Chapter 10
Pulmonary Hemodynamics and Right Heart Catheterization

Saurabh Rajpal, Yonatan Buber, and Michael J. Landzberg

Abstract Hemodynamic assessment of the patient with pulmonary hypertension begins with a careful physical exam and is followed by several noninvasive tests and ultimately right heart catheterization. Proper interpretation of the considerable data that is generated by this process requires a firm working knowledge of the pulmonary circulation and right ventricle along with major factors that can affect pulmonary vascular tone and cardiac output. This chapter reviews normal cardiopulmonary physiology and provides an in depth approach to assessing pulmonary hemodynamics in patients with pulmonary vascular disease. A detailed discussion of the physical exam and techniques used for transthoracic echocardiogram and right heart catheterization are provided along with a guide to interpreting their results. The skills and diagnostic approaches presented are necessary for the proper diagnosis of pulmonary vascular disease and should be used to distinguish patients with pulmonary arterial hypertension from patients with pulmonary hypertension associated with left heart failure or chronic thromboembolic pulmonary hypertension.

Keywords Pulmonary hypertension • Pulmonary arterial pressure • Cardiac output • Pulmonary vascular resistance • Right heart catheterization • Pulmonary artery catheter

S. Rajpal, M.D.
Louisiana State University School of Medicine, Shreveport, LA, USA

Boston Adult Congenital Heart (BACH) and Pulmonary Hypertension Group, Brigham and Women's Hospital and Children's Hospital, Harvard Medical School, Boston, MA, USA

Y. Buber, M.D.
Boston Adult Congenital Heart (BACH) and Pulmonary Hypertension Group, Brigham and Women's Hospital and Children's Hospital, Harvard Medical School, Boston, MA, USA

Sheba Medical Center, Sackler School of Medicine, Tel Aviv, Israel

M.J. Landzberg, M.D. (✉)
Boston Adult Congenital Heart (BACH) and Pulmonary Hypertension Group, Brigham and Women's Hospital and Children's Hospital, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital,
300 Longwood Avenue, Bader, 2nd Floor, Boston, MA 02115, USA
e-mail: Mike.Landzberg@CARDIO.CHBOSTON.ORG

J.R. Klinger, R.P. Frantz (eds.), *Diagnosis and Management of Pulmonary Hypertension*, Respiratory Medicine 12, DOI 10.1007/978-1-4939-2636-7_10

Abbreviations

AT	Acceleration time
CCB	Calcium channel blocker
CP	Constrictive pericarditis
CTEPH	Chronic thromboembolic pulmonary hypertension
CVP	Central venous pressure
dPAP	Diastolic pulmonary artery pressure
DPG	Diastolic pressure gradient
FAC	Fractional area change
ICU	Intensive care unit
IJ	Internal jugular
IVC	Inferior vena cava
JVP	Jugular venous pulse
LAP	Left atrial pressure
LV	Left ventricle
mLAP	Mean left atrial pressure
MPA	Main pulmonary artery
mPAP	Mean pulmonary artery pressure
NO	Nitric oxide
PAH	Pulmonary arterial hypertension
PAOP	Pulmonary artery occlusion pressure
PAP	Pulmonary artery pressure
PBF	Pulmonary blood flow
PCWP	Pulmonary capillary wedge pressure
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RAP	Right atrial pressure
RCM	Restrictive cardiomyopathy
RHC	Right heart catheterization
RV	Right ventricle
RVH	Right ventricle hypertrophy
RVOT	Right ventricle outflow tract
RVSP	Right ventricular systolic pressure
sPAP	Systolic pulmonary artery pressure
TAPSE	Tricuspid annulus plane systolic excursion
TPG	Transpulmonary gradient
TRV	Tricuspid regurgitation velocity
TTE	Transthoracic echocardiography
VTI	Velocity time integral

Definition of Pulmonary Hypertension Based on Hemodynamics

The conventional definition of pulmonary hypertension (PH) used in clinical studies includes a mean pulmonary artery pressure (mPAP) of greater than 25 mmHg at rest in the setting of a normal pulmonary arterial wedge pressure of 15 mmHg or less with a pulmonary vascular resistance (PVR) greater than 3 Wood units [1, 2]. Cardiac catheterization and hemodynamic assessment are essential for the diagnosis of PH. Of note, the current US and European PH care guidelines do not support the use of pulmonary artery hypertension (PAH) specific medications without a hemodynamic evaluation by right heart catheterization [2, 3]. Table 10.1 lists the hemodynamic definition of pulmonary hypertension [3].

The Pulmonary Vasculature

The lung has a dual blood supply from the bronchial and pulmonary circulations. While bronchial blood flow is a small part (2 %) of the left ventricular output; the pulmonary circulation carries the entire output of the right ventricle (RV) which in the absence of significant intravascular shunting equals left ventricular output and supplies the lung with the mixed venous blood draining all the tissues of the body [4]. It is the blood in the pulmonary circulation that participates in the gas exchange process.

Table 10.1 Hemodynamic definitions of pulmonary hypertension [3]

Definition	Characteristics	Clinical group(s)
Pulmonary hypertension (PH)	Mean PAP ≥25 mmHg	All
Pre-capillary PH	Mean PAP ≥25 mmHg	1. Pulmonary arterial hypertension
	PWP ≤15 mmHg	3. PH due to lung diseases
	CO normal or reduced	4. Chronic thromboembolic PH
		5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	Mean PAP ≥25 mmHg	2. PH due to left heart disease
	PCWP >15 mmHg	
	CO normal or reduced	
Passive	TPG ≤12 mmHg	
Reactive (out of proportion)	TPG >12 mmHg	

CO cardiac output, *PAP* pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *PH* pulmonary hypertension, *TPG* transpulmonary gradient

Despite typically similar blood flow, the pulmonary and systemic circulation have major differences. The pulmonary artery and its branches have thinner walls (comprised of less smooth muscle and elastin), and greater internal diameters when compared to the systemic arteries; as well, there are no smaller denominators of pulmonary artery that correspond to the highly muscular systemic arterioles [5]. As the result of these factors the pulmonary arteries have lower resistance and are both more distensible and compressible when compared to systemic arteries (Fig. 10.1). The location of pulmonary vessels in the thorax subjects them to alveolar and intrapleural and intrathoracic pressure changes that occur with respiration [4, 5]. These characteristics combine to underscore the importance of considering transmural pressure gradient (during both spontaneous as well as mechanical ventilation) as a determinant of PVR. It is important to know during which respiratory phase pulmonary vascular pressures are measured and a standard should be followed when reporting such.

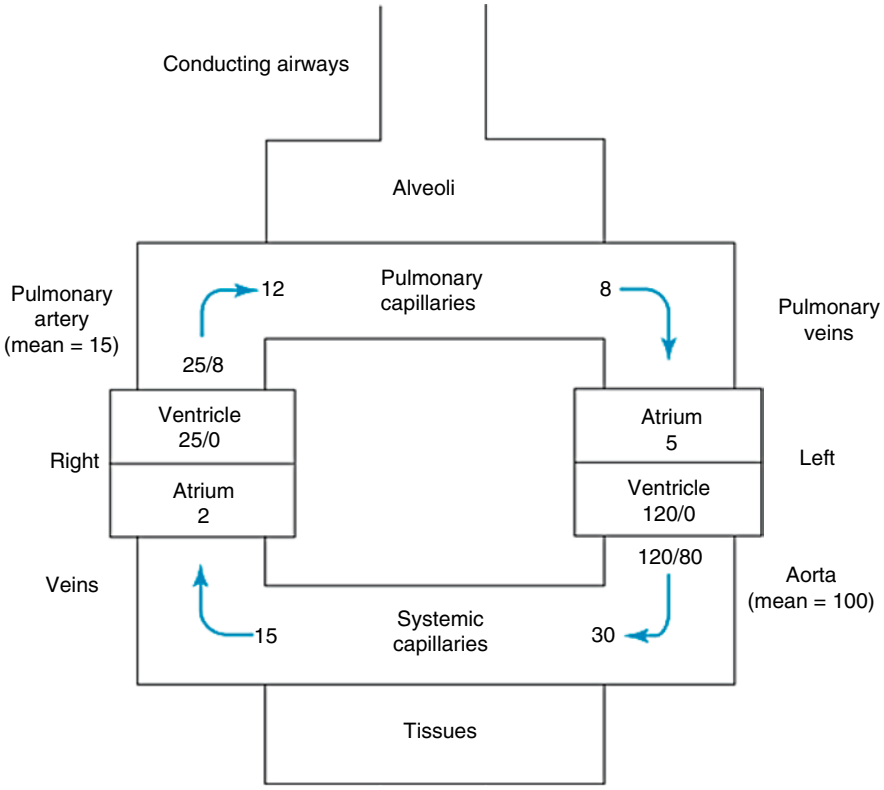

Fig. 10.1 Normal cardiac chamber pressures

Pulmonary Vascular Resistance (PVR)

PVR cannot be measured directly, but must be calculated. According to Hagen–Poiseuille's law that assumes laminar flow, non-compressible fluid and no flow acceleration, the pressure difference across a non-distensible tube is equal to flow multiplied by resistance represented by the equation $P1 - P2 = Q \times R$, where P1 is pressure at beginning of the tube, P2 is pressure at the end of the tube, Q is flow and R is resistance. Extrapolating this to pulmonary circulation, PVR = (mPAP − mLAP)/PBF, where PVR is pulmonary vascular resistance, mPAP is mean pulmonary artery pressure, mLAP is mean left atrial pressure and PBF is pulmonary blood flow which in the absence of significant intravascular shunting is equal to systemic cardiac output [4, 6].

As intravascular pressures, resistance, impedance, and afterload are lower in the pulmonary circulation as contrasted to the systemic arterial circulation, the left ventricle has greater metabolic demand and is thicker than the right ventricle. Under normal physiologic conditions, pulmonary arterial pressure (PAP) need not be as high as the systemic arterial pressure to overcome the effects of gravity, nor to distribute blood flow among several vascular beds. While in systemic circulation the majority of vascular resistance lies in the systemic arterioles, in the pulmonary circulation vascular resistance is evenly distributed among the pulmonary arteries, capillaries and veins. As the pulmonary circulation holds the same amount of blood with lower pressures, under normal circumstances PVR is one sixth to one ninth of the systemic vascular resistance. In addition to intrinsic vascular factors that regulate pulmonary vascular smooth muscle tone (Table 10.2), extravascular or mechanical factors (Table 10.3) are important in the regulation of PVR.

Gravitational Distribution of Pulmonary Blood Flow

Traditionally, gravity is considered to be an important factor affecting distribution of pulmonary blood flow (Fig. 10.2). In this classical model the lung is considered to have three zones: zone 1 has higher alveolar pressure than PAP and hence no blood flow occurs, in zone 3, PA and pulmonary vein pressure (PVP) are both greater than the alveolar pressure and hence blood flow occurs based on the pressure gradient between the PA and the PV, and in zone 2 PA pressure is higher than alveolar pressure and the driving force for pulmonary blood flow is the pressure difference between alveoli and pulmonary artery [7].

Although gravity has a measurable effect on pulmonary blood flow, recent studies have shown that gravity may not be the most important factor affecting distribution blood flow in lung as compared to anatomy and anatomic structure of the pulmonary arterial tree [8, 9]. While measuring PAP and PVR during catheterization this concept of zones of lungs is important to keep in mind especially if pressures are being measured in an upright patient.

Table 10.2 Factors affecting PVR specifically pulmonary vascular smooth muscle (modified from Levitzky MG. Chapter 4. Blood flow to the lung. In: Levitzky MG. eds. Pulmonary Physiology, 8e. New York, NY: McGraw-Hill; 2013)

Increase	Decrease
Stimulation of sympathetic innervation (may have greater effect by decreasing large vessel distensibility)	Stimulation of parasympathetic innervation (if vascular tone is already elevated)
Norepinephrine, epinephrine	Acetylcholine
Alpha adrenergic agonists	B-adrenergic agonists
PGF2A	PGE1
PGE2	PGI2
Thromboxane	Nitric oxide
Endothelin	Bradykinin
Angiotensin	
Histamine	
Alveolar hypoxia	
Alveolar hypercapnea	
Low pH	

Table 10.3 Factors affecting PVR—passive or mechanical factors (modified from Levitzky MG. Chapter 4. Blood flow to the lung. In: Levitzky MG. eds. Pulmonary physiology, 8e. New York, NY: McGraw-Hill; 2013)

Factor	Effect on PVR	Mechanism
Lung volume increase above functional residual capacity (FRC)	Increases	Lengthening and compression of alveolar vessels
Lung volume decrease above FRC	Increases	Compression of and less traction on extra-alveolar vessels
Increased pulmonary artery pressure; increased left atrial pressure; increased pulmonary blood volume; increased cardiac output	Decreases	Recruitment and distention *Long term effect of these factors could be elevation in PVR due to vascular remodeling*
Gravity; body position	Decreases in gravity-dependent regions of the lungs	Hydrostatic effects lead to recruitment and distention
Increased (more positive) interstitial pressure	Increases	Compression of vessels
Increased blood viscosity	Increases	Viscosity directly increases resistance
Positive-pressure ventilation		
Increased alveolar pressure	Increases	Compression and de-recruitment of alveolar vessels
Positive intrapleural pressure	Increases	Compression of extra-alveolar vessels; compression of vena cava decreases pulmonary blood flow and leads to derecruitment

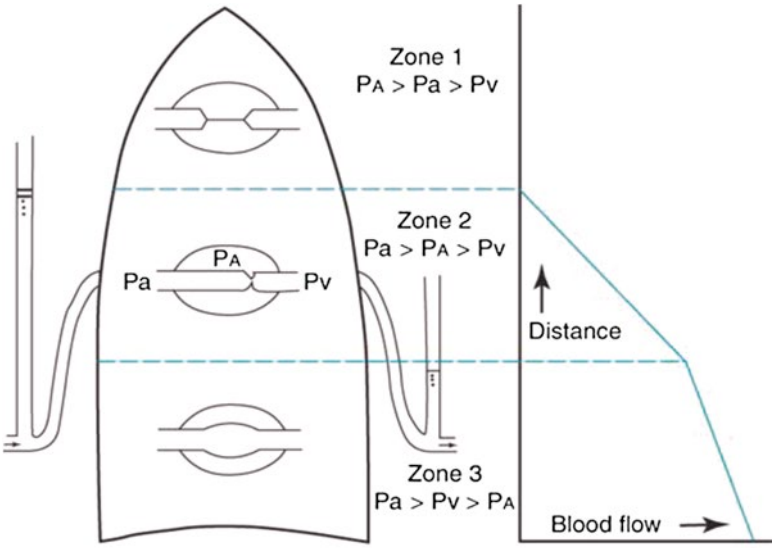

Fig. 10.2 Lung zones in gravitational distribution of pulmonary blood flow model

Hypoxic Pulmonary Vasoconstriction

Hypoxia has important physiologic effects on pulmonary vascular tone, typically balancing less ventilated and more poorly oxygenated alveoli with reduced blood flow under normal conditions. Arteriolar vasoconstriction (Fig. 10.3) in the less oxygenated alveoli, reduces the blood flow and hence decreases contamination of the pulmonary venous blood with poorly oxygenated blood [10].

