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REVIEW

Pulmonary hypertension in remote and disadvantaged population: overcoming unique challenges for improved outcomes

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Abstract

Pulmonary hypertension (PH) is a common and debilitating medical condition with high mortality. PH research has traditionally focused on pulmonary arterial hypertension and its management in expert PH centres. Other forms of PH such as PH associated with cardiac or respiratory disease are more common, less well-understood and associated with higher mortality. Epidemiology of PH in disadvantaged, remote and rural regions, remains largely undocumented. In this review, we discuss the unique challenges in identifying PH in rural and disadvantaged populations using the Top End region of the Northern Territory of Australia as an example. We propose a simple diagnostic approach, ideally suited to regions where resource allocation is scarce, using clinical skills, echocardiography, and an escalation algorithm. The brief history, epidemiology and current literature on PH are summarised to inform the busy clinicians. We highlight two case examples from the Top End to illustrate the challenges and potential solutions.

Introduction

Pulmonary hypertension (PH) is complex, heterogenous and usually multifactorial in origin. PH is currently hemodynamically defined as a mean pulmonary artery pressure (mPAP) of more than 20 mmHg measured with right heart catheterisation (RHC) at rest and classified into five distinct groups (Fig. 1), each having differing prognosis and management.[1,2] Physiologically, PH can be classified into pre-capillary PH where pressure elevation is primarily in the arterial side of the pulmonary circulation, and post-capillary PH where the pressure elevation occurs in pulmonary venous system or the left heart which then secondarily raises the PAP.[3] Pre-capillary physiology is a hallmark of all PH groups, except group 2 (PH due to left heart disease (PH-LHD)) where pulmonary vascular resistance (PVR) is usually normal but may be accompanied by a degree of pulmonary vascular remodelling. Post-capillary PH is seen mainly in PH-LHD patients and some patients with group 5 PH. Owing to limited awareness of PH among the medical community and public, there are considerable diagnostic delays leading to poor outcomes even in the developed world.[4,5] Recent reports suggest that the burden of PH is higher in remote and disadvantaged regions than in the major cities where PH referral centres are usually located.[6,7]

Growing evidence suggests a rising prevalence of all forms of PH.[8] The data from National Echocardiography Database of Australia have shown that, regardless of underlying aetiology, patients with severe PH face a 5-year mortality of nearly 10 times higher than people without PH. Even with mildly elevated right ventricular systolic pressure (RVSP = 30–40 mmHg), patients were more likely to die than those with RVSP <30 mmHg.[9] This lower RVSP threshold of 30 mmHg corresponds almost exactly to a mPAP of 20 mmHg (measured during RHC) and creates both a potential opportunity to improved outcomes as well as a dilemma as to how to identify these individuals at an earlier stage in their illness.[10,11] The worldwide prognosis of patients with

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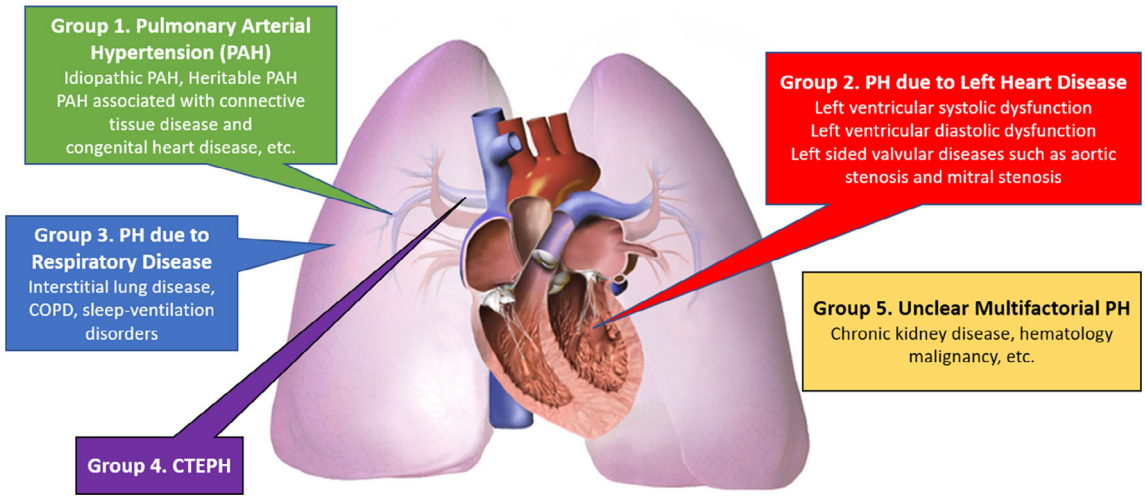

