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Section

The Nuts and Bolts of Interpreting Hemodynamics in Pulmonary Hypertension Associated With Diastolic Heart Failure



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IMPORTANCE OF CARDIAC CATHETERIZATION

The definitions of PAH and of PH associated with DHF illustrate why cardiac catheterization is critical in the differentiation of these conditions (Table 1). PAH is defined by a pulmonary artery (PA) mean pressure ≥ 25 mm Hg while the left heart filling pressure (either the pulmonary capillary wedge pressure [PCWP] or LV end-diastolic pressure [LVEDP]) is \leq 15 mm Hg. Many also believe that a pulmonary vascular resistance (PVR) ≥ 3 Wood units is necessary for the diagnosis (discussed below in "Important Calculations"). In contrast, PH associated with DHF is defined by a PA mean pressure \geq 25 mm Hg, while the PCWP or LVEDP is >15 mm Hg. The PVR may be normal or elevated; an elevated PVR (\geq 3 Wood units) raises the possibility of PH out of proportion to the severity of the underlying DHF. This entity is described in more detail below in "Errors in Data Interpretation."

In addition to confirming the diagnosis, cardiac catheterization also provides critical prognostic information: in patients with PAH, findings consistent with right heart failure (elevated right atrial [RA] pressure [\geq 15 mm Hg], and depressed

With the widespread application of transthoracic echocardiography as a screening tool for pulmonary hypertension (PH), we have come to appreciate the prevalence of PH associated with diastolic heart failure. Diastolic heart failure (DHF, sometimes called heart failure with preserved, or normal, left ventricular ejection fraction [HFpEF]) is quite common, and PH appears to be a fairly frequent component of DHF.¹⁻³ The epidemiology of these conditions is described in the article by Dr Soto in this issue of Advances. There is a complex relationship between DHF and PH: the 2 may exist independent of each other or in combination; and when they exist in combination, the PH may be in proportion or out of proportion to the DHF. Cardiac catheterization is critical in differentiating among these patterns, and this distinction may lead to important modifications in treatment strategy. This requires, however, a full understanding of the proper performance and interpretation of cardiac catheterization, as well as the potential pitfalls that can limit the utility of the procedure. This article will discuss these aspects of cardiac catheterization as they pertain to patients with pulmonary arterial hypertension (PAH) and PH associated with DHF. A number of important aspects of cardiac catheterization are not covered here due to space limitations but can be obtained in a more detailed text.⁴

cardiac index [CI] ($\leq 2.2-2.5 \text{ L/kg/min}^2$]) confer a poor prognosis, while a positive response to acute vasodilator testing confers a better one.⁵⁻⁷ These catheterizationbased prognostic markers also help with initial management decisions: poor prognostic markers indicate the need for more aggressive therapies,⁸ and filling pressures can be valuable in guiding fluid management. Finally, cardiac catheterization is an important part of patient followup, indicating the need for treatment modifications and consideration of lung transplantation.⁹

BASICS OF CARDIAC CATHETERIZATION Safety

When combined with clinical assessment and echocardiography, right heart catheterization (RHC) alone is usually sufficient for making the diagnosis of PAH or PH associated with DHF. In selected patients, however, full right and left heart catheterization may be required. Cardiac catheterization is both necessary and safe in this patient population. It is necessary because the definitions of PAH and PH associated with DHF literally depend on catheterization-derived values. And RHC is safe, as documented in a study of over 7000 such procedures performed over a 5-year period at 20 PH centers by experienced operators.¹⁰ In this study there was a 1.1% significant complication rate (mostly related to venous access) and a 0.05% procedural mortality. Left heart catheterization carries a somewhat higher risk.⁴ It is generally agreed that the benefits of catheterization in these patients outweigh the risks in almost all cases, and should be performed unless clearly contraindicated.

Technique

The technique of cardiac catheterization has been described in detail in textbooks devoted to the subject.⁴ Briefly, after sterilizing the skin and administering local anesthetic to the access site, the vessel is entered and a J-wire advanced to secure access. For a RHC, after appropriate position is confirmed and a sheath is placed over the wire, a balloon-tipped PA catheter is placed into the venous system. The catheter is advanced into the right heart and pressures are recorded from the RA, right ventricle (RV), PA, and PCWP positions. Under most circumstances, the PCWP is an accurate reflection of left heart filling pressure. In certain circumstances, however, this is not the case, and measurement of LVEDP is necessary. Most commonly, this arises when there are technical difficulties in wedging the catheter properly, or in clinical situations

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Figure 1: Normal right heart catheterization pressure waveforms. From left to right: right atrium (RA), right ventricle (RV), pulmonary artery (PA), and pulmonary (capillary) wedge pressures (PW) are shown. Note in the RA tracing, "a" and "v" waves can be seen immediately following the P and T waves of the ECG, respectively.

where the LVEDP is expected to be abnormal or the PCWP is suspected to be falsely elevated (discussed below in "'Over-' and 'Under-Wedged' Catheters").

