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Pulmonary Hypertension and Measurement of Exercise Capacity Remotely: Evaluation of the 1-min Sit-to-Stand Test (PERSPIRE) – a cohort study

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Shareable abstract (@ERSpublications)

This study has demonstrated the in-hospital safety of the 1-min sit-to-stand test in pulmonary hypertension, and its submaximal characteristics, positive correlation with the incremental shuttle walk test and potential role in remote risk assessment <https://bit.ly/3PgcqAo>

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Abstract

Background Multiparameter risk assessment is recommended to aid treatment decisions in patients with pulmonary arterial hypertension. The 1-min sit-to-stand test (1MSTS) has been validated for use in other respiratory illnesses. The aim of this study was to evaluate its safety in the hospital setting and potential utility in remote assessment in patients with pulmonary hypertension.

Methods In a prospective cohort study design patients performed the 1MSTS and incremental shuttle walk test (ISWT) on the same day. The primary aim of the study was to assess safety signals and correlations with other metrics used in risk assessment.

Results 60 patients with pulmonary arterial hypertension and 15 with chronic thromboembolic pulmonary hypertension were enrolled. No adverse events were recorded. Post-test change in physiological parameters was lower for the 1MSTS than for the ISWT in heart rate (mean±SD change +9.4±8.0 versus +38.3±25.9 beats per min, $p<0.001$), oxygen saturation ($-3.8\pm4.0\%$ versus $-8.9\pm7.3\%$, $p<0.01$) and systolic blood pressure ($+10.1\pm10.5$ versus $+17.7\pm19$ mmHg, $p<0.001$). There were significant correlations between the 1MSTS and ISWT ($r=0.702$, $p<0.01$), World Health Organization functional class ($r=-0.449$, $p<0.01$), emPHAsis-10 (-0.436 , $p<0.001$) and N-terminal pro-b-type natriuretic peptide ($r=-0.270$, $p=0.022$). 97% of patients were willing to perform the test at home.

Conclusion This study has demonstrated the safety, sub-maximal characteristics of the 1MSTS in pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension in the hospital setting, its positive correlation with the ISWT and potential role in remote risk assessment. Further evaluation of this exercise test is now warranted.

Background

Pulmonary hypertension is a chronic, progressive, life-limiting condition with a number of causes [1]. An increase in pulmonary vascular resistance (PVR) and right ventricular afterload arise from remodelling of the pulmonary arterioles in pulmonary arterial hypertension (PAH), and obstruction of the vasculature by chronic clot and a variable vasculopathy in chronic thromboembolic pulmonary hypertension (CTEPH) [1]. The diagnosis of pulmonary hypertension is confirmed by right heart catheterisation and is currently defined in guidelines as a mean pulmonary arterial pressure (mPAP) of ≥ 20 mmHg [2]. Patients will typically demonstrate symptoms of breathlessness and limited exercise capacity [1].

Drug therapies for PAH and CTEPH are focussed on slowing disease progression and minimising symptom burden. In selected patients with CTEPH, pulmonary endarterectomy (PEA) offers the prospect



of cure, whilst balloon pulmonary angioplasty (BPA) is also associated with significant symptomatic and haemodynamic benefits [3]. Due to the progressive nature of PAH, guidelines recommend regular multiparameter risk assessment and stratification, which may prompt a change in treatment [2]. A number of risk assessments exist. All of these include measures of World Health Organization functional class (WHO-FC), exercise capacity and right ventricular function. Hospital-based objective measures of exercise capacity used in risk assessment in PAH include the submaximal 6-min walking test (6MWT) [4], and maximal tests including the incremental shuttle walk test (ISWT) [5] and cardiopulmonary exercise testing (CPET) [6]. In CTEPH, data have also shown that the 6MWT can be used in the risk assessment of patients [7].

The onset of the COVID-19 pandemic has increased the use of remote clinical consultations, and highlighted the need to develop and validate alternatives to hospital-based exercise testing to aid risk assessment and stratification [8]. The 1-min sit-to-stand test (1MSTS) is a simple exercise test in which patients are asked to stand up from a chair repeatedly for 1 min. It has been evaluated in healthy subjects and patients with cardiorespiratory conditions including chronic obstructive pulmonary disease (COPD) [9], in whom it has been shown to correlate with the 6MWT [10, 11], quadriceps strength [12] and levels of physical activity [13]. The 1MSTS does not rely on patients having access to equipment or infrastructure, and is therefore widely accessible and suggested for use in the home setting [14, 15].