Figure 1 Simple illustration of different pulmonary hypertension groups according to the updated clinical classification by the 6th World Symposium on Pulmonary Hypertension Task Force. CTEPH, chronic thromboembolic pulmonary hypertension; PH, pulmonary hypertension.

pulmonary arterial hypertension (PAH; or group 1 PH) has significantly improved due to advanced PH therapies.[12] However, the prognosis of other PH groups remains poor. Improving outcomes of all groups of PH requires a meticulous approach to diagnosis and treatment, creating unique challenges in rural and disadvantaged regions. The two case examples below highlight the challenges the patients and clinicians face in managing complex PH patients who reside in less privileged regions.

Case study 1

Mrs KF is a 25-year-old indigenous mother with systemic lupus erythematosus (SLE) from a regional town 300 km south of Darwin, who had two episodes of life-threatening illnesses requiring intensive care unit (ICU) admissions in late 2019. Her initial echocardiogram showed severe PH with right ventricular failure, Cor Triatriatum Sinister and right ventricular hypertrophy. She had cardiac arrests requiring multiple rounds of cardiopulmonary resuscitations. Her repeat echo after discharge from ICU showed complete recovery of right heart failure. She again represented with similar illness and was admitted to ICU 2 weeks after the initial discharge. The Ventilation-perfusion (VQ) scan revealed two areas of VQ mismatch in left lung suspicious of PE and she was anticoagulated with warfarin. After a prolonged complicated admission and slow recovery, she was discharged home to be with her young children.

Follow up investigations were arranged but she failed to attend for initial appointments in Darwin as she did not want to leave her children behind. She finally agreed to get investigated after multiple attempts and persistent encouragement from local health care providers and PH clinical nurse. The RHC performed 10 months after the initial referral demonstrated pre-capillary PH (mPAP = 27 mmHg) with pulmonary artery wedge pressure of 12 mmHg. The transpulmonary gradient (TPG) of 15 mmHg was regarded as suggestive of PAH. The definitive diagnosis of PAH was not possible without the data on cardiac output to enable calculation of PVR which is an essential parameter in PAH definition.[1] Her trans-oesophageal echocardiogram confirmed the Cor Triatriatum with incomplete membrane and peak gradient of 6 mmHg. There was also a small secundum atrial septal defect (ASD). High resolution CT scan of her chest excluded lupus pneumonitis. After telehealth case conference with a PH specialist from Sydney, patient was commenced on a phosphodiesterase 5 inhibitor therapy for possible PAH associated with SLE and ASD. This case demonstrated complexity of care for remote patients with PH and importance of multidisciplinary team involvement in their management.

Case study 2

Mr JM is a 65-year-old Aboriginal man from a remote town, located 630 km east of Darwin. He had rheumatic fever as a young boy and suffered from rheumatic heart disease (RHD), requiring mechanical mitral valve replacement at the age of 56 years in 2011. His first outreach echocardiogram revealed moderate rheumatic mitral stenosis and regurgitation in 2004. He had repeat echocardiograms in 2006 and 2007 when mitral valve disease remained moderate with normal right heart

function and mild TR. The next echo in May 2010 revealed severe mitral stenosis. He was also symptomatic at that time requiring transfer to Darwin for pre-operative assessment. By then he already developed moderate TR and severe PH (estimated RVSP = 73 mmHg). His case was discussed with the MDT heart team involving a major referral centre in South Australia and promptly accepted for surgery. However, he underwent surgery more than 1 year later in July 2011 due to various personal factors. Operation report recorded a normally appearing tricuspid valve but annular dilatation consistent with 'functional' TR secondary to longstanding PH.

His RVSP improved post operatively to 43 mmHg in February 2012 but never normalised. His estimated RVSP continued to increase over the years and at the end of 2019, he was hospitalised for severe right heart failure. His RVSP was estimated at 52 mmHg by echocardiography in the presence of severe TR. His mechanical mitral valve had a haemodynamic profile within the reference interval for the valve type. His management was challenging not only due to complexity of his medical conditions including PH-LHD, but also logistical and care coordinating issues associated with patients from remote communities. This case highlights importance of regular echocardiographic and clinical follow up for RHD patients and timely corrective surgery to prevent irreversible pulmonary vascular disease.

