Early Decline in Six-Minute Walk Distance from the Time of Diagnosis Predicts Clinical Worsening in Pulmonary Arterial Hypertension

Julie Huang Sanjay Mehta Marco Mura

Southwest Ontario Pulmonary Hypertension Clinic, Division of Respiriology, Department of Medicine, Schulich School of Medicine and Dentistry, Western University, London, Ont., Canada

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Key Words

Pulmonary hypertension · Six-minute walk distance · Clinical worsening · Outcome · Survival

Abstract

Background: The six-minute walk distance (6MWD) is commonly used to assess pulmonary arterial hypertension (PAH). However, the role of 6MWD in predicting outcomes in PAH is controversial. Clinical worsening is being increasingly considered as a clinically meaningful end point in PAH. **Objectives:** We aimed to investigate whether early longitudinal changes in 6MWD (Δ 6MWD) in meters and percent predicted (%pred) from the time of diagnosis predict clinical worsening of PAH. **Methods:** One hundred patients with group I PAH were retrospectively assessed. 6MWD was calculated using American (%pred US) or Canadian (%pred CAN) reference equations. Δ 6MWD at 6 months were recorded. Clinical worsening was defined as either: development of right heart failure, hospital admission for PAH, referral for lung transplantation or initiation of prostanoids after oral therapy failed. Optimal 6-month differences in 6MWD to detect worsening were defined with receiver operating characteristics (ROC) analysis. **Results:** Progressors, i.e. patients with clinical worsening, and nonprogressors showed significant differences in Δ 6MWD. The most clinically significant declines in 6MWD at 6 months were ≥ 35 m, $\geq 8\%$ pred US and $\geq 6\%$ pred CAN. ROC and Cox proportional hazard analyses showed equivalent results for 6MWD %pred and meters. Six-month

declines in 6MWD predicted worsening with a high specificity (94%) but a low sensitivity (33%). **Conclusions:** Early declines in 6MWD (within the first 6 months) predict future clinical worsening of PAH with high specificity. Δ 6MWD may still be part of a comprehensive assessment of a patient's clinical status. However, given the poor sensitivity, a decline in 6MWD should be used with other clinical tools to make an appropriate assessment of the progression of PAH.

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Introduction

Pulmonary arterial hypertension (PAH) is a condition characterized by vascular remodeling leading to increased pulmonary vascular resistance (PVR), with progression of disease and development of right heart failure. Despite major improvements in the medical therapy for PAH, the prognosis remains poor and the condition is still one of the major indications for lung transplantation (LTx) [1, 2].

As significant morbidity and mortality exist despite PAH-targeted therapy, clinically meaningful predictors of clinical worsening are needed. Six-minute walk distance (6MWD) is a commonly used surrogate end point for assessing the clinical status of patients with PAH. Randomized controlled trials (RCTs) have demonstrated that improvements in 6MWD over short periods of time reflect short-term benefits from pharmacotherapy [3–5]. How-

ever, reports on the overall prognostic performance of the 6MWD are contrasting, and its association with long-term outcomes has been questioned [6–8]. Another limitation is represented by the ‘ceiling effect’, i.e. that effective therapy may not further improve exercise capacity in subjects with a relatively preserved baseline 6MWD [9]. Most studies have focused on the improvement in 6MWD as a measure of treatment effect [7, 10, 11], but despite short-term improvements in 6MWD in response to pharmacotherapy, this has not been correlated with a decreased risk of worsening [12]. In contrast, longitudinal declines in 6MWD as predictors of outcome have received less attention. Moreover, although the 6MWD is highly dependent on patients’ variables, studies on PAH report the absolute 6MWD value expressed in meters, with only 1 study to date evaluating the percent predicted (%pred) value, based on the height, weight and age of patients [13].

