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Society Position Statement

Canadian Cardiovascular Society/Canadian Thoracic Society Position Statement on Pulmonary Hypertension

Primary Panel: Naushad Hirani, MD,[a,‡] Nathan W. Brunner, MD,[b,‡] Ali Kapasi, MD,[c] George Chandy, MD,[d] Lawrence Rudski, MD,[e] Ian Paterson, MD,[c] David Langleben, MD (Co-Chair),[e] Sanjay Mehta, MD (Co-Chair),[f] and Lisa Mielniczuk, MD (co-chair),[g] for the CCS/CTS Pulmonary Hypertension Committee[§]

[a] *University of Calgary, Calgary, Alberta, Canada;* [b] *University of British Columbia, Vancouver, British Columbia, Canada;* [c] *University of Alberta, Edmonton, Alberta, Canada;* [d] *Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada;* [e] *Jewish General Hospital, McGill University, Montréal, Quebec, Canada;* [f] *London Health Sciences Centre, Western University, London, Ontario, Canada;* [g] *University of Ottawa Heart Institute, Ottawa, Ontario, Canada*

ABSTRACT

The landscape of pulmonary hypertension (PH) has changed significantly since the last Canadian Cardiovascular Society/Canadian Thoracic Society position statement in 2005. Since then, advances in our understanding of the pathophysiology of PH and improvements in diagnostic and therapeutic options have transformed the care of patients with PH. Globally, PH has an estimated prevalence of 1%, increasing to 10% in those aged 65 years and older, most commonly due to left heart or lung disease. Although pulmonary arterial hypertension (PAH) is less common, the morbidity and mortality is significant and early diagnosis and treatment are essential. This document is targeted at clinicians and describes a framework for screening and diagnosis of PH, with recommendations for performance and interpretation of echocardiography, cardiac magnetic resonance imaging, and right heart catheterization. In addition, the current approach to

RÉSUMÉ

Le paysage de l'hypertension pulmonaire (HP) a beaucoup changé depuis que la Société canadienne de cardiologie et la Société canadienne de thoracologie ont émis leur dernier énoncé de position à ce sujet en 2005. L'évolution des connaissances de la physiopathologie de l'HP et les améliorations des options diagnostiques et thérapeutiques ont transformé les soins prodigués aux patients atteints d'HP. Selon les estimations, l'HP a une prévalence de 1 % dans le monde, prévalence qui atteint 10 % chez les personnes de 65 ans ou plus, et elle est le plus souvent attribuable à une cardiopathie gauche ou à une atteinte pulmonaire. Bien que l'hypertension artérielle pulmonaire (HAP) soit plus rare, la morbidité et la mortalité qui y sont associées demeurent importantes, et un diagnostic et un traitement précoces sont cruciaux. Les auteurs de cet article décrivent, à l'intention des cliniciens, un cadre pour le dépistage et le diagnostic de l'HP et

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‡These authors are co-primary authors.

§See page 989 for Secondary Panel Members.

Corresponding author: Dr Lisa M. Mielniczuk, Department of Medicine, Divisions of Cardiology and Cellular and Molecular Medicine, University of Ottawa Heart Institute, 40 Ruskin St, Ottawa, Ontario K1Y 4W7, Canada. Tel.: +1-613-696-7274.

E-mail: lmielniczuk@ottawaheart.ca

The disclosure information of the authors and reviewers is available from the CCS on their guidelines library at www.ccs.ca.

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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PAH management in Canada including risk stratification and pharmacologic therapy aimed at achieving a low-risk profile is discussed. The rationale to avoid specific PAH therapy in patients with left heart disease and lung disease-related PH is emphasized, along with special considerations for the diagnosis and management of chronic thromboembolic PH. Future advancements in the identification of novel pathways and therapies, personalized approaches to direct therapy, as well as interventional approaches such as balloon pulmonary angioplasty for chronic thromboembolic PH promise to continue the rapid evolution of this field.

formulent des recommandations pour l'exécution et l'interprétation des examens d'échocardiographie, d'imagerie cardiaque par résonance magnétique et de cathétérisme du cœur droit. Ils traitent également de l'approche actuelle en matière de prise en charge de l'HAP au Canada, qui comprend une stratification des risques et une pharmacothérapie visant l'atteinte d'un profil à faible risque. Les arguments justifiant qu'un traitement ciblant spécifiquement l'HAP soit évité chez les patients atteints d'une HP liée à une cardiopathie gauche ou à une atteinte pulmonaire sont présentés, ainsi que les considérations particulières relatives au diagnostic et à la prise en charge de l'HP thromboembolique chronique. Les percées à venir en matière de stratégies et de traitements novateurs, d'approches thérapeutiques directes personnalisées et d'approches interventionnelles, comme l'angioplastie pulmonaire par ballonnet dans les cas d'HP thromboembolique chronique, permettent de croire que ce domaine continuera d'évoluer rapidement.

rare, with an estimated incidence of up to 7.6 cases per million adults and prevalence up to 26-100 per million adults.[4,5] The morbidity and mortality remain significant and early diagnosis and treatment are essential. This document is targeted at clinicians and intended to: (1) provide a framework for screening and diagnosis of PH; and (2) highlight the current approach to PH management in Canada, including specifically PAH as well as other types of PH.

Methods

This statement was initiated by CCS members, and the senior authorship group assembled experts from major centres across Canada with representation from the Canadian Thoracic Society and CCS clinicians experienced in the treatment of patients with PH. Literature was reviewed by individuals who authored each section, and the primary panel had editorial input into each section. The Grading of Recommendations, Assessment, Development, and Evaluation scale was used for rating the strength of recommendations and the quality of evidence (http://ccs.ca/en/guidelines/development-process). A consensus was reached for each recommendation using an iterative voting process.[6] Feedback was incorporated after the document was reviewed by the secondary panel, the CCS Guidelines Executive Committee, and the Canadian Thoracic Society (Pulmonary Vascular Disease Clinical Assembly, Canadian Respiratory Guidelines Committee, Executive Committee). Formatting of the document conforms to CCS standards.

Diagnosis

The evaluation of suspected PH requires a detailed history and physical examination along with integration of several key diagnostic tests, including cardiac catheterization. Dyspnea is the earliest but a nonspecific symptom of PH. Later symptoms and signs can include syncope, angina, and peripheral edema. Algorithms for the work-up of PH (Fig. 1) are extensively discussed elsewhere.[7-9] Briefly, echocardiography establishes the initial probability of PH. A multimodality assessment integrating several additional tests—including electrocardiography, pulmonary function tests, and chest imaging enables the classification of PH. The ventilation/perfusion (V/Q) scan remains the most sensitive test to rule out CTEPH.[10]

Table 1. Updated clinical classification of PH

Group 1: PAH
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH
1.4 PAH associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 PAH long-term responders to calcium channel blockers
1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
1.7 Persistent PH of the newborn syndrome
Group 2: PH due to left heart disease
2.1 PH due to heart failure with preserved LVEF
2.2 PH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to postcapillary PH
Group 3: PH due to lung diseases and/or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders
Group 4: PH due to pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
Group 5: PH with unclear and/or multifactorial mechanisms
5.1 Hematological disorders
5.2 Systemic and metabolic disorders
5.3 Others
5.4 Complex congenital heart disease

LVEF, left ventricular ejection fraction; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease.