To date, the 1MSTS has not been evaluated in patients with pulmonary hypertension. This study has investigated the safety of the 1MSTS in the hospital setting, and its potential for use in remote risk assessment of patients with PAH and CTEPH.

Methods and materials

In this prospective cohort study, patients with PAH and CTEPH were identified from the Sheffield Pulmonary Vascular Disease Unit between June and December 2021.

Inclusion criteria required patients to be ≥ 18 years of age with a diagnosis of PAH or CTEPH following multimodality testing including right heart catheterisation, as defined in guidelines [2].

Patients were excluded if they also presented with significant mobility issues, uncontrolled systemic hypertension (systolic >220 mmHg or diastolic >120 mmHg) or hypotension (systolic <90 mmHg or diastolic <60 mmHg), resting tachycardia (>130 beats per min), or cognitive impairment that would prohibit informed consent. Also excluded were patients who had experienced surgery, myocardial infarction, pneumothorax or stroke within the past 8 weeks, or chest pain, haemoptysis or syncope within the last 2 weeks. To avoid selection bias, all patients attending on days where recruitment occurred were screened for the study.

Sample size estimation

Sample size in correlation studies can be estimated by using estimates of the effect size in t-test calculations [16]. In this study, effect sizes were estimated using comparable studies in COPD which included samples of 48 and 52 participants [10, 17], and identified correlation coefficients between 1MSTS and 6-min walk distance (6MWD) of between $r=0.57$ and $r=0.67$. Based on these values, assuming a Type I error rate of 0.05 and Type II error rate of 0.2, a sample size between $n=22$ ($r=0.5$) and $n=15$ ($r=0.6$) was indicated [16]. To capture participants with a range of exercise capabilities, a stratified sample was selected across three bands of ISWT distance: ≤ 180 , 190–330 and ≥ 340 m [5]. To accommodate this, a total sample of 75 was sought, with a minimum of 22 participants in each of the three ISWT bands.

Exercise testing and data collection

The ISWT was conducted first, on a 10-m corridor and performed using a standard protocol [18]. As per American Thoracic Society guidelines for repeat exercise testing, participants rested for ≥ 30 min before undertaking the 1MSTS test [18].

The 1MSTS used an armless chair of 46–48 cm height and was performed as previously described [10]. Participants were instructed to stand up and sit down as many times as they could within 1 min, without using their arms. They were advised to fully stand up on each repetition, and either come fully to sitting or tap their bottom on the chair before standing back up. They were advised to use rest periods if needed, and to stop before the end of the test if necessary. They were informed when 15 s of the test time remained [10]. As the ISWT is standardly conducted in the study setting without supplemental oxygen, regardless of

whether patients are on long-term or ambulatory oxygen therapy [5], the same approach was adopted for the 1MSTS.

The number of completed levels on the ISWT was recorded and expressed as metres and the number of full repetitions in the 1MSTS was recorded. Heart rate, blood pressure and oxygen saturations were captured before and after both tests, along with a patient reported measure of dyspnoea [19]. Adverse events, for example, dizziness, syncope or the participant becoming unwell, were also recorded. When participants stopped the test within 1 min, the reason for stopping was captured. Routine clinical assessments recorded on the day of testing were also captured, including N-terminal pro-b-type natriuretic peptide (NT-proBNP), emPHasis10 (patient-reported outcome measure in pulmonary hypertension) [20] and WHO-FC.

Survey

On completion of testing a short survey was conducted to assess the potential for a future study assessing the 1MSTS performed by patients at home. Participants were asked if they would be happy to perform the test at home, and if they had access to device to measure physiological parameters including blood pressure, weight, heart rate and oxygen saturations.

Statistics

Descriptive statistics were used to describe demographics and key characteristics at diagnosis and at the time of testing. Spearman's rank correlations were used to compare the two tests. Paired t-tests were used to examine differences in physiological characteristics of the tests. Where data were normally distributed, results are presented as mean \pm SD; otherwise, median (interquartile range) is shown.

Patients identified and approached by the Pulmonary Hypertension Association UK (the UK patient charity for patients with pulmonary hypertension) were consulted with for the study design, involved in the development of study materials and participated in the study steering committee.

