VALIDATION AND RESPONSIVENESS OF WEARABLE BIOMETRIC TECHNOLOGY TO MONITOR CARDIAC AND VENTILATORY PARAMETERS AT REST AND DURING EXERCISE IN COPD

by

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ABSTRACT

Introduction: The use of wearable technology for ambulatory physiological monitoring has become increasingly popular in recent years. However, only about five percent of these wearable devices have been formally validated in healthy adults, let alone in people with chronic obstructive pulmonary disease (COPD). **Objectives**: To assess (a) the validity of the Hexoskin biometric smart shirt for measuring cardiopulmonary parameters at rest and during exercise in people with COPD and (b) the responsiveness of the Hexoskin biometric smart shirt to detect changes in minute ventilation (V'_E), tidal volume (V_T), respiratory rate (RR), heart rate (HR), inspiratory capacity (IC) and inspiratory reserve volume (IRV) during exercise following a 7-8 week pulmonary rehabilitation (PR) program. **Methods**: Cardiopulmonary parameters were collected using Hexoskin and the SensorMedics Vmax 229d metabolic cart in 14 adults with COPD (Forced expiratory volume in 1-sec = 69 ± 26% predicted) during a pre-PR incremental cardiopulmonary cycle exercise test (CPET) (n=13), and both a pre- (n=13) and post-PR (n=8) constant workload cycle CPET performed at 75% of the peak power output achieved during the pre-PR incremental CPET. **Results**: Temporal patterns recorded by Hexoskin and Vmax were very similar in all CPET trials for the cardiopulmonary parameters measured. Strong correlations were found between the two devices for measuring V'_E (R^2=0.80-1.00), V_T (R^2=0.48-1.00), RR (R^2=0.69-1.00), HR (R^2=0.71-1.00), IC (R^2=0.62-1.00) and IRV (R^2=0.58-1.00) throughout CPET as well as their magnitudes of change from rest to peak exercise (R^2=0.69-0.90). Individual subject pre- to post-PR changes in each of the cardiopulmonary parameters were highly correlated between the two devices (R^2=0.54-0.97). **Conclusion**: Hexoskin is a valid and responsive tool for measuring cardiac and ventilatory parameters at rest and during exercise in people with COPD.

RÉSUMÉ

Introduction: L'utilisation de la technologie portable pour la surveillance physiologique ambulatoire est devenue de plus en plus populaire ces dernières années. Cependant, seulement cinq pour cent de ces appareils portables ont été officiellement validés pour des adultes en bonne santé, et encore moins pour ceux avec la maladie pulmonaire obstructive chronique (MPOC). **Objectifs:** Évaluer (a) la validité de la chemise intelligente biométrique Hexoskin pour mesurer des paramètres cardiopulmonaires au repos et pendant l'exercice dans les adultes avec l'MPOC, ainsi que (b) sa capacité de détecter les changements en ventilation minute (V'_E), volume courant (V_T), fréquence respiratoire (RR), fréquence cardiaque (HR), capacité inspiratoire (IC) et volume de réserve inspiratoire (IRV) pendant l'exercice suivant un programme de réadaptation pulmonaire (PR) de 7-8 semaines. **Méthodes:** En utilisant Hexoskin et le SensorMedics Vmax 229d carte métabolique, les paramètres cardiopulmonaires ont été recueillis pour 14 adultes subi de l'MPOC (Volume expiratoire maximal en une seconde = 69 ± 26% prévus) pendant un test d'effort cardiopulmonaire (CPET) incrémentielle pré-PR (n=13), ainsi qu'un pré- (n=13) et post-PR (n=8) CPET de charge constante à 75% de la puissance maximale atteinte au cours de la CPET incrémentielle pré-PR. **Résultats:** Les schémas temporels enregistrés par Hexoskin et Vmax étaient très similaires dans tous les CPETs pour les paramètres cardiopulmonaires mesurés. Des hautes corrélations ont été trouvées entre les deux appareils pour mesurer V'_E (R^2=0.80-1.00),V_T (R^2=0.48-1.00), RR (R^2=0.69-1.00), HR (R^2=0.71-10.00), IC (R^2=0.62-1.00) et IRV (R^2=0.58-1.00) au courant de CPET, ainsi que leurs variances en amplitude de repos à l'effort maximale (R^2=0.69-0.90). Pour chaque individu, les changements de pré- à post-PR pour tous les paramètres cardiopulmonaires mesurés étaient fortement corrélées entre les deux appareils (R^2=0.54-0.97).

Conclusion: Hexoskin est un outil valide et sensible pour mesurer les paramètres cardiaques et ventilatoires au repos et pendant l'exercice dans les adultes atteintes de l'MPOC.

PREFACE AND CONTRIBUTION OF AUTHORS

Raffoul, D was the primary author and played the principle role in the analysis and interpretation of the data as well as in the preparation of this thesis and the accompanying manuscript.

Murray, S and Tracey, L played the principle role in the collection of the data, and Frank Niro contributed to the extraction of the data.

