Diagnosis and Assessment of Pulmonary Arterial Hypertension

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The diagnosis and assessment of pulmonary arterial hypertension is a rapidly evolving area, with changes occurring in the definition of the disease, screening and diagnostic techniques, and staging and follow-up assessment. The definition of pulmonary hypertension has been simplified, and is now based on currently available evidence. There has been substantial progress in advancing the imaging techniques and biomarkers used to screen patients for the disease and to follow up their response to therapy. The importance of accurate assessment of right ventricular function in following up the clinical course and response to therapy is more fully appreciated. As new therapies are developed for pulmonary arterial hypertension, screening, prompt diagnosis, and accurate assessment of disease severity become increasingly important. A clear definition of pulmonary hypertension and the development of a rational approach to diagnostic assessment and follow-up using both conventional and new tools will be essential to deriving maximal benefit from our expanding therapeutic armamentarium.

Definition of Pulmonary Hypertension (PH)

PH has been defined as a resting mean pulmonary arterial pressure (mPAP) >25 mm Hg, or an mPAP with exercise >30 mm Hg. The subgroup of PH known as pulmonary arterial hypertension (PAH) adds the criterion that the pulmonary arterial wedge pressure must be ≤15 mm Hg. Some definitions have also included pulmonary vascular resistance (PVR), requiring that it be ≥2 or 3 Wood units. Potential weaknesses of the current definition include the fact that the level, type, and posture of exercise have not been specified. Furthermore, the normal exercise pulmonary arterial pressure (PAP) varies with age (1).

Clarification of the definition based on available evidence was an important initial objective of the 4th World Symposium on Pulmonary Hypertension, which took place in Dana Point, California, in early 2008. Members of the Working Group on Diagnosis and Assessment of PAH reviewed the literature and identified 47 studies describing 72 populations of healthy volunteers that were examined for PAH during rest and physical exercise (2–51). Normal resting mPAP was approximately 14 ± 3.3 mm Hg. The upper limit of normal (ULN) was approximately 20.6 mm Hg. During slight exercise (heart rate [HR] 100 to 110 beats/min), the ULN for mPAP was 32 (supine) and 30 mm Hg (upright). During submaximal exercise (HR 130 to 135 beats/min), the ULN was 31 (supine) and 35 mm Hg (upright), and during maximal exercise (HR 160 beats/min), it was 37 (supine) and 35 mm Hg (upright). If only studies were considered that strictly excluded exercise-induced hypertension, the data were not significantly different (1).

According to age group, there were only minor differences in PAP at rest; however, during slight and submaximal exercise, mPAP was significantly higher in older subjects (>50 years old). During slight exercise, the ULN was 29 and 30 mm Hg for people age <30 and 30 to 50 years,
respective, whereas for those age >50 years, the ULN was 45 mm Hg. During submaximal exercise, the ULN for subjects age <30, 30 to 50, and >50 years were 33, 36, and 47 mm Hg, respectively.

**Recommendations.** Based on this literature review, we recommend simplifying the definition of PH, as follows:

- The exercise and PVR criteria should be eliminated.
- A resting mPAP of 8 to 20 mm Hg should be considered normal, based on available evidence.
- The proposed new definition of PH is a resting mPAP ≥25 mm Hg.

Further studies are needed to better determine the natural history of patients with mPAP 21 to 24 mm Hg.

**Screening and Diagnosis**

**Noninvasive estimation of PAP—echocardiography.** With the introduction of Doppler echocardiography, approximate evaluation of PAP became feasible. Although this method is helpful in detecting or excluding significant PH, its intrinsic and operator-dependent limitations make early PH diagnosis and screening challenging (52,53). In the presence of a tricuspid insufficiency peak gradient (TIPG) ≥30 mm Hg, some investigators have used arbitrary criteria for noninvasive diagnosis of PH (54). During a meeting on PH held in Evian, France, in 1998, mild PH was arbitrarily defined as a tricuspid jet velocity (TJV) 2.8 to 3.4 m/s, which corresponds to TIPG 31 to 46 mm Hg and to PAP 36 to 51 mm Hg, if a fixed right atrial pressure (RAP) estimate of 5 mm Hg is used (55). It seems reasonable to consider TJV >2.8 m/s and TIPG ≥31 mm Hg at rest as elevated, except in elderly and/or very obese patients (56) (Table 1).