The study protocol was approved by the National Health Service Health Research Authority (protocol reference number 21/EE/0074). The study was registered at www.ClinicalTrials.gov (identifier number NCT04903704). Written informed consent was obtained.

Results

Participant characteristics

Of 75 participants, 60 (80%) had a diagnosis of PAH. 15 (20%) were diagnosed with CTEPH, of whom six had residual pulmonary hypertension following PEA surgery, three had residual pulmonary hypertension following BPA, three were ineligible for PEA or BPA, and three had declined these interventions. 58 (77%) of participants were female.

At diagnosis, the mean \pm SD age was 52 \pm 16.8 years, 95% of participants were in WHO-FC III or IV with a mPAP of 48 \pm 13.3 mmHg, pulmonary arterial wedge pressure 10 \pm 5 mmHg and PVR of 764 \pm 388 dyn \cdot s \cdot cm $^{-5}$ (table 1). A detailed breakdown of PAH subgroups is in the supplementary material (table S1). On the day of testing, patients were, on average, 4.3 \pm 4.2 years post-diagnosis. 68% were in WHO-FC III or IV, with an ISWT of 281 \pm 174.4 m, median (interquartile range) NT-proBNP 339 (120–723) ng \cdot L $^{-1}$ and an emPHasis10 score of 27 (19–34) (table 2).

Safety and adverse events

75 hospital-based 1MSTS tests were conducted with no adverse events. One participant reported feeling anxious at the end of the 1MSTS test, recovering after <5 min of rest. Two participants terminated the test before the end of 1 min, after 50 and 55 s, due to shortness of breath and leg pain (table S2).

Comparison of exercise tests

Compared to the 1MSTS, patients undergoing the ISWT had a significantly greater fall in oxygen saturation from baseline when compared to post-test measures (3.8 \pm 4.0% versus 8.9 \pm 7.3%, p <0.01), and a greater rise in heart rate (9.4 \pm 8.0 versus 38.3 \pm 25.9 beats per min, p <0.001), systolic blood pressure (10.1 \pm 10.5 versus 17.7 \pm 19 mmHg, p <0.001), diastolic blood pressure (2.9 \pm 7.8 versus 10.3 \pm 15.1 mmHg, p <0.01) and Borg breathlessness score (2.8 \pm 1.7 versus 3.7 \pm 2.2, p <0.001) (table 3).

There were significant correlations between the 1MSTS and the ISWT (r =0.702, p <0.01). Correlations within the risk stratification bands were: high risk (r =0.391, p =0.044; n =27), intermediate risk (r =0.300, p =0.165; n =23) and low risk (r =0.667, p <0.01; n =25). The 1MSTS correlated significantly with WHO-FC

TABLE 1 Participant characteristics at diagnosis

Characteristics	PAH	CTEPH	All
Patients, n	60	15	75
Age, years	49.1±16.4	64.0±13.8	52±16.8
Female, n (%)	47 (78.3)	11 (73.3)	58 (77.3)
BMI, kg·m ⁻²	28.8±7.3	30.4±8.7	29.2±7.6
WHO-FC, n (%)			
Class II	4 (6.7)	0 (0)	4 (5.3)
Class III	49 (81.7)	15 (100)	64 (85.3)
Class IV	7 (11.7)	0 (0)	7 (9.3)
ISWT distance, m	222±161	192±155.9	216±159
Haemodynamics			
mRAP, mmHg	10±6.2	10±5.5	10±6.1
mPAP, mmHg	49±13.7	42±11.1	48±13.3
PAWP, mmHg	10±4.6	12±6.4	10±5.0
Cardiac output, L·min ⁻¹	4.49±1.60	4.26±1.33	4.44±1.54
Cardiac index, L·min ⁻¹ ·m ⁻²	2.54±0.94	2.21±0.58	2.46±0.87
PVR, dyn·s·cm ⁻⁵	796±401	645±322	764±388
Mixed venous S _{po₂} , %	64.3±10.7	63.0±7.64	64.0±10.0
Pulmonary function			
FEV ₁ , L [#]	2.09±0.72 (77% pred)	2.09±0.82 (82% pred)	2.09±0.73 (78% pred)
FVC, L [#]	2.82±1.1 (88% pred)	3.08±1.3 (96% pred)	2.87±1.1 (90% pred)
T _{LCO} , mmol·min ⁻¹ ·kPa ⁻¹ [#]	4.41±1.9 (51% pred)	4.96±1.9 (64% pred)	4.51±1.8 (54% pred)
emPHasis10, median (IQR)	33 (25–41)	29 (22–36)	31 (23–39)
Comorbidities, n (%)			
Systemic hypertension	8 (13.3)	5 (33.3)	13 (17.3)
Atrial fibrillation	5 (8.3)	2 (13.3)	7 (9.3)
Diabetes	6 (10)	2 (13.3)	8 (10.7)
Ischaemic heart disease	2 (3.3)	1 (6.7)	3 (4.0)
COPD	1 (1.7)	1 (6.7)	2 (2.7)
Interstitial lung disease	7 (11.7)	0 (0)	7 (9.3)
Chronic kidney disease	1 (1.7)	0 (0)	1 (1.3)