While there is good evidence that baseline and post-treatment improvements in 6MWD are good predictors of survival [6, 7, 14, 15], it remains unclear whether a decline in 6MWD can predict clinical worsening in PAH. Furthermore, there have been no studies investigating whether 6MWD %pred is a better predictor of worsening than 6MWD in meters. We hypothesized that an early decline in 6MWD from the time of diagnosis may be a predictor of clinical worsening in PAH, and also assessed the predictive value of 6MWD %pred compared to 6MWD in meters.

Materials and Methods

Patients diagnosed with World Health Organization (WHO) group I PAH at the Southwest Ontario Pulmonary Hypertension Clinic of the Western University, were retrospectively considered. Baseline was the time of diagnosis. Patients with incomplete data and those with PAH other than group I were excluded. The study was approved by the Research Ethics Board of Western University (protocol No.103784).

PAH was defined as a mean pulmonary arterial pressure (mPAP) of ≥ 25 mm Hg and a pulmonary capillary wedge pressure of ≤ 15 mm Hg upon right heart catheterization [16, 17]. Baseline characteristics were captured at the time of diagnosis before the initiation of treatment, and these included age, body mass index (BMI), WHO functional class (WHO FC), 6MWD, right ventricle systolic pressure (RVSP) obtained with echocardiography, mPAP, PVR and the diffusion lung capacity for carbon monoxide (DLCO). After diagnosis, patients received follow-up at intervals of 3–6 months, at the direction of the attending physician. 6MWD was obtained at each follow-up visit, as part of standard of care. 6MWD at 6 months from the time of diagnosis was recorded and changes in 6MWD ($\Delta 6$ MWD) were calculated.

The primary end point was clinical worsening of PAH within 18 months of diagnosis, defined as either: the development of clin-

ical features of right heart failure, admission to hospital for PAH-related respiratory or cardiac causes, initiation of intravenous prostanoids after failing oral therapy or referral for LTx (WHO FC III–IV symptoms in spite of medical therapy or rapidly progressive disease) [18–22]. Worsening-free survival was defined as the interval from the time of diagnosis to clinical worsening. The secondary end point was LTx-free survival, defined as the time from diagnosis to death or LTx.

Pulmonary function tests and 6MWD tests were performed according to the ATS guidelines [23, 24]. 6MWD %pred was calculated using reference equations based on US and Canadian populations (i.e. %pred US and %pred CAN) [25, 26].

Statistical Analysis

Values were expressed as mean $\pm$ standard deviation. Comparisons were made with unpaired Student *t* tests or Mann-Whitney *U* tests, where appropriate. Receiver operating characteristics (ROC) analysis was used to determine the cut-off values and longitudinal changes for the detection of the end point. Cut-offs for determining the best 6MWD baseline values to detect the outcome were those that provided the optimal (i.e. the best sum of) sensitivity and specificity (accuracy). Cut-offs for determining the best interval declines of 6MWD to detect the outcome were those that provided the optimal accuracy as well. Time to end point was evaluated using Kaplan-Meier curves and log-rank tests. Kaplan-Meier distributions were realized with cut-offs from the ROC analysis. Cox proportional hazards regression analysis was used to identify significant variables predicting end points, which were then evaluated with multivariate regression analysis. Results were summarized as hazard ratios (HR). $p < 0.05$ was significant. JMP (SAS Institute, Cary, N.C., USA), GraphPad (MacKiev, San Diego, Calif., USA) and MedCalc (MedCalc, Mariakerke, Belgium) software was used.

Results

One hundred patients were included. Patients’ characteristics at the time of diagnosis are shown in table 1. After diagnosis, patients received PAH-targeted therapies [16, 17], including endothelin receptor antagonists (51%), phosphodiesterase type-5 inhibitors (27%) or a combination of the two (10%). Six patients were started on intravenous prostanoids at the time of diagnosis. Follow-up from the time of diagnosis was 40 ± 27 months.