Noninvasive Hemodynamic Assessment of Pulmonary Hypertension

Clinical Examination

The noninvasive evaluation of a patient starts with clinical examination. Patients who are using pulmonary vasodilator pharmacologic therapy have a distinct facial flushing which can mask effects of systemic arterial vasoconstriction due to low systemic cardiac output (and at times can simulate distributive physiology). Use of sphygmomanometric response of systemic blood pressure to valsalva maneuver is extremely useful in estimating pulmonary capillary wedge pressure (PCWP) [11]. Inflation of brachial cuff to blood pressure 15 points higher than systemic arterial systolic blood pressure, performance of valsalva maneuver for up to 10 s and observation of phase 2 response allows for reliable and reproducible estimation of PCWP.

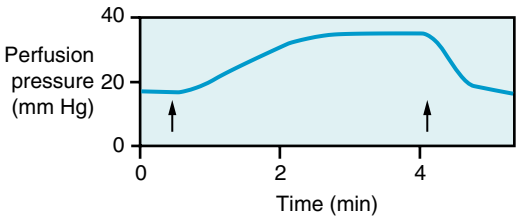

Fig. 10.3 Effect of hypoxia on vascular resistance of an isolated rat lung. The lung was perfused with blood at a constant flow. When the O_2 tension of the inspired air was reduced (between the *arrows*), the pulmonary resistance vessels constricted, as indicated by the substantial rise in perfusion pressure

Normally, Korotkoff sounds are heard during the initial phase of Valsalva then stop and return again at the end of Valsalva (phase 2). The persistence of Korotkoff sounds for either ≥4 beats but <10 s after the start of Valsalva, or for ≥10 s ("square root response") predicts elevated PCWP. Jugular venous pulsations (JVP) are elevated, at times with prominent "v" waves if significant tricuspid regurgitation is present. An elevated JVP signifies an elevated RV end diastolic pressure and hence RV failure and poor prognosis. Venous hypertension can also be examined by provoking the abdominojugular reflux sign, which indicates a volume-overloaded state and limited compliance of the systemic venous system. The abdominojugular reflux sign is provoked by applying consistent pressure over the right upper abdominal quadrant, for at least 10 s. A sustained rise of >3 cm in the venous pressure for at least 15 s is a positive response [12]. It is also important to note how quickly the JVP "falls" when the abdominal pressure is removed to assess the compliance of the systemic venous system.

Clubbing may be present and is a marker of chronic hypoxemia. The RV is anteriorly positioned, directly behind the sternum and chest wall; a palpable "right ventricular" heave is variably present when it is enlarged. Auscultation may include a loud pulmonary component of the second heart sound (P2), a holosystolic murmur of tricuspid regurgitation, a diastolic murmur of pulmonary insufficiency and a third sound of RV origin. Tricuspid regurgitation in the setting of markedly elevated RV systolic pressure and an enlarged RV may produce a high-pitched murmur. Lung sounds are usually normal; "wet" crackles suggest elevated left ventricular end diastolic pressure, disease, while "dry" inspiratory crackles may point towards interstitial lung disease [13]. Hepatomegaly, elevated JVP, peripheral edema, ascites, and cool extremities are consistent with low output right heart failure, indicating more advanced disease.

Chest X-Ray

A chest X-ray cannot be used for diagnosis of PH; however, certain findings can suggest important hemodynamics even though these findings are not sensitive or specific. An increased diameter of the right descending pulmonary artery may suggest significant elevated PAP. Increased hilar thoracic index (the horizontal

distance between the outer borders of the right and left pulmonary arteries divided by the maximum transverse diameter of the thoracic cage. A ratio <0.35 is considered to be normal) is also suggestive of elevated PAP [14, 15]. In a prospective study of idiopathic pulmonary arterial hypertension (IPAH), the chest radiograph demonstrated prominence of the main pulmonary artery in 90 % of patients, enlarged hilar vessels in 80 %, and decreased peripheral vessels in 50 %. All three abnormalities were seen in just over 40 % of subjects, and the presence of all three abnormalities was associated with a higher mPAP and lower cardiac index [16]. The PCWP can be estimated by observing the vascular pattern and the presence of interstitial or alveolar edema on chest radiographs. It has been suggested that PCWP greater than 13 but less than 18 mmHg indicates the presence of vascular redistribution with relative hypervascularity of the upper lung fields. When PCWP is 18–25 mmHg, interstitial pulmonary edema is seen and when greater than 25 mmHg, alveolar edema and often pleural effusion is present [17, 18]. Such changes may be absent in the presence of remodeling changes within the pulmonary vascular bed.

CT Scan

CT scan and angiography are pivotal in diagnosing pulmonary embolism and chronic thromboembolic pulmonary hypertension (CTEPH), peripheral pulmonary arterial stenosis, and mechanical or other etiologies of obstruction within the pulmonary vasculature as causes of PH (as well as for ruling out significant primary parenchymal lung disease). However, for direct hemodynamic assessment of PH, CT has a limited role. Some CT findings that can predict hemodynamics include the main pulmonary artery (MPA) caliber, segmental artery to bronchus ratio [19, 20, 22], and presence of pericardial effusion [21]. MPA caliber greater than 29 mm measured 2 cm from the pulmonary valve has 84 % sensitivity, 75 % specificity, and 97 % positive predictive value for the presence of pulmonary arterial hypertension. Also, if the MPA has a maximum transverse diameter greater than that of the proximal ascending thoracic aorta, sensitivity is 70 %, specificity 92 %, and positive predictive value 96 % for the presence of pulmonary arterial hypertension. Segmental artery to bronchus ratio greater than 1.25 times the caliber of the adjacent bronchus suggests elevation of PAP [21] and pericardial thickening or effusion is suggestive of mPAP>35 mmHg.

MRI

The use of MRI in management of patients with PH is evolving. Phase contrast MRI calculated pulmonary vascular index, acceleration time (defined as time from onset of PA forward flow to maximum velocity), the ratio between acceleration time and RV ejection time are being evaluated to calculate PAP but results have been variable [23]. Kuehne and colleagues showed that PVR assessment using MRI-guided catheterization and MRI velocity mapping provided more reproducible results than the

traditional thermodilution method. In addition, this technique seems to provide the ability to sample PVR more comprehensively (including both overall and branch-specific resistance) than can be achieved using Doppler guidewires [24].

Electrocardiogram

Electrocardiogram (ECG) lacks sensitivity and specificity in diagnosing PH. In patients with PH, sinus tachycardia may be the only abnormality present (EKG could be completely normal). RV strain, right ventricular hypertrophy (RVH), incomplete right bundle branch block and increased P wave amplitude are common findings [25]. On occasion, in patients in whom PAH attenuating treatment has been very effective, dramatic ECG changes from a pattern corresponding with RVH to a (near)-normal pattern have been reported [26]. P wave amplitude has been shown to predict prognosis in PAH [27].

Echocardiogram

The transthoracic echocardiogram (TTE) remains a core element of RV assessment with applications in the initial and longitudinal diagnosis and screening of pulmonary hypertension, discrimination between contributors to etiology, as well as in assessment of RV and valvular function. The European Society of Cardiology guidelines for the diagnosis and treatment of PH suggest the following: (1) PH is unlikely for tricuspid regurgitation velocity (TRV) $\leq$2.8 m/s, systolic PAP (sPAP) $\leq$ 36 mmHg (assuming RAP of 5 mmHg), and no additional echocardiographic signs of PH; (2) PH possible for TRV $\leq$ 2.8 m/s and sPAP $\leq$ 36 mmHg, but the presence of additional echocardiographic signs of PH or TRV of 2.9–3.4 m/s and SPAP of 37–50 mmHg with or without additional signs of PH; and (3) PH likely for TRV > 3.4 m/s and sPAP > 50 mmHg with or without additional signs of PH [3]. Combined with well-validated hemodynamic calculations, focused TTE can provide very close approximations of the pulmonary vascular and RV hemodynamics.

Systolic Pulmonary Artery Pressure (sPAP)

TTE-based estimation of sPAP most frequently relies upon determination of Doppler-based peak TVR and use of the modified Bernoulli equation (Δpressure = 4 × velocity [2]) to approximate differences between RV and right atrial (RA) pressure. Further addition of TTE-guided estimation of RA pressure (RAP) allows for calculation of RV systolic pressure (which in the absence of obstruction to RV outflow represents sPAP). As central venous pressure (CVP) and RAP are essentially equivalent in the absence of anatomic obstruction, the latter is commonly evaluated by measuring the size, flow patterns and the respiratory variation of the inferior

vena cava (IVC). Generally, IVC diameter <2.1 cm and collapse greater than 50 % on inspiration would correspond to a normal RAP of 0–5 mmHg. The presence of either greater diameter or lesser collapse (but not both) correspond to RAP of 5–10 mmHg, and a diameter greater than 2.1 cm with less than 50 % collapse corresponds to a high RAP of 10–20 mmHg [28, 114]. These criteria are relatively poor indicators of RAP, however, and this should be acknowledged when estimating PAP [29]. Patients who cannot comply with taking a deep inspiration to demonstrate collapsibility of the IVC can be asked to perform a "sniff" maneuver, which causes a decrease in intrathoracic pressure.

Although widely accepted as a screening test, the precision of this echocardiographic estimate of PAP is modest. In studies that have compared echocardiographically estimated values and values measured by right heart catheterization (RHC), the mean difference ranged from 3 to 40 mmHg, and sPAP was underestimated with the echocardiographic method by >20 mmHg in 31 % of patients studied [30]. To minimize error in acquisition of the TR envelope by Doppler, it is recommended that TRV be measured in multiple views and the maximal velocity jet found should be used for the calculation. Inadequate regurgitant signals can be enhanced with the use of contrast. It should always be remembered that sPAP evaluation with Doppler methods, however, cannot definitively diagnose PH and has limited role in the decision to treat patients or to monitor therapy efficacy.

Mean Pulmonary Artery Pressure (mPAP)

The simplest method of calculating the mPAP may be by using sPAP as follows:

$$\text{mPAP} = 0.61 \times \text{sPAP} + 2\,\text{mmHg}\ [31].$$

As the only variable in the above equation is sPAP, this calculation carries the same pitfalls as measurement of sPAP mentioned above.

Doppler-based measure of diastolic pulmonary valve regurgitation may be difficult to obtain, and therefore may be absent on particular studies. When present and complete, use of the peak pulmonary valve regurgitation velocity (typically early in diastole) in the modified Bernoulli equation allows estimation of peak pressure difference between RV and PA in early diastole. The peak pulmonic regurgitation velocity represents the diastolic pressure gradient between the pulmonary artery and the RV. Adding the RAP to such calculation often provides acceptable estimation of mPAP ($\text{mPAP} = 4 \times (\text{peak pulmonic valve regurgitation jet velocity})^2 + \text{RAP}$) [32].

RV–RA Mean Systolic Gradient

When TTE-based estimation of RAP is added to TR Doppler-velocity based approximation of peak systolic RA–RV systolic pressure difference, a value is obtained that has excellent correlation with mPAP measured during an invasive RHC [33]. Critical to use of this methodology is capture of complete and accurate tricuspid regurgitation Doppler envelope.

Diastolic Pulmonary Artery Pressure (dPAP)

Application of the modified Bernoulli equation to the end-diastolic pulmonary regurgitation velocity allows estimation of the end-diastolic gradient between the RV and PA, which, when added to the TTE-based estimation of RA pressure, estimates diastolic PA pressure, (dPAP), with a high correlation with invasive dPAP measurements [34]. Similar estimation can be obtained by Doppler-based assessment of the earliest systolic gradient at the time of pulmonary valve opening (closely approximating end-diastolic gradient between RV and PA) and adding TTE-based estimation of RA pressure, yielding estimate of dPAP [35, 36].