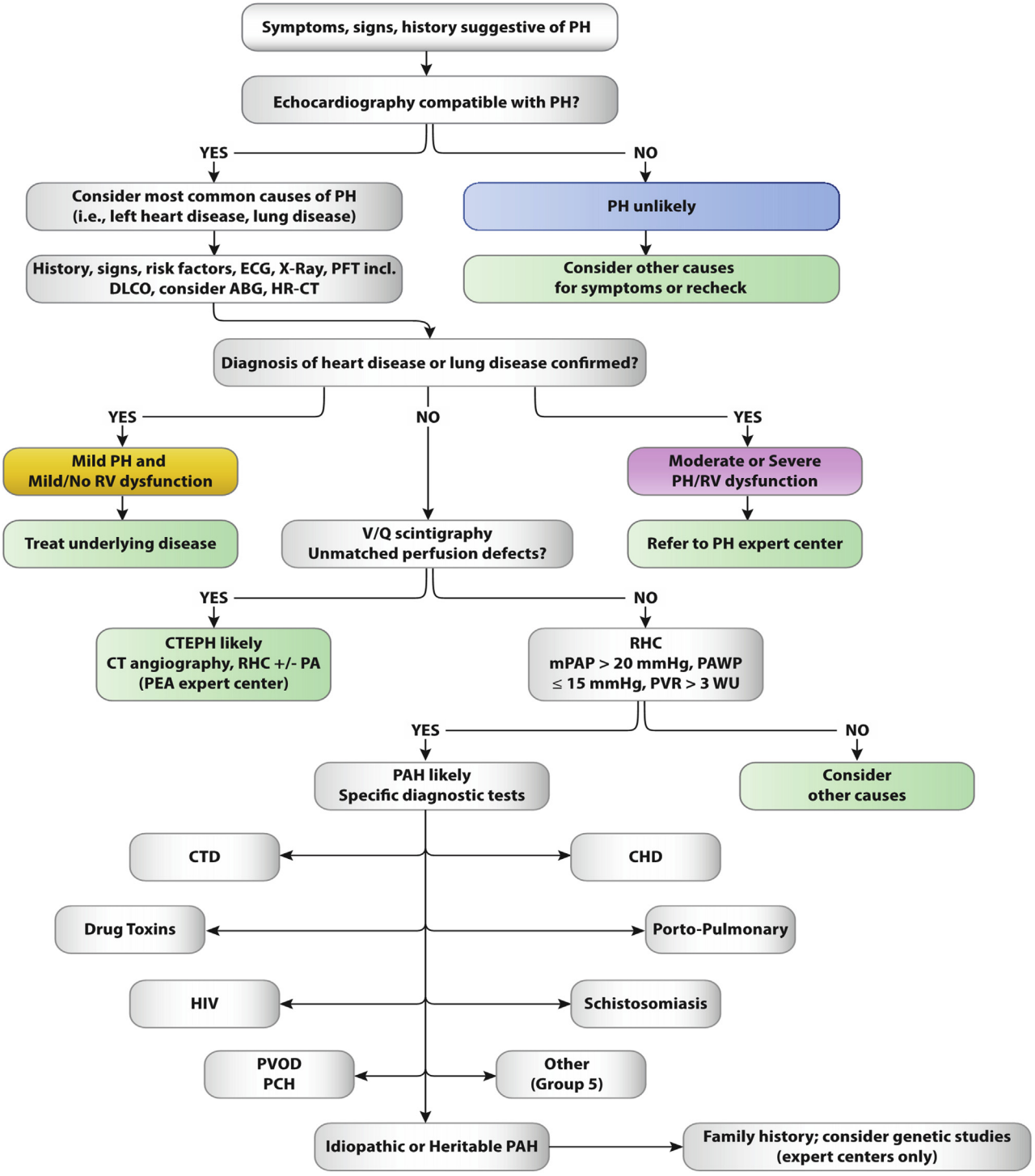

Figure 1. An algorithm for the work-up of pulmonary hypertension (PH). ABG, arterial blood gas; CHD, congenital heart disease; CT, computed tomography; CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; DLCO, diffusion capacity of the lung for carbon monoxide; ECG, electrocardiogram; HR-CT, high-resolution computed tomography; mPAP, mean pulmonary artery pressure; PA, pulmonary angiography; PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; PCH, pulmonary capillary hemangiomatosis; PEA, pulmonary endarterectomy; PFT, pulmonary function testing; PVOD, pulmonary veno-occlusive disease; PVR, pulmonary vascular resistance; RHC, right heart catheter; RV, right ventricle; V/Q, ventilation/perfusion; WU, Wood unit; x-ray, chest radiograph. Modified from Haddad et al.[8] with permission from Elsevier.

Figure 2. Canadian pulmonary hypertension (PH) centres. CTEPH, chronic thromboembolic pulmonary hypertension.

Coordinated care of PH patients in a specialized centre provides several advantages including the development of expertise and fostering of research on this rare disease.[11] The clinical care of PH is highly resource-intensive. There is universal recognition that the best clinical care is delivered by highly experienced multidisciplinary teams rather than isolated practitioners with limited experience in treating PH.[12] The delivery of PH care in Canada has evolved into focused