While 6MWD in meters did not show a significant correlation with mPAP ($r = -0.20$, $p = 0.0511$), 6MWD %pred US ($r = -0.32$, $p = 0.0018$) and %pred CAN ($r = -0.32$, $p = 0.0019$) showed a significant, inverse relationship (online suppl. fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000370124). Similarly, a significant, negative correlation was observed between PVR and 6MWD %pred US and CAN ($r = -0.28$, $p = 0.0100$ and $r = -0.23$, $p = 0.0379$, respectively), but not between 6MWD in meters and PVR ($r = -0.09$, $p = 0.43$).

Fig. 1. a Worsening-free survival up to 18 months after diagnosis. **b** Worsening-free survival. **c** LTx-free survival.

Table 1. Baseline characteristics of patients included in the study

Male/female (% of males)	76/24 (24)
Age at diagnosis, years	59±16
BMI, kg/m ²	29±8
Etiology	
Idiopathic PAH	50 (50)
CTD PAH	37 (37)
CHD PAH	13 (13)
Function and hemodynamics	
WHO FC	2.8±0.5
DLCO, %pred	49±18
RVSP, mm Hg	73±24
mPAP, mm Hg	49±15
PVR, dyn·s·cm ⁻⁵	697±423
6MWD at baseline	
In meters	323±115
%pred US	67±22
%pred CAN	49±16
6MWD at 6-month follow-up	
In meters	334±127
%pred US	69±25
%pred CAN	50±18
Therapy started after diagnosis	
ERA	51 (51)
ERA and PDE5i	10 (10)
PDE5i	27 (27)
IV PGI ₂	6 (6)
Diuretics only	3 (3)
Calcium-channel blocker	3 (3)

Values are n (%) or mean ± SD. Baseline characteristics were recorded before the initiation of treatment.

CHD PAH = Congenital heart disease-associated PAH; CTD PAH = connective tissue disease-associated PAH; ERA = endothelin receptor antagonist; IV PGI₂ = IV prostacyclin analog; PDE5i = phosphodiesterase type 5 inhibitor.

Twenty-eight patients (28%) experienced clinical worsening within 18 months of diagnosis. The average interval from diagnosis to worsening was 10 ± 6 months. During the total study period, 19 patients died and 1 received LTx. The average time to death or LTx was 30 ± 29

months. Worsening-free survival and LTx-free survival curves are shown in figure 1.

The baseline and longitudinal characteristics of progressors (defined as patients with clinical worsening) versus nonprogressors were compared (table 2; online suppl. table 1). With respect to hemodynamics, mPAP and PVR were significantly higher in progressors. Both 6MWD in meters and %pred at baseline were significantly different between the groups. The Δ6MWD from time of diagnosis also showed significant differences: among progressors, a significant decline in 6MWD was observed, compared to non-progressors [Δ6MWD (m)]. ROC analysis was used to determine the baseline cut-off values that best predicted clinical worsening in terms of sensitivity and specificity (fig. 2; table 3). Baseline 6MWD (≤342 m, ≤63%pred US or 51%pred CAN) all predicted worsening with similar, intermediate sensitivity and specificity. The area under the curve (AUC) was highest for %pred US (0.71; fig. 2; table 3).

ROC analysis determined 6-month Δ6MWD that best predicted clinical worsening in terms of sensitivity and specificity (fig. 2; table 3; see online suppl. table 2 for a detailed analysis). Declines in 6MWD at 6 months of ≥35 m, ≥8%pred US and ≥6%pred CAN all predicted worsening with exactly the same low sensitivity (33%) and with high specificity (94, 94 and 91%, respectively; table 3).