Pulmonary Vascular Resistance

Accurate assessment of PVR provides an understanding of the mechanism of elevated PAP and aids in selecting therapy for PH. As a result of its clinical importance, numerous TTE-based estimations of PVR have been developed. Noninvasively, one can relate trans-pulmonary gradient (TPG) to pulmonary blood flow by determining the ratio between the tricuspid regurgitation velocity and the velocity time integral of the pulmonary flow at the RV outflow tract. This equation simplifies to:

$$\begin{aligned} &10 \times \text{tricuspid valve velocity} \\ &/\text{velocity time integral at the RV outflow tract}\left(\text{RVOT}\right) \\ &\approx \text{PVR}\left(\text{Wood units}\right) \end{aligned}$$

Individuals with ratios <0.2 have been demonstrated to likely have low PVR values (<2 WU), with 70 % sensitivity and 90 % specificity, even in the presence of increased Doppler sPAP [37].

Alternatively, relating sPAP by the heart rate-corrected velocity time integral (VTI) at the RVOT, namely sPAP/(HR × VTIRVOT), also estimates PVR but takes into account RAP and heart rate (cutoff value of 0.076 with >80 % sensitivity and specificity in a population with PVR > 15 Wood units) [38, 39].

Additional analysis of the pre-ejection systolic time (the period of the cardiac cycle between onset of tricuspid regurgitation and beginning of elevation of PAP) related to systolic acceleration time (period of time between the beginning of ejection and peak flow velocity), normalized for total systolic (ejection and non-ejection) time linearly correlates with invasively measured PVR between 0 and 9 Wood units [40].

An additional technique to estimate PVR is based on the fact that mid systolic notching of the RVOT envelope relates to pathologic wave reflection in the setting of elevated pulmonary artery impedance and PVR of at least 3 Woods units [41]. The ratio of sPAP Doppler to RVOT tract VTI with or without a constant value of 3 designates presence of RVOT VTI midsystolic notching. {PASP/RVOTVTI + 3 if midsystolic notching of RVOT envelope is present} provides superior agreement with catheterization estimates of PVR across a wide range of values.

Morphology of the Doppler Velocity Curves

The Doppler pulmonary flow velocity curve has a dome-like appearance in subjects with normal pulmonary pressures; this is transformed to a somewhat "triangular" shape in patients with PH. Acceleration time (AT) is decreased in the presence of elevated sPAP and mPAP, with peak velocity appearing earlier in systole. An AT <93 ms correlates well with invasive PAP elevation [42, 43]. At times of concomitant abnormality of PA compliance, capacitance or PVR, a second slower rise in velocity during mid-systolic flow deceleration can be observed, resulting in so-called "midsystolic notching" [44].

The combination of assessment of presence or absence of mid systolic notching of the RVOT envelope with estimate of Doppler acceleration time is one of the most utilized echocardiographic techniques to determine if PVR is elevated.

Estimates of RV Function

In response to pressure overload, the RF typically dilates and develops concentric hypertrophy. The TTE-based apical "4-chamber" view allows an expansive view of the heart. Transition of the RV from a triangular to a more globular or rounded shape can be demonstrated. Similarly as the RV expands in size, it may replace the LV in forming part or all of the cardiac apex. While quantification of the size of the RV remains a limitation of echocardiography, the ratio between the diastolic inflow diameters and the areas of the RV and the LV (0.6–1 mild, >1 severe) appear to correlate well with the degree of RV dilatation [45].

More complex methodology requires tracing of RV endocardium during systole and diastole to calculate the fractional are change (FAC) (RVFAC = (end-diastolic area − end-systolic area)/end-diastolic area × 100, normal being ≥35 %) as a correlate of RV systolic function [28, 46].

One of the most utilized indices of RV contractile function is perhaps one of the simplest to obtain. The longitudinal tricuspid annulus plane systolic excursion or TAPSE is calculated via M-mode echocardiography (though two-dimension estimates are often performed) of the right ventricular annulus. Normal values are >2.0 cm and are reduced in case of RV dysfunction [47]. Important limitations to this method include its dependency on proper image acquisition angle and RV load dependency, its focus on a small part of the RV myocardium, independent changes that occur after surgical or other penetration of the pericardium, and the fact that the tricuspid annulus motion may be very well affected by the overall heart motion [48]. TAPSE values of less than 1.8 cm correlate with worse 1 and 2 year prognosis in patients with groups 1 and 2 PH.

While the myocardial performance Tei index (sum of isovolumetric contraction time and isovolumetric relaxation time indexed to the total LV ejection time [(IVCT + IVRT)/(LVET)]) has been correlated with invasive hemodynamics and clinical outcomes, its use in care practice has been limited [49]. Additional complex hemodynamic assessments from TTE include tissue Doppler and strain assessment.

Current American Society of Echocardiography guidelines regarding right-heart assessment recommend that basal RV free wall $S' < 10$ cm/s should be considered a marker of RV dysfunction [28]. Mitral annular velocity should be checked to consider the presence of elevated left-sided filling pressures. Strain imaging can suggest RV dysfunction in the presence of decreased RV longitudinal strain and impairment of left ventricular segmental longitudinal and circumferential strain (when greater for the interventricular septum than for the LV free wall) [50].

The "reverse Bernheim effect" suggests RV and LV interaction such that poor RV function in the face of marked afterload can worsen LV filling and output [51]. The ratio of the long axis to short axis diameters of the left ventricle, both in diastole and in systole, otherwise known as the "eccentricity index" assesses LV compression, differentiates between volume and pressure overload, and is assessed on the two-dimensional short-axis view of the LV [52]. In addition, RV dilatation also causes abnormal left ventricular filling which may be assessed by evaluating the Doppler appearance of the mitral inflow. Abnormal relaxation pattern is often a surrogate to LV cavity compression in patients with more severe forms of PH.

The presence of pericardial effusion may be due in part to poor pericardial drainage in the setting of RA hypertension and lower cardiac output. While presence of effusion is a poor prognostic finding, tamponade is not a typically encountered clinical sequelae due to the high pressure in the RA and RV [53].

Right to left intravascular shunting (and resultant hypoxemia unresponsive to oxygen administration) through a patent foramen ovale can be demonstrated with agitated saline or echocardiographic contrast injection, and may be aggravated in the setting of elevation of RA pressure either at rest or with exercise,.

Right Heart Catheterization

Invasive hemodynamic assessment of PH is a dynamic process that often requires continuous recordings of multiple variables and thus, the need for RHC. For the assessment of PH, RHC typically includes vasoreactivity testing and may include exercise and fluid challenge as well as angiography. RHC remains essential for accurate diagnosis of most forms of PH including PAH. Standard of care practice guidelines strongly recommend that patients suspected of having PH after noninvasive evaluation undergo RHC prior to initiation of therapy.

Indications

In the evaluation of patients with PH, RHC is usually indicated for the following [2, 3]

(a) In all patients with PAH to confirm the diagnosis, to evaluate severity and to assist in selection of PAH specific therapy.
(b) For confirmation of efficacy of PAH-specific therapy.

Table 10.4 Essential components of invasive hemodynamic assessment [2]

Oxygen saturations (SVC, IVC, RA, RV, PA's, SA)
Right atrial pressure
Right ventricular pressure
Pulmonary artery pressure, systolic, diastolic, mean
Pulmonary arterial wedge pressure, left atrial pressure, or left ventricular end-diastolic pressure
Cardiac output/index
Pulmonary vascular resistance
Systemic blood pressure
Heart rate
Response to acute vasodilator

(c) For confirmation of hemodynamic effects of suspected clinical deterioration and as baseline for the evaluation of the effect of treatment escalation and/or combination therapy.

RHC may have limited benefit when an alternative diagnosis is obvious on non-invasive testing. Similarly, RHC may have specific but limited use when elevated PAP pressures on non-invasive testing can be explained by left heart disease, diastolic dysfunction, or chronic lung disease.

Table 10.4 lists the essential components of invasive hemodynamic assessment of PH. The addition of exercise testing, vasoreactivity testing or fluid challenge, and angiography to RHC is discussed in appropriate sections below.

Indications for Coronary Angiography with Right Heart Catheterization for Evaluation of Pulmonary Hypertension

It is not infrequent that assessment of coronary anatomy may carry import implications when performed as part of RHC to evaluate PH. The reasons for such include, but are not limited to, evaluation of the coronary anatomy as part of surgical planning, presence of coronary-fistula to the right-sided chambers as a possible source of left to right shunt, presence of atherosclerotic coronary artery disease as a possible reason for impaired LV function or elevated filling pressure, and evaluation of the anatomic relations between the coronary arteries and the pulmonary arteries for specific procedures (e.g., percutaneous prosthetic pulmonary valve implantation).

Safety

RHC, although technically demanding, is a safe procedure when performed by experienced operators [54]. Hoeper and colleagues reported on 5,727 RHC procedures retrospectively and 1,491 prospectively, for a total of 7,218 procedures. The overall number of serious adverse events was 76 (1.1 %, 95 % confidence interval 0.8–1.3 %). The most frequent complications were related to venous access (e.g., hematoma, pneumothorax), followed by arrhythmias and hypotensive episodes related to vagal reactions or pulmonary vasoreactivity testing. The vast majority of these complications were mild to moderate in intensity and resolved either spontaneously or after appropriate intervention. Four fatal events were recorded in association with any of the catheter procedures, resulting in an overall procedure-related mortality of 0.055 % (95 % confidence interval 0.01–0.099 %). Of the four fatal complications only two were related to the procedure itself (PA rupture and both electromechanical dissociation and intrapulmonary hemorrhage) [55]. Adequate patient preparation such as management of anticoagulation issues can help in reducing vascular access complications. It should be remembered that RHC as an elective, planned procedure is a very safe procedure and is very different from placement of a pulmonary artery catheter (PAC) in patients admitted to the intensive care unit (ICU) where the use of PAC has, in some studies, been associated with increased mortality. Also while a PAC placed in an ICU patient may stay in situ for several days, thus increasing vascular, infectious, and thromboembolic complications, diagnostic RHC is typically a short outpatient procedure lasting under an hour.

Patient Preparation

Policy regarding fasting status of patients, use of peripheral IV, and withholding of particular medications (such as hypoglycemics, vasodilators, diuretics, or anticoagulants) should be dependent upon individual laboratory preference, health status of the patient, and whether sedative use is planned. A clear plan for such though, should be constructed and documented. For example, the calculation of risk-benefit ratio of sustaining therapeutic INR up until catheterization for an individual patient in whom anticoagulation has been prescribed for mechanical mitral valve and atrial fibrillation may well be different than that of another patient in whom warfarin is prescribed for primary prevention of stroke with atrial fibrillation. Clear description of such logic should be available to personnel within the team assisting in catheterization (Table 10.5).

Sedation

While concern has been raised regarding safety and influence of sedatives used during catheterization on medical status and physiologic indices including loading conditions and inotropy, this is probably of minor concern unless liver and

Table 10.5 Anticoagulation management in case decision is made to withhold anticoagulation (modified from Massicotte A. A practice tool for the new oral anticoagulants. Can Pharm J (Ott). Jan 2014) [56]

Drug and creatinine clearance	Recommendation in preprocedure period	Recommendation in postprocedure period	Bridging with heparin needed
Warfarin	Stop 48 h prior until INR <1.7 (varies per institutional policy).	Resume therapy when hemostasis is adequate and clinical condition allows	Needed if moderate to high risk of thromboembolism
Dabigatran ≥80 ml/min	Stop 24 h before surgery.	Resume therapy when hemostasis is adequate and clinical condition allows	Needed only if patient cannot take oral medications and there is moderate to high risk of thromboembolism
Dabigatran 50 to <80 ml/min	Stop 1–2 days before surgery.	Resume therapy when hemostasis is adequate and clinical condition allows	Needed only if patient cannot take oral medications and there is moderate to high risk of thromboembolism
Dabigatran <30 ml/min	Stop at least 5 days before surgery.	Use alternative anticoagulation agent	NA
Rivaroxaban ≥30 ml/min	Stop at least 24 h before surgery.	Resume therapy when hemostasis is adequate and clinical condition allows	Needed only if patient cannot take oral medications and there is moderate to high risk of thromboembolism
Rivaroxaban <30 ml/min	Last dose on day −3.	Use alternative anticoagulation agent	NA
Apixaban >50 ml/min	Stop at least 24 h before surgery.	Resume therapy when hemostasis is adequate and clinical condition allows	Needed only if patient cannot take oral medications and there is moderate to high risk of thromboembolism

kidney functions are significantly impaired [57–59]. Nonetheless, it is becoming more common practice to avoid standard use of systemic sedation prior to or during RHC.

Right Heart Catheterization in a Mechanically Ventilated Patient

Complex influences by mechanical ventilation must be considered when assessing measured hemodynamics. Positive pressure ventilation, particularly in the setting of PEEP, variably increases RV afterload with resultant decline in RV contractility, and can contribute to elevated measure of PCWP particularly during inspiration [60, 61]. Additional influences may include baseline vascular and myocardial loading conditions and compliance of the chest wall and lungs. General practice is to discount

meaningful influence of PEEP <10 cm H_2O on measured PCWP, with correction of PCWP when PEEP ≥10 cm H_2O by 2–3 cm for every 5 cm H_2O increment in PEEP [62, 63]. Another cause of falsely elevated PCWP in a mechanically ventilated patient is the monitoring catheter being located outside zone 3 (during positive pressure ventilation less of the lung is zone 3 due to elevated alveolar pressures). Care should be taken to demonstrate catheter tip placement within zone 3, gravitationally below the level of the left atrium [64].