Waveforms and Interpretation

An example of normal RHC pressure waveforms is shown in Figure 1. It is best to interpret waveforms in relation to the ECG. This allows for proper recognition of the "a" and "v" waves in the RA or PCWP tracings. The "a" wave occurs just after the P wave of the ECG and represents the pressure increase from atrial contraction (in patients with atrial fibrillation, it occurs just before the QRS complex and represents the peak of atrial filling pressure). The "v" wave occurs just after the QRS complex, often on the T wave, and represents the pressure increase from ventricular contraction (Figure 1). Many catheterization laboratories report

computer-generated mean pressures for the RA, PA, and PCW pressures. These are arguably acceptable in most patients, but can yield erroneous values in certain situations where dramatic respiratory variation in pressure is present (discussed below in "Errors in Data Interpretation"). Considering the critical importance in deriving accurate hemodynamics, it is recommended that pressure measurements be read at end-expiration (Figure 2).

Cardiac Output Measurement

Cardiac output (CO) is measured often by both thermodilution and modified Fick techniques, which require oxygen saturation measurements from the pulmonary and systemic arteries (the latter is often done noninvasively with oximetry). If the PA oxygen saturation is high, oxygen saturation measurements should also be made throughout the right heart including the central veins to rule out a left to right shunt. Thermodilution CO is felt to be particularly subject to error in patients with severe tricuspid insufficiency, intracardiac shunts, and extremely high or low CO. Accordingly, with the patient in the resting state, and with no physiological issues (such as metabolic derangements or general anesthesia) that would render the assumed oxygen consumption erroneous, the modified Fick method is likely the more accurate measurement. It is important to recognize, however, that when the assumed oxygen consumption is not valid, such as with exercise, the Fick method cannot be used unless a direct measure of oxygen consumption is made. Even in the best of circumstances, there can be significant disagreement in the CO values obtained by these 2 techniques (Figure 3)¹¹; which method is entered into calculations may come down to operator preference and sense of which is more accurate, and technique type should be documented.

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Important Calculations

Two calculations using data from the RHC are critical in the diagnosis of PAH and PH associated with DHF. The transpulmonary gradient (TPG) is calculated as the difference between the PA mean pressure and the PCWP; a normal value is ≤ 12 mm Hg. The PVR is calculated as the TPG divided by the CO; a normal value is <3 Wood units (or 240 dynessec-cm-5). In pediatric patients, the PVR is often indexed to body surface area. The PVR calculation illustrates the importance of trying to record as accurate a CO as possible. TPG and PVR values are included in Table 1 for easy reference.

Provocative Maneuvers

Provocative maneuvers, including acute vasodilator testing, volume loading, or exercise, may be performed during RHC to confirm the diagnosis of DHF if not apparent on the resting hemodynamic data. These results can help refine the diagnosis, provide important prognostic and therapeutic information, and yield insights into the mechanisms underlying a patient's functional limitation.

ACUTE VASODILATOR TESTING

Consensus guidelines recommend that acute vasodilator testing be performed at the time of RHC in patients diagnosed with PAH.⁵ The rationale for this is that a robust positive response indicates a more favorable prognosis and identifies patients more likely to benefit from calcium channel blocker therapy. A positive response is currently defined as a fall in mean PA pressure of at least 10 mm Hg, to a value \leq 40 mm Hg, with no compromise in CO. Acute vasodilator testing can be performed with a number of different agents, including inhaled nitric oxide, intravenous adenosine, or intravenous epoprostenol.⁵ However, it should be noted that for patients with markedly decompensated right heart failure and RV dysfunction where calcium channel blockers would not be an appropriate long-term therapy, acute vasodilator testing may not be advised. Likewise, it is important to recognize that administering one of these selective pulmonary vasodilators in patients with PH associated with DHF risks



Figure 2: Dramatic respiratory variation in the pulmonary capillary wedge pressure tracing. Note that the end-expiratory pressure, approximately 17 mm Hg, is significantly higher than the computer-generated mean pressure (read as 14, ranging from 8-15 mm Hg). In the absence of dramatic respiratory variation, the computer-generated mean pressure is generally acceptable.

precipitating pulmonary edema and thus should be avoided. If it is felt that acute vasodilator testing may be valuable for such a patient, a balanced systemic and pulmonary vasodilator (such as nitroprusside or nitroglycerine) would be a safer choice.