Univariate Cox proportional hazard analysis identified some baseline variables as significant predictors of clinical worsening, including a higher WHO FC, mPAP and PVR, and a lower DLCO (table 4). Age, BMI and RVSP were not predictors of clinical worsening. Considered as continuous variables, a higher baseline %pred US (HR 0.97) and %pred CAN (HR 0.96) were more significantly protective towards worsening than 6MWD in meters (HR 0.99). Similarly, as categorical variables, 6MWDs

Table 2. Baseline characteristics and 6-month changes comparing progressors (patients who developed clinical worsening) to nonprogressors

	Progressors (n = 28)	Non progressors (n = 72)	p value
Male/female (% of males)	10/18 (36)	14/58 (19)	n.s.
Age at diagnosis, years	63±13	57±17	n.s.
BMI, kg/m ²	28±5	30±8	n.s.
<i>Etiology</i>			
Idiopathic PAH	17 (61%)	34 (47%)	n.s.
CTD PAH	9 (32%)	28 (39%)	n.s.
CHD PAH	2 (7%)	10 (14%)	n.s.
<i>Function and hemodynamics</i>			
WHO FC	3.0±0.2	2.7±0.5	0.0178 ^a
DLCO, %pred	43±19	52±18	n.s. ^a
RVSP, mm Hg	77±28	72±22	n.s. ^a
mPAP, mm Hg	57±15	46±14	<0.0001
PVR, dyn·s·cm ⁻⁵	1,027±462	549±309	<0.0001
<i>6MWD at time of diagnosis</i>			
In meters	265±115	346±107	0.0012
%pred US	55±22	71±21	0.0007
%pred CAN	41±16	52±15	0.0016
<i>At 6-month follow-up</i>			
Δ6MWD in meters	-25±91	23±43	0.0016 ^a
Δ6MWD %pred US	-5±19	5±9	0.0022 ^a
Δ6MWD %pred CAN	-3±14	2±8	0.0157 ^a
<i>Therapy started after diagnosis</i>			
ERA	18 (64)	32 (44)	n.s.
ERA and PDE5i	3 (11)	7 (10)	n.s.
PDE5i	5 (18)	23 (32)	n.s.

Values are n (%) or mean ± SD. For abbreviations, see table 1.

^a Results obtained with Mann-Whitney U test (see online suppl. table 1 for median and quartiles).

Fig. 2. ROC curves of 6MWD variables at the time of diagnosis versus upon worsening. See table 3 for further details. **a** 6MWD in meters. **b** 6MWD %pred US. **c** 6MWD %pred CAN. **d** 6MWD in meters at 6-month decline (either ≥35 m or ≥8%pred US – results were identical).

Table 3. ROC analysis of 6MWD variables at the time of diagnosis versus clinical worsening

Variable	AUC	Standard error	p value	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Baseline 6MWD					
In meters	0.69	0.059	0.0010	75 (55–89)	54 (42–66)
%pred US	0.71	0.060	0.0005	68 (48–84)	69 (57–80)
%pred CAN	0.69	0.058	0.0013	79 (59–2)	56 (43–67)
6MWD in meters at 6-month decline (≥ 35 m)	0.64	0.048	0.0044	33 (16–54)	94 (86–98)
6MWD %pred US at 6-month decline ($\geq 8\%$)	0.64	0.048	0.0044	33 (16–54)	94 (86–98)
6MWD %pred CAN at 6-month decline ($\geq 6\%$)	0.62	0.049	0.0124	33 (16–54)	91 (82–97)

The criterion found for baseline 6MWD was ≤ 342 m, 63%pred US and 51%pred CAN. Abbreviations as in table 1. See online supplementary table 2 for details on the choice of 6-month declines. AUC = Area under the curve.

Table 4. Predictors of clinical worsening according to the univariate analysis

	HR	95% CI	p value
Age at diagnosis	1.02	0.99–1.05	n.s.
BMI, kg/m ²	0.98	0.92–1.02	n.s.
WHO FC	5.61	2.06–14.73	0.0005
DLCO, %pred	0.97	0.95–0.99	0.0320
RVSP, mm Hg	1.01	0.99–1.03	n.s.
mPAP, mm Hg	1.04	1.01–1.07	0.0022
PVR, dyn·s·cm ⁻⁵	1.00	1.00–1.00	0.0001
6MWD, m (continuous)	0.99	0.99–0.99	0.0005
6MWD ≤ 342 m	3.09	1.38–7.85	0.0055
6MWD %pred US (continuous)	0.97	0.95–0.98	0.0003
6MWD %pred US ($\leq 63\%$)	4.01	1.63–10.31	0.0014
6MWD %pred CAN (continuous)	0.96	0.94–0.98	0.0008
6MWD %pred CAN ($\leq 51\%$)	3.79	1.63–10.31	0.0014
6MWD in meters at 6-month decline (≥ 35 m)	4.86	2.07–10.59	0.0006
6MWD %pred US at 6-month decline ($\geq 8\%$)	4.86	2.07–10.59	0.0006
6MWD %pred CAN at 6-month decline ($\geq 6\%$)	3.87	1.65–8.44	0.0027

