in patients who are critically ill with PH, but also in the perioperative period after lung transplantation to help medical stabilization

The other technology worth mentioning is the Novalung, which allows you to bypass the pulmonary circuit by returning blood back to the left atrium. It's an interesting idea because you utilize the high right-sided pressure to passively drive blood through the oxygenator, so no pump is necessary. One of the problems I've encountered with salvage VA ECMO is that we get to patients too late and there's not enough reversible disease to allow the patient to survive to transplant before a lot of other organ systems start to fail.

Ray, I know you are also very involved with transplantation. Could you share your experience for us?

Dr Benza: This is something that we have certainly tried to approach very carefully in the PH patients. I was part of the writing team for the World Symposium on PH looking at RV support for the PH patient. The discussions during that committee meeting were very lively around this issue. I am in support of trying to develop right heart support systems for PH patients. I think that's the right thing to do. However, with the current technology, the delivery of blood flow from the device is still to the pulmonary circulation. In light of that, we have to be very careful with the flows that we put through the lung because shear damage to the pulmonary architecture with high flow can result in very significant hemorrhagic problems. Now, as long as you can keep the flow low, I think that is something that will certainly help with a lot of these patients as we bridge them to transplant, although it may not be a good long-term solution for those patients who are not eligible for transplant. Flows devices that can give you low flows, like 2 L, 2 1/2 L, like the CircuLite device, might be a very appropriate device for a patient with right heart failure related to high pulmonary vascular resistance.

Dr Rame: Just to weigh back in, and following up on what Ray has said—truly, the current roadmap for these companies is the design of a low-flow, partial-support device. I just want to point to the work of Bart Meyns from the medical center in Leuven, Belgium, and his team. They have done a number of studies with large-animal PAH models and demonstrated the ability to support them in the acute postimplant and intermediate term. It's important to note exactly what Ray said—the low flow has been demonstrated to be so imperative because of the absent autoregulation that you actually have in the pulmonary bed when these patients are so acutely and chronically ill. Not only do you risk pulmonary hemorrhage, but you can probably induce more angiopathic changes in the pulmonary vasculature, and these patients are more likely to get worse and not better if this design element is not well incorporated.

But the good news is that so far these models have actually shown both pathologically and clinically that they can actually get better with low-flow paradigms. The idea is to relieve the low cardiac output state, decongest, and assist the right side. I think these patients could do well with low flow, partial assist, and achieve decongestion. This is the hypothesis. Just to be very clear, very few people have achieved a long term with an isolated RVAD, especially in patients with RV pressure overload. These RVADs have a tendency to clot. They see a very high dynamic resistance and the devices thrombose.

The other reason that RVADs tend to clot is because once you assist the RV, even partially, and it recovers function, you then have a parallel circuit with native competitive flow and the devices will thrombose as RVAD flows drop. I think there is a lot to learn in this area. The good news is, like Ray said, there is some enthusiasm to try and support these patients who are truly the "walking wounded," who are crippled with end-stage right heart failure due to PAH.

Dr Benza: The current designs of VADs are meant for supporting the left-sided circulation, not the right side, although they're structurally small enough and can support the right heart in the absence of severe PAH. As these devices are meant to run at 4 L, you can have issues when you reduce the flow down to 2 L, as we were just mentioning, because thrombosis can become a big issue. I think we have the right idea. I don't know if we have the right design yet, and that's what we really have to work at, getting the right design to develop a pump that can deliver low flow without clotting off, that doesn't increase shear stress, and doesn't progress the angiopathic changes in the pulmonary circulation.

Dr Krasuski: There are a lot of challenges involved, but I think we've made great advances in this area and there certainly remains a lot to think about.