Jensen, D contributed to the conception, design and financial support of this study, as well as to the analysis and interpretation of data and the preparation of this thesis and accompanying manuscript.

CHAPTER 1. Review of Literature

1.1 Pathophysiology and Impact of COPD

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality in Canada [1-6]. In fact, it is the only chronic disease with increasing mortality, currently estimated to be the third leading cause of death worldwide by 2020 [7, 8].

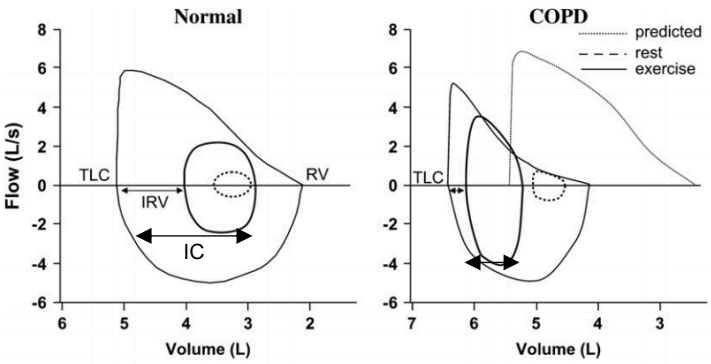


FIGURE 1.1. Tidal flow-volume loops at rest and during exercise in relation to maximal flow-volume loops in a) health and b) COPD [27].

COPD is a progressive and debilitating disease that is characterized by persistent respiratory symptoms (i.e., shortness of breath, cough and sputum production) and airflow limitation [8-10]. Specifically, expiratory flow limitation is the pathophysiologic hallmark of the disease, and it is caused by a mixture of chronic obstructive bronchiolitis (i.e., small airway disease) and pulmonary emphysema (i.e., parenchymal destruction) [8, 9]. Chronic inflammation contributes to the narrowing of the small airways, mucus hypersecretion and the destruction of the lung parenchyma [8, 9, 11]. The combination of these pathophysiological abnormalities (increased airway resistance and decreased lung elastic recoil) make the airways susceptible to collapse and hinders their ability to remain tethered-open during expiration [12]. In other words, it is difficult for COPD patients to empty their lungs prior to taking their next breath in, since their end-expiratory lung volume (EELV) is unable to decline back to the normal relaxation volume of the respiratory system prior to the next inspiration [8, 9, 13]. Ultimately, at rest, this leads to pulmonary gas trapping and static lung hyperinflation (SH), which explains the increased total lung capacity (TLC) in COPD [14-16]. However, despite having bigger lungs, it is important to note that these patients have less room to breathe compared to healthy individuals [14, 15]. This is evidenced by the fact that inspiratory

capacity (IC), which represents the true operating limits for tidal volume (V_T) expansion in flow-limited individuals, is diminished in COPD [17]. As well, this is shown by the flow-volume loops in Figure 1.1 that illustrate the erosion of both IC and inspiratory reserve volume (IRV) in COPD compared to health [18].

Furthermore, under conditions of increased ventilatory demands and reduced expiratory time (e.g., exercise), COPD patients dynamically hyperinflate (DH) and are forced to breathe at increasingly higher operating lung volumes that approach TLC [15, 19, 20]. More specifically, DH occurs since, unlike healthy individuals who can expand their V_T during exercise by simultaneously increasing their end-inspiratory lung volume (EILV) and decreasing their EELV, the majority of COPD patients can only expand V_T during exercise by increasing EILV [18]. Thus, while vital capacity (VC) represents the operating limits for V_T expansion in health, inspiratory capacity (IC) represents the operating limits for V_T expansion in COPD [15, 18, 20]. In other words, each tidal breath becomes increasingly limited by higher EELVs and forces COPD patients to breathe at the upper alinear portion of the respiratory system's sigmoidal pressure-volume curve where elastic loading and functional weakening of the inspiratory muscles is heightened (Figure 1.2) [18, 21, 22]. In order to

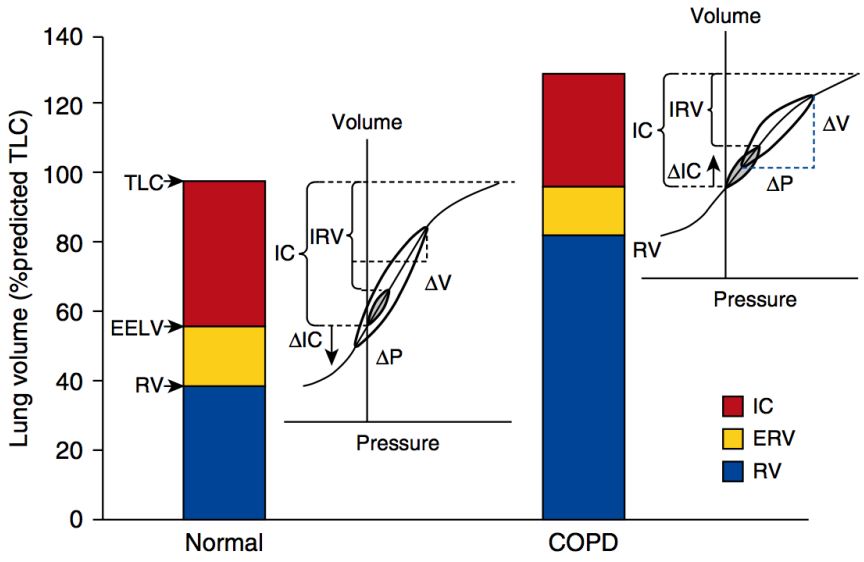


FIGURE 1.2. Resting lung volumes and the respiratory system's pressure-volume (P-V) curves in COPD versus health. Tidal P-V curves are shown at rest (filled area) and during exercise (open area) [22].

