Pulmonary Circulation

Early intervention: should we conduct therapeutic trials for mild pulmonary hypertension before onset of symptoms?

Jessica H. Huston[1], Robert P. Frantz[2] and Evan L. Brittain[1,3]

[1]Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, TN, USA; [2]Department of Cardiovascular Disease, Mayo Clinic, Rochester, MN, USA; [3]Vanderbilt Translational and Clinical Research Center, Vanderbilt University Medical Center, Nashville, TN, USA

Abstract

Pulmonary arterial hypertension (PAH) is a rare disease that carries a poor prognosis. For 45 years, the definition of pulmonary hypertension (PH) has been a mean pulmonary arterial pressure (mPAP) $\geq$ 25 mmHg, based on expert opinion. Recent data indicate that the mortality risk starts in the mPAP range of 21–24 mmHg, which has recently been reflected in the World Symposium on PH consensus document defining PH as a mPAP $>$ 20 mmHg. The mortality associated with these lower levels of pulmonary pressures suggests that these values reflect a more advanced disease stage than previously recognized. It is unknown whether interventions targeting patients with mPAP values in the range of 21–24 mmHg in the absence of left ventricular or hypoxic lung disease are of clinical benefit. Here we present historical perspective on the hemodynamic definition of PH, discuss recent epidemiologic data, and outline obstacles to enrolling and evaluating response to therapy in mild PAH patients, as well as potentially useful study designs.

Keywords

trial, epidemiology, catheterization, echocardiography

Date received: 7 January 2019; accepted: 25 March 2019

Pulmonary Circulation 2019; 9(2) 1–8
DOI: 10.1177/2045894019844994

Defining mild pulmonary hypertension

Pulmonary hypertension (PH) received a consensus definition at the first World Symposium on Pulmonary Hypertension meeting as a mean pulmonary arterial pressure (mPAP) $\geq$ 25 mmHg obtained from resting invasive catheterization.[1] The original definition was based on expert opinion due to the lack of high-quality, large-scale normative data and was focused on defining pulmonary arterial hypertension (PAH), defined as pre-capillary PH with a pulmonary arterial wedge pressure (PAWP) $\leq$15 mmHg.[2] Participants in subsequent Symposia have recognized the potential for a population with abnormal but sub-diagnostic (i.e. "borderline") PAP values but declined to alter the definition due to lack of epidemiologic data demonstrating adverse outcomes.

The best contemporary normative data are presented in a systematic review from Kovacs et al., who examined results of 1187 right heart catheterizations (RHC) from 47 studies in patients free of clinical symptoms and with only minor medical conditions deemed not to effect hemodynamics.[3] The average mPAP on RHC was 14 mmHg ($\pm$3 mmHg) with the upper limit of normal extrapolated to be 19–20 mmHg (2 standard deviations above the mean). A mPAP of 25 mmHg is almost 4 standard deviations above the mPAP found in this study, a departure from how upper limits are defined for many biologic measurements. As current treatment guidelines stand, there are many patients with clearly abnormal mPAP in the 20–24-mmHg range who are not recognized to have disease or perceived to require further evaluation. Although we primarily focus on potential interventions for early PAH in this commentary, these concepts may also apply to those with WHO Group II or III PH, albeit employing different

Corresponding author:
Evan L. Brittain, Division of Cardiovascular Medicine, 2525 West End Avenue, Suite 300-A, Nashville, TN 37203, USA.
Email: Evan.brittain@vumc.org

therapeutic strategies. As current treatment guidelines stand, these ''mild'' PAH patients do not have recommendations for treatment with pulmonary vasodilator therapy because efficacy has not been tested in this population.

Prognostic implications of invasively measured mild PH

Multiple studies have shown increased mortality risk in patients with invasively measured mPAP in the 20–24-mmHg range. Patients with sickle cell anemia were the first to be shown to have an increased mortality associated with mild PAH.[4] Similar findings exist for patients mildly elevated PAPs in heart failure, chronic respiratory diseases, HIV, and systemic sclerosis.[5–10] These relatively small, disease-specific cohorts demonstrate a signal that mild elevations of pulmonary pressures have an association with increased clinical events. However, large-scale epidemiologic outcome data in unselected populations referred for RHC were lacking until recently.

In 2016, Maron et al. used the Veteran Affairs Clinical Assessment Reporting and Tracking database to describe the largest cohort of patients with borderline PH linked to clinical outcomes.[11] They evaluated 21,727 veterans with RHC data and found that increased risk for mortality started at a mPAP of 19 mmHg. Similar findings were shown by Assad et al. in a retrospective cohort of 4343 patients with RHC data.[12] This group found the co-morbidity-adjusted mortality associated with mPAP of 21–24 mmHg was 31% higher compared with patients with mPAP $\leq$ 15 mmHg. Douschan et al. studied a group of 547 patients with RHC data and found that patients with mPAP 20.6–24.9 mmHg had increased mortality compared to reference (hazard ratio [HR] = 3.20; 95% confidence interval [CI] = 1.56–6.60; $P = 0.002$).[13] Although these data may not be generalizable to the community at large, these referral cohorts reflect patients seeking care in clinical practice.