Stepping back for a second, Jamil, I'd like to apply our congenital knowledge to other patients with PAH. Although it may be a little controversial, patients with Eisenmenger syndrome appear to have better clinical outcomes than patients with other types of PAH. There are obviously a lot of embryologic RV adaptations that may be beneficial, but one of the hemodynamic benefits may be the presence of the shunt to serve as a "pop-off valve." Septostomy has been around for a very long time. Personally, I've done a few, but they were performed as a last-gasp effort and although initially successful, the longer-term outcome was poor. We recently published a meta-analysis of the studies of septostomy and found short-term outcomes to be fair, but long-term outcomes to be poor. It's a dangerous procedure and you're exchanging one set of problems, a low cardiac index, for another, hypoxia.

The use of the percutaneous Potts shunt, where the right-to-left shunt is from the left PA to the descending aorta, may be more favorable. The shunt is beyond the coronary and brain blood supply, so you are not creating cyanosis at the neurological and heart level. It's a little bit more appealing to think about improving cardiac output but not dropping the systemic saturation to the most vital organs. Can you give us a little bit

of background on this shunt? Have you had any experience with it?

Dr Aboulhosn: The first time I became aware of a percutaneous Potts shunt in a human being was actually by reading about the work that was being done by the great James Lock at Boston Children's. They ended up publishing a case series of Potts shunts that they did in patients and they were successful. They did have some technical issues, but they were successful in doing them. I think the concept is an interesting one. It goes back to this, that patients with Eisenmenger syndrome who have patent ductus arteriosis (PDA) tend to do a lot better than patients, say, with Eisenmenger-type physiology who have a pretricuspid valve shunt. Those who have ventricular septal defects and PDAs seem to do better, but the PDAs seem to do best out of those 3 groups. There are some important reasons for that, and you alluded to the main one, which is that you are not sending highly deoxygenated blood to the brain and, importantly, to the carotid bodies—the chemoreceptors that we have in our carotid bodies that end up driving our respiratory rate and increasing our minute ventilation when there's a detection of hypoxia or elevation in CO_2 levels. It's a nice idea that you would put your right-to-left shunt beyond the subclavian artery and just desaturate your lower body.

As far as the technical aspects of it, it's a very challenging procedure, frankly. What you have to try to do is either use a radiofrequency wire or a transseptal needle, but preferably a radiofrequency wire, and try to go from the descending aorta into the left PA, which is basically what used to be called in the old days, when done surgically, a Potts shunt. That's what you're trying to create here. Then you need to snare the wire on the PA side, create a wire rail, and then put in a short covered stent that doesn't obstruct the aorta and doesn't obstruct flow in the PA. Usually, obstruction of flow in the PA is not an issue here. Why? Because the left PA tends to be severely dilated in a patient with severe PAH who is being considered for this procedure, but in someone with a low cardiac output state who has severe PH, the aorta might be quite small. So how far that stent sticks into the aorta, especially if you're using a covered stent, could be an issue.

Now, one could potentially consider a fenestrated closure device, such as the AFR device, for example. Could something like that be utilized in this space to create an aorta pulmonary window and not have a large stent in the aorta? One of the issues with the surgical Potts shunts in the congenital population, and why they've been completely abandoned as a palliative shunt, is the difficulty with controlling pulmonary blood flow in patients who have low PA resistance. So if you put it into a child, for example, with pulmonary atresia who has limited pulmonary blood flow, you will have torrential blood flow to the pulmonary arterial bed, usually the left PA.

The work of Abraham Rothman in Las Vegas is very applicable here, actually, for the creation of these kinds of Potts shunts in large-animal models. The consequences of uncontrolled pulmonary blood flow into the left PA are that the left PA thromboses, and you accelerate the pulmonary vascular disease process of completely distorting the architecture of the pulmonary vascular bed on that side. Those are the technical issues involved with this.

One case that I did see a few years ago when I was in Europe and at a meeting of the congenital heart society there in Munich was a case where they used a Melody valve in a large PDA. They put it into a PDA in a patient with severe PH, which is a really interesting concept, because what you're doing here is essentially valving this kind of shunt. Oftentimes, if you look at patients with PDAs who have Eisenmenger-type physiology, what you're going to get is a near equalization or equalization in systolic pressures, or maybe the PA systolic pressure would be higher than the aortic systolic pressure. But often you will have a lower PA diastolic pressure than aortic pressure. What's happening there is that you're shunting right-to-left in systole and left-to-right in diastole, but having a valve would prevent that. The valve would close during diastole and you wouldn't end up getting the excess pulmonary blood flow at that point. You'd have a pure right-to-left shunt in that location. I know I'm getting a little bit too technical here, but this is how I think of it: that this would be a fascinating intervention to do, but there are a lot of technical challenges to it. It's not widely utilized, but I do think there are some major advantages to doing it.