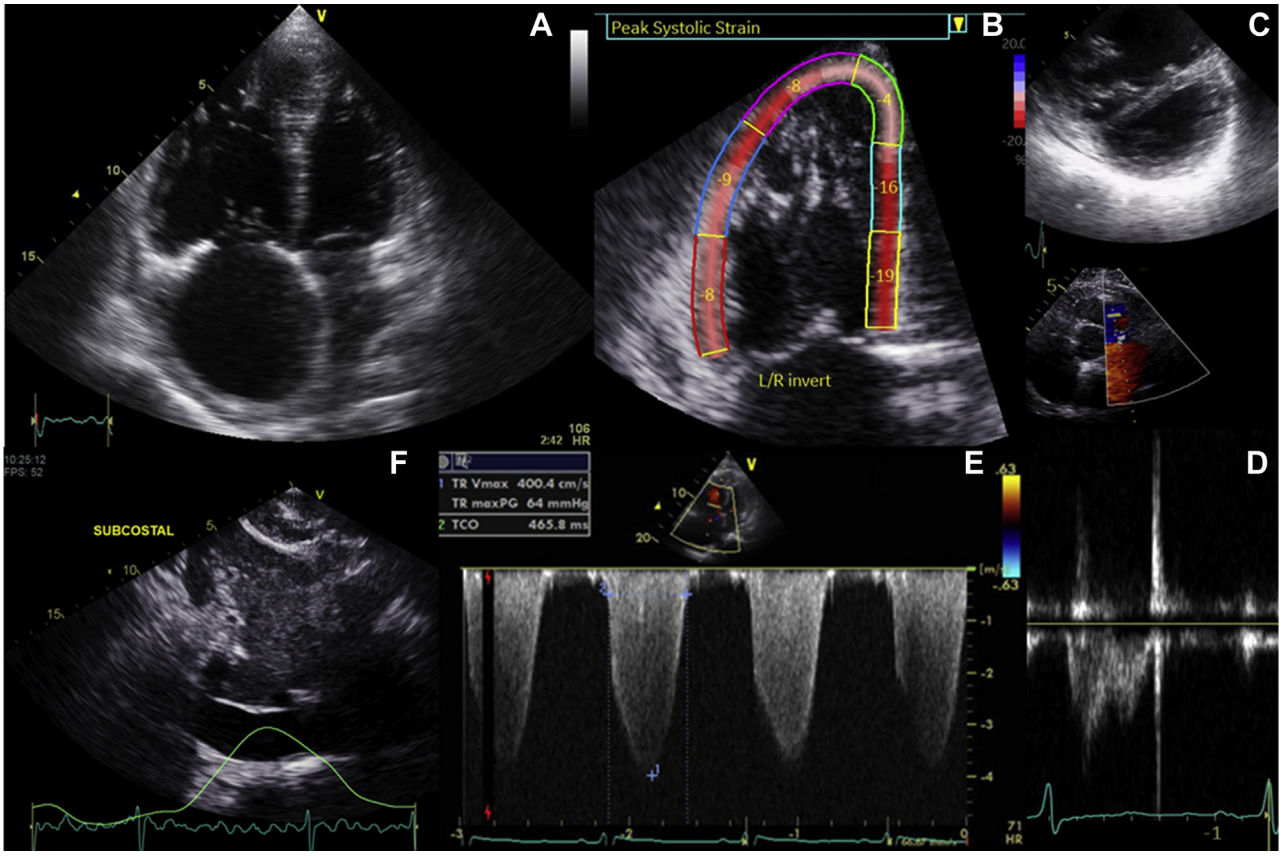

Figure 3. Echocardiography for evaluation and prognostication in pulmonary hypertension. (**A**) Apical 4-chamber view showing right atrial and right ventricular enlargement. (**B**) Measurement of right ventricular strain. (**C**) Parasternal short axis view showing a shift of the interventricular septum. (**D**) Midsystolic notching of the pulmonary outflow velocity. (**E**) Measurement of pulmonary artery systolic pressure from the tricuspid regurgitation jet. (**F**) Subcostal view showing dilation of the inferior vena cava.

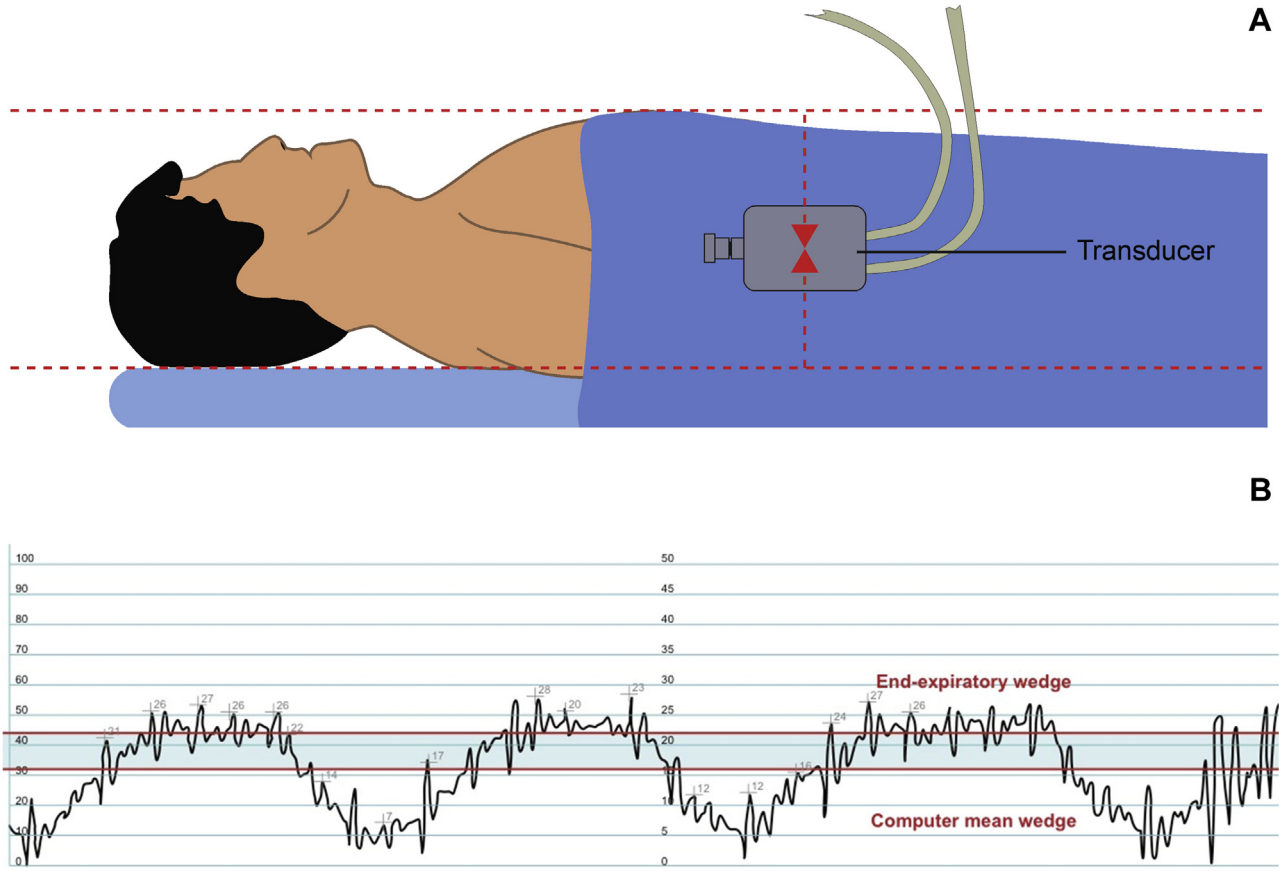

Figure 4. Technical considerations in right heart catheterization. (**A**) Appropriate positioning of pressure transducer at midchest height. (**B**) Measurement of wedge pressure at end expiration.

clinical centres primarily located at academic institutions. Currently, there are 22 centres that facilitate the assessment, diagnosis, and therapy of children and adults with PH in their respective clinical catchment areas (see Fig. 2 and https://phacanada.ca/Living-with-PH/PHCentres). Although such care is principally delivered directly, the advent of telemedicine provides a more convenient option for follow-up of patients located in remote regions of Canada, especially when it can complement the care from local nonspecialist providers.

In the following sections we discuss the role of selected PH testing that is often interpreted by cardiologists.

Echocardiography

Echocardiography is the most common cardiac imaging test used in the evaluation of dyspnea; it can identify clinically significant PH, indicate pre- vs postcapillary etiology, and provide prognostic information (Fig. 3).