Two large French studies have attempted prospective verification of abnormal echocardiographic results, both taking into account the presence of dyspnea. The ItinerAIR study (57) enrolled 599 patients with scleroderma. In patients with TJV >3.0 or with dyspnea and TJV 2.5 to 3.0 m/s, right heart catheterization (RHC) was performed, regardless of symptoms. Among the 33 patients who met those criteria, 14 had mild to moderate PH on RHC at rest, and an additional 4 developed mPAP >30 mm Hg at exercise. These results were compatible with the 45% false-positive results seen with echo-Doppler screening. The second trial assessed the prevalence of PH in patients with human immunodeficiency virus infection (58); 10% of patients presented with dyspnea, and 247 were included in the screening program and were eligible for echocardiography. Among 18 patients with TJV >2.5 m/s, only 5 were found to have PAH on RHC. The results should be interpreted with caution because the sensitivity of echocardiography for the detection of PH in this setting is not known.

Doppler echocardiography may be performed during exercise to estimate PAP. One report found an excellent correlation with catheter measurements of PAP performed simultaneously (r = 0.98) (59). Exercise echocardiography has been used to assess systolic PAP >40 mm Hg in several groups of patients (60), including those with chronic lung disease, heart transplantation (61), atrial septal defect (62), and susceptibility to high-altitude lung edema (63), as well as asymptomatic carriers of a PH gene mutation (60). In all groups, PAP significantly increased during exercise compared with control subjects (63). One group has arbitrarily defined systolic PAP <40 mm Hg, calculated after assuming fixed RAP of 5 mm Hg, as a normal hemodynamic response to exercise (60). A multicenter trial that used exercise echocardiography to assess genetic predisposition to PH among family members of index patients with idiopathic pulmonary arterial hypertension (IPAH) found more pronounced rise of Doppler-derived systolic PAP in family members compared with healthy control subjects (64).

**New modalities in noninvasive screening.** Cardiac magnetic resonance (CMR) may offer more reliable data both at rest and during exercise or acute vasodilator testing, but so far it cannot be used as a screening test. Biomarkers, such as

<table>
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<tr>
<th>Table 1</th>
<th>Reference Ranges for Normal Systolic Pressure Gradients Assessed With Doppler Between RV and RA (TIPG)</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>n</td>
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<tr>
<td>&lt;20</td>
<td>856</td>
</tr>
<tr>
<td>20–29</td>
<td>669</td>
</tr>
<tr>
<td>30–39</td>
<td>650</td>
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<tr>
<td>40–49</td>
<td>494</td>
</tr>
<tr>
<td>50–59</td>
<td>344</td>
</tr>
<tr>
<td>≥60</td>
<td>199</td>
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</table>

Data have been extracted from a table in McQuillan et al. (56) and used with permission.

CI = confidence interval; RA = right atrium; RV = right ventricle; TIPG = tricuspid insufficiency peak gradient.
brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP), may be useful in early detection of PAH. In an otherwise healthy, young, and mildly symptomatic person with borderline echocardiographic results, elevated BNP levels may justify follow-up.

**Prevalence and characteristics of PH in selected associated conditions.** The prevalence of PAH varies substantially depending on the type, etiology, and underlying condition. Table 2 is a summary of the best available data from a variety of sources (57,65–95).

**Genetic assessment and counseling.** Genetic testing is discussed in another section of this supplement (95). When testing and counseling are performed for genetic mutations, they should be done as part of a comprehensive program that includes discussion of the risks, benefits, and limitations of the test results. When used for genetic testing and counseling, molecular testing for the mutation should be performed only in a clinically approved and certified molecular genetics laboratory.

**Staging and Follow-Up Assessment**

**Prognostic parameters.** Although the tools used to diagnose and assess patients with PAH have improved, the number and complexity of therapeutic interventions have increased, making it even more challenging to accurately predict prognosis. The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on PAH, published in 2004, provide an excellent review of prognosis in PAH (96). Following is an update to that review.

**Survival in PAH. Historical perspective.** The natural history of IPAH was described in the National Institutes of Health (NIH) registry, which followed up 194 patients