A brief history and changes in definition of pulmonary hypertension

As early as the late 19th century, reports of young women dying from right heart failure emerged.[13] However, it was not possible to demonstrate pulmonary haemodynamic and diagnose PH until after the introduction of cardiac catheterisation in humans.[14] The first World Symposium of Pulmonary Hypertension (WSPH) was held in 1973 to promote research and find a cure for PH, an elusive objective yet to be achieved.[15] PH was initially defined arbitrarily as a mPAP ≥25 mmHg at rest measured by RHC at the first WSPH to provide a threshold for involvement in clinical trials, as a therapeutic target, and to avoid inclusion of patients with 'borderline' PH in clinical studies. Since then, the definition and classification of PH have been changed and refined multiple times at each WSPH to be in line with contemporary research. In 2018, the 6th WSPH was held in Nice, France and the new haemodynamic definition of PH was introduced as mPAP >20 mmHg, consistent with original data derived from normal humans.[1] This presents the potential for expanded therapeutic application for PH treatments.[10,11]

Roles of right heart catheterisation and echocardiography in pulmonary hypertension

Although PH is defined based on haemodynamic parameters from RHC, echocardiography (echo) plays a key role in diagnosis of PH.[16,17] Echo not only is an important screening tool for PH but also can provide information on underlying pathologies such as left heart disease and congenital heart disease (CHD). It is also useful for prognostication and follow up. The most commonly used echo marker of PH is estimation of RVSP by measuring the maximal tricuspid regurgitation velocity (TRV_{max}) using continuous-wave Doppler and applying the modified Bernoulli equation ($\Delta P = 4\ V^2$)[18] as demonstrated in Figure 2A. This pressure represents the systolic pressure gradient between right ventricle and right atrium, and RVSP can be calculated by addition of estimated right atrial pressure to this gradient. The Doppler profile of right ventricular out flow tract (RVOT) may also be used to detect PH. Shorter time to peak velocity of Doppler envelop (the Acceleration Time) is associated with PH. Systolic notching and triangular shape of RVOT Doppler profile are associated with increased PVR. Other echocardiographic signs of PH include dilatation of right heart chambers (Fig. 2B), inferior vena cava (Fig. 2C) and pulmonary artery. Flattening of interventricular septum is also seen in PH patients due to pressure and volume overload of right ventricle (Fig. 2D).

However, there are several limitations of echocardiographic PH assessment. First, tricuspid regurgitation may not be sufficient nor measurable in every patient. Like all Doppler measurements, measurement of TRV_{max} is operator dependent. It may be underestimated if the Doppler alignment is not parrel to the regurgitant jet and overestimated if higher indistinct peak TRVmax signal is used.[19]

With the increasing prevalence of all forms of PH, it is not possible or practical to perform RHC in every patient in whom PH is suspected. On the other hand, RHC is the gold standard method to define PH and differentiate PH physiologies. Moreover, it is mandatory to demonstrate precapillary PH physiology (elevated PVR) by RHC to diagnose PAH and receive Pharmaceutical Beneficiary Subsidy funded advanced PH therapy in Australia. The TPG and PVR are important parameters to differentiate precapillary PH from post capillary PH. Reliable non-invasive techniques to predict TPG and PVR are necessary for better patient selection, especially in area with limited resources. The potential contenders are echocardiographic pulmonary to left atrial ratio (ePLAR) to predict TPG[20] and echocardiographic PVR (PVR_{echo}) formulae.