Prognostic implications of non-invasively measured mild PH

Currently, echocardiographically measured tricuspid regurgitant velocity (TRV) is used to estimate pulmonary arterial systolic pressure (PASP) as the primary method of screening for PAH.[14] Echocardiography is an imperfect screening test, as PASP can be both over and underestimated by >10 mmHg in up to 50% of the time.[15] Moreover, absence of a measurable TRV does not always signify absence of elevated pulmonary pressure.[16] Despite unreliability of TRV on echocardiogram, there can still be clues of abnormal PAPs including right ventricular (RV) dilation and dysfunction, pericardial effusion, interventricular septal flattening, or pulmonary arterial dilation.

As a non-invasive measure of pulmonary pressures, echocardiography is an important tool to determine risk in large-scale population studies. Echocardiographically estimated PASP in the mild PH range (33–39 mmHg) has been associated with higher mortality. Examination of a cohort of 8296 veterans showed increased mortality with PASP in the mild range, particularly among individuals with HIV but also among uninfected veterans.[17] In a referral population of >43,000 patients, those with PASP of 35 mmHg or TRV of 2.7 m/s had nearly double the mortality risk compared to reference.[18] In a recent meta-analysis and systematic review, Kolte et al. examined 15 studies including >16,000 patients referred for either RHC or echocardiography.[19] They found consistent increases in all-cause mortality in the mild PH range (PASP 19–24 mmHg) on RHC and corresponding estimates on echocardiography.

A new definition

In response to the epidemiologic data discussed above, participants in the 2018 World Symposium on PH elected to redefine PH as a mPAP > 20 mmHg and differentiated pulmonary vascular disease (i.e. pre-capillary PH or PAH) as also requiring a pulmonary vascular resistance (PVR) of $\geq$3 Woods Units (WU) and pulmonary capillary wedge pressure $\leq$15 mmHg.[20,21] This statement acknowledges increased risk in patients with pulmonary vascular disease and mPAP of 21–24 mmHg, specifically risk of disease progression and worsened survival among this group. Pulmonary venous hypertension is now defined as a mPAP > 20 mmHg and pulmonary capillary wedge pressure or left ventricular (LV) end-diastolic pressure >15 mmHg. We expect these recent changes will prompt investigations into clinical effectiveness of interventions in patients with mPAP in the range of 21–24 mmHg.

What we don't know can hurt us

Several questions remain unanswered as to how to optimally evaluate and treat patients with mild PAH. First, the natural history of PAH in at-risk subgroups needs to be better defined. The limited available data suggest that mild PAH is a progressive condition. Valerio et al. studied 228 systemic sclerosis patients who were referred for RHC to evaluate possible PAH.[5] They identified 86 patients with mPAP in the range of 21–24 mmHg. Over a mean interval of four years (±2.9 years), 38 of those patients underwent repeat RHC, of which 42% had progression to overt PAH (mPAP $\geq$ 25 mmHg). A small study (n = 32) suggested that systemic sclerosis patients with asymptomatic PAH identified via screening have improved survival compared to those diagnosed after onset of symptoms, although this finding may suffer from lead-in bias.[22] In an unselected population referred for two RHCs over a median interval of 35 weeks (interquartile range [IQR] = 12–124 weeks), Assad et al. reported that 61% of individuals with mPAP of 19–24 mmHg on the initial RHC subsequently converted to mPAP > 25 mmHg.[12] The majority of these participants were diagnosed with WHO Group II PH.

These retrospective findings suffer from referral bias and therefore may not reflect the true natural history of mild PH, but nonetheless suggest a signal that patients with mild PH are at risk of progression.

There are limited data on interventions for prevention of progression in mild PAH. Kovacs et al. treated 10 systemic sclerosis patients with mild PAH diagnosed by mPAP < 25 mmHg at rest and >30 mmHg with exercise with bosentan to evaluate progression of disease over six months.[23] They observed significant decreases in mPAP at rest and with 50 W of exercise compared to baseline and a preceding 12-month observation period.[23] Similar effects were observed with ambrisentan in 30 patients with exercise-induced increase in mPAP.[24] Notably there was no significant difference in peak VO_2 between groups in either of these studies and long-term outcomes associated with these therapies are not known.