VOLUME LOADING

Occasionally, acute administration of intravenous fluid may help elucidate a patient's underlying pathophysiology. An example of this maneuver would be for a patient with a high probability of DHF, and a RHC showing elevated pulmonary pressures but with low cardiac filling pressures. In this instance acute administration of intravenous fluid may unmask underlying DHF. In this scenario, care should be taken that only enough fluid to demonstrate a clinically significant rise in left heart filling pressures be administered so as not to provoke pulmonary edema.

EXERCISE

Frequently, patients present with cardiorespiratory symptoms predominantly or exclusively with exercise. If resting RHC





Figure 3: Relatively poor agreement between cardiac output (CO) measured by the thermodilution and Fick methods. Note that this is seen regardless of whether CO is preserved or depressed, and in the presence or absence of severe tricuspid regurgitation (TR). Reprinted with permission from: Hoeper MM, et al. Determination of cardiac output by the Fick method, thermodilution, and acetylene rebreathing in pulmonary hypertension. Am J Respir Crit Care Med. 1999;160(2):535-541.

data do not elucidate an explanation for the symptoms, one can consider repeating measurements while the patient is exercising. A variety of exercise types (arm "flies" while holding saline bags, bicycle ergometry) and patient positions (supine, upright) have been employed.^{12,13} The goal of exercise is to increase heart rate, blood pressure, and CO sufficiently to reproduce the patient's symptoms. Hemodynamics (pressures and CO) are measured at intervals and at peak exercise. It's important to remember that the Fick method is not valid for CO measurement during exercise unless direct measures of oxygen consumption are made. In work performed at our institution, we have identified 4 distinct hemodynamic subsets with RHC during exercise: normal, exercise-induced PH, exercise-induced DHF, and exercise-induced PH with DHF. These are illustrated in Figure 4. This is an area under active discussion and, at present, the optimal approach to treating these subsets of patients is unknown and requires further investigation.

PITFALLS OF CARDIAC CATHETERIZATION

Aside from the relatively low risk of procedural complications when performed by an experienced operator, the pitfalls of cardiac catheterization fall into 2 general categories, which include errors in data acquisition and errors in data interpretation.

Errors in Data Acquisition

The most paramount requirement for accurate data acquisition is that laboratory equipment be maintained and set up properly. Laboratory staff and the operator should both take responsibility for ensuring that catheters, tubing, and manometers are connected and flushed properly; that the manometer is accurately leveled and calibrated; and that recording equipment is functioning appropriately. All personnel should scrutinize waveforms to ensure they are not dampened (usually from poor flushing leaving air bubbles within the lumen of the catheter or tubing) or affected by "whip" (from excessive catheter movement within the heart) (Figure 5).

"Over-" and "Under-Wedged" Catheters

Care must be taken when obtaining the PCWP to ensure that the catheter is neither "over-" nor "under-wedged." Overwedging results from excessive inflation pressure in the catheter balloon. It usually

				PH associated with HF	
	Normal	РАН	HF	"in proportion"	"out of proportion"
RA (mm Hg)	0-5	nl or ↑	nl or ↑	nl or ↑	nl or ↑
RV (mm Hg)	15-25/0-10	>30/nl or ↑	nl or ↑	>30/nl or ↑	>30/nl or ↑
PA (mm Hg)	15-25/6-12	>30/>15	nl or ↑	>30/>15	>30/>15
PA mean (mm Hg)	<25	≥25	nl or ↑	≥25	≥25
PCWP (mm Hg)	≤12	≤15	>15	>15	>15
CO (L/min)	>5	nl or ↓	nl or ↓	nl or ↓	nl or ↓
CI (L/min/m2)	>2.4	nl or ↓	nl or ↓	nl or ↓	nl or ↓
TPG (mm Hg) (=PA mean-PCWP)	≤12	>12	nl	nl	↑
PVR (units) (=TPG/CO)	≤3	>3	nl	nl	1

Table 1: Hemodynamic Definition. PH, pulmonary hypertension; HF, heart failure; PAH, pulmonary arterial hypertension; RA, right atrium; RV, right ventricle; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; TPG, transpulmonary gradient; PVR, pulmonary vascular resistance; nl, normal; \uparrow , elevated; \downarrow , depressed. Note that when PH exists "in proportion" to HF, the elevation of PA pressure is completely explained by the elevation of PCWP. The TPG and PVR are normal. When PH exists "out of proportion" to HF, the elevation of PA pressure exceeds that expected for the degree of PCWP elevation. The TPG and PVR are elevated