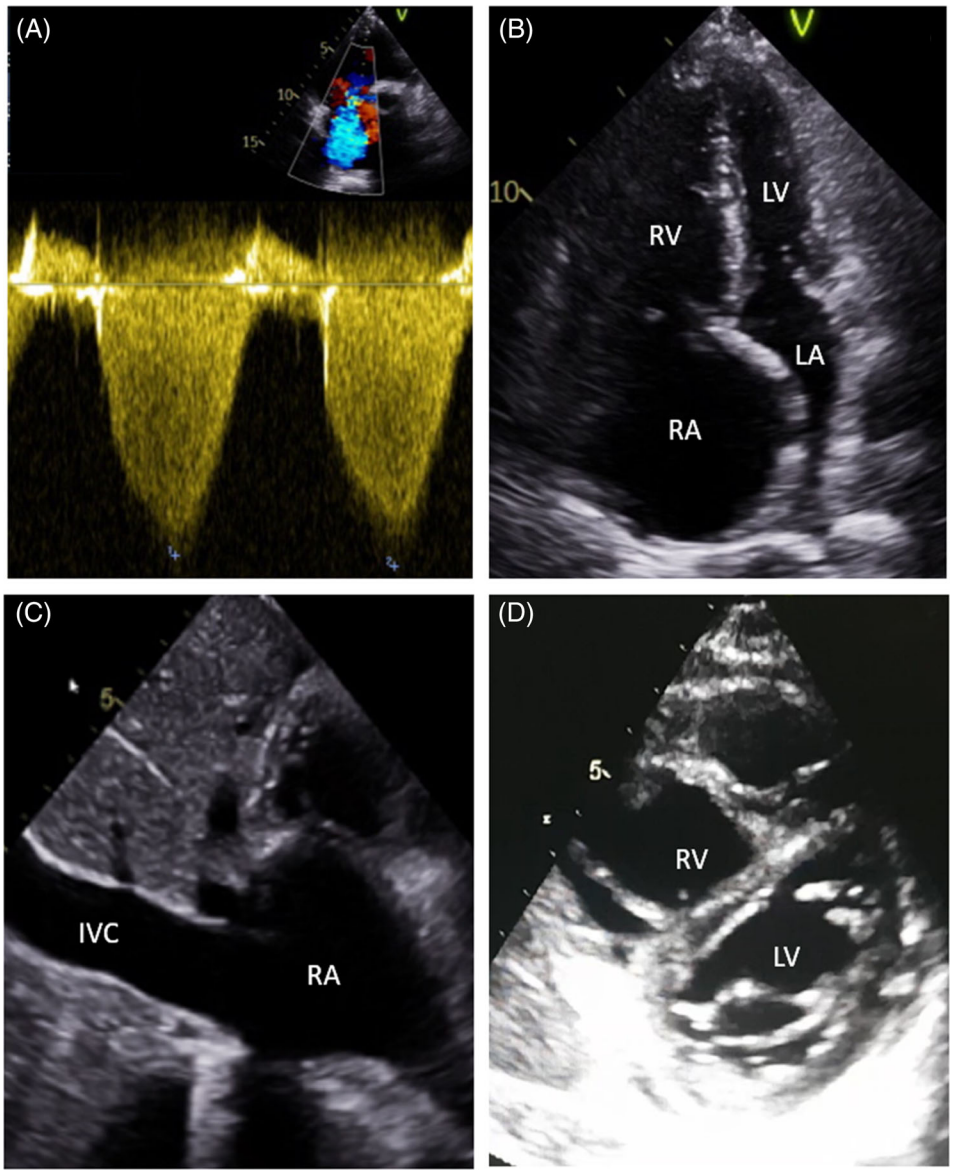

Figure 2 (A) From Apical four-chamber view of transthoracic echocardiogram, right ventricular systolic pressure was estimated from the tricuspid regurgitation velocity is measured by continuous wave Doppler using the modified Bernoulli equation ($\Delta P = 4\ V^2$). P, change in pressure; V, velocity of flow. (B) Dilatation of right ventricle and right atrium in a patient with pulmonary hypertension. (C) Inferior vena cava dilatation in a patient with pulmonary hypertension. (D) Flattening of interventricular septum resulting in a D-shaped left ventricle in a patient with pulmonary hypertension.

Epidemiology of pulmonary hypertension worldwide

Early epidemiology data from PAH registries from the developed world suggested low population prevalence, resulting in PAH having 'orphan' disease status as summarised in Table 1.[21–27] Therefore, the current knowledge on PH epidemiology worldwide has a tendency of bias towards the data on PAH patients who are managed at major referral centres. More recent reports on community-based studies filled the knowledge gap in epidemiology of other groups of PH.[6–8] The study from Armadale, Western Australia[8] reported a much higher prevalence of PAH at 15 cases per 100 000 inhabitants compared with 52 per million population reported in the Scottish registry[24] and 6.6 cases per million reported in the United Kingdom and Ireland registry.[25] The prevalence of all forms of PH was 326 cases per 100 000 inhabitants with majority attributable to PH-LHD at 250 cases per 100 000 inhabitants of Armadale.