Considerations for targeting asymptomatic mild PAH

The weight of the evidence that mild PH is associated with adverse outcomes has become difficult to ignore. Depending on the underlying disease process and hemodynamic state, the mild PH may be simply a marker of underlying disease severity, in which case specifically targeting the PH with vasodilators may not be useful or may even be harmful (e.g. most PH related to lung disease, group III in the classification system). In such patients, the best treatment for the patient and for the mild PH may be more aggressive oxygen supplementation or moving toward active consideration of lung transplantation. Accordingly, decisions to treat mild PAH, or to conduct clinical trials in mild PAH, must rest on a sound physiologic rationale for the proposed treatment. Part of this process is careful evaluation and screening of the proposed study population to ensure the underlying pathophysiology driving mild PAH is more likely to respond to pulmonary vasodilators (i.e. exclusion of parenchymal lung disease and diastolic heart failure). In patients in whom there is sound physiologic rationale for specific PAH treatment, but where the minimally symptomatic nature of the PAH makes the need for treatment unclear, the therapeutic concept rests on the precedents for treating asymptomatic conditions in clinical medicine. Systemic hypertension is a good example of this concept, where therapy of early blood pressure elevation is beneficial in preventing end organ damage such as heart failure, stroke, renal dysfunction, and coronary disease.[25]

Asymptomatic PAH does not equal mild pulmonary vascular pathology

By the time dyspnea due to PAH comes to medical attention and estimated PAPs on echocardiography are sufficiently elevated to prompt RHC, the extent of involvement of the pulmonary vascular bed is usually quite substantial

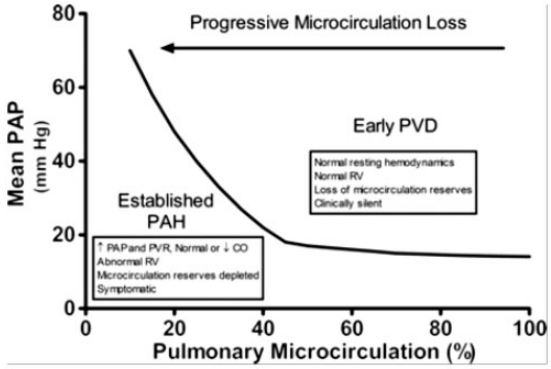

Fig. 1. Schematic representation of the relationship between pulmonary microcirculation loss and PAP. The high capacitance of the pulmonary circulation implies that early microcirculation loss is not accompanied by a change in resting PAP. Many of the current screening modalities are dependent on detecting a rise in PAP and thus will fail to detect the early stages of PVD. PAP, pulmonary artery pressure; PVD, pulmonary vascular disease; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; CO, cardiac output; RV, right ventricle.[28]

(Fig. 1).[26] On detailed questioning, many patients report significant symptoms long before presentation. The diagnosis of PAH is delayed a mean of one year after initial presentation with symptoms and on average four years after symptom onset. Based on this timeline, disease is often caught late in reference to the onset of pathology in pulmonary vasculature.[27] This provides further impetus for including patients with milder symptoms and more preserved functional capacity in clinical trials. This concept is fully in keeping with the FDA guidance on clinical trial design in rare diseases:[28]

- for rare diseases, practical considerations may warrant inclusion of a broader range of disease stage (e.g. severity of manifestations, development of manifestations secondary to long-standing primary disease manifestations) or phenotype than might be used for studies of common diseases;
- if some disease manifestations occur later than when the patients could be identified and enrolled in a study, then targeting patients for treatment before secondary manifestations develop may be important.

Clinical trials in mild PAH: what are the issues?

Inclusion criteria in clinical trials are designed based upon the nature of the endpoint, the estimates of statistical power to identify a particular difference in the endpoints, and the feasibility of identifying adequate numbers of patients to complete the study in an acceptable time frame. The relative importance of these issues is greatly influenced by the size of

the target patient population. For a common disease (e.g. hyperlipidemia), thousands of appropriate patients can readily be identified, obviating many of the potential concerns about study feasibility. For a rare disease such as PAH, the issues are far different. In this section, we will discuss the nature of these issues, the rationale for changes in how we conceptualize clinical trials in PAH, and the growing rationale for inclusion of earlier stages of PAH in the design of clinical trials.

Accordingly, it seems appropriate to consider including asymptomatic or only mildly symptomatic patients in phase II clinical trials in PAH, if the endpoints are of a nature that could be achieved in such patients. Nevertheless, the main barriers to this concept are threefold:

1. identifying early stage PAH patients is challenging, especially in those without known risk factors;
2. for novel agents where phase I safety data are limited, or there is potential for significant off target effects, the risk/benefit ratio for enrolling early stage disease patients is less favorable than in more advanced patients clearly in need of a new approach; and
3. early stage patients may be less interested in participating in clinical trials.