### Table 2: Prevalence and Characteristics of PH in Associated Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>PAH</td>
<td>15/million (65)</td>
</tr>
<tr>
<td>IPAH</td>
<td>5.9/million (65)</td>
</tr>
<tr>
<td>FPAH</td>
<td>Vanderbilt: 107 U.S. families (300 PAH patients among 2,300 individuals; includes 1 kindred with 19 women and 2 men)</td>
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<td></td>
<td>(James Loyd, MD, personal communication, February 2008)</td>
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<tr>
<td></td>
<td>Columbia: 100 U.S. families (353 PAH patients among 3,400 individuals) (personal communication from Robyn J. Barst, MD on behalf of Jane Morse, MD [deceased], February 2008)</td>
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<tr>
<td></td>
<td>Utah: 28 U.S. families (C. Gregory Elliott, MD, personal communication, February 2008)</td>
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<tr>
<td></td>
<td>Possible overlap between registries</td>
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<tr>
<td>APAH–scleroderma</td>
<td>Prospective echocardiographic study of scleroderma and MCTD in 50 U.S. community practices: prevalence of PH (estimated RVSP &gt; 40 mm Hg) of combined previously screened and unscreened patients = 26.7% (66).</td>
</tr>
<tr>
<td></td>
<td>8 Canadian CTD centers: PH detected on echocardiography (RVSP &gt; 30 or 35 mm Hg depending on center) in 21% of limited and 26% of diffuse scleroderma patients (67).</td>
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<td>Prospective study in French registry, 599 scleroderma patients without severe lung dysfunction: 29 had known PH, 33 more suspected by echocardiography (VTR &gt; 3.0 m/s or &gt; 2.5 m/s with unexplained dyspnea); 18 of 33 had PAH (mPAP 30 ± 9 mm Hg) on RHC. Thus, 47 of 599 (8%) had confirmed PAH. Patients with known PH had mPAP 49 ± 17 (67).</td>
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<td>18.3% (36 of 97) moderate–severe PH suspected in patients who had screening echocardiography (retrospective); confirmed by RHC in 89% (68); PH in 12 of 67 (17.9%) patients without ILD vs. 24 of 110 (21.8%) patients with ILD (69).</td>
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<tr>
<td>Portopulmonary hypertension</td>
<td>PH in 1% to 6% of patients with portal hypertension (70–72).</td>
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<td>8.2% (101 of 1,233) of candidates for OLT had echocardiographic RVSP &gt; 50 mm Hg; of these 90 had RHC mPAP &gt; 25 mm Hg; of these 66 had PAH (others had PH explained by high cardiac output or PAWP), so prevalence of PAH in OLT candidates is 66 of 1,235 (5.3%) (73).</td>
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<tr>
<td>Sickle cell disease</td>
<td>32% of sickle cell patients have TRV ≥ 2.5 m/s and 9% ≥ 3.0 m/s (80,81,95).</td>
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<td>Further hemodynamic studies may be necessary to better characterize pulmonary hypertension in sickle cell disease.</td>
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<tr>
<td>Thyroid diseases</td>
<td>PH can be detected in up to 41% of patients with hypothyroidism (82) and 49% of those with hypothyroidism (83), and usually responds to treatment of the thyroid disease (84,85).</td>
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<tr>
<td>Schistosomiasis</td>
<td>20.6% of 34 patients with S. mansoni portal hypertension had mPAP &gt; 20 mm Hg (11.8% &gt; 25 mm Hg) (86).</td>
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<td>In an endemic area of Brazil, those with PH by echocardiography had a higher prevalence of S. mansoni (80%) than those without PH (69%) (25% of the screened population of 246 people had PH by the echocardiographic criteria) (87).</td>
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<td>In 2 Brazilian PH centers, 30% of 123 cases were associated with schistosomiasis (50% IPAH and 10% CTD) (88).</td>
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<tr>
<td>Myeloproliferative disorders</td>
<td>Literature does not provide meaningful data (89,90).</td>
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<tr>
<td>Post-splenectomy</td>
<td>11.5% of IPAH patients have had splenectomy (91).</td>
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<td></td>
<td>8.6% of CTEPH patients have had splenectomy (vs. 2.5% among IPAH patients in this study) (92).</td>
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In CTD patients who are newly screened with echocardiography, the degree of PAH, if present, detected at RHC is usually mild, and the future course is unknown. Based on estimated prevalence of scleroderma 210 to 276/million (68) and U.S. population of 302 million, the number of scleroderma cases is 250 × 302 = 75,500, so approximately 7,550 (10%) people would be expected to have PAH by right heart catheterization criteria. In African Americans, 0.15% have sickle cell disease (homozygotes) and 8% have sickle cell trait (heterozygotes).

**IPAH** = associated pulmonary hypertension; **CTD** = connective tissue disease; **CTEPH** = chronic thromboembolic pulmonary hypertension; **IPAH** = familial pulmonary arterial hypertension; **mPAP** = mean pulmonary arterial pressure; **PH** = pulmonary hypertension; **RHC** = right heart catheterization; **RV** = right ventricular; **RVSP** = right ventricular systolic pressure; **TRV** = tricuspid regurgitation velocity; **VTR** = peak velocity of tricuspid regurgitation.
enrolled at 32 centers from 1981 to 1985 (97). The estimated median survival was 2.8 years, with 1-, 3-, and 5-year survival rates of 68%, 48%, and 34%, respectively. Survival in associated PAH has also been evaluated. Stupi et al. (98) reported a 2-year survival of 40% among patients with scleroderma and isolated PAH. Several series have suggested that patients with scleroderma-associated PAH have a worse prognosis than those with IPAH, with hazard ratios for death ranging from 2.32 to 2.9 (99,100). In contrast, patients with PAH occurring in association with congenital heart disease have a better prognosis. Hopkins et al. (101) described an actuarial survival in patients with Eisenmenger syndrome who did not receive transplantation of 97%, 89%, and 77% at 1, 2, and 3 years, respectively, compared with 77%, 69%, and 35% at 1, 2, and 3 years for patients with IPAH. A national registry in France showed a 1-year survival rate in PAH of 88% in the incident cohort (65).