Hemodynamic pressure measurements should reflect the time of most neutral intrathoracic pressure (in spontaneously respiring patients this occurs at end expiration, with converse in patients utilizing positive pressure ventilation), rather than sole recording of mean pressure. Esophageal manometry is rarely utilized to estimate the effects of high swings of intrathoracic pressure seen with labored breathing. When possible, the patient should be instructed to expire slowly to allow pressure recording that may assist in accuracy of hemodynamic measure [72].

Percutaneous Access Sites

Commonly used access sites include internal jugular (IJ) vein, femoral vein, brachial vein, and subclavian vein. Knowledge of prior procedures, venous and arterial obstructions, compressions, complex anatomical course and prior procedural complications is necessary to choose access site in an individual patient. The IJ vein is usually the preferred site because of its ease of access, lower complication rate and because it allows patients to be discharged early after procedure [54, 55, 65]. Proximal arm veins provide ready access to RHC, but catheter manipulation may be difficult and catheter size choice is limited. Some operators may prefer femoral vein if concomitant left heart catheterization is planned via femoral artery. Ultrasound guidance should be considered for both IJ and femoral access sites. Patients with kidney disease, congenital heart disease, pacemakers, or prior indwelling venous access for other reasons (e.g., TPN) are more likely to have had multiple prior procedures and consequent vascular injury or thrombosis. Imaging of the vascular bed may be established by various modalities (ultrasound, computed tomography and magnetic resonance angiography) and should be considered by the operator when deemed appropriate. The use of a micropuncture kit with a 21-gauge needle and introducer can minimize potential trauma from inadvertent puncture of the carotid artery. Table 10.6 lists the advantages and disadvantages of different catheterization access sites.

While it is relatively easy to pass the catheter in to the RV and out to the PA from the right IJ, brachial or subclavian vein access, it may be challenging to do so via femoral access especially when the right-sided chambers are dilated. Figure 10.4 shows different techniques to pass the catheter into the PA via femoral access; individual operators may employ different and specific maneuvers to assist in passage through the right heart that include use of various shaped catheters and guidewires both within or external to the maneuvered catheter. Care must be taken at all times to avoid inadvertent contact and manipulation of intracardiac and intravascular structures that could result in arrhythmia or cardiac and vascular trauma.

Table 10.6 Access sites for right heart catheterization

Catheter site	Advantages	Disadvantages
Internal jugular vein	Easier access, lower complication rate, quicker discharge	Risk of carotid injury, difficult in obese with thick neck
Femoral vein	Easier catheter manipulation	Higher complication rate esp. bleeding, longer post procedure monitoring
Brachial vein	Easy access, less invasive	Catheter manipulation difficult

Catheter Choice

For adequate evaluation of pressures during the catheterization, large-bore catheters (e.g. 6 or 7 F) that yield high-quality hemodynamic data should be utilized. Of note, the internal catheter lumen diameter appears most important in this consideration. Thus, a large catheter with multiple ports (e.g., an 8 F catheter with RA, thermodilution, and PA ports) will generally produce tracings with lower frequency response than a single-port catheter of smaller bore but greater luminal diameter. The larger lumen diameter also allows the passage of conventional 0.035- and 0.038-in. diameter guidewires when necessary. Guidewire use inside large bore catheter may be required in cases where the PA is difficult to reach or when RHC is attempted from the femoral vein. Pre-shaped catheters such as coronary catheters can be used to help direct wire to a particular segment of the pulmonary artery (e.g. in cases of CTEPH, peripheral pulmonary arterial stenosis, or pulmonary venous obstruction, where selective PA segment access is required) and then exchanging for a balloon tipped end hole catheter.

End hole catheters are best adapted for use in obtaining wedge samples and pressures or when discerning pressures, gradients, or sampling within or over relatively small areas. Side hole catheters assist in avoidance of measures that may be dampened by inadvertent wedge positioning. The Swan-Ganz multi-port PA balloon end hole catheter has potential for thermodilution based measure of cardiac output, and is one of the most commonly used catheters for measuring right-heart pressures. This catheter's port system includes an end-hole, a side-hole 30 cm from the catheter tip, and a thermistor for measurement of cardiac output when using the thermodilution method. Simpler non-thermistor single and double-lumen balloon end-hole catheters exist and may have greater ease in manipulation through enlarged or distorted hearts and vascular structures.

Coronary angiography has evolved considerably to use the smallest-bore catheters, with many catheterization laboratories using 5 F or even 4 F catheters to decrease vascular complications. The radial artery is an increasingly used access site for coronary engagement and visualization, and is also used at the time of direct pressure measurement at the left cardiac chambers (such as direct left ventricular end diastolic pressure measurement). This approach allows immediate ambulation following the procedure, as well as improved coronary visualization (compared with smaller 4 F-diameter femoral catheters), and reduced bleeding complications (compared with femoral access). An Allen test should be performed to ensure that

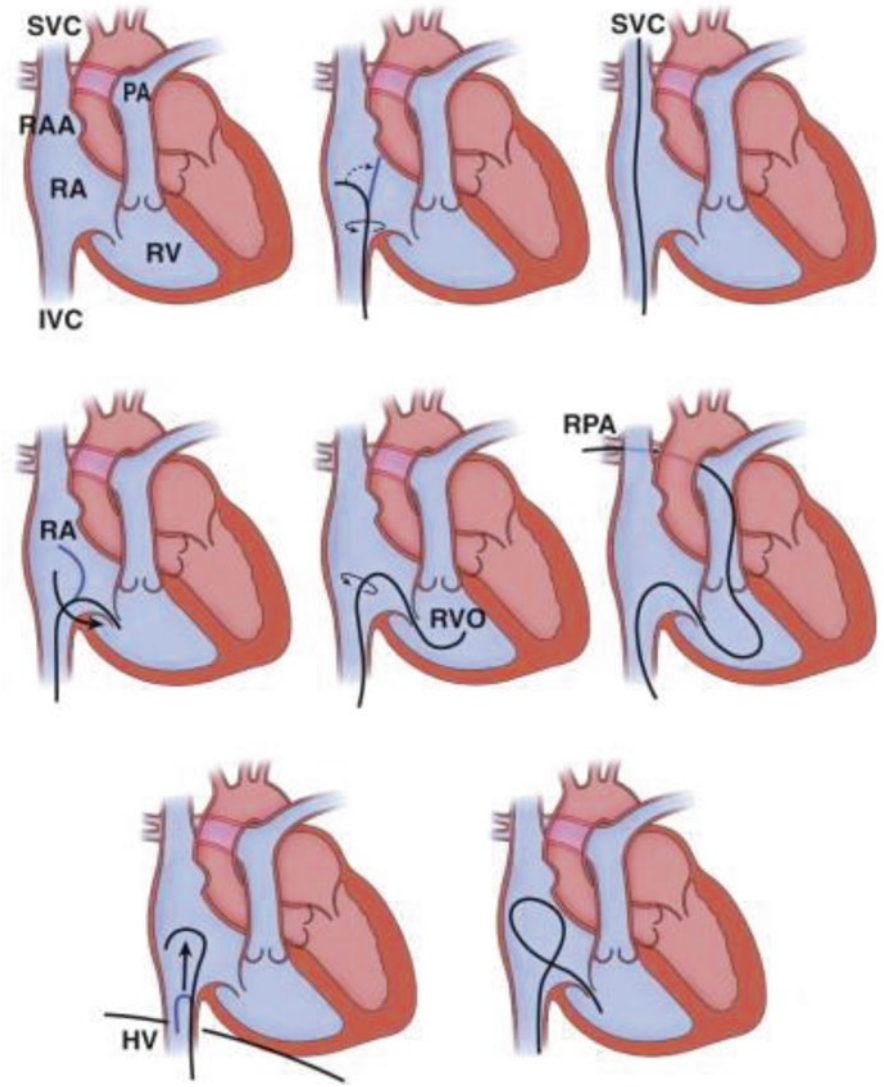

Fig. 10.4 Right-heart catheterization from the femoral vein, shown in cartoon form. *Top row*, the right-heart catheter is initially placed in the right atrium (RA) aimed at the lateral atrial wall. Counterclockwise rotation aims the catheter posteriorly and allows advancement into the superior vena cava (SVC). Although it is not evident in the figure, clockwise catheter rotation into an anterior orientation would lead to advancement into the right atrial appendage (RAA), precluding SVC catheterization. *Center row*, the catheter is then withdrawn back into the right atrium and aimed laterally. Clockwise rotation causes the catheter tip to sweep anteromedially and to cross the tricuspid valve. With the catheter tip in a horizontal orientation just beyond the spine, it is positioned below the right ventricular outflow (RVO) tract. Additional clockwise rotation causes the catheter to point straight up, allowing advancement into the main pulmonary artery and from there into the right pulmonary artery (RPA). *Bottom row*, two maneuvers useful in catheterization of a dilated right heart. A larger loop with a downward-directed tip may be required to reach the tricuspid valve and can be formed by catching the catheter tip in the hepatic vein (HV) and advancing the catheter

the ulnar artery is patent in the event of radial artery occlusion, though the true utility of this remains unclear and an abnormal Allen test does not preclude radial arterial access. However, it should be remembered that left heart catheterization although extremely safe, contributes to a higher risk of complications due to potential for bleeding, increased risk of renal complications because of contrast use and usually a higher radiation exposure (as well as adding a small but definable risk of stroke and death). Relative contraindications to cardiac catheterization are listed in Table 10.7 below.

Equipment Selection for the Hemodynamic Study

Most cardiac catheterization laboratories utilize fluid-filled transducers that are mounted on the catheterization table. Typically these pressure transducers are disposable and usually arrive pre-calibrated, but require initial confirmation and repeated "zeroing," a term that refers to the establishment of a reference point (typically the patient's mid-chest at the level of the second intercostal space, as an estimation of the patient's right atrium) for subsequent pressure measurements. Some laboratories choose to avoid hydrostatic errors in diastolic pressure measurement theorized to be present with such zeroing technique by using a transducer zero reference position of uppermost blood level of the chamber being sampled or measured, Regardless of method employed, failures to ensure appropriate zero reference account for some of the most common pressure measure errors. [67–69].

Table 10.7 Relative contraindications to diagnostic cardiac catheterization [66]

Acute gastrointestinal bleeding
Severe hypokalemia
Uncorrected digitalis toxicity
Anticoagulation with international normalized ratio >1.8 or severe coagulopathy
Previous anaphylactoid reaction to contrast media
Acute stroke
Acute renal failure or severe chronic non-dialysis-dependent kidney disease
Unexplained fever or untreated active infection
Severe anemia
Uncooperative patient

Fig. 10.4 (continued) quickly into the right atrium. The reverse loop technique (*bottom right*) gives the catheter tip an upward direction, aimed toward the outflow tract. *IVC* inferior vena cava, *PA* pulmonary artery, *RV* right ventricle (from Baim DS, Grossman W: Percutaneous approach, including transseptal and apical puncture. In Baim DS, Grossman W [eds]: Cardiac Catheterization, Angiography, and Intervention. 7th ed. Philadelphia, Lea & Febiger, 2006, p 86)

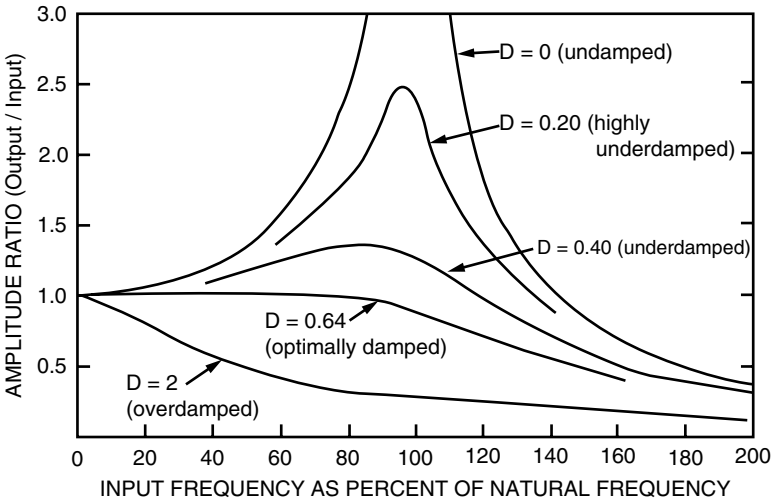

Fig. 10.5 Frequency response curves of a pressure measurement system, illustrating the importance of optimal damping. The amplitude of an input signal tends to be augmented as the frequency of that signal approaches the natural frequency of the sensing membrane. Optimal damping dissipates the energy of the oscillating sensing membrane gradually and thereby maintains a nearly flat natural frequency curve (constant output/input ratio) as it approaches the region of the pressure measurement system's natural frequency. *D* damping coefficient (from Baim, D.S. and W. Grossman, Grossman's cardiac catheterization, angiography, and intervention. 7th ed. 2006, Philadelphia: Lippincott Williams & Wilkins)

Choice of catheters (shortest, widest bore, non-compliant) and transmission fluid (low-density) used for pressure measurements, combined with elimination of air bubbles, as suggested earlier, optimizes effects of energy dissipation, or damping [70] (Fig. 10.5). Loss of high-frequency events with subsequent underestimation of the systolic pressure and overestimation of the diastolic pressure may occur with over-damping; narrow, sharp pressure wave upstrokes, or "ringing," can occur with under-damping.