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produces a dampened waveform, devoid of distinct "a" and "v" waves, and can lead to artificially high or low values. Beyond inaccurate data, over-wedging also increases the risk of PA rupture, a potentially fatal complication, and thus should be assiduously avoided. A more common error is under-wedging. Under-wedging results from the catheter balloon incompletely occluding the branch PA, producing a hybrid waveform composed of elements of both the PA tracing and the PCWP tracing. As a rule this artificially increases the PCWP value (Figure 6). Under-wedging is a frequent problem in patients with very high PA pressures, likely related to poor compliance of their pulmonary vascular beds.

The best strategy for correcting overand under-wedging is to adjust balloon inflation pressure and/or catheter position. In the case of over-wedging, partial deflation of the balloon is usually all that is required. For under-wedging, 2 different strategies can be attempted: the balloon can be deflated and then slowly re-inflated (often only partially) until the catheter wedges more distally and more completely; or, the catheter can be withdrawn to the main PA, and then manipulated into a different PA branch where it may be properly wedged. In either case, proper wedge position should be confirmed by fluoroscopy, waveform inspection, and, if possible, by confirming that the oxygen saturation of the blood withdrawn from the distal port while in the wedge position is in the systemic arterial range. If there is any doubt about the PCWP being accurate, a left heart catheterization should be performed to directly measure the LVEDP. While a large study demonstrated poor agreement between PCWP and LVEDP,¹⁴ there is a general consensus that RHC is sufficient in most patients undergoing evaluation for PH. The entire clinical picture of the patient should be considered when judging the accuracy of the PCWP and therefore the need for a left heart catheterization. For example, if the patient has a high probability of DHF (eg, advanced age, systemic hypertension, and obesity), the finding of an elevated PCWP is more consistent with the clinical picture than if a patient lacks other comorbidities





Figure 4: Change in pulmonary artery (PA) and pulmonary capillary wedge (PCW) pressures with graded supine bicycle exercise. Patients are grouped by response: normal (normal resting pressures and neither PCW nor transpulmonary gradient [TPG] increase by >5 mm Hg from baseline with exercise); pulmonary arterial hypertension (PAH; either resting PAH as described in the text, or an exercise-induced increase in PA mean to >30 mm Hg, with PCW <18 mm Hg, and TPG increase >5 mm Hg from baseline); diastolic heart failure (DHF; either resting PCW >15, or an exercise-induced increase in PCW to >18, and TPG increase <5 mm Hg from baseline); and DHF + pulmonary hypertension (DHF + PH; either resting PCW >15 mm Hg, or an exercise-induced increase in PCW to >18, and TPG increase >5 mm Hg). The meaning of these categories is uncertain, and there are as yet no data to support specific therapies aimed at exercise-induced hemodynamic changes. Unpublished data, courtesy of Dr David Ishizawar.

seen frequently in association with DHF. Again, if there is any doubt about the reliability of a PCWP measurement that might impact treatment course, a leftsided cardiac catheterization should be performed. A practical approach to ensuring an accurate measure of left heart filling pressure in patients with PAH or PH associated with DHF is shown in Figure 7.

ERRORS IN DATA INTERPRETATION

Even when accurate RHC data are acquired, errors can be made in the interpretation of these data. A number of clinical conditions can lead to these errors, and others can be difficult to interpret even in the absence of any errors being committed. Among the conditions that can lead to errors in the interpretation of RHC data are advanced parenchymal lung or airway disease, morbid obesity, severe mitral regurgitation, and DHF in a patient with volume depletion. With advanced lung disease, intrathoracic pressure fluctuation is exaggerated, and the PCWP at endexpiration can differ considerably from the mean PCWP. Relying on the mean in this circumstance will significantly underestimate the true PCWP. Morbid obesity often produces the same phenomenon, and can have the added confounding influences of elevated PCWP from DHF and elevated CO. Severe mitral regurgitation usually results in large "v" waves in the PCWP tracing. These "v" waves will drive the mean PCWP up significantly; many advocate reading the PCWP at the "a" wave to account for this expected change. In the volume depleted patient with DHF, elevated PA pressures may be misinterpreted as PAH because intracar-



Figure 5: Panel A: Dampened right ventricular (RV) pressure tracing. Note the overly smooth waveforms. Panel B: Pulmonary artery (PA) pressure tracing with excessive "whip" induced by catheter movement. Note the spikes in the pressure waveform.

diac filling pressures will be low. As described above, volume loading in this instance may bring out the true pathophysiology.

