Assessment of Instantaneous Heart Rate and Accelerometry Changes During 6-minute Walk Tests in Pulmonary Hypertension Using a Multi-modality Patch

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Abstract

The 6-minute walk test (6MWT) is widely used in the assessment in patients with pulmonary arterial hypertension (PAH) to measure disease progression or demonstrate improvement after adding additional treatments. Incorporating continuous heart rate monitoring during 6MWT, Cardiac Effort, has provided more granular information on physiologic stress during 6MWT. With the increased availability for patients to use remote monitoring, we developed an experimental setup and analytical tools to help patients conduct a 6MWT from home by incorporating a wearable device to measure changes in heart rate variables and acceleration. We enrolled 50 *subjects and computed a list of ECG and accelerometry measurements at rest, during the 6MWT, and after the test that could be measured easily in the home setting. We studied the reproducibility and absolute values of these measurements across multiple cohorts of PAH (stable and requiring therapy) and healthy subjects. The measurements were reproducible in healthy and stable PAH subjects. In the future, we envision the integration of these variables in a self-administered home 6MWT or other functional assessment to improve remote monitoring in PAH. This will further support patient care and healthcare professionals by detecting changes in clinical status early, especially as more therapies become available and are administered in the home setting.*

1. Introduction

The six-minute walk test (6MWT) is a frequently used submaximal exercise test to objectively measure functional capacity in chronic cardiopulmonary diseases [1]. It is widely used in patients with pulmonary arterial hypertension (PAH) to assess disease progression or the efficacy of drug treatment. In a clinical setting , the test is performed in a designated unobstructed hallway (>30 m) where patients can be monitored for safety and compliance [1]. Cardiac Effort, the number of heart beats used during the 6MWT/walk distance, has been shown to correlate with stroke volume and brought light into the idea of incorporating heart rate changes when interpreting walk distance [2].

In recent years there has been a push to perform the 6MWT in the home setting. The initial reporting of a home 6MWT in PAH did not incorporate technology and was very similar to the ATS guidelines [3]. New digital health solutions, such as smartphone fitness applications and wearable devices, have been evaluated to facilitate conducting the 6MWT remotely in PAH on a modified walking space [4]. Importantly, both studies showed it was safe and feasible to perform 6MWT in a home setting to remotely assess patients' functional exercise capacity. Similar findings have also been reported with acceptable levels of reliability and reproducibility in chronic obstructive pulmonary disease [4].

When assessing a home 6MWT, it is paramount to develop a method that not only is reliable, safe, but also assesses whether the effort the individual performing the self-testing engages into the test. For the 6MWT to be most beneficial for interpretation for clinicians, it is essential that patients perform the exercise with a level of physical exertion that ensures they can walk as far as they can with maximal effort to accurately assess changes overtime. This decreases variability in the measurement. Additionally, the distance covered in 6 minutes must be recorded accurately. Additional physiological measurements such as heart rate (HR) provide physiologic insight into limitations into walk distances achieved.

We propose a method that uses a multi-modal ECG patch loaded with an accelerometer as a home-based solution to implement accurate self-tested 6MWT in patients with PAH that encompasses physiological measurements in addition to the accurate measurement of the distance walked by the patients.

2. Methods

We analysed paired 6MWT data from 50 subjects enrolled in an IRB-approved study involving PAH patients and healthy subjects[1]. This included 13 health subjects (H) and 37 PAH subjects, including 18 stable (S), 7 requiring treatment intensification (TI) on

background therapy, and 12 with newly diagnosed PAH starting oral therapy (TN). The 6MWT were performed according to ATS guidelines on an obstructed 30 m walking space [2]. 6MWT included in the analysis were repeated twice within 30 days (+/-7 days) in the healthy control and stable group and between 1-3 months in the treatment groups.

2.1. Monitoring Equipment

During the 6MWT, all subjects wore a Biostamp nPoint ECG patch (MC10, Cambridge, MA) which collected single-lead ECG and accelerometry signals in a continuous manner. The data was transmitted to a web platform via Wi-Fi network and all data were de-identified and stored in a HIPAA compliant cloud server.