Catheter whip artifact (motion of the tip of the catheter within the measured chamber) can be problematic in the accurate measurement of PA pressures. It has the potential to produce superimposed waves, typically of ±10 mmHg, but on occasion even greater deviation from true measure [71]. Catheter tip or luminal obstruction, at times due to catheter-vessel mismatch or internal thrombus formation, can cause significant changes in pressure contour. End-pressure artifact may occur when an end-hole catheter measures an artificially elevated pressure because of streaming or high velocity of the pressure wave. Another artifact similar to but distinct from whip artifact is catheter impact artifact, which can occur when walls of a cardiac chamber or valve hit the end of the measuring catheter. It can affect pressure measurements when a pigtail is used to measure LV pressures, and is impacted by mitral valve motion [70].

To avoid these artifacts, we strongly encourage the practice of taking multiple measurements, rebalancing the zero baseline during pressure evaluation at each

chamber or vessel and intermittent catheter flushing with heparinized saline. The ability to "zero" prior to measurement of pressure in each chamber, assisted by visual confirmation of catheter placement in the appropriate chamber in catheterization laboratory is a distinct advantage compared to placement of Swanz-Ganz catheter in the ICU/stepdown setting.

Another way to measure intracardiac pressure besides the fluid filled system is via use of micromanometer catheters. Small transducers have been constructed that can fit on the distal tip of standard catheters and be used as intracardiac manometers. Micromanometer catheters are currently not routinely used during RHC, but rather they form the basis of the pressure wire used for measurement of intracoronary pressures and are usually used for hemodynamic measurements as part of more detailed research efforts.

Pressure Measurements and Cardiac Output Determination

Hemodynamic catheterization, a combined experience of pressure measurement, sampling, catheter advancement, and angiography, is an interactive procedure where data obtained from each chamber is compared to previously obtained data; the accuracy of measurements may require additional confirmation and additional tests may be added and performed to answer new questions that arise. As there can be multiple sources of error as discussed above, measurements should be repeated if a single value does not fit with the overall emerging picture. Frequent "zeroing," and looking for air bubbles in the catheter system and "flushing" all ensure most accurate measurements.

Based on the findings, further testing and interventions are considered; such may include nitric oxide (NO) or adenosine administration assessing pulmonary vasoreactivity (see below), oxygen supplementation as therapy for systemic arterial desaturation (when responsive to such), diuretic or nitrate therapy for isolated elevated LV end-diastolic pressures, limited angiography, and balloon-closure of a patent inter-chamber or intravascular communication (if seen or detected).

Right Atrial Pressures and Waveform

In normal RA pressure tracings (Fig. 10.6), the "a" wave (atrial systole) is higher than the "v" wave (passive filling of the RV, reflecting RA and RV compliance) in contrast to the LA. Elevated "v" waves on the RA tracing in a patient with PH may be caused by tricuspid regurgitation, RV failure with secondary lowering of compliance, or restrictive cardiomyopathy. Constrictive pericarditis and tamponade typically demonstrate equalization of the "a" and the "v" waves.

Normal RAP is 2–6 mmHg. The finding of elevated RAP at the time of the right heart study usually implies worse RV function. Elevated RAP has been shown in several studies to be an adverse prognostic factor in patients with PH [74, 75], whereas normal RAP during RHC is reassuring.

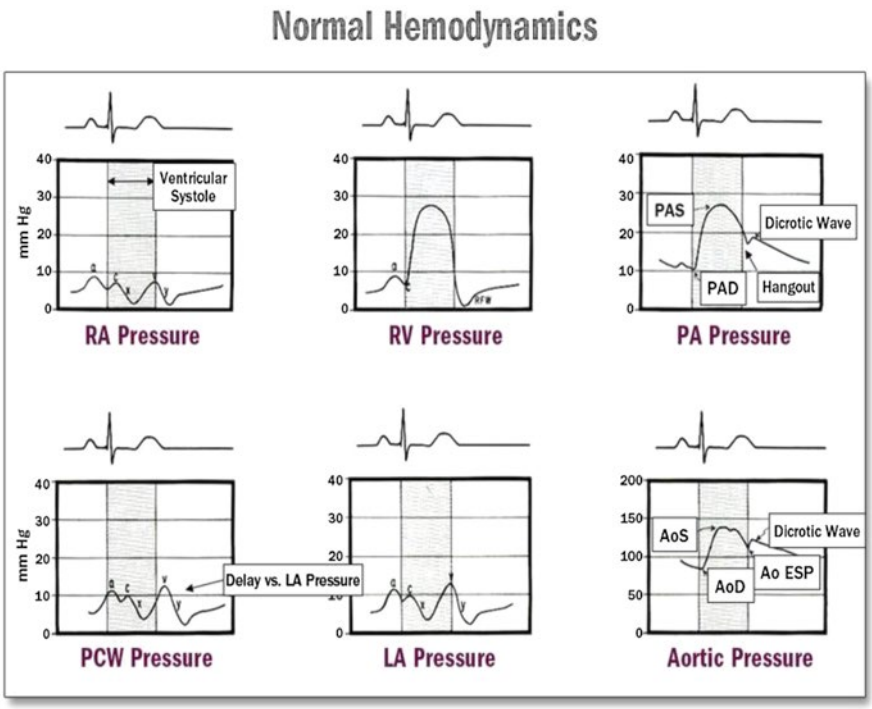

Fig. 10.6 Hemodynamic tracings of the cardiac chambers under normal conditions

Right Ventricle Pressure and Waveform

Normal RV systolic and end-diastolic pressures are 20–30 and 0–8 mmHg, respectively (Fig. 10.6). There may be a small (5 mmHg) systolic gradient between the RV and the PA. End-diastolic pressure is measured at the C point, which is the rise in ventricular pressure at the onset of isovolumic contraction. When the C point is not well seen, a line is drawn from the R wave on the simultaneous EKG recording to the ventricular pressure waveform.

Long-standing elevation of RV afterload leads to concentric RV hypertrophy and elevation of filling pressures, progressive tricuspid regurgitation (via annular dilation) and RV diastolic and eventually systolic dysfunction [76, 77]. These changes occur in a staged manner and should be interpreted with caution and never in isolation. Elevated RV systolic pressure or PA pressure by itself is not considered to be a prognostic factor for PH as a low or normal RVSP could signify a normal RV or a failing RV that cannot generate a high enough RVSP, depending on stage of the disease. In the early stages of disease when RV is able to mount a pressure response to afterload, RV pressure rise may be increased by up to ten times the normal value [78]. Occasionally, "a" waves will be present on the RV waveforms at this

stage, indicating "restrictive physiology" with decreased compliance of the RA and RV. (Normally, the highly compliant RV is able to "accommodate" the contraction of the RA without a rise in pressure, making the "a" waves non-visible in a normal tracing.) In more severe forms of RV dysfunction, depressed upstroke and delayed relaxation may appear on the pressure tracings. Generally, RV end-diastolic pressure >12 mmHg, especially if accompanied by a mean RAP >8 mmHg, is suggestive of RV failure and carries poor prognosis [74].

Pulmonary Artery Pressure and Waveform

The resistance of the normal pulmonary circulation is relatively low, with little or no resting vascular tone. The PA tracing consists of a systolic wave, the incisura (indicating closure of the pulmonary valves), and a gradual decline in pressure until the following systole (Fig. 10.6). The determining factors of the mPAP are the hydrostatic pressure, the intra-alveolar pressure, LAP and alveolar gases. Normal sPAP is 20–30 mmHg and normal dPAP is 4–12 mmHg. If there is a systolic pressure difference between the RV and the PA, the possibilities of pulmonic valve stenosis or pulmonary artery (main or branch) stenosis or obstruction should be considered.

The PAP should be measured bilaterally and in multiple lobes, both proximally and distally to ensure absence of stenotic lesions and also because CTEPH may involve only certain lobar vessels. PA pressures should always be measured in the lower lobes (zone 3), as ventilation perfusion mismatch is least in lower lobe vessels. The diurnal variation of PAP is well known and it can be as much as 50–100 % with higher pressures often noted at night [79].

Pulmonary Capillary Wedge Pressure

Estimation of the pulmonary venous and pulmonary capillary pressure can be usually achieved via the wedge technique, accomplished on the basis of measuring the pulmonary wedge pressure. The PCWP waveform is similar to the LAP waveform, but is more damped and delayed as a result of transmission through the lungs (Fig. 10.6). Normally, dPAP is equal to mean PCWP as the pulmonary resistance is low. However, when PVR is elevated dPAP overestimates LAP.

Finessing the Wedge

There are several ways to confirm the appropriateness of catheter "wedging" and that the quality of PCWP measurement is high. The best way is to check either angiographic stability (reserved to personnel with experience in PA catheterization and angiography), or oxygen saturation within the wedge position. Oxygen saturation >90 % typically suggests an adequate wedge position [68]. Alternative is via *wedge angiography* [80], where 1–2 cc of contrast is hand injected distal to a

"wedged" PAC to opacify the distal pulmonary vasculature. A satisfactory wedge position should have no evidence of contrast "washout" due to incompletely occluded proximal flow. (True wedge angiography can be performed with balloon deflation after injection, allowing contrast to flow through the pulmonary vasculature, thus outlining the physical appearance of the branch pulmonary arteries and revealing when present, the presence of distal pulmonary artery obstruction, pulmonary arteriovenous malformations, normal pulmonary venous drainage and possible evidence of pulmonary venous obstruction). Optimal PCWP is obtained with the measuring catheter positioned to ensure viewing of "a" and "v" waves without dampening or under wedging. Slow balloon inflation proximally and then advancing balloon catheter, or very slow distal inflation, or using a wire to obtain optimal distal placement, may help in accurate positioning of the catheter.

PCWP and PAOP (Pulmonary Artery Occlusion Pressure)

Elevated PAP can create difficulty in obtaining a true "wedge" with even small amounts of proximal flow around the balloon resulting in inaccurately high estimates of PCWP [81, 82]. When such error is suggested, the balloon can be deflated by 0.2–0.5 ml with slight forward pressure on the catheter, allowing the catheter and balloon to move forward within a smaller portion of the branch vessel thereby securing a better lodging and wedge.

Care must be taken to ensure measure of PCWP under conditions that sustain physiologic zone 3 (pulmonary venous pressure exceeding alveolar pressure). Wedging of the catheter can, in and of itself, lead to lack of distension of the effected distal vascular bed, leading to underestimating of true capillary pressure. In addition to positive pressure ventilation (as discussed earlier), both hypovolemia and advanced parenchymal lung disease can contribute to making alveolar pressure exceed pulmonary venous pressure, adding error to estimate of true pulmonary venous pressure.

On special occasion when subsegmental venous obstruction such as occurs in pulmonary veno-occlusive disease is suspected, occlusion of a larger, more proximal PA known as pulmonary artery occlusion pressure (PAOP) (Fig. 10.7) may provide a more accurate summed representation of more distal pulmonary venous and LAP. In this circumstance, PCWP has potential to reflect local or subsegmental pulmonary venous pressure (in the setting of increased local vascular resistance) rather than LAP [83]. Assessment of the curve of the decay from PAP to PAOP may be of assistance in determining the site of predominant increase in resistance (Fig. 10.8) [85].

Transpulmonary Gradient and Diastolic Pressure Gradient

The transpulmonary gradient (TPG) is calculated by subtracting the mean LAP (or PCWP, as a surrogate of post-capillary pressure) from the mPAP. TPG can be used to differentiate pre-capillary and post-capillary forms of PH [86]. A TPG of >12 mmHg

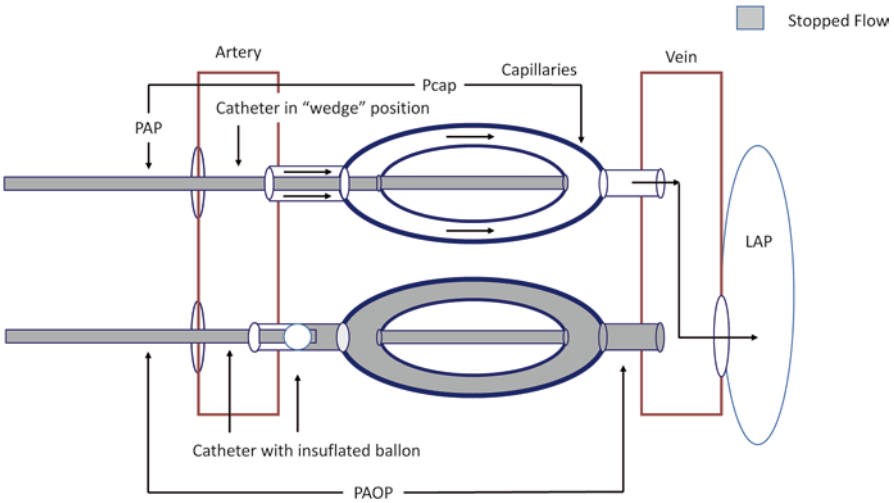

Fig. 10.7 Pulmonary artery occlusion pressure and pulmonary capillary wedge pressure

has been used classically to distinguish pre-capillary PH, which is the result of intrinsic pulmonary vascular disease, from post-capillary PH which is due to pulmonary venous or left atrial hypertension. Post-capillary PH may be expected to reverse when the cause of pulmonary venous hypertension is removed (such as seen in patients with mitral stenosis or diastolic heart failure). However, it is possible for diastolic heart failure or mitral stenosis to cause irreversible changes in PH and lead to pre-capillary hypertension as well.