**THE IMPACT OF MEDICAL THERAPY.** An open-label, randomized controlled trial (RCT) involving 81 IPAH patients showed a survival advantage with epoprostenol therapy over a period of 12 weeks (102). Subsequent longer-term case series have compared survival on epoprostenol therapy with historical control subjects or with predictions based on an equation described in the NIH registry study discussed above (97). Shapiro et al. (103) reported 1-, 2-, and 3-year survival rates in IPAH patients treated with epoprostenol of 80%, 76%, and 49%, respectively. Sitbon et al. (104) followed up 178 patients and reported survival rates at 1, 2, 3, and 5 years of 85%, 70%, 63%, and 55%. McLaughlin et al. (105) reported on 162 patients with IPAH treated with epoprostenol. Observed survival rates at 1, 2, 3, 4, and 5 years were 88%, 76%, 63%, 56%, and 47%, respectively. A recent meta-analysis of RCTs in PAH, conducted by Galie et al. (106), suggested that active treatments were associated with a reduction in mortality of 43% (relative risk: 0.57; 95% confidence interval: 0.35 to 0.92; p = 0.023).

The effects of anticoagulant therapy on survival in patients with IPAH have been evaluated in 2 studies. Foster et al. (107) reported an apparent survival benefit of warfarin in a retrospective, uncontrolled, single-center study of 120 patients. Rich et al. (108) described a better outcome among patients treated with warfarin who were not calcium-channel blocker responders. The 1-, 3-, and 5-year survival rates in patients treated with warfarin were 91%, 62%, and 47%, respectively, compared with 52%, 31%, and 31% in those not treated with warfarin.

McLaughlin et al. (109) reported that first-line therapy with bosentan, with the subsequent addition of or transition to other therapy as necessary, resulted in Kaplan-Meier survival estimates of 96% at 12 months and 89% at 24 months, compared with predicted survival rates from the NIH registry formula of 69% and 57%, respectively. Sitbon et al. (110) compared survival in patients with WHO (World Health Organization) functional class (FC) III IPAH treated with bosentan with historical data from similar patients treated with epoprostenol. Kaplan-Meier survival estimates at 1 and 2 years were 97% and 91%, respectively, in the bosentan cohort, and 91% and 84% in the epoprostenol cohort.

**Testing to predict prognosis in PAH.** Hemodynamics. The NIH registry (97) suggested that 3 hemodynamic variables were associated with increased risk of death: increased PAP, increased RAP, and decreased cardiac index. Sandoval et al. (111) reported on 61 IPAH patients and found that increased mean RAP, decreased cardiac index, and decreased mixed venous oxygen saturation were predictive of survival. Other studies evaluated prediction of survival in IPAH based on hemodynamics (112–115). With 1 exception (112), lower cardiac output (CO) or cardiac index seems to have been predictive. The prognostic value of baseline hemodynamics may be impacted by epoprostenol therapy. Sitbon et al. (104) found that lower mPAP and higher mean RAP had negative prognostic implications by univariate analysis, whereas only mean RAP was predictive by multivariate analysis. In 162 patients with IPAH treated with epoprostenol, McLaughlin et al. (105) found that only mean RAP was predictive of survival in a univariate analysis.

**Response to acute vasodilator therapy.** Sitbon et al. (116) reported the results of a retrospective analysis of 557 IPAH patients tested acutely with intravenous epoprostenol or inhaled nitric oxide. Using a definition of a ≥20% decrease in mean PAP and PVR, only 70 patients (12.6%) showed vasoreactivity. Long-term calcium channel blocker responders were defined as patients in New York Heart Association (NYHA) FC I or II with sustained hemodynamic improvement after at least 1 year without the addition of other PAH-specific therapy. Of the 70 patients showing acute vasoreactivity, only 38 (6.8% of the overall study group) had a favorable long-term response to calcium-channel blocker therapy.

**Echocardiography.** An early study of patients with IPAH in the late 1980s showed the severity of pericardial effusion to be predictive (117). Hinderliter et al. (118) analyzed the echocardiograms of 79 of 81 IPAH patients who participated in an RCT of epoprostenol (102) and found pericardial effusions in 43 patients. Larger effusions correlated with more severely impaired exercise performance and right atrial (RA) dilation. Effusion size was correlated with death or a composite of death or lung transplantation at 1 year. Longer follow-up showed that the presence of a pericardial effusion and RA area index were predictive of survival (119). A series of 53 IPAH patients showed the value of the right ventricular (RV) index (120). These studies suggest that pericardial effusion, indexed RA area, and RV index have prognostic value.