of ≤ 342 m, $\leq 63\%$ pred US and $\leq 51\%$ pred CAN were associated with a 3.09-fold ($p = 0.0055$), 4.01-fold ($p = 0.014$) and 3.79-fold ($p = 0.0014$) risk of worsening, respectively (table 4).

A decline in 6MWD at 6 months of ≥ 35 m, $\geq 8\%$ pred US or $\geq 6\%$ pred CAN (online suppl. table 2) from the time of diagnosis was associated with significantly increased risk of worsening (HR 4.86, $p = 0.0006$ for 6MWD in meters and %pred US; HR 3.87, $p = 0.0027$ for %pred CAN; table 4). Multivariate Cox proportional hazard analysis showed that the best independent predictors of worsening were baseline 6MWD %pred US $\leq 63\%$ and a 6-month decline in 6MWD %pred US $\geq 8\%$, combined with baseline mPAP (table 5).

Kaplan-Meier curves confirmed that patients with a decline in 6MWD (in meters or %pred) 6 months after diagnosis experienced a significantly higher rate of worsening than patients with stable 6MWD ($p < 0.0001$; fig. 3). Within 18 months from the time of diagnosis, 69% of the subjects with a 6-month decline in 6MWD experienced clinical worsening.

Regarding the secondary end point, LTx-free survival, significant differences in 6MWD baseline values and 6-month $\Delta 6$ MWD were also found between survivors and nonsurvivors (online suppl. table 3). ROC analysis showed that baseline 6MWD values and 6-month declines were significant predictors of mortality (online suppl. table 4). Baseline 6MWD %pred US was a slight-

Fig. 3. A 6-month decline in 6MWD from the time of diagnosis predicts worsening. Kaplan-Meier worsening analysis grouped by 6MWD 6-month decline (either ≥ 35 m or $\geq 8\%$ pred US – the results were identical). $p < 0.0001$ (log-rank).

Table 5. Predictors of clinical worsening according to the multivariate analysis

	HR	95% CI	p value
mPAP	1.04	1.01–1.07	0.0143
6MWD %pred US ($\leq 63\%$)	4.56	1.98–11.43	0.0003
6MWD %pred US at 6-month decline ($\geq 8\%$)	7.21	2.76–18.04	0.0002

ly better predictor of the need for LTx or of mortality than 6MWD in meters and 6MWD %pred CAN. However, the 6MWD %pred provided no additional advantage over 6MWD in meters with respect to changes at 6 months (online suppl. tables 3–5). Clinical worsening was a strong risk factor for mortality during the observation period (HR 12.46; online suppl. table 5). Multivariate analysis (online suppl. table 6) identified a baseline 6MWD %pred US of $\leq 63\%$ and its 6-month decline of $\geq 8\%$ as independent predictors of mortality.

Discussion

In this study, we assessed whether short-term declines in 6MWD can predict clinical worsening in PAH. Longitudinal $\Delta 6\text{MWD}$ were evaluated from the time of diagnosis. Clinical worsening of PAH was defined with a con-

servative approach based on widely accepted criteria, without considering subjective variables such as WHO FC. Our data show that early declines in 6MWD can predict future worsening of PAH, including death and the need for LTx. Our study also evaluated, for the first time, the use of %pred 6MWD, calculated using US and Canadian reference equations [25, 26]. While baseline 6MWD %pred provided some advantage in predicting outcomes, longitudinal changes were equivalent predictors of worsening when compared to 6MWD in meters. Declines in 6MWD of ≥ 35 m and $\geq 8\%$ pred US at 6 months were identical in predicting worsening with high specificity but low sensitivity. Early postdiagnosis declines in 6MWD were also strong predictors of mortality.