There are other areas where you can also create shunts, and these we have done, which is at the ventricular septal level. You can stent the muscular ventricular septum, and you can do that safely, thereby creating a muscular ventricular septal defect as a pop-off for a severely hypertensive RV. It can work well and can decrease the RV systolic pressure. However, it does lead to this issue of more severe desaturation and the consequences thereof, especially the desaturation caused by the right-to-left shunting at the ventricular septal level that is taking place proximal to the cerebral vessels for the reasons I described earlier.

As far as the septostomies go—atrial-level septostomies and the creation of atrial-level shunts—I think that's gotten a lot safer with the advent of radiofrequency wires and needles. For example, the Bayliss systems that are now commercially available are great because if you have a tiny left atrium and a huge right atrium with a septum that is bulging deep into the left atrium, in prior years we would have to use the Brockenbrough needle and try to push until we broke through, and the needle could go through the septum and end up going right through the back wall of the left atrium. Now that risk is much lower with the use of radiofrequency needles and wires. I think performing the procedure is safer and we do have more choices now with the fenestrated devices for attempting to control the size of any fenestration that you create. I do think that the future for these shunts probably lies in the transcatheter Potts shunt, and I think the basic hemodynamic principles and physiologic principles when it comes to the Potts shunt do make it superior to an atrial-level shunt and even to a ventricular septal–level shunt. Really, the key here is going to be the technical details

and making this more widely applicable as opposed to something that's done by a few people around the world who are highly skilled, and done in variable ways at that.

Dr Krasuski: Thank you for that very erudite discussion, Jamil. While you were discussing shunts and fenestrated devices, I thought it would be worth noting that companies are now designing devices that create an atrial shunt for patients with heart failure and preserved ejection fraction. In this case they are decompressing the left atrium into the right to reduce pulmonary congestion. One company in particular, Corvia, is pretty far along now in their clinical trials and may get FDA approval soon. Who knows, maybe this technology may one day be applied in PAH to facilitate the creation of a more effective septostomy. In addition to the problem you noted (perforation of the left atrium), there's also been the issue of the creation of shunts that are just too large, resulting in excessive hypoxia or the septostomy site itself closes afterwards, undoing the benefit and requiring reintervention. The use of such a device may eventually eliminate these problems.

Well, this roundtable has been extremely educational for me, and I hope it will be for our readers as well. I'd like to thank you all for taking time out of your busy schedules to join me. It's certainly a welcome respite from the COVID-19 pandemic, a great chance to sit down and talk about anything other than the coronavirus. Thank you, gentlemen, on behalf of myself and our readers.

ASK THE EXPERT

Is There a Role for Percutaneous or Surgically Implanted Right Ventricular Assist Devices in Pulmonary Arterial Hypertension?

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The development of right ventricular (RV) failure in patients with pulmonary arterial hypertension (PAH) is associated with a dismal prognosis. While phosphodiesterase-5 inhibitors, prostacyclin analogs, endothelin receptor antagonists, and other medications have transformed the prognosis of PAH, these therapies have limited effectiveness. A subset of patients develops right heart failure in the face of severely elevated pulmonary vascular resistance (PVR) despite optimal medical management. The appropriate role for mechanical support of the failing RV in the context of PAH remains undefined.