Finding the target: clinical endpoints in PAH trials

Selection of trial endpoints is challenging in a population of patients with mild disease at relatively low (but not trivial) risk of clinical outcomes. Surrogate endpoints are often required because accruing an adequate sample size to demonstrate a reduction in ''hard'' endpoints is prohibitive in a low-risk population. Below, we discuss possible physiologic and biochemical surrogate endpoints for trials targeting patients with mild PAH. However, it is important to realize that differentiating meaningful changes in surrogate endpoints may be difficult in a low-risk population. Composite clinical endpoints may also be of value in this patient population, such as onset of symptoms, time to clinical worsening, or hospitalization.

Six-minute walk distance

Historically, phase III PAH trials have used 6-min walk distance (6MWD) as a primary endpoint. This has been highly effective in achieving regulatory approval for an array of therapies, particularly if patients could not be on any background therapy, since the placebo group in such trials typically deteriorates, magnifying the treatment effect. Trials have generally included patients with 6MWD in the range of 150–450 m. The lower end has been to exclude patients so ill that the probability of success is low, and the upper end to exclude patients where it is difficult to show improvement in an already good walk distance (so called ceiling effect).[29] The ceiling effect limitation is particularly relevant to individuals with mild or asymptomatic disease. Limitations of 6MWD include bias related to patient effort and limited prognostic value. In a meta-analysis of 3112 PAH patients in 22 trials, Savarese et al. demonstrated that improvements in 6MWD do not correlate with improved clinical outcomes including all-cause death, PH-associated hospitalization, lung transplantation, or start of PAH rescue therapy.[30] Activity monitoring may be a more sensitive measure of functional capacity that incorporates physiological and environmental inputs. Physiologic measures obtained on cardiopulmonary exercise testing such as peak oxygen consumption (VO_2) or VE/VCO_2 may also be more sensitive than 6MWD. As phase III clinical trial design has evolved to include composite clinical endpoints, generally including components of hospitalization, death, clinical worsening, and unacceptable clinical response, it has been possible to extend the range of eligible patients. For example, allowing more functional class II patients, and a blend of treatment-naïve and background therapy, has proven effective.

However, patients with earlier stage disease (asymptomatic and/or with well-preserved 6MWD) have often continued to be excluded from both phase II and phase III trials due to concern that showing a benefit will be too difficult. In addition, asymptomatic or mildly symptomatic patients are less likely to agree to enroll in clinical trials since the burden of doing so may seem more than the burden of the disease. This is particularly true in a disease where it is not clear that the available predominantly vasodilator therapies are disease modifying with regard to the underlying pulmonary vascular process. However, thinking is evolving as the focus for new therapies shifts from vasodilators (which usually have anti-proliferative, anti-inflammatory, and/or anti-fibrotic effects in animal models but without definitive evidence of these effects in humans) to specifically anti-proliferative, immunomodulatory, and anti-inflammatory agents. The endpoints for such studies (at least for proof-of-concept, phase II studies) can include parameters such as PVR (a commonality with some vasodilator studies, which have sometimes included a hemodynamic sub-study). Use of such endpoints opens up the field to allow enrollment of less advanced individuals where it may be possible to achieve an endpoint such as PVR in a setting where 6MWD is already too high to be likely to improve.

Pulmonary vascular resistance

For proof-of-concept studies, PVR is an excellent endpoint appropriate for a wide range of disease severity. A fall in PVR from 4 WU to 2 WU may be just as meaningful as a signal of treatment effect as a fall from 10 WU to 8 WU. In addition, a priori it is not known which range of disease severity may be most likely to respond, so restricting enrollment to only the higher range of PVR may both needlessly complicate feasibility, while risking missing a meaningful

signal of effect. The rationale for restricting to more ill patients may nonetheless be compelling if the therapy has substantial risk of serious toxicity, where risk/benefit in the milder population may seem doubtful.

The main concern with use of PVR as primary endpoint is the expense and invasiveness of performing serial RHCs. In addition, a time frame for the repeat RHC must be somewhat arbitrarily chosen, which can either make the trial last longer than necessary if PVR falls quickly or miss a successful result if performed too soon. Calculation of PVR also requires accurate measurement of cardiac output, mPAP, and pulmonary artery occlusion pressure, which can sometimes be challenging in multicenter studies.

PVR also has, thus far, not been viewed by regulatory agencies as an acceptable primary endpoint for a phase III study, since situations can be envisioned such as successful reduction in PVR combined with a decline in RV function, obviating clinical benefit. Accordingly, PVR or other surrogate endpoints are generally utilized in phase II trials as part of an array of endpoints searching for proof of concept and signals of efficacy, and as supportive secondary endpoints in phase III trials.