Echocardiography for identification of PH. Systolic pulmonary artery pressure (sPAP) is estimated using the simplified Bernoulli equation from the tricuspid regurgitation jet velocity (TRV) and estimated right atrial (RA) pressure, and is well established in the screening for PH.[13] Nonsimultaneous echocardiography vs right heart catheterization (RHC) studies have shown significant discrepancy among these modalities, particularly at high pulmonary artery pressure (PAP), and estimation of RA pressure according to inferior vena cava size and collapsibility is sometimes inaccurate.[14,15] A TRV of $>$ 2.8 m/s or estimated sPAP of $>$ 35 mm Hg suggests possible PH. Mean PAP can be estimated using echocardiograph-determined sPAP and simple validated correlation methods, but this must still be confirmed using RHC.[16-20]

RECOMMENDATION

1. We recommend transthoracic echocardiography for initial assessment of all patients with clinically suspected PH or unexplained dyspnea (Strong Recommendation, Moderate-Quality Evidence).
2. We recommend a complete echocardiographic assessment when PH is suspected, including estimation of sPAP using the TRV jet, measurement of inferior vena cava size, and degree of inspiratory collapse, as well as assessment of "secondary" signs of PH, such as RA or right ventricular (RV) enlargement, RV hypertrophy, septal flattening, and RV dysfunction (Strong Recommendation, Moderate-Quality Evidence).

Practical tip. Each laboratory should follow echocardiographic guidelines[13] for standardization of imaging and interpretation techniques to minimize variability and improve accuracy.

Echocardiography for classification of PH. Echocardiography can help distinguish precapillary from postcapillary PH and provide insights into mixed etiologies. The presence of left heart disease such as left ventricular hypertrophy, systolic or diastolic dysfunction, aortic or mitral valvular disease, and indexed left atrial volume are strong predictors of postcapillary PH.[21,22] A severely dilated and remodelled right ventricle, notching of the RV outflow tract Doppler flow profile (Fig. 3D) and absence of the previously described left-sided pathology suggest a precapillary etiology. Agitated saline contrast and/or transesophageal echocardiography should be routinely performed to rule out shunt in the setting of enlarged right heart chambers or suspected significant PH.

RECOMMENDATION

3. We recommend transthoracic echocardiography in all PH patients to detect any abnormality of left-sided chambers or valves, which can indicate the possibility of postcapillary PH (Strong Recommendation, Moderate-Quality Evidence).

Echocardiographic prognosticators in patients with PH. Prognosis for PH depends on the ability of the right ventricle to adapt to the greater load imposed by elevated PAP. Echocardiographic measures of RV systolic function include measurements of basal function (tricuspid annular plane systolic excursion and S'), regional function (RV free wall strain), and global function (RV ejection fraction using 3D echocardiography, RV index of myocardial performance, and fractional area change). RV free wall strain using speckle tracking appears to strongly predict outcomes.[23-26] Other echocardiographic parameters that predict outcome include the presence of a moderate or large pericardial effusion, RA area, and severity of tricuspid regurgitation.[27-31]

RECOMMENDATION

4. We recommend that PH patients should have baseline and follow-up echocardiograms that measure systolic PAP, RA size, tricuspid regurgitation severity, and presence/severity of pericardial effusion. Additionally, indices of RV systolic function should be assessed using tricuspid annular plane systolic excursion, S', or RV index of myocardial performance, with free wall strain using 2-dimensional speckle tracking being a recommended method in laboratories with suitable equipment and expertise (Strong Recommendation, Moderate-Quality Evidence).

Recognizing PAH in high-risk groups

Patients with connective tissue disease (especially scleroderma), HIV,[32] congenital heart disease (CHD), portal hypertension, and carriers of PAH-associated genetic mutations, have a higher prevalence of PAH than the general population and might be appropriate for consideration of targeted screening. The Evidence-Based Detection of Pulmonary Arterial Hypertension in Systemic Sclerosis (DETECT) study included 644 patients with a diagnosis of scleroderma for > 3 years and diffusion capacity of the lung for carbon monoxide $< 60\%$, because impaired diffusing capacity can be an early marker of pulmonary vascular disease; it correlates with functional parameters, and when abnormal is associated with worse prognosis.[33] This algorithm involved the assessment of 8 variables in a 2-step decision tree, improving the sensitivity of identifying PAH from 71% to 96%.[34,35] Interstitial lung disease, coronary disease and left ventricular diastolic dysfunction associated with scleroderma should be considered when screening for PAH because these entities can cause similar symptoms.[36,37]

Although the prevalence of PAH associated with HIV infection is only 0.5%, echocardiography should be considered in such patients with unexplained dyspnea or multiple risk factors for HIV-PAH.[7,38] Screening echocardiography in CHD patients should also be performed at centres with adult CHD expertise, because nearly 10% of these patients might have PAH.[7,39] Portopulmonary hypertension is associated with poor prognosis in the absence of medical therapy, with some studies suggesting 5-year survival to be as low as 14%.[40,41] Liver transplantation is contraindicated in patients with a moderate to severe degree of portopulmonary hypertension because the prognosis worsens with the severity of PH. Echocardiographic screening in liver transplant candidates has been shown to have a sensitivity and specificity of 97% and 77%, respectively.[42-44]

RECOMMENDATION

5. We recommend annual echocardiography and measurement of lung diffusing capacity for carbon monoxide to screen for PH in all patients with scleroderma (Strong Recommendation, Low-Quality Evidence).
6. We recommend echocardiography to screen for PH in all patients with portal hypertension being assessed for liver transplantation (Strong Recommendation, Low-Quality Evidence).

Right heart catheterization

Cardiac catheterization is essential to evaluate PH and cannot be replaced by noninvasive imaging. A normal echocardiogram does not exclude postcapillary PH related to left heart disease.[45,46] RHC also enables acute vasodilator testing, typically with inhaled nitric oxide (NO), to identify acutely vasoresponsive PAH. This condition is distinct from other types of PAH and has a unique treatment approach discussed in the management section.

Historically, PAH diagnosis has required a mean PAP $\geq$ 25 mm Hg, a wedge pressure of $\leq$ 15 mm Hg, and a

pulmonary vascular resistance (PVR) > 3 Wood units.[33] However, recently a lower mean PAP cutoff of > 20 mm Hg (with PVR > 3 Wood units) has been recommended.[3] Mean PAP elevation to this degree is already 2 SDs above the normal mean of 14 mm Hg, and is associated with worse clinical outcomes in many types of PH.[47-50]

RHC for PH requires rigourous standardization, should be tailored to the individual patient, and performed in high-volume expert PH centres. This minimizes measurement errors, which can alter the classification of PH and the choice of therapy, as well as repeat testing, which causes inconvenience and risk to the patient.

RECOMMENDATION

7. We recommend RHC in all patients with suspected PAH or CTEPH to confirm the hemodynamic diagnosis of precapillary PH and to assess the severity of PH (Strong Recommendation, Moderate-Quality Evidence).
8. We recommend RHC in PH patients be performed only in centres with technical expertise and experience to accurately assess cardiopulmonary hemodynamics and to diagnose and appropriately classify the cause of PH (Strong Recommendation, Low-Quality Evidence).

Practical tip. See Table 2: Technical considerations for RHC.

Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) imaging provides the most accurate assessment of right ventricle size and function and is an attractive imaging modality for the serial assessment of PH because it is noninvasive and does not use ionizing radiation. CMR has been used to predict mean PAP, cardiac output, wedge pressure, and PVR with accuracy.[58-60] Although studies have shown promise in differentiating precapillary from postcapillary PH, the data were derived from small, single-site experiences and many have lacked validation cohorts. Larger studies are needed before CMR can be considered as an alternative to RHC for the diagnosis of PH.