Data are presented as mean±sd or n (%), unless otherwise stated. emPHasis10 is a patient-reported outcome measure in pulmonary hypertension, scored on a scale of 0–50. PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; BMI: body mass index; WHO-FC: World Health Organization functional class; ISWT: incremental shuttle walk test; mRAP: mean right atrial pressure; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; S_{po₂}: oxygen saturation measured by pulse oximetry; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; T_{LCO}: transfer factor of the lung for carbon monoxide; IQR: interquartile range. #: % predicted values are given in parentheses.

TABLE 2 Participant characteristics on day of testing

Characteristics	PAH	CTEPH	All
Patients, n	60	15	75
Age, years	53.9±14.9	68.1±12.5	56.7±15.5
Time since diagnosis, years	4.4±4.4	3.9±3.1	4.3±4.2
BMI, kg·m ⁻²	29.4±8.0	29.7±5.7	29.5±7.5
WHO-FC, n (%)			
Class I	0 (0.0)	2 (13.3)	2 (2.7)
Class II	18 (30.0)	4 (26.7)	22 (29.3)
Class III	41 (68.3)	9 (60.0)	50 (66.7)
Class IV	1 (1.7)	0 (0.0)	1 (1.3)
ISWT distance, m	278±174	291±184	281±174
NT-proBNP, pg·mL ⁻¹	437 (111–830)	219 (127–378)	339 (120–723)
emPHasis10	29 (20–35)	22 (9–27)	27 (19–34)

Data are presented as mean±sd or median (interquartile range), unless otherwise stated. emPHasis10 is a patient-reported outcome measure in pulmonary hypertension, scored on a scale of 0–50. PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; BMI: body mass index; WHO-FC: World Health Organization functional class; ISWT: incremental shuttle walk test; NT-proBNP: N-terminal pro-b-type natriuretic peptide.

TABLE 3 Change in physiological parameters in response to 1-min sit-to-stand (1MSTS) and incremental shuttle walk (ISWT) tests

	1MSTS	ISWT	Mean difference (95% CI)	p-value
S_{po₂}, %				
Baseline	95±3.4	94±4.1	1.0 (0.4–1.8)	0.002*
Post-test	91±6.2	85±8.9	6.2 (4.6–7.7)	<0.001*
Change from baseline	–3.8±4.0	–8.9±7.3	5.0 (3.5–6.7)	<0.001*
Heart rate, beats per min				
Baseline	79±13.1	80±13.3	–0.52 (–2.5–1.4)	0.593
Post-test	89±14.9	118±24.3	–29.4 (–34.9– –23.9)	<0.001*
Change from baseline	9.4±8.0	38.3±25.9	–28.8 (–34.8– –22.9)	<0.001*
Systolic blood pressure, mmHg				
Baseline	126±19.1	119±17.9	7.1 (3.9–10.2)	<0.001*
Post-test	136±21.4	136±28.2	0.0 (–4.9–4.9)	0.995
Change from baseline	10.1±10.5	17.7±19.0	–7.6 (–12.0– –3.2)	<0.001*
Diastolic blood pressure, mmHg				
Baseline	75±11.1	74±14.8	1.4 (–1.4–4.3)	0.32
Post-test	78.8±13.0	84.4±17.6	–5.6 (–8.8– –2.4)	<0.001*
Change from baseline	2.9±7.8	10.3±15.1	–7.4 (–10.7– –4.0)	<0.001*
Borg breathlessness				
Baseline	0.85±1.1	0.92±1.1	–0.1 (–0.24–0.09)	0.34
Post-test	3.6±1.8	4.6±2.0	–1.0 (–1.37– –0.62)	<0.001*
Change from baseline	2.8±1.8	3.7±2.2	–0.9 (–1.3– –0.6)	<0.001*

Data are presented as mean±SD unless otherwise stated. Borg breathlessness is scored on a scale of 0–10. S_{po₂}: oxygen saturation measured by pulse oximetry. *: p<0.05.