More recent studies have suggested that novel echocardiographic parameters might be of value. Forfia et al. (121) reported that tricuspid annular plane systolic excursion (TAPSE) predicted survival in PH. In a cohort of 63 patients with PH, a TAPSE <1.8 cm was associated with
greater RV systolic dysfunction. In patients with PAH (n = 47), survival estimates at 1 and 2 years were 94% and 88%, respectively, in subjects with a TAPSE ≥1.8 cm, and 60% and 50%, respectively, in subjects with a TAPSE <1.8 cm. Gurudevan et al. (122) reported that in 50 patients with suspected chronic thromboembolic PH, the systolic velocity of the tricuspid annulus had an inverse relationship with mPAP and PVR. Mahapatra et al. (123) found that a measure of pulmonary vascular capacitance, as determined by Doppler echocardiography, is a predictor of mortality in patients with IPAH and adds prognostic value to conventional risk markers.

**EXERCISE CAPACITY.** Measurements of exercise capacity in PAH have generally included 6-min walk distance (6MWD) and bicycle ergometry cardiopulmonary exercise testing (CPET). Miyamoto et al. (124) compared these measures in 27 patients with IPAH and found good correlation between maximum oxygen consumption and 6MWD. The 6MWD is simpler to perform and reproducible. Barst et al. (102) used 6MWD as the primary outcome measure in an RCT of chronic epoprostenol therapy in 81 patients with IPAH. The 6MWD was less in the nonsurvivors versus the survivors from both treatment groups, and it was found to be an independent predictor of survival. Miyamoto et al. (124) studied 43 patients with IPAH. Patients walking fewer than 332 m had a significantly lower survival rate than those walking farther than 332 m. In a study of long-term intravenous epoprostenol therapy in patients with IPAH, Sitbon et al. (104) reported that a 6MWD of ≤250 m was associated with a poor outcome. Humbert et al. (65) reported the results of a French registry on PH, showing that the 6MWD correlates with NYHA FC in all forms of PAH. A number of important studies in PAH have used the 6MWD as the primary outcome measure (102,125–132) or an important part of the primary end point (133). Wensel et al. (134) studied 86 patients with IPAH, 70 of whom were able to undergo CPET, and found that maximum oxygen consumption was an independent predictor of survival.

**FC.** In the NIH registry of patients with IPAH (before modern therapy), the risk of death was higher among patients in NYHA FC III or IV than among those in FC I or II (97). Median survival was nearly 6 years among those in NYHA FC I or II, 2.5 years among those in FC III, and 6 months among those in FC IV. A study of 91 patients with PAH, all treated with epoprostenol, showed that patients in WHO FC IV, compared with FC I, II, and III, had a significantly decreased survival (99). In a study of 178 patients with IPAH treated with epoprostenol, Sitbon et al. (104) reported that survival was lower for those starting therapy in NYHA FC IV compared with FC III, and that the persistence of FC III or IV after 3 months of therapy was associated with poor survival.

**Biomarkers—BNP.** Nagaya et al. (135) measured BNP in 60 patients with IPAH at diagnostic catheterization, together with atrial natriuretic peptide, norepinephrine, and epinephrine. According to multivariate analysis, baseline plasma BNP was an independent predictor of mortality. Patients with a supramedian baseline BNP (≥150 pg/ml) had a significantly lower survival rate than those with an inframedian level, according to Kaplan-Meier survival curves (p < 0.05). The BNP in survivors decreased significantly during the follow-up (217 ± 38 pg/ml to 149 ± 30 pg/ml, p < 0.05), whereas that in nonsurvivors increased (365 ± 77 pg/ml to 544 ± 68 pg/ml, p < 0.05).

Fijalkowska et al. (136) found that NT-proBNP levels correlated with 6MWD, cardiac index, PVR, and RAP, but not with PAP in 55 patients. The NT-proBNP levels were also related to the ratio of the diastolic area of the RV and left ventricle (LV) and to pericardial effusion during echocardiography.

Williams et al. (137) evaluated NT-proBNP, 6MWD, hemodynamics or tricuspid gradient, and survival in 109 patients with systemic sclerosis (SSc). Sixty-eight subjects had PAH, and 41 did not. In patients with normal PAP, 1-year survival was 100%, compared with 83.5% in those with SSc-PAH (p < 0.05). Patients without PAH had a mean NT-proBNP level of 139 pg/ml; those with SSc-PAH had a significantly higher mean NT-proBNP level of 1,474 pg/ml (p = 0.0002). Among patients with PAH, for every order of magnitude increase in NT-proBNP level, there was a 4-fold increased risk of death (p = 0.002 for baseline level and p = 0.006 for follow-up level). Baseline NT-proBNP levels correlated positively with mPAP and PVR and inversely with 6MWD.