Table 1 Summary of registries and cohort studies on pulmonary hypertension epidemiology

Registry/Study	Timeline	Number of patients studied	Prevalence of all type of PH	Prevalence of PAH	1-year survival unless otherwise stated
National Institute of Health PAH Registry (USA)[21]	1981–1985	194 PAH patients from 32 US centres	–	–	68% (95% CI, 61%–75%)
Chinese Registry[22]	1999–2004	72 idiopathic and familial PAH patients	–	–	68%
REVEAL Registry (USA)[23]	2006–2011	1515 PAH patients from 55 US centres	–	–	91% (95% CI, 89.9%–92.1%)
Scottish Registry[24]	1986–2001	All hospitalisation for PAH in Scottish population	–	52 per million	–
UK and Ireland Registry[25]	2001–2009	482 incident PAH patients in eight PH centres in UK and Ireland	–	6.6 per million	92.7%
France Registry[26]	2002–2003	674 adult PAH patients from 17 university hospitals	–	15 per million	88%
Armadale Cohort Study[8]	2003–2009	936 patients with echo evidence of PH in Armadale, Western Australia	326 per 100 000	15 per 100 000	Mean survival 4.3 ± 0.1 years
PHSANZ Registry[27]	2012–2016	220 consecutive incident cases of PAH			95.6% (95% CI, 92.8%–98.5%)
Central Australia Cohort Study[7]	2005–2016	182 all type of PH patients in Central Australia	385 per 100 000	27 per 100 000	Median survival of 9 years (IQR 7.2–13.2)
Top End PH Study[6]	2010–2015	1764 patients with echo evidence of PH in Top End of Australia	955 per 100 000	37 per 100 000	40% 5 year-mortality

PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PHSANZ, Pulmonary Hypertension Society of Australia and New Zealand; REVEAL, registry to evaluate early and long-term PAH disease management; UK, United Kingdom; USA, United States of America.

Recent reports indicate higher incidence of PH in the developing world owing to the prevalence of risk factors common in disadvantaged population.[28] The burden of RHD remains significant in the poor regions[29] and may contribute to high prevalence of PH in these regions. CHD-related PH is also common in the developing world due to late diagnosis and delayed correction of congenital cardiac defects.[30,31] The high prevalence of infectious diseases such as human immunodeficiency virus infection and schistosomiasis may also contribute to the burden of PH in the developing countries.[32]

Despite a relatively high prevalence of PH-LHD and respiratory disease related PH, the epidemiology on these groups is not as well established as that of PAH.[33] To date, there are no PH-specific treatments available for these patients, with treatment options focused on the underlying disease state rather than the PH itself.[2] Due to increasing prevalence of risk factors, the prevalence of heart failure with preserved ejection fraction is also on the rise,[34] and it is estimated that between 50% and 83% of these patients will develop PH.[35]

Pulmonary hypertension in disadvantages regions and unique challenges

Unique climate, higher prevalence of chronic diseases, social and health inequity, poor health literacy, geographical isolation with poor access to health care are responsible for increased prevalence of PH and its risk factors in remote and rural regions such as the Top End of Australia. Culturally, indigenous patients may choose not to leave their communities to seek medical advice, investigation, or treatment, which may play a further role in late diagnosis and increased prevalence of underlying risk factors for PH.

Our group has recently reported a prevalence of PH in the Top End.[6] The minimal indicative prevalence of all forms of PH was 955 per 100 000 population, approximately three times that of the Armadale population.[8] PH was more common in indigenous people with the minimal indicative prevalence of 1587 per 100 000 population, almost five times that of the Armadale group. Modifiable risk factors such as hypertension, smoking, RHD and diabetes were found to be very common among the PH patients in the region. Indigenous patients were younger at diagnosis but suffered higher mortality. The majority (58%) of patients suffered from PH-LHD, consistent with global PH data. However, valvular heart disease was the main underlying cause, reflective of high prevalence of RHD in the territory. The PAH related to CHD was the most common form of PAH, suggestive of delayed diagnosis and correction of CHD in the region. The data on PAH is

limited by small numbers of RHC performed in this population. A significant portion (17%) of the patients in the study could not be classified into a PH group due to apparent underinvestigation.