The natural history of PAH is characterized by a 1-year mortality of 15% and a median survival of 2.8 years, in the absence of PAH-targeted therapy [17, 27]. In our population, 28% of the subjects experienced worsening within 18 months of diagnosis, and 20% died or received LTx over an average period of 30 months from diagnosis. Clinical worsening of PAH is emerging as a key measure of long-term outcome and was the main end point in a recent RCT that used macitentan treatment [14, 28, 29]. In our study, clinical worsening was defined according to widely recognized, objective criteria [18–22]. Since 6MWD continues to be the most commonly used objective test for monitoring the functional severity of PAH in clinical practice, it is critically important to establish its role in predicting worsening. Unfortunately, the reliability of 6MWD as a marker of disease worsening in PAH remains surrounded by controversy [7]. In the EARLY (Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary Arterial Hypertension Patients) study, a significant effect of bosentan treatment on time to worsening was observed without a statistically significant $\Delta 6\text{MWD}$ [9]. A meta-analysis of 22 RCTs that included over 3,000 patients demonstrated no relationship between $\Delta 6\text{MWD}$ and clinical indicators of worsening, despite a significant treatment-associated impact on 6MWD and other key outcomes, including survival and hospitalization [8]. It is important to note that we included incident cases from the time of diagnosis only, but that the meta-analysis results were based on prevalent cases from RCTs in which patients were enrolled at different stages of the disease, meaning that subjects with severe or aggressive PAH may have been excluded. The rate of survival in incident and prevalent cases differs remarkably [30].

In several studies, a low baseline 6MWD has been shown to be associated with higher mortality, with cut-off

values varying between <165 and <332 m [15, 16, 18, 31–33]. We found a significant difference in both baseline 6MWD in meters and 6MWD %pred in survivors versus nonsurvivors. In our study, there was also a significant difference in baseline 6MWD, in meters or %pred, between progressors and nonprogressors. A previous study reported that a baseline 6MWD of ≤ 367 m was predictive of a greater risk of clinical worsening [14]. However, this particular study used a definition of worsening which incorporated a 15% reduction in 6MWD from baseline, the baseline was not necessarily defined as the time of diagnosis and the longitudinal changes were not considered [14].

As baseline 6MWD is generally measured at the time of diagnosis and before starting therapy, it is expected that a patient's subsequent 6MWD on therapy should improve. Indeed, the Δ 6MWD has been the primary outcome measurement in most of the RCTs on all the currently available PAH-targeted therapies. Meta-analyses of these RCTs found a mean improvement of 6MWD of between 22.4 and 42.8 m at 12–16 weeks after the initiation of therapy [7, 16, 34]. However, longitudinal Δ 6MWD in response to PAH therapy has not been shown to be associated with survival benefit [22, 35]. Moreover, Gabler et al. [7] recently showed only a modest association between Δ 6MWD and clinical improvement, while Rubin et al. [36] showed a deterioration of 6MWD after starting sildenafil which was associated with poor survival. Δ 6MWD has also been shown to be predictive of patient-centered outcome measurements, such as health-related quality of life [35–37].

In this study, a decline in 6MWD of ≥ 35 m 6 months after diagnosis predicted worsening with a high specificity (94%). In contrast to the improvement expected once PAH therapy has been started, an early decline in 6MWD at this stage could identify subjects with more aggressive disease. The high rate of worsening, death or LTx suggests that the population included in this study had moderate to severe disease at baseline. Worsening strongly predicted mortality (HR 12.46); this was previously shown by Frost et al. [18].