N terminal pro brain natriuretic peptide (NTproBNP)

Brain natriuretic peptide (BNP) levels are associated with prognosis in PAH; change in BNP levels further inform regarding improving or worsening patient prognosis.[31] However, BNP degrades fairly readily particularly if blood samples are not handled meticulously and is not suitable for multicenter clinical research studies where sending samples to a core lab for analysis is the norm. NTproBNP is superior in this regard, and there is good evidence for its value as a simple, cost-effective, robust marker of disease severity in PAH. Values <300 pg/mL are generally associated with excellent outcome, while values >1200 pg/mL are associated with a worse outcome. Several of the clinical trials resulting in approval of currently available PAH therapies included NTproBNP as a secondary endpoint, often with finding of reduction in values that then served as additional supportive evidence of efficacy. The utility of NTproBNP is unclear in these low-risk populations, as the ability to detect a meaningful change in an asymptomatic population may be difficult. Biochemical endpoints, such as NTproBNP, for clinical trials could help detect sub-clinical changes in hemodynamics or pathobiology; however, a more detailed understanding of biochemical changes in a low-risk population are needed.

Cardiopulmonary exercise testing

Patients with well-preserved 6MWD nonetheless usually have demonstrable limitations on cardiopulmonary exercise testing, including peak oxygen consumption, abnormalities in oxygen pulse, and elevation in VE/VC02 ratios. Though the history of using these tests as endpoints in multicenter clinical trials is checkered, this most likely reflected inconsistency in performance and interpretation across sites, and should be mitigated by systematic training protocols, use of a core lab for interpretation, and restriction to its use to expert centers.

Invasive cardiopulmonary exercise testing

The same concerns about variation in conduct and interpretation of invasive cardiopulmonary exercise testing apply, with the added element of need for interpretation of exercise hemodynamics. Nonetheless, this type of testing is becoming more widespread and more standardized, so that consideration of such testing as part of proof-of-concept trials in PAH is now reasonable. Resting hemodynamic measures will be available for serial comparison and the exercise measures, particularly the slope of the relationship between the mPAP and the cardiac output (mPAP/CO), may add ability to show improvement in earlier stage disease. Novel endpoints including parameters on non-invasive or invasive cardiopulmonary exercise testing may improve the ability to show change in less patients with less advanced pulmonary vascular disease.

Measures of RV function

Incorporation of imaging endpoints could help detect earlier changes in end organ damage by evaluating RV response to therapy. RV morphology and function can be assessed by echocardiography via RV diameter and area, RV/LV size ratio, eccentricity index, tricuspid annular plane systolic excursion (TAPSE), RV free wall strain, and other measures.[32] Cardiac magnetic resonance imaging (MRI) is also an excellent modality for assessing cardiac compensation in PAH. For patients with milder disease, the ability to show change may be more limited, but these measures also serve as safety parameters. For example, an investigational drug that has potential impact on cell proliferation and apoptosis that is hoped to improve the pulmonary vasculature may also have some potential for either beneficial or adverse effects on the right ventricle, so including such measures is helpful in understanding pleotropic effects of the drug.

Potential trial design in asymptomatic mild pulmonary vascular disease

Significant challenges are also present for study design in low-risk, rare patient populations such as mild PAH. The inherent difficulties in diagnosing asymptomatic patients with mild disease hold true including the current inability to identify which patients may progress and which will remain stable over time. The requirements of large sample size and long-term follow up (due to low event rates) may make associated costs prohibitive. As such, alternative clinical trial designs may help overcome these limitations, these have been discussed in detail previously.[33] To enhance our

early understanding of therapeutic benefits in mild PAH, the initial target populations may be those known to be at risk for developing more advanced PAH such as scleroderma or patients with known causative genetic mutations. This would allow identification of a population at higher risk of progression to clinically overt disease.

Patient population heterogeneity is a significant issue in studying PAH that permeates trials across all WHO groups of disease. In this patient population, a precision medicine approach could involve molecular phenotyping to allow identification of potential therapeutic responders. Promising examples of this include identification of calcium channel blockers on the basis of peripheral blood RNA expression profiles and ET-1 pathway polymorphisms associated with response to endothelin receptor antagonists.[34,35] However, a priori identification of likely responders is not currently a part of clinical practice.

Non-traditional trial designs may help delineate effective therapies for mild PAH patients (Fig. 2). Factorial designs allow multiple therapeutics and hypotheses to be tested concurrently, although there is a need to account for possible drug interactions. An example of this would be similar to the Ambition trial (Fig. 3a). Difficulty in recruiting patients is a significant consideration for factorial trial design, given the need for larger numbers when compared to crossover trial. A randomized discontinuation trial (RDT) is one such design that allows for evaluation therapies with the ability to initially weed out those with adverse reactions and non-adherence. A RDT has two phases: initially all patients are treated with a therapy, then those who are stable or have no progression are randomized to placebo or study drug; additionally, those who initially responded are able to continue the drug. This design helps identify patients with the greatest benefit potential and eliminate those with early adverse reactions and poor adherence.[36] This type of trial requires 20–50% sample size of a traditional randomized controlled clinical trial, which is helpful in studying a low prevalence disease. However, the possibility of carry-over effects is a limitation in this design.