(–0.503, p<0.01), emPHAsis10 (–0.436, p<0.001) and NT-proBNP (–0.262, p=0.028). There were also significant correlations between the ISWT and WHO-FC, emPHAsis10 and NT-proBNP (table 4). Scatterplots of 1MSTS versus ISWT distance, WHO-FC, NT-proBNP and emPHAsis10 scores are shown in figure 1. Figure 2 shows box plots of 1MSTS in each of the risk stratification bands.

Survey results

97% of participants surveyed (n=67) indicated that they would conduct a 1MSTS test at home as part of a remote assessment, with 90% having access to weighing scales, 45% an oxygen saturation monitor and 40% a sphygmomanometer at home (table S3).

Discussion

To our knowledge, this is the first study to examine the 1MSTS test in patients with PAH and CTEPH. We have demonstrated that it is a safe, submaximal test that correlates strongly with ISWT distance and other

TABLE 4 Correlation of outcomes for 1-min sit-to-stand test (1MSTS) test and incremental shuttle walk test (ISWT)

	1MSTS		ISWT	
	r	p-value	r	p-value
1MSTS			0.702	<0.001*
High risk			0.391	0.044*
Intermediate risk			0.300	0.165
Low risk			0.667	<0.001*
WHO-FC	–0.503	<0.001*	–0.592	<0.001*
NT-proBNP	–0.262	0.028*	–0.286	0.012*
emPHAsis10	–0.436	<0.001*	–0.479	<0.001*
Age	–0.393	<0.001*	–0.445	<0.001*

emPHAsis10 is a patient-reported outcome measure in pulmonary hypertension. r: Spearman's rank correlation coefficient; WHO-FC: World Health Organization functional class; NT-proBNP: N-terminal pro-b-type natriuretic peptide. *: p<0.05.