The ECG signal was captured at 250 Hz sampling frequency with an amplitude resolution of 16 bit/mV. The data was prefiltered following the standard method recommended by AAMI standard for ambulatory ECG analyses. The accelerometer data was sampled at 31.25Hz with time stamps enabling us to synchronise ECG and XYZ acceleration tracings after signal resampling. Mean amplitude deviations (MAD) of vector magnitude counts .

2.2 Comprehensive Measurements for the 6-Minute Walk Test

The ECG signal and accelerometer data all have specific timestamps. Each data point for HR and MAD are average value spans 4 seconds accommodating the sampling rate of the accelerometer. Cardiac beats were automatically detected and HR was extracted for several periods after data was manually adjudicated for the presence of arrhythmias (ventricular and atrial ectopic beats), and artefacts. We report HR at baseline (HRb), maximum HR (HRm), HR acceleration during exercise (HRa), HR at 1-minute recovery (HRr), SDNN during recovery (SDNr), and number of laps (NL). These measurements are described in Figure 1.

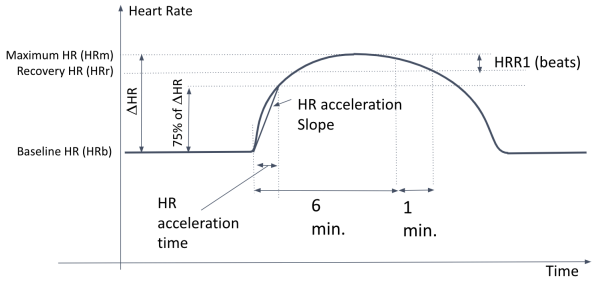

Figure 1. Illustration of the measurements computed based on heart rate continuously monitored during the 6 MWT. The plot represents the HR changes over time from the start of the test to the end of the recovery period. We present our results using the absolute value (val), the so-called test-retest variability (TV) or within subject variability, and the coefficient of variation (CV) across the patient cohorts. TV was computed as in (1):

$$(1) TV = \frac{1}{N}\sum_{i=1}^{N}\frac{\left|test_i - restest_i\right|}{(test_i + restest_i)/2}.\ 100\%$$

2.3 Study Population

Subjects were recruited from University of Rochester's Pulmonary Hypertension Association-accredited Comprehensive Care Center. The study was undertaken during the pandemic, from June 2020 to October 2021. PAH patients were adults (age >18 years old), they must have had a diagnosis of WHO Group 1 PAH to be eligible for enrollment into the study [1]. They were enrolled at the time of a clinic visit. The study also included a control group consisting of 13 healthy subjects. Enrollment criteria for the 4 categories were as below.

Table 1. Summary of the inclusion/exclusion criteria for patient selections.

Group	Inclusion/exclusion criteria
Healthy (N=13)	healthy controls
Stable PAH (N=18)	Patients without indication to change therapies (or those on maximal therapy) were assigned to the stable group
PAH+treatment initialization (N=12)	Treatment naïve patients
PAH+treatment intensification (N=7)	Patients with clinical indications (persistent breathlessness or exercise intolerance thought to be responsive to additional therapy) prescribed with additional PAH therapy.

2.4 6-minute walk test (6MWT)

All subjects performed two 6MWT according to American Thoracic Society guidelines [1]. All 6MWT were performed without a mask.

3. Results

Our study population included 50 subjects with 28 females, age: 54±16 years old. The patient cohort was primarily caucasian with one Black woman.

The time of the second 6MWT varied between subjects and were as follows: Healthy: 8 ±8 days, Stable PAH:19 ± 19 days, PAH+treatment initialization: 51 ± 19 days, and PAH+Treatment intensification: 58 ± 31 days.

3.1 Reliability Analysis

We investigated the reproducibility and variability of the measurements proposed in Figure 1.

Table 1 provides the values for the measurements of heart rate before, during and after the 6MWT, as well as the measurements of dynamic recovery factors, namely, HRr and SDNr measurements. It illustrates the stability of the measurements across the patient categories and phases of the 6MWT.