As for the many physiological parameters, exercise capacity is dependent on anthropometric factors [38, 39] and %pred may be a more robust method to control for individual differences compared to 6MWD in meters. The use of 6MWD %pred versus 6MWD in meters in idiopathic pulmonary fibrosis [40, 41], chronic lung diseases [42] and congestive heart failure [43] better reflects patients' clinical status. In PAH, despite the long-stand-

ing use of 6MWD, it is largely unknown whether the %pred is a better marker of disease severity than 6MWD in meters; Lee et al. [13] showed that %pred was not better for predicting mortality. Our data showed that, while only a small advantage was provided by baseline 6MWD %pred over 6MWD in meters, 6-month declines in %pred were equivalent to 6MWD in meters for predicting clinical worsening. However, multivariate analysis showed that the best independent predictors of worsening were a low baseline 6MWD %pred US combined with its 6-month decline. 6MWD %pred US and %pred CAN also showed a better correlation with hemodynamic data than 6MWD in meters. Compared to the US reference equations, which performed slightly better in predicting outcome, the Canadian equations did not take into account patients' BMI [25]. From the literature, there appears to be wide variability between reference equations from different countries [44].

The main limitation of this study was its retrospective nature, which meant that patients with rapidly progressive disease may have been excluded from the analysis. Our center is, however, a regional tertiary referral center to which severe cases are often referred. Our results need to be confirmed in prospective studies. The lack of follow-up hemodynamic data in most of the patients was also a limitation.

Conclusions

Early decline in 6MWD in the first 6 months after diagnosis predicts clinically important worsening of PAH with high specificity. Therefore, despite recognized limitations, the regular assessment of 6MWD still provides valuable information for the clinical management of group I PAH. 6MWD %pred obtained with the currently available equations did not provide a significant advantage over 6MWD in meters for predicting worsening or mortality. In addition, declines in 6MWD at 6 months after diagnosis predicted worsening with a poor sensitivity. 6MWD should therefore not be used in isolation for assessing patients with PAH. Outcomes can be predicted more accurately when the 6MWD is used in conjunction with a panel of other parameters.

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Erratum

The authors of the article entitled ‘Long-term data from the Swiss pulmonary hypertension registry’ [*Respiration* 2015;89:127–140, DOI: 10.1159/000370125] wish to publish the following correction. On page 127, the name of an author has been published incorrectly: Guido Domenighetti should read Guido Domenighetti. The correct author list should be as follows:

Séverine Mueller-Mottet^a Hans Stricker^b Guido Domenighetti^c
 Andrea Azzola^d Thomas Geiser^e Markus Schwerzmann^f Daniel Weilenmann^g
 Otto Schoch^h Jean-Marc Fellrathⁱ Thierry Rochat^j Frederic Lador^j
 Maurice Beghetti^k Laurent Nicod^l John-David Aubert^l Vladimir Popov^m
 Rudolf Speich^a Stephan Keusch^a Elisabeth Hasler^a Lars C. Huber^a
 Peter Grendelmeierⁿ Michael Tammⁿ Silvia Ulrich^a

^aPulmonary Clinic, University Hospital Zurich, Zurich, ^bClinic of Internal Medicine, Ospedale La Carità, and ^cPulmonary Clinic, Cantonal Hospital Locarno, Locarno, ^dPulmonary Clinic, Cantonal Hospital Lugano, Lugano, ^ePulmonary Clinic and ^fDivision of Cardiology, University Hospital Bern, Bern, ^gDivision of Cardiology and ^hPulmonary Clinic, Cantonal Hospital St. Gallen, St. Gallen, ⁱPulmonary Clinic, Cantonal Hospital Neuchâtel, Neuchâtel, ^jPulmonary Clinic, University Hospital Geneva, and ^kPediatric Cardiology Unit, University Children’s Hospital, Geneva, ^lPulmonary Clinic, University Hospital Lausanne, Lausanne, ^mPulmonary Clinic, Cantonal Hospital Lucerne, Lucerne, and ⁿPulmonary Clinic, University Hospital Basel, Basel, Switzerland