The role of CMR in the prognostication of PAH is better established. A recent meta-analysis has shown RV ejection fraction to be a strong predictor of mortality, along with RV volumes.[61] RV measures on CMR also predict favourable treatment responses[62] and late disease progression.[63] Recently, parameters of RA function have been associated with PH prognosis.[64,65]

RECOMMENDATION

9. We suggest CMR imaging in PAH patients when accessible to assess right ventricle size and function to help guide management (Weak Recommendation, Moderate-Quality Evidence).

Practical tip. At present, CMR is best used as a second-line imaging test for difficult PH cases or for the assessment of concurrent adult CHD. There are insufficient data to recommend it for routine serial assessment.

Approach to Management of PAH

A diagnosis of PAH is reached by excluding the more commonly seen PH due to left heart disease, lung disease, and CTEPH. Risk stratification using a combination of clinical, hemodynamic, and imaging features such as functional class, 6-minute walk test distance, brain natriuretic peptide levels, and cardiac index helps to prognosticate at the time of diagnosis and is essential to guide management and follow-up (Table 3). In this section we discuss specific issues surrounding the management of PAH followed by a brief discussion of management of PH due to left heart and lung disease.

Supportive measures

After a definitive diagnosis, all PAH patients should be provided disease-specific education, psychosocial support, safe physical activity though structured rehabilitation programs,[66]

Table 2. Technical considerations for right heart catheterization

Reference level	The choice of reference level can lead to substantial variability in measured pressures, with mid-thoracic height best approximating the level of the left atrium.[51] See Figure 4A
Wedge pressure	Mean PAP may be determined at end-expiration, or with a mean throughout the respiratory cycle. With obesity or obstructive lung disease, respiratory swings in intrathoracic pressure can be substantial, affecting interpretation of the hemodynamics. Computer-derived mean pressure measurements instead of end-expiratory pressures can change PH classification in 25%-30% of patients.[52,53] We recommend pressure measurement at end expiration. Values should be taken using examination of traces containing several respiratory cycles and not the automatic digital estimation by recording devices. See Figure 4B When a reliable assessment of pulmonary arterial wedge pressure is not possible, consideration should be given to performing a left heart catheterization to obtain a left ventricular end diastolic pressure. This is particularly important when mixed etiologies of PH are being considered
Cardiac output	Although most accurate, the direct Fick estimation of cardiac output is rarely feasible. The commonly used techniques are the TD and indirect Fick methods. They correlate with direct Fick, but the agreement between methods is only fair.[54,55] Because TD correlates better with RV function and mortality, it should be used[56,57]
Additional manoeuvres	• Vasodilator challenge is essential in the hemodynamic evaluation of suspected idiopathic, heritable, and drug-induced PAH • Saline loading during catheterization might unmask left heart disease • Catheterization with exercise might identify early pulmonary vascular disease • A shunt run can also help to identify left-to-right shunts that might not have been detected noninvasively

PA, pulmonary angiography; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PH, pulmonary hypertension; RV, right ventricular; TD, thermodilution;

Table 3. Measures to consider in risk stratification of pulmonary arterial hypertension patients

Parameter	Low risk	Intermediate risk	High risk
WHO/NYHA functional class	I-II	III	IV
Clinical right heart failure	Absent	Absent	Present
Syncope	No	Occasional	Repeated
Symptom progression	No	Slow	Rapid
Six-minute walk distance, m	> 440	165-440	< 165
NT pro-BNP, ng/mL or BNP, ng/L	< 300 < 50	300-1400 50-300	> 1400 > 300
RAP, mm Hg	< 8	8-14	> 14
CI, L/min/m^2	>2.5	2.0-2.4	<2.0
SvO2	> 65%	60%-65%	< 60%
Echo/CMR RA area, cm^2	< 18	18-26	> 26
Pericardial effusion	None	None or minimal	Present
CPET peak VO2, mL/min/kg	> 15	11-15	< 11
VE/VCO2 slope	< 36	36-45	> 45

BNP, brain natriuretic peptide; CI, cardiac index; CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise test; Echo, echocardiography; NT pro-BNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; RA, right atrial; RAP, right atrial pressure; SvO2, mixed venous oxygen saturation; VE/VCO2, ventilatory equivalents for carbon dioxide; VO2, oxygen consumption; WHO, World Health Organization.

Adapted from Galie et al.[83] with permission from Oxford University Press.

and contraception. Supportive medical therapy includes carefully titrated diuretics to reduce fluid overload, and long-term oxygen therapy for resting or exertional hypoxemia.

RECOMMENDATION

10. We recommend general supportive (education, psychosocial support, contraception) measures in all PAH patients to improve understanding and self-management (Strong Recommendation, Low-Quality Evidence).
11. We recommend supervised exercise rehabilitation be considered in PAH patients to improve functional capacity and health-related quality of life (HRQoL; Strong Recommendation, Moderate-Quality Evidence).
12. We suggest general medical therapeutic measures (diuretics for volume overload, and oxygen for resting hypoxemia) in all PAH patients (Weak Recommendation, Low-Quality Evidence).

Anticoagulation

There is evidence for pulmonary arterial *in situ* thrombosis in patients with PAH, and therefore anticoagulation might be of benefit.[67] However, no randomized controlled trials (RCTs) have addressed this, and registry data have raised questions regarding this practice.[68] Anticoagulation with warfarin (international normalized ratio 2-3) is recommended in selected PAH patients, such as those with central venous catheters, without significant bleeding risk.[69] These recommendations do not address the patient who might have another indication for systemic anticoagulation (outside of PAH). There are no studies to support the use of direct oral anticoagulants in patients with PAH, but they might be acceptable in patients who show intolerance or unsafe variability with warfarin.

RECOMMENDATION

13. We suggest systemic anticoagulation with warfarin in selected PAH patients (idiopathic PAH [IPAH], heritable PAH [HPAH], drug- and toxin-induced [DPAH]) in the absence of elevated bleeding risk (Weak Recommendation, Low-Quality Evidence). We recommend against systemic anticoagulation in patients with PAH associated with connective tissue disease, CHD, portal hypertension, and HIV (Strong Recommendation, Low-Quality Evidence).

Calcium channel blockers

Acute vasodilator testing remains essential to identify the 10%-15% of selected PAH patients (IPAH, HPAH, or DPAH) who have a marked short-term hemodynamic improvement that predicts a high likelihood of long-term response to treatment with high doses of calcium channel blockers (CCBs; amlodipine or diltiazem).[70,71] These patients have > 95% survival over 5 years, but high-dose CCB treatment can be dangerous in nonvasoreactive patients and is contraindicated. Patient selection for high-dose CCB vasodilator therapy requires careful clinical and hemodynamic assessment and should only be done in a PH expert centre. Moreover, regular clinical and hemodynamic follow-up in expert centres are required to confirm a strong therapeutic response and the achievement of a low-risk clinical status.

RECOMMENDATION

14. We recommend acute vasodilator testing (with inhaled NO, intravenous [I.V.] epoprostenol or adenosine) in selected PAH patients (IPAH, HPAH, DPAH) (Strong Recommendation, Low-Quality Evidence). Marked vasodilator responsiveness (decrease in mean PAP $\geq$ 10 mm Hg to < 40 mm Hg and stable/increased cardiac output) identifies a subgroup of patients more likely to respond to high-dose CCBs, which should be initiated in PH expert centres (Strong Recommendation, Low-Quality Evidence).