These data highlight how a constellation of factors conspire together to produce a massive disease burden in an already disadvantaged population. It also compels a deeper examination into strategies that could address the imbalance, such as simple and portable diagnosis and management algorithms. To assist in identifying individuals at-risk of PH in areas with limited resource availability, we have developed a new diagnostic approach, which is summarised below.

Proposed diagnostic approach for pulmonary hypertension in disadvantaged regions

Although definitive diagnosis of PH requires comprehensive investigations including RHC,[2] this approach is not feasible as an early investigation in areas where resources are scarce. We have developed a new approach, summarised in Figure 2, which focusses on clinical markers of disease. The approach is simple and practical, and can be realistically achieved by a multidisciplinary outreach team, which includes a physician, community-based echocardiography and X-ray equipment.[36]

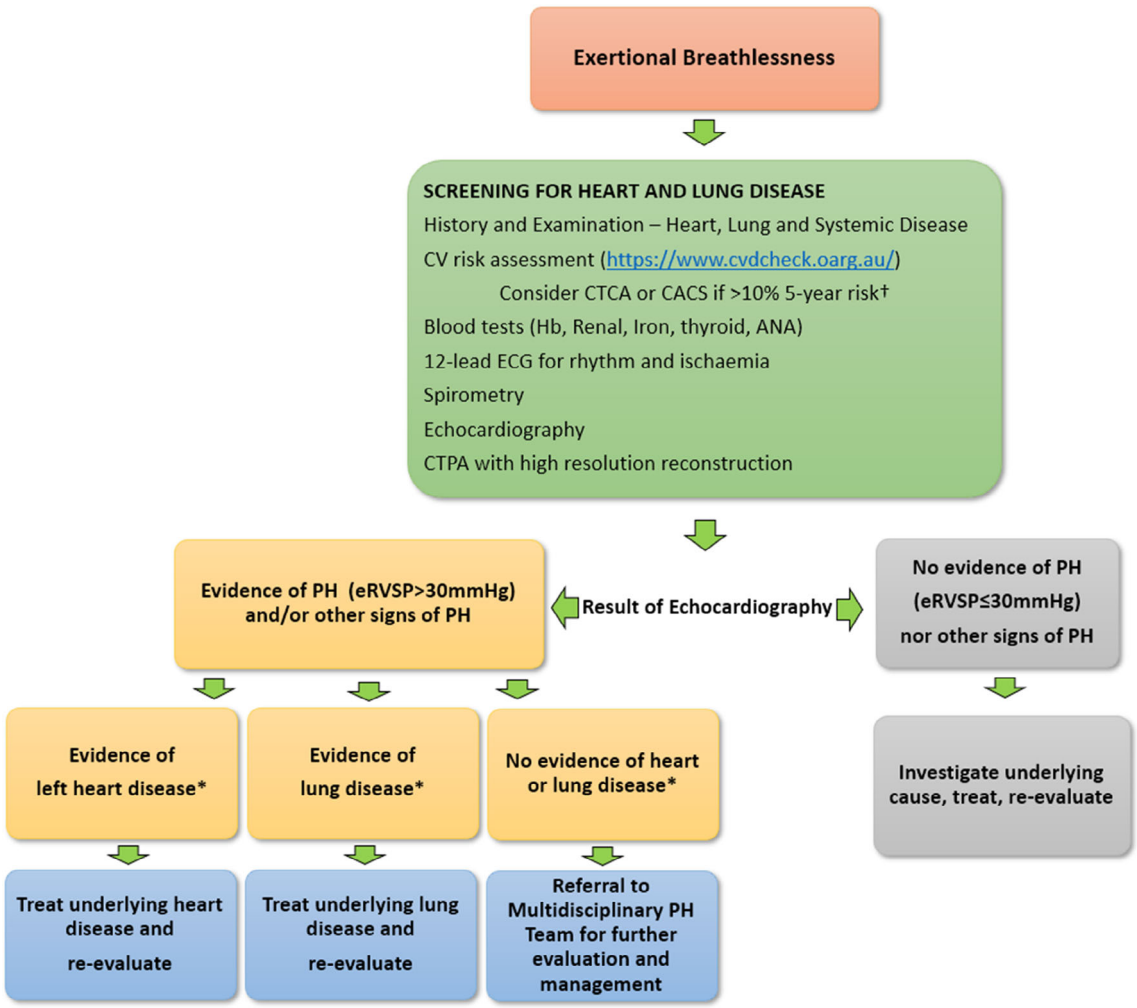

Figure 3 (Central Illustration). Proposed simple diagnostic algorithm for detection of pulmonary hypertension in breathless patients in the Top End of Australia. †In patients with cardiovascular risk factors especially if no cause was found after the initial investigations. *It is important to make sure that the heart and lung diseases are proportionate to the degree of PH. CTCA, CT coronary angiogram; CTPA, computed tomography pulmonary angiogram; CV, cardiovascular; ECG, electrocardiogram; eRVSP, estimated right ventricular systolic pressure; FBE, full blood examination; Hb, haemoglobin; PH, pulmonary hypertension.