Andreassen et al. (138) assessed plasma NT-proBNP in 61 consecutive patients with pre-capillary PH. Compared with age-matched control subjects (n = 10), NT-proBNP was significantly greater in those with IPAH (n = 16), chronic pre-capillary PH associated with other diseases (n = 26), and chronic thromboembolic disease (n = 19), and was correlated with hemodynamic variables and functional capacity. In 17 medically treated patients, a significant decrease in NT-proBNP levels correlated with improved hemodynamics. Baseline NT-proBNP was an independent predictor of mortality.

Park et al. (139) examined BNP levels in 20 PAH patients as a marker of response to epoprostenol therapy. A decrease in BNP level of ≥50% during the first 3 months on epoprostenol was strongly predictive of event-free survival (p = 0.003).

**Summary of prognostic parameters.** A variety of disease characteristics and diagnostic measurements have been found to be predictive of prognosis in patients with PAH, including etiology, therapeutic interventions, hemodynamics (cardiac index and RAP), echocardiographic findings (pericardial effusion, RV-Tei index, TAPSE), exercise capacity (6MWD, peak oxygen consumption), NYHA FC, and BNP levels.
Follow-up assessment. The follow-up of patients with PAH has never been standardized, and has not been included in current guidelines (140–142). Two different follow-up strategies can be identified: a clinical strategy and a goal-oriented strategy. It is not known which strategy is superior.

CLINICAL STRATEGY. This strategy is based principally on the symptoms and signs reported on clinical examination. If the FC is considered satisfactory (WHO FC I and II) and no signs of right heart failure are detected, no changes in therapy are proposed (143). Noninvasive examinations can also be included—for example, electrocardiography, chest radiography, echocardiography, and 6MWD—but no pre-specified goals are considered, and results are used for confirming clinical stability or deterioration. In this case, the intervals between patient evaluations are variable, ranging from 3 to ≥6 months.

GOAL-ORIENTED STRATEGY. Goal-oriented therapy has been proposed to optimize treatment (144–146). The objective is to correct parameters considered prognostically relevant and to escalate treatment until a threshold is reached. Goal-oriented therapy requires: 1) identification of the parameters to be measured; 2) establishment of levels to be achieved for each parameter; and 3) intervals of assessments. In an example described by Hoeper (144), patients were assessed by 6MWD or CPET; goals were 6MWD >380 m, peak oxygen consumption >10.4 ml/min/kg, and peak systolic blood pressure >120 mm Hg during exercise; intervals were 3 to 6 months. Treatments were escalated to triple combination therapy if required. This strategy led to better survival compared with historical control subjects.

A similar strategy, but with different parameters and goals, has been used at the University of Bologna (146). Parameters considered relate to symptoms (World Health Organization FC), functional capacity (6MWD), and RV function as assessed by RHC. The goals are FC I or II, 6MWD ≥500 m in patients <50 years old and ≥380 m in older patients, with RAP ≤10 mm Hg, and cardiac index ≥2.5 l/min/m². Assessments are performed at baseline and after 3 to 4 months of first-line treatment. If the goals are reached, the patient is followed up at 3- to 4-month intervals with a noninvasive approach. In case of subsequent deterioration, hemodynamic confirmation is required. If the first-line treatment is not sufficient to reach the pre-specified goals, combination therapy is initiated and a subsequent evaluation is performed after 3 to 4 months. Noninvasive follow-up is carried out in cases of goal fulfillment. In cases with nonsatisfactory results, triple combination therapy is initiated and patients are considered for transplantation.

RV function in PAH. The usual cause of death in PAH is RV failure. Both diastolic (147,148) and systolic (148) dysfunction are likely contributors to RV failure. Diastolic RV dysfunction is thought to be related to RV hypertrophy and/or chronic pressure overload, with prolonged isovolumetric relaxation time (148,149) being a prominent feature. With systolic RV dysfunction, isovolumetric contraction time is prolonged and ejection time is shortened. An echocardiographic, Doppler-derived index of combined RV systolic and diastolic function correlates with symptoms (149) and seems to be a predictor of survival in patients with PAH (148). Evidence of advanced clinical disease in patients with PAH is apparent, with elevated jugular venous pressure, presence of a third heart sound (S3), and peripheral edema. Combined with increasing symptoms, decreased RV contractility, elevated RAP, and decreased CO, these findings suggest decompensated RV function.

It is difficult to assess the inotropic properties of prostanoids because of the strong vasodilative effects of these substances. Epoprostenol has a positive inotropic effect on the RV (150), but this may be caused by baroreflex activation. In isolated cardiomyocytes, treprostinil per se had no positive inotropic effects, but it significantly amplified the positive inotropic effects of catecholamines (151). This effect of prostanoids, along with inhibition of platelet aggregation and smooth muscle cell contraction and proliferation (152,153), may be in part responsible for its clinical benefit. A PAH treatment strategy based on measures that better reflect RV function may be superior to the traditional strategies outlined in consensus guidelines.