A TPG value of 12 mmHg is considered to signify intrinsic pulmonary vascular disease, as this degree of PH is "out of proportion" to elevated pulmonary venous pressures. Some authors suggest that the diastolic gradient between dPAP and PCWP, or diastolic pressure gradient (DPG), is a better measure of "out of proportion" PH than TPG, as the TPG is affected by both stroke volume and also by the large v waves that can occur in the PCWP waveform (Fig. 10.9) [87].

Pulmonary Vascular Resistance (PVR)

Presence of PH does not delineate presence or absence of elevation of PVR. Definition of PAH requires additional hemodynamic criteria that include a PVR >3 Wood units and a PCWP <15 mm Hg. PVR is calculated using Ohm's Law in Wood units, as follows:

$$\text{PVR} = \frac{(\text{mPAP} - \text{PCWP})}{\text{Cardiac output}(\text{CO})} = \frac{(\text{TPG})}{\text{CO}}$$

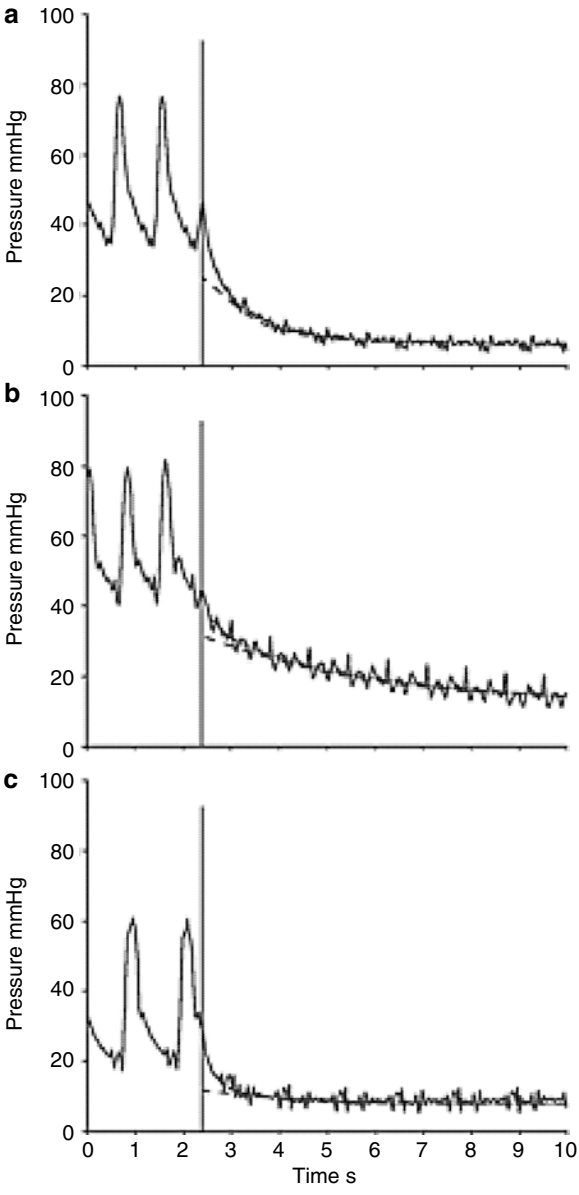

Fig. 10.8 Typical pulmonary artery occlusion recordings used to estimate pulmonary capillary pressure (P_c) in (**a**) a patient with a pulmonary arterial hypertension, (**b**) a patient with pulmonary veno-occlusive disease and (**c**) a patient with chronic thromboembolic pulmonary hypertension. The bi-exponential fittings are shown in *dotted lines*, and the evolution of P_c after occlusion (*vertical solid lines*) calculated with the three-compartment model of the pulmonary circulation in *dashed lines* [85] (from Single arterial occlusion to locate resistance in patients with pulmonary hypertension. Eur Respir J 2001)

Multiplying the resistance calculated in Wood units by 80 converts to the resistance units of dynes s/cm^5. A value of <200 dynes s/cm^5 (or 2.5 Wood units) is considered to be normal. Normal PVR at rest is age dependent, but PVR >2 WU can be considered elevated in all age populations.

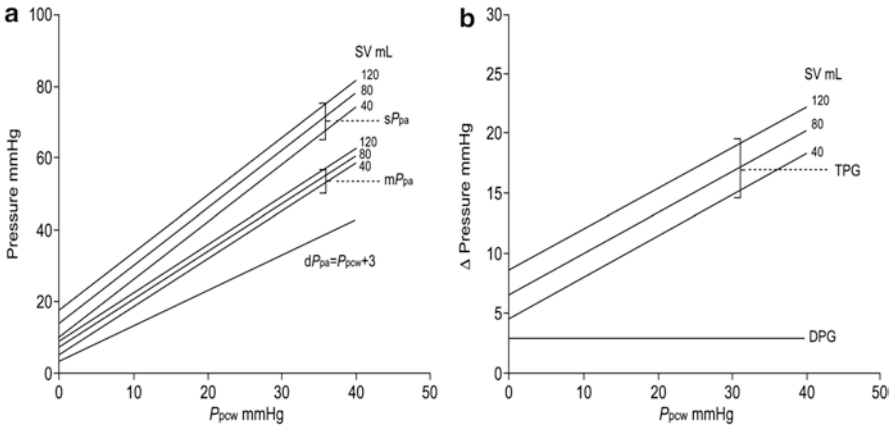

Fig. 10.9 Effects of pulmonary capillary wedge pressure (P_{pcw}) and stroke volume (SV) on systolic (s), diastolic (d), and mean (m) pulmonary arterial pressures (P_{pa}). If diastolic P_{pa} increases more than P_{pcw}, there is an out of proportion increase in systolic P_{pa} and mean P_{pa} that is a function of SV. The transpulmonary pressure gradient (TPG) increases, but the diastolic gradient (DPG) is independent of both pulmonary capillary wedge pressure (P_{pcw}) and SV

Pulmonary Vascular Resistance Index (PVRI)

It is generally recommended that PVR should be indexed to the patient's body size (PVRI) [88]. Using PVR instead of PVRI has been shown to be responsible for significant underestimation of PH in patients with high body mass index. PVRI is considered to mainly reflect the functional status of pulmonary vascular endothelium and smooth muscle cells and is positively related to blood viscosity and to changes in perivascular alveolar and pleural pressure. Unlike mPAP, PVRI increases with age: the upper limit for PVRI in normal subjects increases from about 2.8 indexed Wood units (6–10 years) to 3.2 (32–45 years) to 4.6 (60–83 years) indexed Wood units [1, 89–92].

Cardiac Output

There is no completely accurate method of measuring cardiac output in all patients. However, the two commonly used methods include the Fick and thermodilution techniques.

For comparison among patients, cardiac output should be corrected for the patient's body surface area and expressed as cardiac index (CI).

Fick Method

The basis of the Fick principle is that the rate of human oxygen consumption must equal the rate of oxygen addition to the body. This tenet also assumes a constancy of blood flow into and out of the lungs, free of shunt [93, 94]. This principle can be expressed as:

$$\text{Pulmonary blood flow}\left(\text{l}/\text{min}\right) = \frac{\text{O}_2\ \text{consumption}\left(\text{ml}/\text{min}\right)}{\left(\Delta\text{O}_2\ \text{concentration entering and leaving lungs}\right)}$$

or,

$$\text{Cardiac output}\left(\text{l}/\text{min}\right) = \frac{\text{oxygen consumption}\left(\text{ml}/\text{min}\right)}{\text{A}\ \ \text{VO}_2 \times 1.36 \times \text{Hemoglobin}\left(\text{mg}/\text{dL}\right) \times 10}$$

where A-VO_2 is the arterial-venous oxygen saturation difference and the constant 1.36 is the oxygen-carrying capacity of hemoglobin (expressed in ml O_2/g Hgb). As contrasted to thermodilution methodology, the Fick calculation of cardiac output necessitates minimal waver in mean flow over time, and carries less error at lower measures of blood flow; therefore, it is typically utilized in patients with heart failure syndromes. Accuracy of measure falls away in subjects with inspiratory O_2 fractions larger than 60 %, and in those with significant mitral or aortic regurgitation [97].

Determination of cardiac output by catheterization based Fick method requires measure of the A-VO_2 content difference which requires knowledge of serum hemoglobin and determination of systemic arterial (as a surrogate for pulmonary vein) and mixed venous blood oxygen saturation (classically PA O_2 saturation, but SVC O_2 saturation is often used as a surrogate) as well as determination of oxygen consumption. All measurements should be collected as close in time to each other as possible, so as to avoid theoretic changes in ventilation, loading conditions and contractility. Steady state oxygen consumption, or uptake, should ideally be measured, via a fitting gas exchange mask that collects and measures the oxygen content of expired air, directly in the catheterization laboratory. Many catheterization laboratories use an "assumed" value (typically 125 ml/min/m^2 for most adult patients, and 110 ml/min/m^2 for elderly patients) for oxygen consumption. The use of the "assumed" rather than the directly measured O_2 consumption can be a major source of error in the Fick method, but when performed correctly, the total error indetermination of the cardiac output is about 10 % [95–97].

Thermodilution Method

The thermodilution method of estimation of cardiac output requires injection of an indicator substance such as a bolus of liquid (usually sterile normal saline) via the proximal port of a specially adapted multiport catheter. Cardiac output between two points along the catheter (injection and thermistor located more distally) is

determined by knowing temperature at the origin and at the endpoint of measure, as well as assessing this change over time, as demonstrated in a thermodilution curve. The area under this curve, a function of temperature versus time, is inversely correlated with cardiac output, and is rapidly displayed in near real-time in most catheterization laboratories. Thermodilution methodology carries greatest risk of error at lower (and highest) cardiac output and in the presence of tricuspid regurgitation or irregular heart rhythm [100, 101], Nonetheless, due to ease of performance, thermodilution technique remains the most commonly used method for measure of cardiac output in most catheterization laboratories [98, 99].

Direct Measurement of Left-Sided Pressures

Possible conditions in which direct evaluation of the left-sided intracardiac pressures may be required include one or more of the following: (1) Uncertainty about a direct correlation between the PCWP and the LAP/LV end-diastolic pressure, such as in patients with suspected mitral stenosis, pulmonary vein obstruction or cor-triatriatum; (2) Clinical or imaging-based suspicion of restrictive or constrictive physiology, requiring concomitant measurement of RV and LV pressures.

Both constrictive pericarditis (CP) and restrictive cardiomyopathy (RCM) lead to impaired filling of left and right ventricles that result in decreased cardiac output. Both are characterized by initially normal systolic contractile function and are an important differential diagnosis for diastolic dysfunction due to left heart disease. In the cardiac catheterization laboratory concomitant measurement of LV and RV pressures helps in differentiating between these pathologic entities. In constrictive pericarditis (CP), as more blood enters the RV with inspiration, the intrapericardial pressure increases because of the limited space in the pericardium and LV filling is reduced. Hence in CP, RV systolic pressure rises with inspiration while LV systolic pressure decreases. The reverse happens during spontaneous expiration [102]. In contrast, LV and RV systolic pressures do not show discordance in variation with respiration, and will both increase during expiration and decrease during inspiration. Some of the clues that help distinguish between CP and RCM include (a) the persistence of higher left-sided filling pressures maintained in RCM and (b) the magnitude of pulmonary hypertension tends to be greater in RCM (RVSP is >3 times RVEDP) [103]. The “systolic area index” ratio which is calculated as the RV to LV systolic pressure-time area during inspiration versus expiration is shown to have a sensitivity of 97 % and a predictive accuracy of 100 % for the identification of patients with surgically documented CP (see Fig. 10.10) [104].

Suspicion or knowledge of significant left-sided valvular disease may require direct evaluation of the hemodynamics and pressure gradients across the involved valve(s). In these cases transseptal puncture and direct measurement of LAP may be required. If mitral stenosis is suspected and PCWP measurement is not reliable, direct LAP measurement should be performed. If underlying coronary artery disease is suspected to be the cause or contributor to diastolic dysfunction coronary angiography may be considered.