Table 1. Measurement values for test and retest experiments across patients groups. The values are in general in the same range

	6MWT	Healthy	Stable PAH	PAH+TI	PAH+TN
N		13	18	7	12
HRb (bpm)	1	77	82	76	85
	2	73	85	81	88
HRm (bpm)	1	133	131	115	124
	2	138	133	117	129
HRa (bpm)	1	81	111	100	121
	2	111	128	101	133
HRr (bpm)	1	25	19	13	16
	2	30	23	14	16
SDNr (ms.)	1	8.7	6.4	1.3	2.4
	2	9.6	7.4	1.9	1.9
NL (n)	1	21.5	15.7	13.1	13.8
	2	21.5	16.0	13.3	15.2

The values of the measurements described in the Section 2.2 for the first and second 6MWT within the 4 groups of subjects. There are variable heart rate changes for a given walk distance (laps calculated using accelerometry data). In Table 2, we present the test retest variability for the measurement presented in Table 1.

The TV values reveal a lower stability for the measurements associated with the dynamic factors measured during the 6MWT (HRr and SDNr). As expected, greater changes were observed in patients undergoing treatment intensification (PAH+TI), and less variability were observed in the stable groups. The treatment groups showed a higher level of variability in test and retest measurements showing changes in physiology after adding therapy were captured with these variables.

Table 2. Summary of the reliability analysis of the 5 measurements implemented in the 6MWT based on a single-lead ECG patch worn during the test.

		Healthy	Stable PAH	PAH+TI	PAH+TN
TV	HRb	10	8	9	12
	HRm	9	6	8	6
	HRa	49	27	35	38
	HRr	38	42	80	46
	SDNr	36	38	52	41
CV	HRb	22	19	14	26
	HRm	21	17	11	18
	HRa	77	41	39	50
	HRr	52	63	62	57
	SDNr	48	59	47	55

In Table 2, we highlighted the CV values >50% dimmed to have low stability. We note that the HRr has the lowest CV values including in the group of Healthy subjects which tends to demonstrate intrinsic technical instability in the measurement of the HR at 1-min recovery time. In most measurements, we observed CV values of less than 50%, demonstrating that the proposed measurement can be reliably extracted from the signals captured by the ECG patch.

4. Discussion

The 6MWT is a submaximal exercise test that allows for assessing disease progression and evaluation for improvement after adding a treatment. Traditionally, the test is conducted in a clinical setting with supervision, not because it requires extensive medical device support. However, with the advent of home-based monitoring devices for cardiac activities (such as ECG wearables) and physical activities (such as accelerometry and GPS technology), there is now an opportunity to conduct the 6MWT at home (using smartphones or wearables) and more frequently than what is currently done. This could allow for a clinically useful test to be performed seamlessly in a fully remote manner [4,5]. Preliminary investigations in PAH using chest based patch [4] and of this concept when using a smartphone application have been successful and demonstrated a strong usability level and remarkable patient's acceptance [6].

In appropriately selected patients, the remote 6MWT could find utility in monitoring functional status in PAH patient populations when assessing for clinical worsening or while titrating a medication. This tool could be utilised by medically stable, low-risk patients as a self-regulated monitoring method. It has the potential to encourage greater patient participation in their own health monitoring, thereby enhancing their overall engagement in health management. This is particularly beneficial for patients who are unable to attend clinic visits regularly. [7].

Integrating continuous ECG recording during the 6MWT is now feasible remotely and offers significantly more clinically relevant information than relying solely on accelerometry and sparse heart rate values. Continuous

ECG monitoring provides valuable insights into the dynamic aspects of heart rate in relation to energy expenditure, which is likely to yield deeper understanding of the patient's status, treatment effects, and disease progression. Furthermore, the integration of safety notifications could enhance the safety of conducting the test at home. This monitoring technology could also optimise the test by helping patients adjust their performance based on historical data from previous tests and changes in reliability measures over time.

In this project, we have implemented a series of measurements using ECG and accelerometer data collected by a single patch. We provide a preliminary set of results from a series of experiments to determine whether a reliable quantitative assessment of the 6MWT can be performed with these technologies. The tests were conducted in a hospital setting but without support, in order to mimic home conditions. We analysed the measurements post-experiment and provided a simple assessment of intra-patient variability across two tests conducted between 1 and 90 days apart in 52 subjects, including both PAH patients and healthy individuals.

5. Conclusion

We developed a series of parameters to characterise heart rate variations and their dynamics from data captured by a multi-modal patch during a 6MWT in patients with pulmonary hypertension. We evaluated the variation of these parameters in a cohort of healthy subjects and PAH patients. The results support the concept of wearable-based monitoring of 6MWT using such wearable technology.

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