Future Directions

Treatment escalation. Exercise capacity. Aerobic exercise capacity in PAH may be largely dependent on maximum CO and on the maximum flow output of the RV. Gas exchange function of the lungs in PAH is often normal or near normal. Rest- and exercise-induced hypoxemia are caused by a decreased mixed venous oxygenation caused by low CO (154) or right-to-left intracardiac shunting. The 6MWD has served well as a primary end point in most of the RCTs of new therapies in PAH (140) and is a potent predictor of functional state and survival (104,105,124). Two important questions remain concerning exercise capacity in PAH: 1) What is the minimal change in 6MWD effectively perceived by the patients as improvement or deterioration? (In patients with chronic obstructive pulmonary disease it was 54 m [155].) 2) What is the contribution of respiratory and skeletal muscle weakness as well as joint, bone, neurological, and psychological factors to aerobic exercise capacity in PAH?

ECHOCARDIOGRAPHY. Echocardiography can be important in the evaluation of RV function. The most relevant measures are RV and LV surface areas, the eccentricity index on parasternal short axis views, the Tei index (the ratio of the sum of isovolumic contraction and relaxation times divided by ejection time), TAPSE, inferior vena cava dimensions and inspiratory collapsibility, the presence and magnitude of a pericardial effusion, RV and LV diastolic function estimated on tissue Doppler imaging of tricuspid and mitral annuli, and systolic function on tissue Doppler...
imaging measures of tricuspid annular systolic velocity S wave (117,119,121,148,156–159). All are, to a variable degree, sensitive to prognosis (117–119,121,148,157) and therapeutic interventions (156,160).

**INVASIVE HEMODYNAMICS.** Right heart catheterization with the measurement of PAP, CO, RAP, and pulmonary arterial wedge pressure remains the gold standard for the diagnosis of PAH (140,161). Possible areas for improvement include the measurement of PAP at several levels of flow to derive pulmonary vascular pressure–flow relationships that would improve the assessment of pulmonary vascular function and that might prove useful for diagnosis of latent PAH and for understanding the effects of therapy (162,163).

**Imaging: a developing magnetic resonance imaging era?** Magnetic resonance imaging is useful in the noninvasive assessment of the right heart in PH (164–167). It provides excellent spatial resolution, and virtually any plane of cross section can be obtained. Direct assessment of cardiac volumes, muscular mass, and function is possible. Precise flow measurements in the heart and great vessels can be made using velocity-encoded imaging. Interobserver variability is low, which makes magnetic resonance imaging a potential tool for follow-up assessment (168,169). The SERAPH (Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension) study used CMR to compare the effect of bosentan and sildenafil on RV hypertrophy (170).

Three-dimensional flow mapping of the central pulmonary artery may allow assessment of mPAP (171).

The first attempt to assess the value of CMR for monitoring mortality risk in patients with PAH was made by Van Wolferen et al. (172). Assessed at baseline, RV stroke volume index >26 ml/m², RV end-diastolic volume <83 ml/m², and LV end-diastolic volume >41 ml/m² each indicated better survival. In a multivariate analysis, only 6MWD added independently to the prognostic message provided by these CMR variables. Importantly, progressive dilatation of the RV, as well as a decrease in LV diastolic volume and a further decrease in RV stroke volume at 1-year follow-up, were related to worse long-term outcome (172) (Fig. 1).

**RV and PA/RV interactions.** Chronic PH results from an increase in PVR, which is a simple measure of opposition to the mean component of flow. However, given the low resistance/high compliance nature of pulmonary circulation, the pulsatile component of hydraulic load is also critical. Several studies have documented the relationship between pulsatile pressure and flow (impedance) (173–176). These studies have shown that pulsatile load is increased in chronic PH. This abnormal pulsatile load may have detrimental effects on ventricular–vascular coupling, unfavorably loading the still-ejecting RV. Impedance is a measure of the opposition to the pulsatile components of flow. The role of pulmonary arterial input impedance has been under-