There is rapidly growing experience with left ventricular assist devices (LVADs) to provide mechanical circulatory support, both percutaneous and durable surgical options. RV assist devices (RVADs) have also been increasingly used; for example, to provide temporary RV support in patients with acute myocardial infarction involving the RV. PAH, however, is associated with additional obstacles to RV mechanical support. For one, increasing pulmonary flow can cause harm in the setting of fixed, elevated PVR. Risks include pulmonary hemorrhage and pulmonary edema, due to either increasing pulmonary arterial (PA) pressures or indirect adverse effects on left ventricular (LV) filling.[1]

Currently, LV support can be considered in diverse circumstances. A key question is how long mechanical support is likely to be needed; some devices provide temporary support, while others can provide durable support for years. When extrapolated to RV support in PAH, acute RV decompensation can occur at the time of initial PAH presentation, before starting PAH-specific therapies, or in patients with longstanding PAH because of acute illness. In these contexts, temporary RV support could be used until recovery or until optimization of pulmonary vasodilator therapy. Durable RV support can be considered in situations with patients with end-stage PAH and progressive symptomatic RV failure despite optimal medical therapy awaiting organ transplantation. Punnoose et al have explored computational models of RVAD effects on pulmonary vascular, peripheral vascular, RV, and LV hemodynamics at various stages of PAH and RV failure.[1] These models predict that RVAD support would improve RV hemodynamics (eg, higher pulmonary flow, lower right atrial pressure), but at the cost of increased pulmonary pressures. Maintaining low RVAD flow rates may mitigate the associated risk, but this approach would limit benefit and is restricted by rotational limits and related risk of thrombosis.

Key Words—pulmonary arterial hypertension, right ventricular assist device, mechanical circulatory support, right heart failure
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Several options exist for temporary RV support, including the Impella-RP (Abiomed, Danvers, Massachusetts), TandemHeart (LivaNova, London, UK), and CentriMag (Abbott, Chicago, Illinois). Off-label use of durable LVADs surgically implanted in the RV position, such as the HeartWare Ventricular Assist Device (HVAD; HeartWare, Framingham, Massachusetts) and HeartMate III (Abbott), has also been reported. The Impella-RP is an 11 French axial-flow pump placed through a femoral vein with blood inflow provided from the inferior vena cava and outflow directed into the main PA at up to 4.0 L/min. The TandemHeart is an external continuous flow pump that can provide up to 5 L/min of flow with speeds up to 7500 rpm. The use of the TandemHeart with a ProtekDuo catheter (LivaNova) allows for single-site vascular access via the right internal jugular vein; inflow to the pump is from the RA, and outflow is directed to the main PA. Above-the-diaphragm access facilitates patient mobility and rehabilitation. The CentriMag device is an extracorporeal continuous flow pump compatible with various cannulation strategies, placed either surgically or percutaneously, that can provide up to 9.9 L/min of flow. Durable surgical cannulation also enables easier ambulation and rehabilitation and is currently approved for humanitarian use up to 30 days for cardiogenic shock. Both continuous flow pump options, TandemHeart and CentriMag, can incorporate an oxygenator into the circuit to provide oxygenation in addition to hemodynamic support. Finally, the HVAD and the HeartMate III are surgically implanted LVADs which have been used off-label as durable RVADs; currently, there are no FDA-approved durable RVADs.[2,3]

Despite these many options, the published experience using RVADs in patients with PAH remains limited to case reports.[4–6] Rosenzweig et al describe a patient with longstanding PAH with progressive RV failure and recurrent hospitalizations despite maximal medical therapy.[4] Given safety concerns, a staged approach was used. First, a trial of temporary percutaneous RV support was provided with cannulation of the internal jugular vein using a ProtekDuo cannula connected to a CentriMag pump. Low flows (1.0 L/min) were initiated, increasing mean PA pressure ~8 to 10 mm Hg, without complications. Flows were gradually increased to 2.0 L/min with no further increase in PA pressure. Based on this favorable response, a durable HVAD was then implanted. Vullaganti et al also report a patient with RV failure in the setting of chronic thromboembolic pulmonary hypertension.[5] Temporary RVAD support was provided with a ProtekDuo cannula connected to a TandemHeart pump. There were no acute complications, and there was short-term improvement with flows up to 3.7 L/min; durable RVAD support was then pursued with an HVAD. Both patients ultimately died due to septic shock within 1 to 4 weeks after HVAD implantation.