PAH-targeted medications available in Canada

The range of PAH-targeted medications has evolved substantially in the past 2 decades. Ten Health Canada-approved

agents are available, supported by a large body of evidence showing short- and long-term benefits in clinically important outcomes such as improved exercise capacity, reduced disease progression, and improved survival.[4,72,73] Although long-term registry data support improved survival since the introduction of these therapies, only 1 agent has been associated with a survival benefit in the context of an RCT.[74]

Advances in the understanding of PAH pathophysiology have implicated 3 key pathways that are targeted by currently available medications: the prostacyclin, endothelin, and NO pathways.

Prostacyclin pathway. Patients with PAH have deficient levels of prostacyclin. The first and most effective drug approved by Health Canada to treat PAH was epoprostenol, a prostacyclin analogue with a short half-life requiring continuous I.V. administration.[74] This therapy can be a burden for patients, who must aseptically reconstitute the drug, manage an indwelling central venous catheter and delivery system, and deal with multiple side effects. Because of their complexity, many patients are not candidates for parenteral prostanoid infusions, and typically only expert centres have the necessary experience, expertise, and nursing support required to safely manage these treatments. Selexipag, the newest oral PAH-targeted medication, is a nonprostanoid prostacyclin receptor agonist active on the prostacyclin pathway.[75] Agents in this class are typically uptitrated on the basis of adverse effects (Table 4) to the highest tolerable dose.

Endothelin receptor antagonists. PAH is associated with elevated levels of endothelin-1, a potent vasoconstrictor and mitogen. Three oral endothelin receptor antagonists (ERAs) are available that target this pathway (Table 4).[76-78] Some ERA therapy requires regular monitoring of liver enzymes and hemoglobin levels, because of risks of hepatotoxicity and anemia.

NO-cyclic GMP pathway. Deficiency of endogenous NO in patients with PAH can be addressed by 2 families of medication: (1) phosphodiesterase type-5 inhibitors (PDE-5i),[79,80] which target the downstream signalling pathway by reducing the breakdown of cyclic guanosine monophosphate (cGMP); and (2) soluble guanylate-cyclase stimulators (sGCs), which increase the production of cGMP. Riociguat, an sGC stimulator, is indicated to treat PAH and CTEPH patients[81,82] and requires careful uptitration over approximately 8 weeks.

Risk-Based Assessment and Treatment Strategies

All patients with symptomatic (New York Heart Association functional classification [NYHA FC] II-IV) PAH should be treated with PAH-targeted medications to reduce symptoms, improve functional capacity, and to delay progression of PAH, hospitalization, and death. The initial choice of therapy depends on the severity of PAH and RV dysfunction at diagnosis, as well as other individual patient factors, such as cause of PAH, comorbid illnesses, concomitant medications, as well as expected tolerance of known side effects.[83]

Table 4. Pulmonary arterial hypertension-targeted therapies

Drug family	Drug name	Trade name	Route of delivery	Typical dosing	Notable side effects	Health Canada approved	Recommendation/level of evidence*
Prostacyclin pathway agents	Epoprostenol	Flolan, Caripul	Continuous I.V. infusion	10-30 ng/kg/min	Flushing, headache, diarrhea, jaw/bone pain, nausea, hypotension, central line complications, rebound PH	Yes	I/A
	Treprostinil	Remodulin	Continuous SC/I.V. infusion	20-80 ng/kg/min	Flushing, headache, diarrhea, jaw/bone pain, nausea, hypotension, infusion site pain	Yes	I/B, IIb/C
		Orenitram	Oral	3-6 mg bid	Flushing, headache, diarrhea, jaw/bone pain, nausea	No	IIb/B
		Tyvaso	Inhaled	54 µg qid	Flushing, headache, diarrhea, jaw/bone pain, nausea, cough	No	I/B
	Iloprost	Ventavis	Inhaled	5 µg 6-9 times daily		No	I/B
	Selexipag	Uptravi	Oral	200-1600 µg bid	Flushing, headache, diarrhea, jaw/bone pain, nausea	Yes	I/B
Endothelin receptor antagonists	Bosentan	Tracleer, generic	Oral	125 mg bid	Hepatotoxicity, anemia, fluid retention	Yes	I/A
	Ambrisentan	Volibris	Oral	10 mg daily		Yes	I/A
	Macitentan	Opsumit	Oral	10 mg daily		Yes	I/B
Nitric oxide pathway agents	Sildenafil	Revatio, generic	Oral	20-80 mg tid	Headaches, flushing, fluid retention	Yes	I/A
	Tadalafil	Adcirca	Oral	40 mg daily		Yes	I/B
	Riociguat	Adempas	Oral	1.0-2.5 mg tid	Hypotension, headache, gastroesophageal reflux	Yes	I/B

Manufacturer information: Flolan, Volibris (Glaxo Smith Kline, Mississauga, ON); Caripul, Ventavis, Tracleer, Opsumit (Actelion Pharmaceuticals, Toronto, ON); Remodulin, Orenitram, Tyvaso, Adcirca (United Therapeutics, Magog, QC); Revatio (Pfizer Inc, Kirkland, QC); Adempas (Bayer Inc, Mississauga, ON).
bid, twice per day; I.V., intravenous; PH, pulmonary hypertension; qid, 4 times per day; SC, subcutaneous; tid, 3 times per day.
*According to European Respiratory Society/European Society of Cardiology Guidelines.[83]

Recent studies have shown that patient-specific risk stratification using a panel of clinical and hemodynamic variables at baseline and follow-up within 1 year of treatment best predicts survival.[84-88] These variables reflect symptoms, exercise capacity, and right heart function (Table 3). Current treatment paradigms focus on achieving a low-risk status defined by a combination of these prognostic parameters.[89] Not all parameters are routinely repeated serially and might not be available at all centres (eg, cardiopulmonary exercise testing), but a subset can be used, and there are several approaches as to how to combine the most practically obtained measures to guide management.[84-87,89]

Historically, monotherapy with an oral agent has been the first-line approach, but this remains acceptable only in selected low-risk patients. The standard of care is combination PAH-targeted medical therapy for most PAH patients,[44,83] and upfront or initial dual oral combination is now recommended for most patients.[89,90] Patients with high-risk features including NYHA FC IV should be considered for parenteral prostanoid therapy.

Regardless of the choice of therapy, regular, comprehensive re-evaluation and risk stratification of individual patients, with the involvement of a PH centre, is essential for optimal outcomes. Lack of adequate response to any PH-targeted therapy indicates a high risk for progression, complications, and poor clinical outcomes. Achieving and maintaining a low-risk profile is the most important goal of treatment, and in its absence, intensification of therapy and/or consideration of lung transplantation is indicated.

Limitations to Access and Therapy

Canadian patients generally have access to required PAH-targeted medications through private insurance or provincial/territorial government funding. However, there are disparities among provincial formularies, and increasing restrictions in private insurance coverage. Access to macitentan, riociguat, and selexipag is currently limited despite Health Canada approval, because many provinces have not approved funding for these important treatment options.