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**Table 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>6MWT</td>
<td>0.28</td>
<td>0.09</td>
<td>1.18</td>
</tr>
<tr>
<td>Mean RA pressure</td>
<td>5.06</td>
<td>1.85</td>
<td>12.9</td>
</tr>
<tr>
<td>Mean PA pressure</td>
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<td>0.21</td>
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<tr>
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<td>1.44</td>
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<tr>
<td>Stroke volume index</td>
<td>0.14</td>
<td>0.06</td>
<td>0.85</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.98</td>
<td>0.26</td>
<td>3.68</td>
</tr>
<tr>
<td>Mixed venous O₂ saturation</td>
<td>0.23</td>
<td>0.08</td>
<td>1.36</td>
</tr>
<tr>
<td>Cardiac index (MRI)</td>
<td>0.16</td>
<td>0.07</td>
<td>1.00</td>
</tr>
<tr>
<td>Stroke volume index (MRI)</td>
<td>0.10</td>
<td>0.04</td>
<td>0.59</td>
</tr>
<tr>
<td>RV mass index</td>
<td>2.12</td>
<td>0.56</td>
<td>7.79</td>
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<tr>
<td>LV mass index</td>
<td>0.68</td>
<td>0.18</td>
<td>2.54</td>
</tr>
<tr>
<td>RV wall thickness</td>
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<td>7.25</td>
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<td>LV wall thickness</td>
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<td>RVEF</td>
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<tr>
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<tr>
<td>LVEDVI</td>
<td>0.13</td>
<td>0.06</td>
<td>0.77</td>
</tr>
</tbody>
</table>

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**Figure 1** Univariate Analysis of the Change in Variables, Including Magnetic Resonance Imaging Data After 1-Year Follow-Up as a Potential Predictor of Mortality in IPAH

6MWT = 6-min walk test; IPAH = idiopathic pulmonary arterial hypertension; LV = left ventricle; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PA = pulmonary artery; PVRI = pulmonary vascular resistance index; RA = right atrium; RV = right ventricle; RVEDVI = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction. Reproduced from van Wolferen et al. (172) by permission of the European Society of Cardiology.
recognizes in the past; however, there are compelling reasons why this should be evaluated (173–178).

Cardiomyocyte hypertrophy has been considered an adaptive response to increased load, such as hypertension or pressure overload, because it normalizes the increase in wall stress induced by mechanical overload (179). Prolongation of this hypertrophic response leads to contractile dysfunction and heart failure. The distinctions between physiologic and pathologic hypertrophy are many (180).

There is emerging interest in determining the effect of therapy on RV function. Phosphodiesterase-5A expression is increased in the RVs of patients with PAH, and animal models suggest that inhibition of the enzyme results in inotropic activity (181). Magnetic resonance imaging-based studies have shown that acute sildenafil treatment promotes RV relaxation (147). Several other studies in animal models have shown improved RV systolic and diastolic function in response to acute and chronic treatment with prostacyclin analogs, phosphodiesterase-5A inhibitors, and endothelin-receptor antagonists (181,182). Further studies are needed to translate these observations into therapies for people with PH.

**Summary**

As new therapies have been developed for PAH, screening, prompt diagnosis, and accurate assessment of disease severity have become increasingly important. A clear definition of PH and the development of a rational approach to diagnostic assessment and follow-up using both conventional and new tools will be essential to deriving maximal benefit from our expanding therapeutic armamentarium.

**Author Disclosures**

Dr. Badesch has received honoraria for service on steering committees and advisory boards from Actelion (CoTherix), Biogen IDEC, Encysive, Gilead (Myogen), GlaxoSmithKline, Lilly, Lung Rx, MondoBIOTECH, Pfizer, and United Therapeutics; has served as a speaker for CME-certified activities for HLR Communications; and has received grants from Actelion (CoTherix), Gilead (Myogen), Encysive, Lilly (ICOS), Lung Rx, Pfizer, United Therapeutics, and Wyeth. Dr. Champion has served on advisory boards for Actelion, Gilead, Pfizer, and United Therapeutics, and has served as an expert witness in diet drug litigation. Dr. Gomez Sanchez has served on advisory boards for GlaxoSmithKline, Pfizer, and United Therapeutics; has served as an investigator for Actelion, Bayer Schering, Gilead, and United Therapeutics; and has given lectures supported by Actelion, Bayer Schering, Encysive, GlaxoSmithKline, and Pfizer. Dr. Hoeper has received grants from Actelion, Bayer Schering, and Encysive; has received travel accommodations and speaker’s honoraria from Actelion, Encysive, Gilead (Myogen), Pfizer, Schering, and Unither; and has been a consultant to Bayer Schering, Gilead (Myogen), GlaxoSmithKline, and Unither. Dr. Oudiz has received research support, speaker honoraria, and/or consulting fees from Actelion, Bayer Ag, Eli Lilly, Gilead, Pfizer, Lung Rx, and United Therapeutics. Dr. Torbicki has served as a consultant for Eli Lilly, GlaxoSmithKline, and mondoBIO-TECH; has received honoraria from Bayer Schering, Eli Lilly, and Sanofi-Aventis; and has conducted research supported by Bayer Schering, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, mondoBIO-TECH, and Pfizer. Drs. Loyd and Manes report no conflicts of interest.

**REFERENCES**


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