Patients with unexplained breathlessness should undergo thorough clinical evaluation including the careful history taking, physical examination (including height, weight and body mass index), and initial investigations. Initial blood evaluation may include full blood counts, urea and electrolytes, liver and thyroid function, B-type natriuretic peptide (BNP; or NT-proBNP), iron studies, an autoimmune screen, and a lipid profile. Full cardiovascular risk screening should be performed using commercially available software (e.g., www.cvdcheck.org.au). Spirometry and thoracic CT will help detect the presence of lung disease (and coronary CT angiography for detection of coronary artery disease if clinically appropriate), and echocardiography will help identify underlying heart disease and evidence of PH.

The results of the initial investigations should be discussed by a multidisciplinary team and the most suitable pathway chosen, outlined in Figure 3, 4. This approach will allow for initial successful triage of patients and minimise delays. The presence of elevated right ventricular systolic pressure on echocardiography and/or other signs of PH such as right heart chambers, inferior vena cava and pulmonary artery dilatation, in the absence of significant heart or lung disease, should alert the multidisciplinary team to the possibility of PAH and trigger further evaluation at a major centre. Clear referral pathways should be developed and distributed widely in the region. Telehealth and case conferences between the local health providers and PH team will be useful in remote regions with limited resources.

Patients with PH will usually present with nonspecific breathlessness and a high index of clinical suspicion is required for early diagnosis. The common clinical features for PH patients are illustrated in Figure 4. The electrocardiograph of patients with PH may show right axis deviation and right bundle block but their absences do not exclude the diagnosis of PH. Chest X-ray of PH