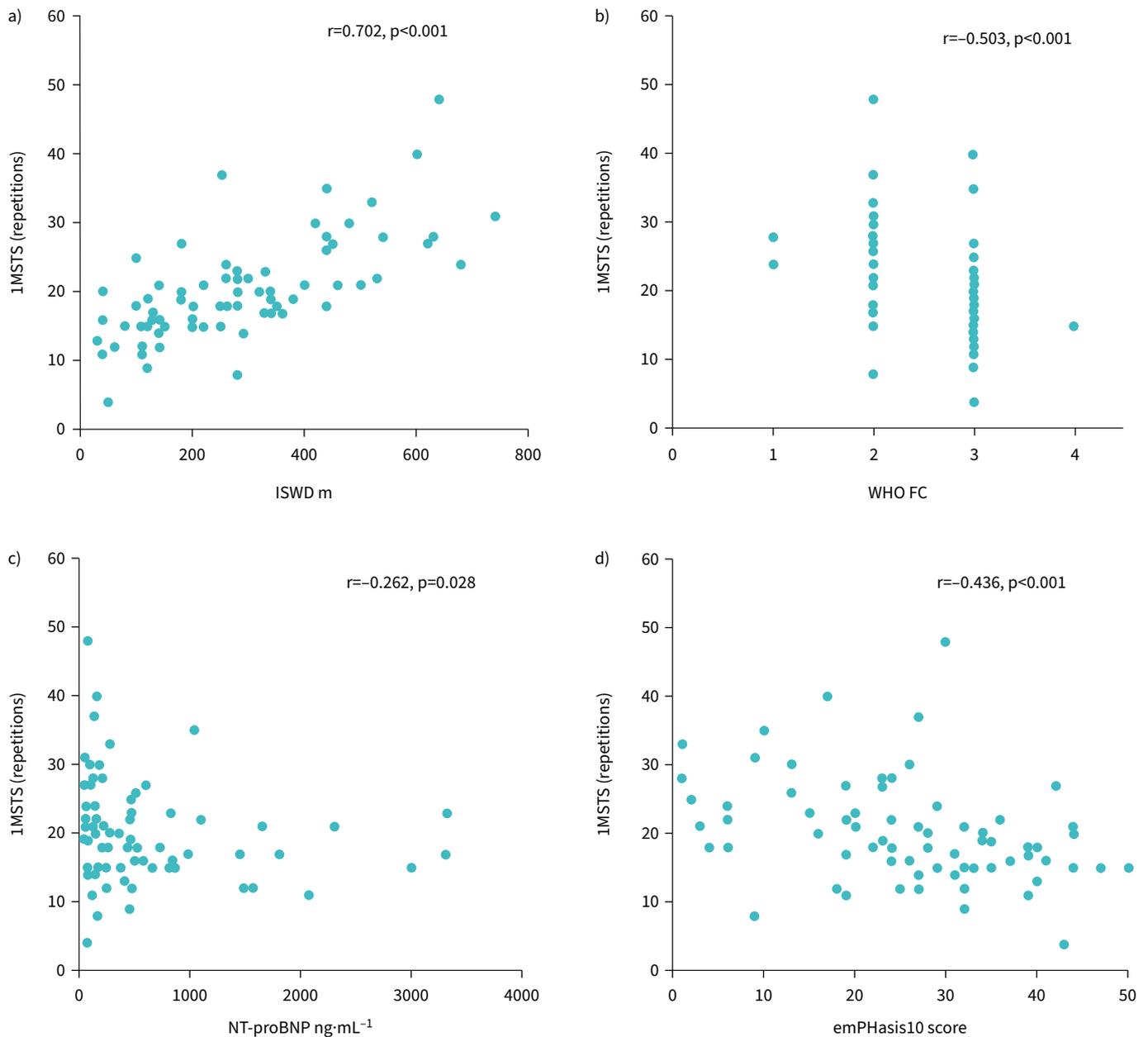


FIGURE 1 Scatter plots of 1-min sit-to-stand (1MSTS) against **a)** incremental shuttle walk distance (ISWD), **b)** World Health Organization functional class (WHO-FC), **c)** N-terminal pro b-type natriuretic peptide (NT-proBNP) and **d)** a patient-reported outcome measure (emPHasis10).

metrics used to assess disease severity, and has the characteristics of an exercise test that can be performed by patients remotely in the home.

Safety

No adverse events occurred in 75 hospital-based 1MSTS tests. This is consistent with an acceptable safety profile, supporting further exploration of the 1MSTS for remote assessment of exercise capacity in the home setting. Two patients undergoing hospital-based testing stopped before the end of the test due to leg pain and shortness of breath, in accordance with the test protocol [18].

Test characteristics

Our study demonstrates the submaximal nature of the 1MSTS when compared to the ISWT in PAH and CTEPH, with lower post-test changes from baseline in heart rate, oxygen saturation, systolic blood pressure

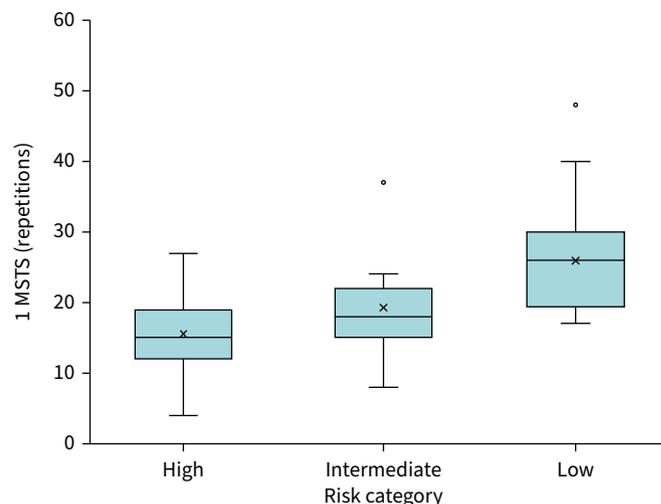


FIGURE 2 Box plot of 1-min sit-to-stand (1MSTS) against risk stratification bands.

and Borg score when compared to changes observed with the ISWT. This is in accordance with the findings of OZALEVLI *et al.* [11], who compared the 1MSTS to the 6MWD in patients with COPD.

This study also shows a strong correlation between the 1MSTS and ISWT ($r=0.702$, $p<0.001$). The 1MSTS also correlates significantly with other measurements used to assess patients with PAH and CTEPH, namely WHO-FC ($r=-0.449$), NT-proBNP ($r=-0.270$) and emPHasis10 ($r=-0.436$). Furthermore, these correlations were similar to those of the ISWT with the same parameters. Comparable studies in COPD, with smaller sample sizes, identified correlation coefficients between 1MSTS and 6MWD of between 0.57 and 0.67 [10, 17] as well as an association with age, quality of life and muscle strength [10, 11, 17].