Most Canadian patients can be treated with dual combination PAH-targeted therapy if required, but access mechanisms vary according to province, commonly Special Authorization programs. There is limited access to triple combination therapy at present. The high costs of targeted therapies are a significant barrier and have led to efforts to limit them, including the Canadian Agency for Drugs and Technologies in Health report in 2015.[91] However, recent studies that show the survival benefit in patients who achieve low-risk features[86,87,92] underline the importance of focusing treatment strategies on patient-specific parameters rather than an approach that emphasizes the lowest cost.

Most provinces limit prescribing of PAH-targeted medications to PH expert centres. Although this might restrict inappropriate use of these expensive medications, it can be a barrier for patients living outside of the urban areas where expert centres are located.

RECOMMENDATION

15. We recommend that all PAH patients be assessed in a recognized PH centre to confirm the diagnosis, direct institution of PH-targeted therapies, and evaluate the response to treatment (Strong Recommendation, Low-Quality Evidence).
16. We recommend initial oral monotherapy (ERA, PDE-5i, or sGCs) only in low-risk (Table 3) treatment-naive PAH patients (Strong Recommendation, High-Quality Evidence).
17. We recommend initial dual oral combination therapy in intermediate-risk treatment-naive PAH patients (Strong Recommendation, High-Quality Evidence).
18. We recommend initial combination therapy including I.V. epoprostenol in high-risk patients who are candidates for such therapies (Strong Recommendation, Low-Quality Evidence). We suggest initial combination therapy including I.V./subcutaneous treprostinil in high-risk PAH patients who are candidates for such therapies (including NYHA FC IV; Weak Recommendation, Low-Quality Evidence).
19. We recommend regular reassessment of all PAH patients using a panel of measures (clinical, functional, hemodynamic, and/or right ventricle size/function [Table 3]; Strong Recommendation, Low-Quality Evidence).

Practical tip. See Table 5 for practical tips for PAH medical therapy

Which PH Patients Should Not Be Treated With PAH-targeted Medications?

PH due to left heart disease (group II PH)

There is no evidence to support the use of PAH targeted therapies in patients with group II PH due to left heart disease.

Management options for group II PH need to address the left-sided cardiac dysfunction (ventricular systolic, diastolic, and valvular abnormalities) as well as the elevation in left sided filling pressures/pulmonary venous congestion that results. Percutaneous valve interventions such as MitraClip (Abbott, Abbott Park, IL)[93,94] and transcatheter aortic valve implantation[95] as well as cardiac resynchronization therapy[96] can reduce group II PH severity. Left ventricular assist devices (LVADs) are frequently used to reduce PH severity in patients being considered for heart transplantation.[97-99] One of the most important goals is optimization of volume status. PA pressure-guided changes in diuretics and vasodilators can reduce heart failure (HF) hospitalization[100] in patients with HF with reduced and preserved ejection fraction.[101]

PAH-targeted therapies have been associated with systemic hypotension, fluid retention, and pulmonary edema as well as increased mortality when left heart disease is present.[102] Many trials are limited by patient heterogeneity, lack of specific criteria for PH at study entry, and variability in drug strategy or dose.[103] Of the several classes of medication that have

Table 5. Practical tips for PAH medical therapy

Initial/combination therapy	No head-to-head trials or other data support any specific initial choice of therapy
	There are no reliable factors that predict the likelihood of an individual PAH patient responding to any specific individual or combination of PH-targeted medical therapies
	The use of ambrisentan with tadalafil in upfront combination therapy is supported by a randomized controlled trial.[90] Other initial therapeutic combinations can be considered, but are less well supported by clinical evidence
	Most combinations of the 4 classes of drugs are acceptable, except the combination of PDE-5i and sGCs which is contraindicated because of the risk of systemic hypotension
Follow-up	Regular comprehensive reassessment of all PAH patients is required to assess response to therapy and establish individual risk for poor clinical outcomes (worse functional status, hospitalization, need for transplantation, or death)
	Reassessment should occur within 3-4 months of institution of initial therapy or any change in therapy. In PAH patients who achieve low-risk status, reassessment could be every 6-12 months, depending on geographic access to the PH expert centre
Risk assessment	The definitions of low, intermediate, and high-risk patient profiles include a combination of measures that appear in Table 3. There are various approaches on the parameters that should be included and how to weight each parameter[84-89]
	After initial PH-targeted therapy, patients who improve to low-risk status upon reassessment can safely continue their individual current maintenance therapy

PAH, pulmonary arterial hypertension; PDE-5i, phosphodiesterase type-5 inhibitor; PH, pulmonary hypertension; sGC, soluble guanylate-cyclase stimulator.

shown consistently negative results, NO pathway agents show some promise in safety and efficacy. Oral PDE-5i medications have strong selectivity for the cGMP pathway in the pulmonary circulation, and have shown mixed results in left heart disease. Benefits have been seen in in patients with left HF,[104-107] and acutely in patients after cardiac transplantation or LVAD implantation.[108-112] However, worse HRQoL and increased risk of hospitalization was shown with PDE-5i use in patients with PH after left-sided valve surgery.[113]

RECOMMENDATION

20. We recommend that the management of patients with group II PH should focus on efforts to optimize ventricular filling pressures and treat the underlying causes of and contributors to left heart disease (Strong Recommendation, Low-Quality Evidence).

Practical tip. Comorbid conditions often accompany group II PH (sleep apnea, obesity, hypertension, or diabetes) and should be addressed and managed in parallel.

RECOMMENDATION

21. We recommend against the routine use of PAH-targeted therapies in patients with group II (post-capillary) PH (Strong Recommendation, Low-Quality Evidence).

Practical tip. The use of pulmonary vasodilator therapy in select short-term scenarios such as post LVAD or cardiac transplantation PH should only be done in centres with significant expertise. Patients with group II PH who have a significant precapillary component and/or significant right HF should be evaluated in an expert PH centre for further diagnosis and treatment strategies.

PH due to lung disease and/or hypoxia (group III PH)

PH in general can be aggravated by the presence of significant hypoxemia. PH can also be a complication of many types of lung disease, including obstructive disease (eg, chronic obstructive pulmonary disease), interstitial lung disease, and sleep-disordered breathing. In particular, combined pulmonary fibrosis and emphysema as well as obesity hypoventilation syndrome commonly cause PH, which is associated with worse functional capacity, worse hypoxemia, and shorter survival.[114]

Published experience with PAH-targeted drugs is scarce, and there is no evidence for improved clinical outcomes with these drugs in patients with group III PH. A potential risk of pulmonary vasodilators is worsening V/Q matching and thus worsening hypoxemia.

Currently there is no specific therapy for group III PH apart from optimal management of the underlying lung disease. However, moderate-severe PH/RV failure is unlikely to be a result of mild lung disease; in this scenario, other potential causes such as left heart disease, CTEPH, or PAH should be considered.

RECOMMENDATION

22. We recommend against routine RHC and against the use of PAH-targeted therapy in patients with mild-moderate World Health Organization group III PH in the absence of RV failure (Strong Recommendation, Moderate-Quality Evidence).
23. We suggest that patients with moderate-severe World Health Organization group III PH (and/or features of RV failure) be referred to a PH centre (Strong Recommendation, Low-Quality Evidence).