Beyond the well-known conditions that may lead to erroneous interpretation of data, there are often other subtler and more frequently encountered clinical situations that leave the care provider in a "gray area" with regard to interpretation of the data. One commonly encountered situation is when PH exists, but is confounded by circumstances that call into question the safety and/or value of initiating PAH-specific therapy. An example is PH "out of proportion" to underlying DHF. In this situation, if the TPG and PVR are significantly elevated, PAHspecific therapy may be of value. A graphic depiction of this situation is shown in Figure 8. As shown, if there is

PH with PCWP <15 mm Hg, this defines PAH and treatment with a PAH-specific agent is clearly indicated. If there is PH but the PCWP is severely elevated (eg, >20-25 mm Hg), treatment with a PAHspecific agent is very unlikely to be tolerated and should not be considered. However, if there is PH with PCWP between 15 and 25 mm Hg, PAH-specific therapy can be considered if the PVR is elevated to a degree that is "out of proportion" and if intracardiac filling pressures can be controlled reasonably well. It must be emphasized that the exact definition of "out of proportion" and the value of using PAH-specific therapy for PH out of proportion to DHF remains uncertain.

Another typical hemodynamic scenario leading to a clinical "gray area" is in the patient with elevated PA pressures and TPG but with high CO and therefore normal or minimally elevated PVR. There is still debate on whether such a patient would benefit from PAH-specific therapy. Examples of this include patients with advanced liver disease and portopulmonary hypertension, and those with chronic kidney disease in whom the CO may be increased in the setting of an arteriovenous fistula for hemodialysis.

CONCLUSION

Cardiac catheterization is an indispensible tool in the diagnosis and management of patients with PAH and those with PH associated with DHF. It allows for differentiation between these conditions, which can appear markedly similar from initial echocardiographic assessments, provides critical input in deriving therapeutic decisions, contributes prognostic information, and figures prominently in patient follow-

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Figure 6: Pulmonary artery (PA) and pulmonary (capillary) wedge (PW) pressure tracings in a patient with severe pulmonary arterial hypertension (PAH). The middle panel shows an "underwedged" tracing composed of elements of the PA pressure tracing and the true PW pressure tracing. The value exceeds that of the true PW pressure tracing shown in the right panel.

up. Provocative maneuvers, including vasodilator challenge, volume loading, and

exercise can help uncover the pathophysiology attributing to patients' symptoms. For all of these advantages, however, the procedure is only valuable if performed



Figure 7: Algorithm for accurate and efficient determination of left heart filling pressure in patients undergoing assessment of pulmonary hypertension. RHC, right heart catheterization; R & LHC, right and left heart catheterization; H&P, history and physical examination; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; dz, disease; PND, paroxysmal nocturnal dyspnea; AV/MV, aortic valve/mitral valve; LVH, left ventricular hypertrophy; AF, atrial fibrillation; LAE, left atrial enlargement; LVEF, left ventricular ejection fraction; RWMAs, regional wall motion abnormalities.



Figure 8: Graphic representation of pulmonary hypertension (PH) in the context of pulmonary capillary wedge pressure (PCWP). When the pulmonary artery (PA) mean pressure exceeds 25 mm Hg and the PCWP is <15 mm Hg, this defines pulmonary arterial hypertension (PAH). When the PA mean pressure is >25 mm Hg and the PCWP is \geq 15 mm Hg, the PH can be considered "out of proportion" to the heart failure (HF) when the transpulmonary gradient (TPG; = PA mean - PCWP) is >12 mm Hg. However, if the PCWP exceeds a certain level (here the cutoff is set at 25 mm Hg), the PH should be considered "in proportion" to the HF regardless of the value of the TPG. This is to caution against the use of PAH-specific therapies in the setting of such elevated left heart filling pressures.

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and interpreted correctly. Common errors to be aware of include improper PCWP recording, relying on computer-generated mean instead of measured end-expiratory pressure readings, and failure to recognize inaccurate output measurements. Furthermore, it is important to understand that certain clinical situations can confuse the interpretation of catheterization data. These include PH out of proportion to underlying DHF, and volume depletion in patients with PH associated with DHF. Despite these potential pitfalls, cardiac catheterization remains a necessary and critical diagnostic tool in the assessment of a broad spectrum of patients with PH.

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