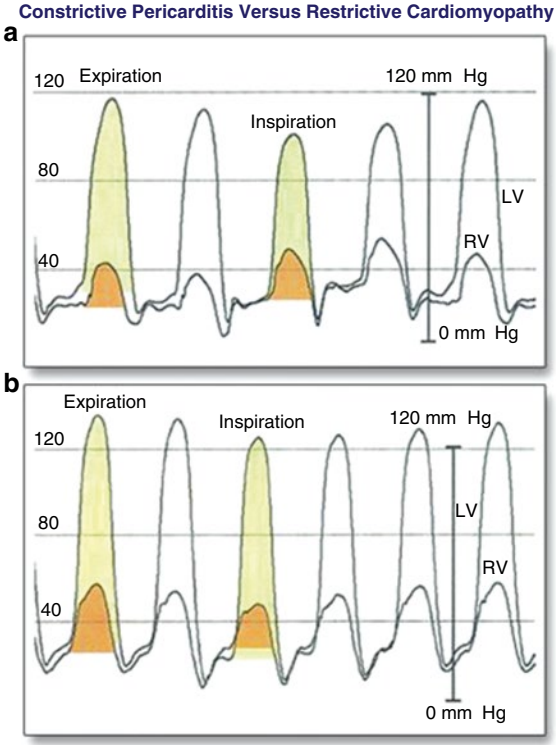

Fig. 10.10 LV and RV high-fidelity manometer pressure traces from two patients during expiration and inspiration. Note that both patients have early rapid filling and elevation and end-equalization of the left ventricular (LV) and right ventricular (RV) pressures at end expiration. (**a**) A patient with surgically documented constrictive pericarditis. During inspiration there is an increase in the area of the RV pressure curve (*orange shaded area*) compared with expiration. The area of the LV pressure curve (*yellow shaded area*) decreases during inspiration as compared with expiration. (**b**) A patient with restrictive myocardial disease documented by endomyocardial biopsy. During inspiration there is a decrease in the area of the RV pressure curve (*orange shaded area*) as compared with expiration. The area of the LV pressure curve (*yellow shaded area*) is unchanged during inspiration as compared with expiration (from Talreja DR, Nishimura RA, Oh JK, Holmes DR. Constrictive pericarditis in the modern era: novel criteria for diagnosis in the cardiac catheterization laboratory. J Am Coll Cardiol. 2008)

Volume Challenge to Unmask PH due to Diastolic Dysfunction

It has been shown in healthy individuals that administration of 1 l of saline over 6–8 min raises the PCWP by a maximum of 3 mm Hg, but not to >11 mmHg [1, 105]. In addition, in a population that is at elevated risk for diastolic dysfunction, administration of 500 ml of saline over 5 min can unmask patients in whom the PCWP increases to >15 mmHg [106]. Fluid volumes larger than 1 l, may cause the PCWP to rise even in healthy volunteers [107]. The diagnostic performance (sensitivity, specificity, and positive and negative predictive values) of fluid

challenge has not yet been sufficiently evaluated nor has the safety of fluid challenge in patients with severe PH. However, when mild to moderate PH exists in the presence of modest suspicion of diastolic dysfunction, fluid challenge appears to be a reasonable test to perform.

Exercise Challenge During Right Heart Catheterization

Getting hemodynamic measurements during exercise can add to the information obtained from RHC done only at rest. For example, elevated PCWP during exercise can point towards diastolic dysfunction as a cause of PH. Borlaug and colleagues recently showed that during exercise, end-expiration PCWP rose to 32 ± 6 mmHg in patients with HFpEF compared with 13 ± 5 mmHg in controls [108]. Exercise hemodynamics may also be useful in distinguishing between PAH and PH associated with LV diastolic dysfunction in patients with the scleroderma (SSc) spectrum of disease [109]. In some patients mPAP may be only slightly elevated at rest, but exercise leads to symptoms and significant elevation in PAP and PVR, thus unmasking more severe PH [110]. Change in PAP during exercise along with symptoms can also be an important measure of response to treatment [110, 111] Exercise testing for PH during RHC is not yet standardized and at present is limited to centers with experience and expertise in interpreting pulmonary vascular responses to exercise [1]. In particular, change in PVR may be more important than the change in PAP and thus, measurement of cardiac output is usually needed to properly interpret pulmonary hemodynamic responses to exercise. Also, PCWP measured during exercise is unreliable due to multiple contributors such as changes in ventilatory pattern abdominal muscle contractions and differs from the recumbent to the upright position of the patient. Further discussion of this topic is presented in Chap. 11.

Pulmonary Angiography for CTEPH

It is quite safe to perform pulmonary angiography (typically isolated to particular PA segments or lobes) even in cases with severe PH, although the risk may be elevated in patients with severe decrease in cardiac output, elevation in RA or RV end diastolic pressure, or super-systemic RV pressures. While performing RHC in a patient with suspected PA or pulmonary vein obstructions, PA pressures should be measured bilaterally and in multiple lobes both proximally and distally. A preshaped catheter such as a coronary catheter can be used for the purpose of accessing specific lobes and then can be exchanged for balloon tipped end hole catheter for checking pressures. It should be kept in mind that there is a reflex rise in PAP and PVR after pulmonary angiography so pressures should be measured prior to performing this procedure. Pulmonary angiography should be performed in cases with suspected CTEPH, peripheral pulmonary artery stenosis, vasculitis, pulmonary AV malformations, or pulmonary venous obstruction [112].

Table 10.8 Agents for acute vasodilator testing (from McLaughlin VV et al, ACCF/AHA 2009 expert consensus document on pulmonary hypertension, Circulation 2009)

	Epoprostenol	Adenosine	Nitric oxide
Route of administration	Intravenous infusion	Intravenous infusion	Inhaled
Dose titration	2 ng/kg/min every 10–15 min	50 mcg/kg/min every 2 min	None
Dose range	2–10 ng/kg/min	50–250 mcg/kg/min	10–80 ppm
Side effects	Headache, nausea, lightheadedness	Dyspnea, chest pain, AV block	Increased left heart filling pressure in susceptible patients

AV atrioventricular

Vasoreactivity Testing

Vasoreactivity or vasodilator testing during RHC is beneficial as it may identify a subset of patients that respond to calcium channel blockers (CCB), or may assist in prognostic assessment. Acute vasoreactivity challenge should be performed with a short-acting pulmonary specific vasodilator that has no or very limited systemic hypotensive effects. The agent most commonly used is inhaled NO, while intravenous epoprostenol or adenosine can also be used as alternatives (with the caveat that they may cause systemic vasodilator effects) (Table 10.8) [1]. A positive acute response is defined as a reduction of mPAP by 10 mmHg *and* to an absolute value of ≤40 mmHg with an increased or unchanged cardiac output. Using these criteria, about 5–10 % of the patients with IPAH will have a positive pulmonary vasodilator response. Positive acute responders are likely to show a sustained response to long-term treatment with high doses of CCB. True vasodilator responders who demonstrate sustained response to CCB have an excellent prognosis, with up to a 95 % survival at 5 years [113]. In one study, however, 44 % of patients with IPAH who demonstrated an acute pulmonary vasodilator response showed no hemodynamic improvement after 1 year of therapy. Thus, the number of patients who can be treated with CCB alone is quite small [113].

References

1. Hoeper MM, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol. 2013;62:D42–50.
2. McLaughlin VV, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. Circulation. 2009;119:2250–94.
3. Galiè N, et al. Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of

Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J. 2009;30:2493–537.
4. Levitzky MG. Chapter 4. Blood flow to the lung. In: Levitzky MG, editors. Pulmonary physiology, 8e. New York, NY: McGraw-Hill; 2013. http://accessmedicine.mhmedical.com/content.aspx?bookid=575&Sectionid=42512982. Accessed 8 Sept 2014.
5. Achilles J, et al. 12—Special circulations, In: Achilles J. editors. Cardiovascular physiology. 10th ed. Philadelphia; 2013. p. 237–62. ISBN 9780323086974, http://dx.doi.org/10.1016/B978-0-323-08697-4.00012-5. (http://www.sciencedirect.com/science/article/pii/B9780323086974000125)
6. Kovacs G, et al. Pulmonary vascular resistances during exercise in normal subjects: a systematic review. Eur Respir J. 2012;39:319–28.
7. Hughes JM, et al. Effect of lung volume on the distribution of pulmonary blood flow in man. Respir Physiol. 1968;4:58–72.
8. Glenny RW, Bernard S, Robertson HT, Hlastala MP. Gravity is an important but minor determinant of pulmonary blood flow heterogeneity in the baboon. FASEB J. 1997;11:1996.
9. Galvin I, Drummond GB, Nirmalan M. Distribution of blood flow and ventilation in the lung: gravity is not the only factor. Br J Anaesth. 2007;98:420–8.
10. Dumas JP, Bardou M, Goirand F, et al. Hypoxic pulmonary vasoconstriction. Gen Pharmacol. 1999;33:289–97.
11. Opotowsky AR, Ojeda J, Rogers F, Arkles J, Liu T, Forfia PR. Blood pressure response to the valsalva maneuver. A simple bedside test to determine the hemodynamic basis of pulmonary hypertension. J Am Coll Cardiol. 2010;56(16):1352–3.
12. Wiese J. The abdominojugular reflux sign. Am J Med. 2000;109(1):59–61.
13. Nath AR, Capel LH. Inspiratory crackles—early and late. Thorax. 1974;29(2):223–7.
14. Simon M, Sasahara AA, Cannilla JE. The radiology of pulmonary hypertension. Semin Roentgenol. 1967;2:368–88.
15. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med. 1987;107(2):216–23.
16. Chetty KG, Brown SE, Light RW. Identification of pulmonary hypertension in chronic obstructive pulmonary disease from routine chest radiographs. Am Rev Respir Dis. 1982;126(2):338–41.
17. Turner AF, Lau FY, Jacobson G. A method for the estimation of pulmonary venous and arterial pressures from the routine chest roentgenogram. AJR. 1972;116:97–106.
18. Milne EN. Physiological interpretation of the plain radiograph in mitral stenosis, including a review of criteria for the radiological estimation of pulmonary arterial and venous pressures. Br J Radiol. 1963;36:902–13.
19. Ng CS, Wells AU, Padley SP. A CT sign of chronic pulmonary arterial hypertension: the ratio of main pulmonary artery to aortic diameter. J Thorac Imaging. 1999;14(4):270–8.
20. Kuriyama K, Gamsu G, Stern RG, Cann CE, Herfkens RJ, Brundage BH. CT-determined pulmonary artery diameters in predicting pulmonary hypertension. Invest Radiol. 1984;19(1):16–22.
21. Baque-Juston MC, Wells AU, Hansell DM. Pericardial thickening or effusion in patients with pulmonary artery hypertension: a CT study. AJR Am J Roentgenol. 1999;172(2):361–4.
22. Tan RT, Kuzo R, Goodman LR, et al. Utility of CT scan evaluation for predicting pulmonary hypertension in patients with parenchymal lung disease. Chest. 1998;113:1250–6.
23. Benza R, Biederman R, Murali S, Gupta H. Role of cardiac magnetic resonance imaging in the management of patients with pulmonary arterial hypertension. J Am Coll Cardiol. 2008;52(21):1683–92.
24. Kuehne T, Yilmaz S, Schulze-Neick I, et al. Magnetic resonance imaging guided catheterisation for assessment of pulmonary vascular resistance: in vivo validation and clinical application in patients with pulmonary hypertension. Heart. 2005;91:1064–9.
25. Henkens IR, Scherptong RW, Kralingen KW, Said SA, Vliegen HW. Pulmonary hypertension: the role of the electrocardiogram. Neth Heart J. 2008;16:250–4.

26. Rich S, Brundage BH. High-dose calcium channel-blocking therapy for primary pulmonary hypertension: evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy. Circulation. 1987;76(1):135–41.
27. Bossone E, Paciocco G, Iarussi D, Agretto A, Iacono A, Gillespie BW, Rubenfire M. The prognostic role of the ECG in primary pulmonary hypertension. Chest. 2002;121(2):513.
28. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010;23:685–713.
29. Fisher MR, Forfia PR, Chamera E, Housten-Harris T, Champion HC, Girgis RE, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med. 2009;179:615–21.
30. McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004;126:14S–34.
31. Skjaerpe T, Hatle L. Noninvasive estimation of systolic pressure in the right ventricle in patients with tricuspid regurgitation. Eur Heart J. 1986;7:704–10.
32. Abbas AE, Fortuin FD, Schiller NB, Appleton CP, Moreno CA, Lester SJ. Echocardiographic determination of mean pulmonary artery pressure. Am J Cardiol. 2003;92:1373–6.
33. Aduen JF, Castello R, Lozano MM, Hepler GN, Keller CA, Alvarez F, et al. An alternative echocardiographic method to estimate mean pulmonary artery pressure: diagnostic and clinical implications. J Am Soc Echocardiogr. 2009;22:814–9.
34. Lee RT, Lord CP, Plappert T, Sutton MS. Prospective Doppler echocardiographic evaluation of pulmonary artery diastolic pressure in the medical intensive care unit. Am J Cardiol. 1989;64:1366–70.
35. Reynolds DW, Bartelt N, Taepke R, Bennett TD. Measurement of pulmonary artery diastolic pressure from the right ventricle. J Am Coll Cardiol. 1995;25:1176–82.
36. Stephen B, Dalal P, Berger M, Schweitzer P, Hecht S. Noninvasive estimation of pulmonary artery diastolic pressure in patients with tricuspid regurgitation by Doppler echocardiography. Chest. 1999;116:73–7.
37. Abbas AE, Fortuin FD, Schiller NB, Appleton CP, Moreno CA, Lester SJ. A simple method for noninvasive estimation of pulmonary vascular resistance. J Am Coll Cardiol. 2003;41:1021–7.
38. Haddad F, Zamanian R, Beraud AS, Schnittger I, Feinstein J, Peterson T, et al. A Novel noninvasive method of estimating pulmonary vascular resistance in patients with pulmonary arterial hypertension. J Am Soc Echocardiogr. 2009;22:523–9.
39. Addonizio LJ, Gersony WM, Robbins RC, Drusin RE, Smith CR, Reison DS, et al. Elevated pulmonary vascular resistance and cardiac transplantation. Circulation. 1987;76:V52–5.
40. Scapellato F, Temporelli PL, Eleuteri E, Corrá E, Imparato A, Giannuzzi P. Accurate noninvasive estimation of pulmonary vascular resistance by Doppler echocardiography in patients with chronic failure heart failure. J Am Coll Cardiol. 2001;37:1813–9.
41. Opotowsky AR, Clair M, Afilalo J, Landzberg MJ, Waxman AB, Moko L, Maron BA, Vaidya A, Forfia PR. A simple echocardiographic method to estimate pulmonary vascular resistance. Am J Cardiol. 2013;112:873–82.
42. Dabestani A, Mahan G, Gardin JM, Takenaka K, Burn C, Allfie A, et al. Evaluation of pulmonary artery pressure and resistance by pulsed Doppler echocardiography. Am J Cardiol. 1987;59:662–8.
43. Burgess MI, Bright-Thomas RJ, Ray SG. Echocardiographic evaluation of right ventricular function. Eur J Echocardiogr. 2002;3(4):252–62.
44. Arkles JS, Opotowsky AR, Ojeda J, Rogers F, Liu T, Prassana V, Marzec L, Palevsky HI, Ferrari VA, Forfia PR. Shape of the right ventricular Doppler envelope predicts hemodynamics and right heart function in pulmonary hypertension. Am J Respir Crit Care Med. 2011;183:268–76.