The 1MSTS test comprises an activity commonly performed in daily life. This functional feature, along with the submaximal characteristics of the test, absence of adverse events in this study, its positive correlation with the ISWT, and scatter and distribution of values, suggests there is potential for its use as an exercise test conducted by patients at home, as a surrogate for hospital-based exercise testing. This is an important finding in the context of the increased use of remote consultations in the management of patients with PAH and CTEPH. The advantages of remote consultation include the potential for more frequent monitoring whilst reducing patient travel, stress and fatigue, improved access for patients with disabilities, and potential cost savings [21]. This approach can also empower patients to take a more active role in their own monitoring and can support patient-initiated follow-up. Increasingly, pulmonary hypertension centres are offering hybrid care models that incorporate both remote and face-to-face clinical consultations, structured to meet the needs of patients [8].

Risk assessment

Due to the progressive nature of PAH and the high risk for rapid deterioration, international guidelines [2] recommend regular risk assessment in PAH to aid treatment decisions. Risk assessment incorporates parameters including exercise testing, NT-proBNP and WHO-FC. Remote consultation without exercise testing diminishes the effectiveness of risk assessment [8].

Investigators have evaluated the use of device-based applications to measure 6MWD as a substitute for hospital-based exercise, using smartphone or physical activity monitors; to date, these studies have been inconclusive [22, 23]. Furthermore, this approach is limited to patients who own a smartphone, have reliable internet access [24] and can confidently walk outdoors. In contrast, these restrictions do not apply in the 1MSTS.

This study was not designed to look at thresholds that could be used to risk stratify patients with PAH. Nonetheless, it has a strong correlation with the maximal exercise test that it was benchmarked against (ISWT), and strong-moderate correlations within each of the risk stratification bands, where sample sizes

were lower. It also correlates with other measurements that can be used to risk stratify patients with PAH, namely WHO-FC, NT-proBNP and emPHasis10 score.

Limitations

This pragmatic study was designed to collect data with minimal disruption to clinical services and patients during the COVID-19 pandemic. To this end, all participants conducted their ISWT before the 1MSTS, which may have contributed to fatigue in the second test. Additionally, a practice test was excluded from the protocol; all participants had conducted at least one ISWT prior to their testing in this study, but none had previously completed the 1MSTS. The 1MSTS has been shown to have a learning effect in patients with COPD [10], and this may therefore have impacted on outcomes.

Further work

While this study supports the safety of the 1MSTS in the hospital setting and illustrates its potential role in risk assessment of patients with PAH and CTEPH, further examination of this exercise test is required. Future studies should compare the 1MSTS with the 6MWT and the results of CPET testing. A larger data set collected across multiple sites with a longer period of follow-up, including testing of home-based safety, would further inform the potential for use in remote risk assessment, along with inclusion of mortality data. Test and re-test to examine the learning effect of the 1MSTS in this patient group would be of value, as would studies to establish minimal clinically important difference of 1MSTS in PAH and CTEPH and its value in measuring response to treatment [17]. The survey results in this study suggest patients would be happy to conduct the 1MSTS at home, but it would be important to ascertain patients' perspectives on the wider use of remote assessment and patient-initiated follow-up. It would also be of interest to explore clinicians' perceptions of patient-recorded assessments, in comparison to the results of hospital-based testing.

Conclusion

This study has demonstrated the submaximal characteristics of the 1MSTS in PAH and CTEPH, its safety in the hospital setting, its positive correlation with the ISWT and potential role in remote risk assessment. Further evaluation of this exercise test is now warranted.

Provenance: Submitted article, peer reviewed.

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This study is registered at www.clinicaltrials.gov with identifier number NCT04903704.

Conflict of interest: C. Keen has received payment for participation in advisory boards, speaker fees and grant funding from Janssen. D.G. Kiely has received payment for participation in advisory boards, speaker fees and support to attend educational meetings from Acceleron, Janssen, GSK and Ferrer; he has received grant funding from GSK and Janssen. There are no conflicts for interest to declare for I. Smith, M. Hashmi-Greenwood or K. Sage.

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