Diagnosis and Management of CTEPH (Group IV PH)

CTEPH is one of the most important causes of PH, because it is common, treatable, and curable with pulmonary endarterectomy (PEA). A small proportion (1%-4%) of survivors of acute PE develop CTEPH, although a significant proportion (30%-50%) of CTEPH patients have no history of documented pulmonary embolism (PE). Treatment with lifelong anticoagulation alone is associated with poor survival, estimated at 10% at 3 years in one study.[115-117]

The presence of dyspnea or exercise intolerance post acute PE should trigger consideration of CTEPH. In patients with unexplained PH, initial V/Q scanning is a sensitive test to help exclude CTEPH.[118,119]

PEA requires cardiopulmonary bypass with deep hypothermic circulatory arrest and is now associated with a mortality of 1%-2%.[120] Less than one-third of CTEPH patients are ineligible for PEA, largely because of either predominantly surgically inaccessible "distal" disease, or because of prohibitive comorbidities. The assessment of operability and decisions regarding other treatment strategies are best made by a multidisciplinary team of experts including an experienced PEA surgeon.

There is evidence to support the use of PAH-targeted medications in CTEPH patients. Riociguat is indicated for the treatment of symptomatic patients with CTEPH, including inoperable CTEPH and residual/recurrent CTEPH post-PEA.[82] Macitentan has also been shown to have benefit in inoperable patients.[121]

Literature describing the efficacy of balloon pulmonary angioplasty has recently emerged, with low complication rates at experienced centres.[122,123] Lung transplantation is an option for CTEPH patients ineligible for PEA or who develop residual/recurrent post-PEA PH and have no other contraindications.

RECOMMENDATION

24. We recommend that patients with residual dyspnea or exercise intolerance after at least 3 months of uninterrupted anticoagulation post acute PE be assessed for CTEPH with echocardiography and V/Q lung scan (Strong Recommendation, Low-Quality Evidence).
25. We strongly recommend that the possibility of CTEPH be assessed with initial V/Q scanning in patients being evaluated for PH (Strong Recommendation, Low-Quality Evidence).
26. We recommend that all potential CTEPH patients be referred to a local expert PH centre for establishment of a formal diagnosis of CTEPH and assessment for the most appropriate treatment (Strong Recommendation, Moderate-Quality Evidence)
27. We strongly recommend that all CTEPH patients be evaluated for PEA in consultation with a PEA centre (Strong Recommendation, Moderate-Quality Evidence).
28. We recommend treatment with riociguat monotherapy in all patients with symptomatic inoperable or residual/recurrent CTEPH post-PEA (Strong Recommendation, Moderate-Quality Evidence). We do not currently recommend for or against combination PH-targeted medical therapy in CTEPH patients.
29. We suggest CTEPH patients who are ineligible for or decline PEA be considered for balloon pulmonary angioplasty (Weak Recommendation, Low-Quality Evidence).

Practical tips.

- Either planar or single-photon emission computed tomography or nuclear V/Q scan are acceptable modalities to screen for CTEPH.
- A normal perfusion (Q) scan effectively rules out the possibility of CTEPH.
- A negative computed tomography pulmonary angiogram does not effectively rule out CTEPH.
- Macitentan improved hemodynamics and functional capacity in inoperable CTEPH patients in a phase II placebo-controlled RCT,[121] but is not yet Health Canada-approved for this indication.
- Low-quality evidence suggests a possible benefit of other PAH-targeted medications (I.V. epoprostenol, subcutaneous treprostinil, oral bosentan, oral sildenafil).[124]

Lung Transplantation for PH

Transplantation remains a final treatment option for many PH patients. Because of the potential delays in assessment and eventual transplantation, referral should be considered for all PAH and CTEPH patients with progressive disease despite maximal therapy, or those who begin I.V./subcutaneous prostanoid infusion treatment. Bilateral lung transplantation is the procedure of choice for PAH and CTEPH whereas heart-lung transplantation is usually reserved for patients with CHD not amenable to surgical correction.

Modalities such as venoarterial extracorporeal membrane oxygenation and centrally cannulated pumpless devices (Pulmonary Artery-to-Left Atrial [PALA] Novalung; Fresenius Medical Care, Waltham, MA) have been used successfully to bridge patients to lung transplantation and early consultation with a specialized centre should be sought for rapidly deteriorating patients. Balloon atrial septostomy is not routinely performed in Canada, but is a surgical option for palliating patients with RV failure who are not transplant candidates.

RECOMMENDATION

30. We recommend that PH patients (especially PAH and CTEPH) with persistent severe PH (NYHA FC III or IV, and/or RV failure) despite maximal medical therapy be referred for lung transplantation assessment (Strong Recommendation, Moderate-Quality Evidence).
31. We suggest that PH patients with refractory RV failure and/or hemodynamic instability be considered for extracorporeal life support as a "bridge" to definitive PH therapy (Weak Recommendation, Moderate-Quality Evidence).

Summary

Significant progress has been made in the landscape of PH diagnosis and management in Canada, however prognosis remains poor for many patients and challenges remain. Referral to a PH centre of excellence is essential when a diagnosis of PAH is suspected, or when the etiology of PH cannot be confirmed with initial investigations. Management is now focused on early diagnosis and a goal-directed approach to achieve a low-risk profile in each patient, which optimizes HRQoL and delays progression. More patients are being aggressively treated with multiple drugs across the 3 therapeutic pathways, with improved survival and better clinical outcomes. At present, there are currently 10 drugs approved for use by Health Canada, however, access to these therapies is

not consistent across provinces, and unfortunately the choice of therapy can be constrained by funding limitations. PAH-targeted medications are not recommended for patients with PH secondary to underlying cardiac or pulmonary disease. Future research is needed to explore novel pathobiologic pathways, identify targeted agents to reverse disease, and explore personalized treatment strategies on the basis of biomarkers known to be causally related to the disease.

Secondary Panel

Stephen Archer, MD, Queen's University, Kingston, Ontario, Canada

Kim Connelly, MBBS, PhD, University of Toronto, Toronto, Ontario, Canada

John Granton, MD, Toronto General Hospital, Toronto, Ontario, Canada

Doug Helmersen, MD, University of Calgary, Calgary, Alberta, Canada

Andrew Hirsch, MD, McGill University, Montréal, Quebec, Canada

Simon Jackson, MD, Queen Elizabeth II Health Sciences Centre, Dalhousie University, Halifax, Nova Scotia, Canada

Lisa Lee, NP(F), Pulmonary Hypertension Clinic, GLDHCC, Vancouver, British Columbia, Canada

Jamie Myrah, BA, Pulmonary Hypertension Association of Canada, Vancouver, British Columbia, Canada

Sharon Proudfoot, B Com, Pulmonary Hypertension Association of Canada, Vancouver, British Columbia, Canada

Steeve Provencher, MD, Laval University, Quebec, Quebec, Canada

Duncan Stewart, MD, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

John Swiston, MD, University of British Columbia, Vancouver, British Columbia, Canada

Anne Van Dam, Director of Knowledge Mobilization, Canadian Thoracic Society, Ottawa, Ontario, Canada

Linda Webster, MN, NP University of Alberta, Edmonton, Alberta, Canada

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