Experience is far too limited to provide confidence in the safety or effectiveness of isolated RV mechanical support with PAH, even for the few patients without alternative options who might be considered. At the same time, the growing experience with and improving outcomes of other approaches, such as extracorporeal membrane oxygenation and pumpless membrane ventilators (eg, Novalung device, Xenios, Heilbronn, Germany), have further narrowed the potential role for RVAD support in PAH.[7,8]

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PH GRAND ROUNDS

Giant Pulmonary Artery Aneurysm and Severe Multifactorial Pulmonary Hypertension: A Case Report

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PRESENTATION

A 63 year-old morbidly obese female with chronic hypercarbic and hypoxic respiratory failure was referred to our program for severe pulmonary hypertension (PH) identified on right heart catheterization (RHC).

On presentation, she complained of increasing shortness of breath on exertion, in setting of PH directed therapy with macitentan and sildenafil prescribed 3 years before. She had initially improved on this regimen and supplemental oxygen. The patient remained compliant with a continuous positive airway pressure device and supplemental oxygen for obstructive sleep apnea. In clinic, vital signs were unremarkable; she had normal O2 saturation on 3 L/min supplemental oxygen. Physical exam revealed no jugular venous distention or right ventricular heave. S1 and S2 were equal; lungs were clear to auscultation bilaterally. Trace lower extremity edema was present. A comprehensive evaluation for pulmonary arterial hypertension (PAH) excluded connective tissue disease and other Group 1 etiologies. A severe restrictive ventilatory defect and impairment of diffusing capacity were reported on pulmonary function testing. Echocardiogram revealed left ventricular ejection fraction of 80%, normal right ventricular size and function, moderate to severe pulmonic regurgitation, and a previously unreported large pulmonary artery aneurysm (PAA), measuring over 7 cm. Computed tomography angiography of the chest confirmed a main pulmonary artery aneurysm of 7.4 cm at its greatest dimension (Figures 1 and 2). Serologies for associated infection (syphilis and tuberculosis) were negative. A repeat RHC demonstrated elevated mean pulmonary arterial pressure of 48 mm Hg, pulmonary capillary wedge pressure 21 mm Hg, pulmonary vascular resistance 5.38 Wood units, and Fick cardiac index 2.49 L/min/m^2. Diuresis was intensified. Patient was referred to an academic center for consideration of surgical management. Her pulmonary function tests and functional status excluded her from surgery. Pulmonary hypertension directed therapy was reconsidered; macitentan was discontinued in view of pulmonary vascular congestion, while sildenafil was continued.

Right heart catheterization repeated 10 months later revealed worsening hemodynamics: mean pulmonary arterial pressure 50 mm Hg, pulmonary capillary wedge pressure 14 mm Hg, pulmonary vascular resistance 7.8 Wood units, and Fick cardiac index 2.34 mL/min/m^2. Selexipag was added and titrated to maximal tolerated dose. Exertional dyspnea, peripheral swelling, and oxygen requirement have improved with continued directed PH therapy. The PAA has remained stable in size on serial computed tomography pulmonary angiography for 2 years.

DISCUSSION

A giant PAA with coexistent severe multifactorial PH represents a man-

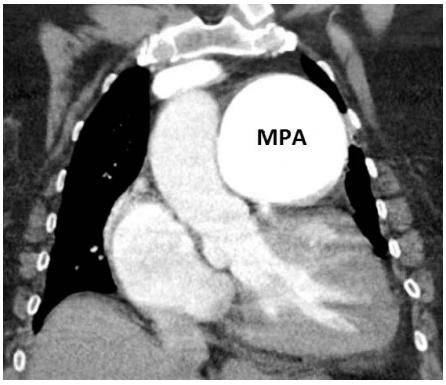

Figure 1: Chest computed tomography angiography, coronal view, demonstrating 7.4 cm main pulmonary artery (MPA).