A multi-phase crossover trial also allows for small test population with patients acting as their own controls, receiving the therapy and placebo in succession. This design would be of potential value when the endpoint is biochemical or physiologic and expect to change relatively quickly such as NTproBNP, but is also limited by carry-over effects. The N-of-1 trial is an alternative as well, trying multiple different treatments over a period of time in an individual patient. However, this is problematic in overt PAH given the short-term morbidity and mortality as this design requires repeated, time-consuming drug challenges. The use of N-of-1 trial design in asymptomatic mild PAH is not reasonable given this is a low-risk population; specifically, there would be difficulty measuring drug effect in an already asymptomatic patient. There is also the risk of presuming efficacy in patients that maintain stability when, in reality, this patient would not have progressed without therapy either over the trial period.

Consider a phase II PAH trial that proposes to utilize 6MWD as the primary endpoint. Traditionally, this trial would need to exclude patients with a preserved 6MWD, e.g. >500 m. An alternative approach would be to utilize a different primary endpoint for patients with a walk distance above the cutoff (Fig. 3b). These patients could be studied utilizing cardiopulmonary exercise testing, with an endpoint such as VO_2 max or VE/VCO_2 ratio, which may be more sensitive to change in less advanced disease. Alternatively,

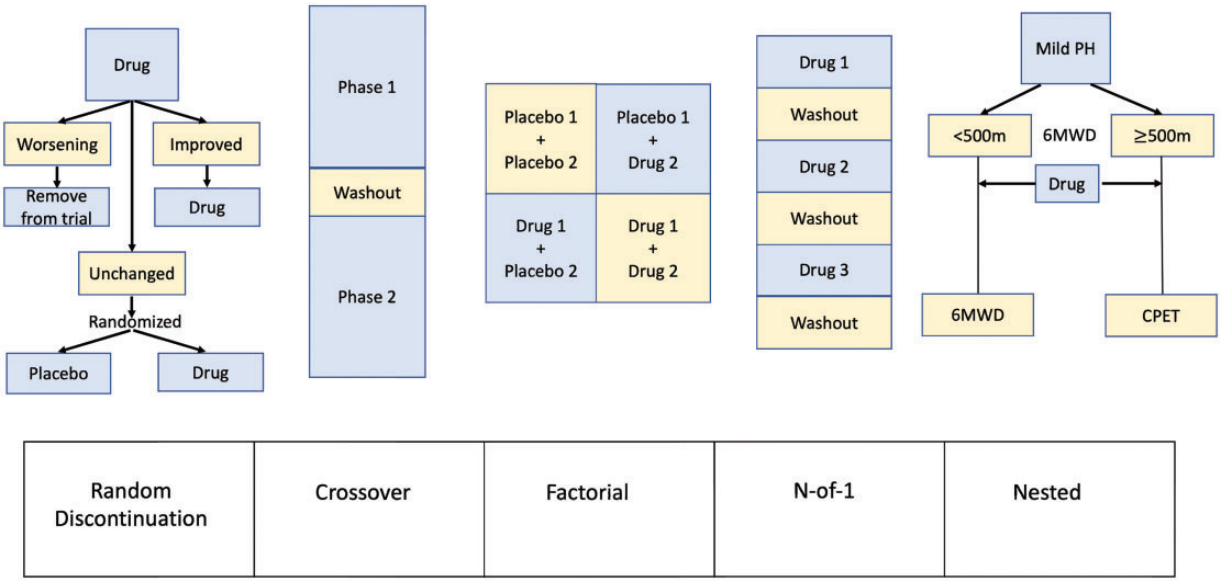

Fig. 2. Schematic of alternative trial designs. Different potential trial designs in pulmonary hypertension include Random Discontinuation, Crossover, Factorial, N-of-1, and Nested. 6MWD, 6-min walk distance.