45. Lai WW, Gauvreau K, Rivera ES, Saleeb S, Powell AJ, Geva T. Accuracy of guideline recommendations for two-dimensional quantification of the right ventricle by echocardiography. Int J Cardiovasc Imaging. 2008;24:691–8.
46. Anavekar NS, Gerson D, Skali H, Kwong RY, Yucel EK, Solomon SD. Two-dimensional assessment of right ventricular function: an echocardiographic-MRI correlative study. Echocardiography. 2007;24:452–6.
47. Forfia PR, Fisher MR, Mathai SC, Housten-Harris T, Hemnes AR, Borlaug BA, Chamera E, Corretti MC, Champion HC, Abraham TP, Girgis RE, Hassoun PM. Tricuspid annular displacement predicts survival in pulmonary hypertension. Am J Respir Crit Care Med. 2006;174(9):1034–41.
48. Badano LP, Ginghina C, Easaw J, Muraru D, Grillo MT, Lancellotti P, Pinamonti B, Coghlan G, Marra MP, Popescu BA, De Vita S. Right ventricle in pulmonary arterial hypertension: haemodynamics, structural changes, imaging, and proposal of a study protocol aimed to assess remodelling and treatment effects. Eur J Echocardiogr. 2010;11(1):27–37.
49. Tei C, Dujardin KS, Hodge DO, Bailey KR, McGoon MD, Tajik AJ, et al. Doppler echocardiographic index for assessment of global right ventricular function. J Am Soc Echocardiogr. 1996;9:838–47.
50. Meris A, Faletra F, Conca C, Klersy C, Regoli F, Klimusina J, et al. Timing and magnitude of regional right ventricular function: a speckle tracking derived strain study of normal subjects and patients with right ventricular dysfunction. J Am Soc Echocardiogr. 2010; 23:823–31.
51. Haddad F, et al. Right ventricular function in cardiovascular disease, part I: anatomy, physiology, aging, and functional assessment of the right ventricle. Circulation. 2008;117(11): 1436–48.
52. Ryan T, et al. An echocardiographic index for separation of right ventricular volume and pressure overload. J Am Coll Cardiol. 1985;5(4):918–27.
53. Hinderliter AL, et al. Frequency and prognostic significance of pericardial effusion in primary pulmonary hypertension. PPH Study Group. Primary pulmonary hypertension. Am J Cardiol. 1999;84(4):481. -4, A10.
54. Ranu H, Smith K, Nimako K, Sheth A, Madden BP. A retrospective review to evaluate the safety of right heart catheterization via the internal jugular vein in the assessment of pulmonary hypertension. Clin Cardiol. 2010;33:303–6.
55. Hoeper MM, Lee SH, Voswinckel R, et al. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. J Am Coll Cardiol. 2006;48:2546–52.
56. Massicotte A. A practice tool for the new oral anticoagulants. Can Pharm J (Ott). 2014; 147(1):25–32.
57. Francis GS, Cohn JN. The autonomic nervous system in congestive heart failure. Annu Rev Med. 1986;37:235–47.
58. Groeneveld AB, et al. Effect of the mechanical ventilatory cycle on thermodilution right ventricular volumes and cardiac output. J Appl Physiol (1985). 2000;89(1):89–96.
59. Couture P, et al. Effects of anesthetic induction in patients with diastolic dysfunction. Can J Anaesth. 2009;56(5):357–65.
60. Biondi JW, et al. The effect of incremental positive end-expiratory pressure on right ventricular hemodynamics and ejection fraction. Anesth Analg. 1988;67(2):144–51.
61. Theres H, et al. Phase-related changes in right ventricular cardiac output under volume-controlled mechanical ventilation with positive end-expiratory pressure. Crit Care Med. 1999;27(5):953–8.
62. Ragosta M. Normal waveforms, artifacts, and pitfalls. In: Textbook of clinical hemodynamics. Philadelphia: Saunders/Elsevier; 2008.
63. Summerhill EM, Baram M. Principles of pulmonary artery catheterization in the critically ill. Lung. 2005;183(3):209–19.
64. Dehmer GJ, Firth BG, Hillis LD. Oxygen consumption in adult patients during cardiac catheterization. Clin Cardiol. 1982;5(8):436–40.

65. Hemnes AR, Forfia PR, Champion HC. Assessment of pulmonary vasculature and right heart by invasive haemodynamics and echocardiography. Int J Clin Pract Suppl. 2009;162:4–19.
66. Bonow R, Mann D, Zipes D, Libby P. Technical aspects of cardiac catheterization. Braunwald's heart disease. http://www.r2library.com/Resource/Title/1437703984/ch0020s0569. (2012). Retrieved 8 Sept 2014.
67. Sabbah HN, Anbe DT, Stein PD. Negative intraventricular diastolic pressure in patients with mitral stenosis: evidence of left ventricular diastolic suction. Am J Cardiol. 1980;45(3): 562–6.
68. Paulus WJ, Vantrimpont PJ, Rousseau MF. Diastolic function of the nonfilling human left ventricle. J Am Coll Cardiol. 1992;20(7):1524–32.
69. Courtois M, et al. Anatomically and physiologically based reference level for measurement of intracardiac pressures. Circulation. 1995;92(7):1994–2000.
70. Baim DS, Grossman W. Grossman's cardiac catheterization, angiography, and intervention, 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2006. xvii, 807 p.
71. Bonow R, Mann D, Zipes D, Libby P. Hemodynamic data. Braunwald's heart disease. http://www.r2library.com/Resource/Title/1437703984/ch0020s0577. (2012)Retrieved 8 Sept 2014.
72. Irvin CG, et al. Effect of breathing pattern on esophageal pressure gradients in humans. J Appl Physiol Respir Environ Exerc Physiol. 1984;57(1):168–75.
73. D'Alonzo GE, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991;115(5):343–9.
74. Thenappan T, et al. Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. Eur Respir J. 2010;35(5):1079–87.
75. Stein PD, et al. Performance of the failing and nonfailing right ventricle of patients with pulmonary hypertension. Am J Cardiol. 1979;44(6):1050–5.
76. Chemla D, et al. Haemodynamic evaluation of pulmonary hypertension. Eur Respir J. 2002;20(5):1314–31.
77. Fishman AP, Fisher AB, American Physiological Society. The respiratory system. Handbook of physiology 1985. Bethesda, MD: American Physiological Society; 1887. Distributed by Williams & Wilkins.
78. Gibbs JS, Cunningham D, Shapiro LM, Park A, Poole-Wilson PA, Fox KM. Diurnal variation of pulmonary artery pressure in chronic heart failure. Br Heart J. 1989;62:30–5.
79. Bell ALL, Shimomura S, Guthrie WJ, Hempel HF, Fitzpatrick HF, Begg CF. Wedge pulmonary arteriography. Its application in congenital and acquired heart disease. Radiology. 1959;73:566.
80. Zidulka A, Hakim TS. Wedge pressure in large vs. small pulmonary arteries to detect pulmonary venoconstriction. J Appl Physiol. 1985;59(4):1329–32.
81. Hellems HK, Haynes FW, Dexter L. Pulmonary capillary pressure in man. J Appl Physiol. 1949;2(1):24–9.
82. Kafi SA, et al. Partitioning of pulmonary vascular resistance in primary pulmonary hypertension. J Am Coll Cardiol. 1998;31(6):1372–6.
83. Fesler P, Pagnamenta A, Vachiery JL, Brimioulle S, Abdel Kafi S, Boonstra A, Delcroix M, Channick RN, Rubin LJ, Naeije R. Single arterial occlusion to locate resistance in patients with pulmonary hypertension. Eur Respir J. 2003;21:31–6.
84. Naeije R, Vachiery JL, Yerly P, et al. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. Eur Respir J. 2013;41:217–23.
85. Gerges C, Gerges M, Lang MB, et al. Diastolic pulmonary vascular pressure gradient. Chest. 2013;143(3):758–66.
86. McGregor M, Sniderman A. On pulmonary vascular resistance: the need for more precise definition. Am J Cardiol. 1985;55(1):217–21.
87. Tartulier MM, et al. Pulmonary arterial pressures in normal subjects. Effects of age and muscular exercise. Bull Physiopathol Respir (Nancy). 1972;8(6):1295–321.
88. Ehrsam RE, et al. Influence of age on pulmonary haemodynamics at rest and during supine exercise. Clin Sci (Lond). 1983;65(6):653–60.

89. Weir EK, Reeves JT. Pulmonary hypertension xiv. Mount Kisco, NY: Futura Pub. Co.; 1984, 442 p.
90. Lankhaar JW, Westerhof N, Faes TJ, et al. Quantification of right ventricular afterload in patients with and without pulmonary hypertension. Am J Physiol Heart Circ Physiol. 2006;291:H1731–7.
91. Cournand A, et al. Measurement of cardiac output in man using the technique of catheterization of the right auricle or ventricle. J Clin Invest. 1945;24(1):106–16.
92. Stead EA, et al. The cardiac output in male subjects as measured by the technique of right atrial catheterization. Normal values with observations on the effect of anxiety and tilting. J Clin Invest. 1945;24(3):326–31.
93. Kendrick AH, et al. Direct Fick cardiac output: are assumed values of oxygen consumption acceptable? Eur Heart J. 1988;9(3):337–42.
94. Fakler U, et al. Assumed oxygen consumption frequently results in large errors in the determination of cardiac output. J Thorac Cardiovasc Surg. 2005;130(2):272–6.
95. Ultman JS, Bursztein S. Analysis of error in the determination of respiratory gas exchange at varying FIO2. J Appl Physiol Respir Environ Exerc Physiol. 1981;50(1):210–6.
96. Moise SF, Sinclair CJ, Scott DH. Pulmonary artery blood temperature and the measurement of cardiac output by thermodilution. Anaesthesia. 2002;57(6):562–6.
97. Lehmann KG, Platt MS. Improved accuracy and precision of thermodilution cardiac output measurement using a dual thermistor catheter system. J Am Coll Cardiol. 1999;33(3): 883–91.
98. 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): 535–41.
99. Hillis LD, Firth BG, Winniford MD. Analysis of factors affecting the variability of Fick versus indicator dilution measurements of cardiac output. Am J Cardiol. 1985;56(12): 764–8.
100. Hurrell DG, Nishimura RA, Higano ST, Appleton CP, Danielson GK, Holmes Jr DR, Tajik AJ. Value of dynamic respiratory changes in left and right ventricular pressures for the diagnosis of constrictive pericarditis. Circulation. 1996;93(11):2007.
101. Tyberg TI, Goodyer AV, Hurst 3rd VW, Alexander J, Langou RA. Left ventricular filling in differentiating restrictive amyloid cardiomyopathy and constrictive pericarditis. Am J Cardiol. 1981;47(4):791.
102. Talreja DR, Nishimura RA, Oh JK, Holmes DR. Constrictive pericarditis in the modern era: novel criteria for diagnosis in the cardiac catheterization laboratory. J Am Coll Cardiol. 2008;51(3):315.
103. Bush CA, Stang JM, Wooley CF, Kilman JW. Occult constrictive pericardial disease. Diagnosis by rapid volume expansion and correction by pericardiectomy. Circulation. 1977; 56:924–30.
104. Robbins IM, Newman JH, Johnson RF, et al. Association of the metabolic syndrome with pulmonary venous hypertension. Chest. 2009;136:31–6.
105. Fujimoto N, Borlaug BA, Lewis GD, et al. Hemodynamic responses to rapid saline loading: the impact of age, sex, and heart failure. Circulation. 2013;127:55–62.
106. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail. 2010;3:588–95.
107. Hager WD, Collins I, Tate JP, et al. Exercise during cardiac catheterization distinguishes between pulmonary and left ventricular causes of dyspnea in systemic sclerosis patients. Clin Respir J. 2013;7:227–36.
108. Tolle JT, Waxman AB, van Horn TL, et al. Exercise-induced pulmonary arterial hypertension. Circulation. 2008;118:2183–9.
109. Oudiz RJ, Rubin LJ. Exercise-induced pulmonary arterial hypertension. A new addition to the spectrum of pulmonary vascular diseases. Circulation. 2008;118:2120–1.

110. D'Alto M, Ghio S, D'Andrea A, et al. Inappropriate exercise-induced increase in pulmonary artery pressure in patients with systemic sclerosis. Heart. 2011;97:112–7.
111. Sitbon O, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation. 2005;111(23):3105–11.
112. Brennan JM, et al. Reappraisal of the use of inferior vena cava for estimating right atrial pressure. J Am Soc Echocardiogr. 2007;20(7):857–61.