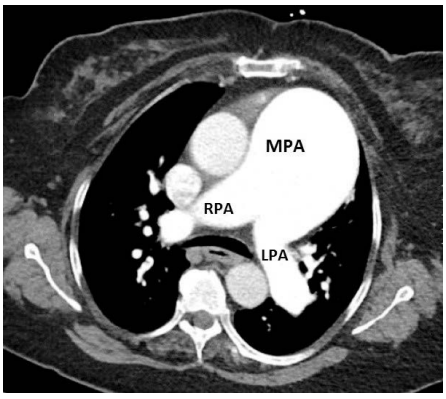

Figure 2: Chest computed tomography angiography, axial view, demonstrating dilated main (MPA), right (RPA), and left pulmonary arteries (LPA).

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agement challenge. Pulmonary artery aneurysm is an unusual defect that can be seen in patients with PH. Pulmonary artery aneurysms are defined by vessel diameter greater than 4 cm and are relatively rare, with a reported incidence of 0.0073%.[1] There is a slight female predominance, with peaks of occurrence in the third and sixth decades.[2] Congenital heart disease with left-to-right shunt accounts for more than half of PAA cases. The remainder are associated with connective tissue disease (vasculitis), infections (including syphilis and tuberculosis), PAH, chronic pulmonary thromboembolic disease, pulmonary vascular neoplasm, and cystic medial necrosis. Of note, prior studies have reported a PAA prevalence of 1.3% to 24% in PAH.[3] However, a recent retrospective cohort study reported 38% of PAH patients having evidence of aneurysmal dilation of one of the proximal pulmonary arteries.[4]

Pulmonary artery aneurysms are often asymptomatic but can present with heart failure symptoms of dyspnea, chest pain, and cough due to mass effect.[5] The mechanism by which PA dilation progresses in PH patients with a PAA remains unclear.[4] Several small studies have suggested PH and PAAs progress independently.[6,7]

Other literature suggests that increased pulmonary pressures superimposed on large-radius aneurysms may increase parietal wall stress, causing intimal tearing and increasing risk for PA dissection or rupture.[8,9] Reducing hemodynamic stress on the PA wall may prevent progression of PAA dilation.[10]

Surgery is the treatment of choice in selected patients, but there is not consensus on a vessel diameter threshold or growth rate for surgery.[5,8] One report suggested operating at a diameter greater than 5.5 cm, based on the guidelines for aortic disease, or with an increase in diameter of greater than 0.5 cm in 6 months.[5] Our patient was not a surgical candidate due to comorbid chronic respiratory failure complicated by coexistent severe PH. Also, a vascular lesion involving a proximal pulmonary artery and more distal arterioles would not be corrected by surgery.[5,11] Therefore, PAH targeted therapy was continued, given RHC data that met the hemodynamic definition of PAH, as well as for potential salutary effect of reduction of shear force on this patient's giant, inoperable PAA.

Our case describes challenges in management of a giant PAA complicated by severe multifactorial PH. Though the patient's PH had characteristics of Group 1 and Group 3 disease, in this case, management with PH directed therapy was associated with decreased oxygen requirement and improved exertional tolerance. The Sixth World Symposium on Pulmonary Hypertension (WSPH) does not currently recognize an indication for PH directed therapy in patients with combined Group 1 and 3 disease.

In conclusion, PH directed medical therapy might be a useful adjunct to management of inoperable PAAs complicated by coexisting PH.

KEY POINTS

- A pulmonary artery aneurysm (PAA) is comparatively rare, with reported incidence of 0.0073% in the general population.
- Congenital heart disease, vasculitis, and infection (mycotic) are recognized etiologies for PAAs. An association of PAAs with pulmonary arterial hypertension is more common than previously thought.
- There is no consensus as to what threshold PAA diameter requires operative intervention. Literature suggests surgical intervention at a diameter greater than 5.5 cm based on guidelines for aortic disease.
- A beneficial effect of PH directed therapy might be seen in management of cases of combined Group 1 and 3 disease, as in this patient with coexistent PAA. However, this is not currently a recognized indication for PH directed therapy.

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