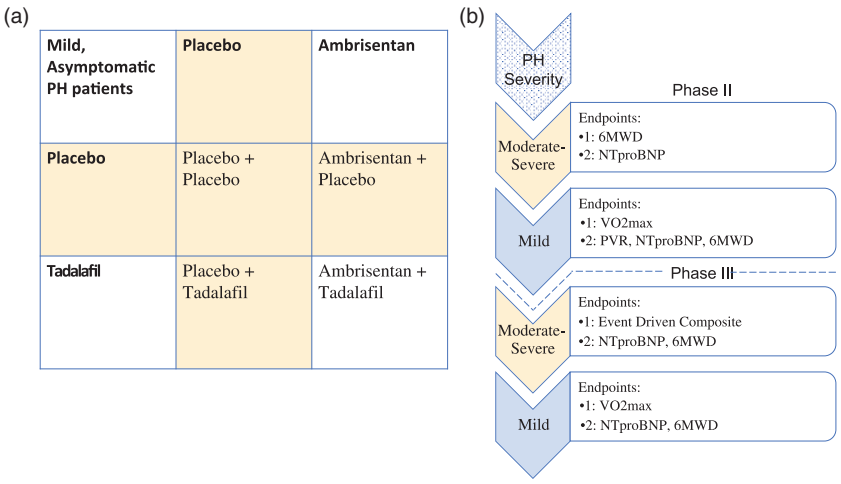

Fig. 3. Examples of alternative trial designs in mild PH. (a) Schematic of a factorial trial design in mild PH testing tadalafil and ambrisentan in a two-factor design. (b) Schematic of a Nested Design of a phase II and phase III PAH trial. Primary endpoint differs depending on disease severity at study entry. NTproBNP, N terminal pro brain natriuretic peptide; PVR, pulmonary vascular resistance; 1°, primary; 2°, secondary.

PVR could be utilized. These are examples of nested or embedded trial design. This approach could be cost-effective, since a large proportion of screened patients would be eligible, and the 6MWD as endpoint for the more advanced patients is inexpensive. At the same time, the less advanced patients would contribute the differing endpoint, which, if positive, further strengthens support for the proof of concept testing and also helps inform phase III trial design. It can be argued that using cardiopulmonary exercise testing as a primary endpoint for both mild and more advanced disease could be successful but may limit conduct of the trial to expert centers, making enrollment more challenging.

Nested trial design for phase III trials is also worthy of consideration. For example, a combined clinical endpoint could include a measure of improvement in cardiopulmonary exercise testing as an optional component that would be performed only at expert centers, either in all individuals able to do so, or only in the milder disease cohort (Fig. 3b). Participants improving VO_2max by a prespecified amount would be considered to have met a suitable component of the composite endpoint and could exit into the extension trial onto a known active drug.

Summary

The rationale for inclusion of asymptomatic patients in clinical trials for rare diseases such as PAH rests on four critical pillars: (1) mildly symptomatic PAH often reflects worrisome pulmonary vascular pathology; (2) potential outcome measures relevant to such patients are now available; (3) innovative concepts in trial design are now available and appear feasible; and (4) the range of potential therapies is growing, necessitating more efficient trial design.

Accordingly, the time is now to move forward with innovative trials that include earlier stages of pulmonary vascular disease.

Conflict of interest

The author(s) declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Hatano S, Strasser T and World Health Organization. Primary pulmonary hypertension: report on a WHO meeting, Geneva, 15–17 October 1973. Geneva: WHO, 1975.
2. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint 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: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J* 2015; 46: 903–975.
3. Kovacs G, Berghold A, Scheidl S, et al. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J* 2009; 34: 888–894.
4. Gladwin MT, Sachdev V, Jison ML, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *N Engl J Med* 2004; 350: 886–895.
5. Valerio CJ, Schreiber BE, Handler CE, et al. Borderline mean pulmonary artery pressure in patients with systemic sclerosis: transpulmonary gradient predicts risk of developing pulmonary hypertension. *Arthritis Rheum* 2013; 65: 1074–1084.
6. Brittain EL, Duncan MS, Chang J, et al. Increased echocardiographic pulmonary pressure in hiv-infected and uninfected individuals in the veterans aging cohort study. *Am J Respir Crit Care Med* 2018; 197: 923–932.
7. Miller WL, Grill DE and Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary

hypertension and heart failure. *JACC Heart Fail* 2013; 1: 290–299.
8. Burrows B, Kettel LJ, Niden AH, et al. Patterns of cardiovascular dysfunction in chronic obstructive lung disease. *N Engl J Med* 1972; 286: 912–918.
9. Kessler R, Faller M, Weitzenblum E, et al. ''Natural history'' of pulmonary hypertension in a series of 131 patients with chronic obstructive lung disease. *Am J Respir Crit Care Med* 2001; 164: 219–224.
10. Kimura M, Taniguchi H, Kondoh Y, et al. Pulmonary hypertension as a prognostic indicator at the initial evaluation in idiopathic pulmonary fibrosis. *Respiration* 2013; 85: 456–463.
11. Maron BA, Hess E, Maddox TM, et al. Association of borderline pulmonary hypertension with mortality and hospitalization in a large patient cohort: insights from the Veterans Affairs Clinical Assessment, Reporting, and Tracking Program. *Circulation* 2016; 133: 1240–1248.
12. Assad TR, Maron BA, Robbins IM, et al. Prognostic effect and longitudinal hemodynamic assessment of borderline pulmonary hypertension. *JAMA Cardiol* 2017; 2: 1361–1368.
13. Douschan P, Kovacs G, Avian A, et al. Mild elevation of pulmonary arterial pressure as a predictor of mortality. *Am J Respir Crit Care Med* 2018; 197: 509–516.
14. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; 28: 1–39.e14.
15. Rich JD, Shah SJ, Swamy RS, et al. Inaccuracy of Doppler echocardiographic estimates of pulmonary artery pressures in patients with pulmonary hypertension: implications for clinical practice. *Chest* 2011; 139: 988–993.
16. O'Leary JM, Assad TR, Xu M, et al. Lack of a tricuspid regurgitation Doppler signal and pulmonary hypertension by invasive measurement. *J Am Heart Assoc* 2018; 7: e009362.
17. Brittain EL, Duncan MS, Chang J, et al. Increased echocardiographic pulmonary pressure in HIV-infected and -uninfected individuals in the Veterans Aging Cohort Study. *Am J Respir Crit Care Med* 2018; 197: 923–932.
18. Huston JH, Huang S, Assad TR, et al. Abstract 15765: Echocardiographic pulmonary arterial pressure estimates and mortality: evidence of increased risk at ''normal'' values. *Circulation* 2017; 136: A15765.
19. Kolte D, Lakshmanan S, Jankowich MD, et al. Mild pulmonary hypertension is associated with increased mortality: a systematic review and meta-analysis. *J Am Heart Assoc* 2018; 7: e009729.
20. Galie N, McLaughlin VV, Rubin LJ, et al. An overview of the 6th World Symposium on Pulmonary Hypertension. *Eur Respir J* 2019; 53: 1802148.
21. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019; 53: 1801913.
22. Humbert M, Yaici A, de Groote P, et al. Screening for pulmonary arterial hypertension in patients with systemic sclerosis: clinical characteristics at diagnosis and long-term survival. *Arthritis Rheum* 2011; 63: 3522–3530.
23. Kovacs G, Maier R, Aberer E, et al. Pulmonary arterial hypertension therapy may be safe and effective in patients with systemic sclerosis and borderline pulmonary artery pressure. *Arthritis Rheum* 2012; 64: 1257–1262.
24. Segrera SA, Lawler L, Opotowsky AR, et al. Open label study of ambrisentan in patients with exercise pulmonary hypertension. *Pulm Circ* 2017; 7: 531–538.
25. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018; 71: e127–e248.
26. Rare Diseases: Common Issues in Drug Development, Guidance for Industry. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM629579.pdf (accessed 10 April 2019).
27. Strange G, Gabbay E, Kermeen F, et al. Time from symptoms to definitive diagnosis of idiopathic pulmonary arterial hypertension: The delay study. *Pulm Circ* 2013; 3: 89–94.
28. Lau EM, Manes A, Celermajer DS, et al. Early detection of pulmonary vascular disease in pulmonary arterial hypertension: time to move forward. *Eur Heart J* 2011; 32: 2489–2498.
29. Grunig E, Maier F, Ehlken N, et al. Exercise training in pulmonary arterial hypertension associated with connective tissue diseases. *Arthritis Res Ther* 2012; 14: R148.
30. Savarese G, Paolillo S, Costanzo P, et al. Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? A meta-analysis of 22 randomized trials. *J Am Coll Cardiol* 2012; 60: 1192–1201.
31. Frantz RP, Farber HW, Badesch DB, et al. Baseline and serial brain natriuretic peptide level predicts 5-year overall survival in patients with pulmonary arterial hypertension: data from the REVEAL Registry. *Chest* 2018; 154: 126–135.
32. Simon MA, Rajagopalan N, Mathier MA, et al. Tissue Doppler imaging of right ventricular decompensation in pulmonary hypertension. *Congest Heart Fail* 2009; 15: 271–276.
33. Ryan JJ, Rich JD and Maron BA. Building the case for novel clinical trials in pulmonary arterial hypertension. *Circ Cardiovasc Qual Outcomes* 2015; 8: 114–123.
34. Hemnes AR, Trammell AW, Archer SL, et al. Peripheral blood signature of vasodilator-responsive pulmonary arterial hypertension. *Circulation* 2015; 131: 401–409; discussion 409.
35. Benza RL, Gomberg-Maitland M, Demarco T, et al. Endothelin-1 pathway polymorphisms and outcomes in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2015; 192: 1345–1354.
36. Kopec JA, Abrahamowicz M and Esdaile JM. Randomized discontinuation trials: utility and efficiency. *J Clin Epidemiol* 1993; 46: 959–971.