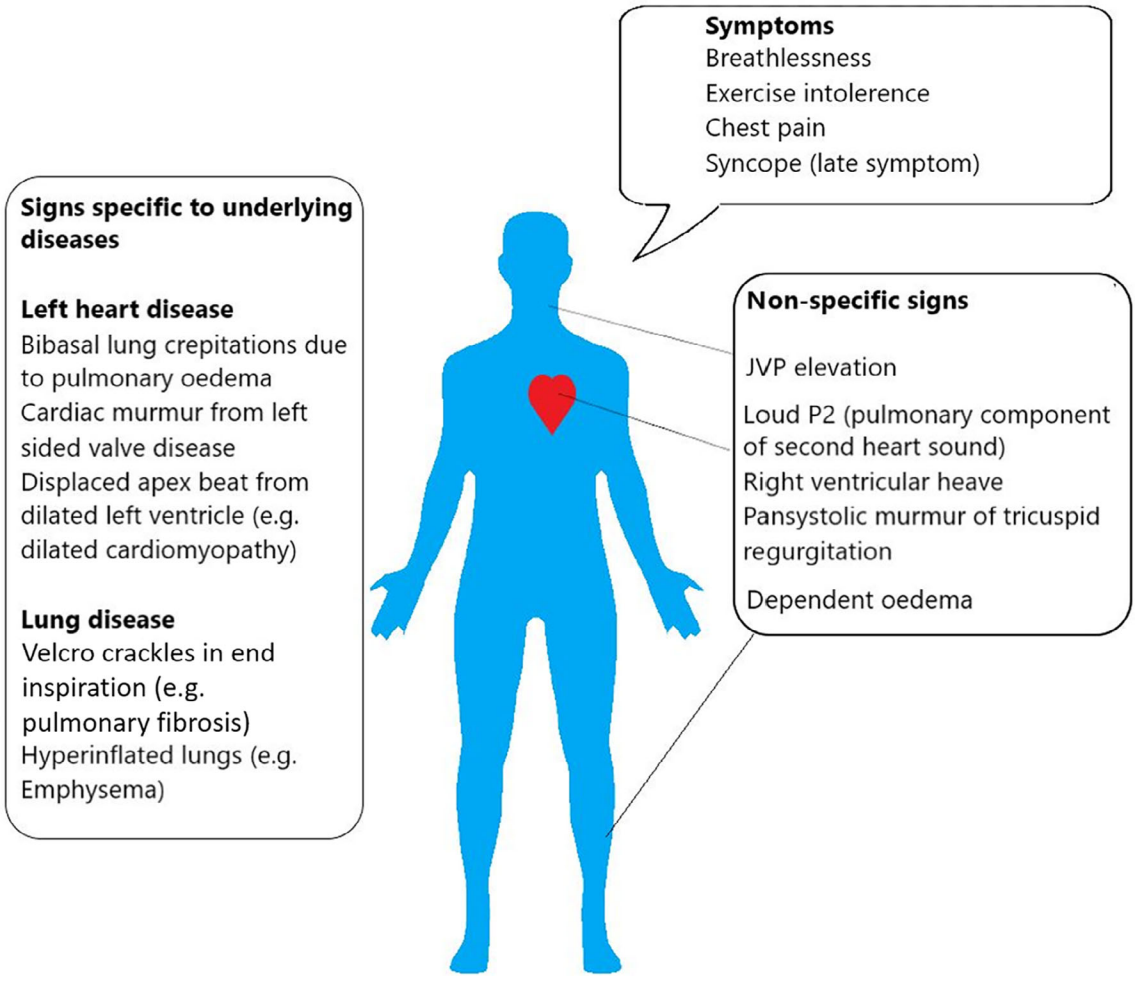

Figure 4 Potential clinical features in patients with pulmonary hypertension. JVP, jugular venous pressure.

patients may show pruning of pulmonary vasculature, but again these changes may not be present. Group 3 PH patients may have radiographic changes due to their underlying lung pathology such as hyperinflated lungs in emphysema. RHC should be offered to patients with suspected PAH or unclear data after careful evaluation by the PH team. This approach will ensure appropriate selection of patients for more invasive investigations resulting in better resource management and patient safety.

Community engagement and patient-centred care

One of the challenges of managing a complex medical problem such as PH in a remote, disadvantaged population is poor engagement with health care secondary to language and cultural barriers as well as poor health literacy. Patient educational materials for PH in indigenous languages should be made available widely to increase awareness of the condition in the community which will facilitate early diagnosis. Training and involvement of local and indigenous health practitioners in the management will promote culturally appropriate care. Our colleagues have recently performed a successful active case findings of RHD in a remote community by involving the local community.[37] Training of community and local health care providers in Point of Care Ultrasound is another way of early case detection, particularly as new artificial-intelligence based machines that can guide an operator with limited training to obtain on-axis and diagnostic quality images. Innovative models of care such as telemedicine, specialist outreach, case conferences and care co-ordinations may also play huge roles in PH management in disadvantaged regions and are more patient centric and cost-effective. Primary care providers such as general practitioners and nurses should also be educated and regularly updated with important information on PH diagnosis and management.

Conclusion

PH is likely to be a significant contributor to the life expectancy gap in remote, rural, and disadvantaged where chronic health conditions are common. Whether caused by pulmonary arterial or lung disease (pre-capillary PH) or left heart diseases (post-capillary PH), PH cause devastating effects on patients, families, and the community. An important goal is to identify early disease, hence a focus towards early diagnosis and prevention at community level. Important diagnostic tools such as echocardiography, chest imaging and pulmonary function testing should be made easily accessible for the patients, using a diagnostic algorithm such as we provide in Figure 3. A multidisciplinary team involving clinicians with experience in managing PH patients, skilled at interpreting initial investigations could act as gatekeepers for the use of more invasive diagnostic tools such as RHC, prescribing advanced therapies, choosing treatment targets and monitoring treatment outcomes. These measures could at least, in part, improve health disparity between the developed and developing regions.

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