compensate for such abnormalities in dynamic respiratory mechanics, greater neural respiratory drive is needed to support a given level of ventilation and pulmonary gas exchange in these patients [23]. Ultimately, these consequences of DH translate into an increased work (and oxygen cost) of breathing (WOB) as well as an increased sensation of dyspnea (breathlessness) with attendant exercise intolerance [18].

Unfortunately, the result of the intolerable dyspnea experienced upon exertion in COPD is typically the avoidance of physical activity [18]. Not only does this make it difficult for COPD patients to perform activities of daily living (ADLs) that require a certain level of exertion, but it further intensifies their respiratory symptoms through the dyspnea-inactivity vicious cycle (Figure 1.3) [9, 24, 25]. Briefly, airflow limitation leads to both lung hyperinflation and COPD exacerbations, which independently contribute to exercise limitation and deconditioning of both the cardiovascular system and locomotor muscles [25]. As well, lung hyperinflation results in increased sensations of dyspnea *via* mechanisms that are beyond the scope of this thesis but described in detail elsewhere [15, 25, 26]. Thus, a vicious cycle occurs where dyspnea leads to physical inactivity, which leads to reduced exercise capacity, which leads to physical deconditioning, which further contributes to sensations of dyspnea [25]. Ultimately, this cycle highlights the consequences of SH and DH and it has meaningful implications for COPD patients considering that chronic breathlessness, physical inactivity and reduced exercise capacity all strongly and independently predict mortality in this patient population [12, 16, 24, 27]. Thus, due

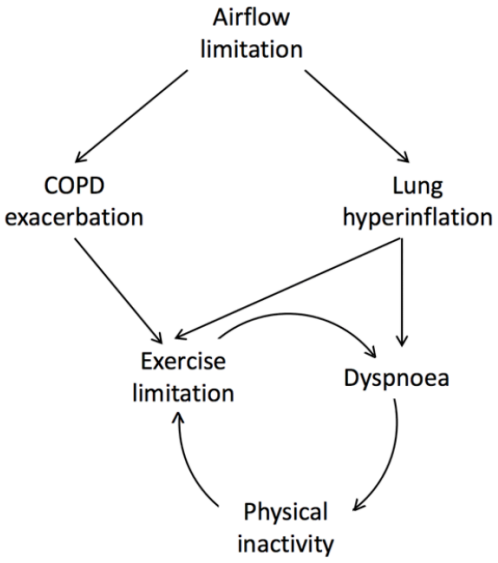


FIGURE 1.3. Dyspnea-inactivity vicious cycle [31].

to the impact of lung hyperinflation, wearable technologies capable of continuously monitoring breathing pattern and tracking the behaviour of dynamic operating lung volumes outside of a clinical care and/or research setting have clear advantages for people with COPD and their health care providers. For instance, wearable biometric technologies may permit health care providers and researchers to advance their understanding of the pathophysiological mechanisms of patient-reported symptoms in daily life that cannot be adequately captured using task-based questionnaires, such as the Medical Research Council dyspnea scale or the Baseline/Transition Dyspnea Index. They may also provide health care providers and researchers with unique opportunities to evaluate the efficacy of therapeutic interventions (e.g., bronchodilators) on sensory-respiratory mechanical relationships during ADLs; for example, an effective intervention may be identified as a patient being able to achieve a higher minute ventilation (V'_E) for a given level of breathlessness because operating lung volumes are more favourable throughout the day and/or breathing pattern is better optimized; that is, EELV and EILV are lower (or IC and IRV are larger); and V_T is bigger, while respiratory rate (RR) is lower.

1.2 Wearable Devices for Physiological Monitoring

The use of wearable technology to monitor human health and fitness has skyrocketed in recent years [28-31]. As illustrated below in Figure 1.4, these technologies include wrist-worn devices, patches, straps, bands and smart garments that make use of sophisticated sensors to capture health data (e.g., heart rate [HR], RR, movement patterns, tissue oxygenation and sleep) and advanced wireless communication protocols to relay the data to remote locations (e.g.,

smartphone) [32-35]. Ultimately, contrary to most laboratory-based technologies and clinical tools, these devices are capable of continuous physiological monitoring in natural environments [35]. Thus, while they are mainly used by healthy adults to track personal wellness, they have potential applications in medical and research contexts where ambulatory physiological monitoring may be beneficial. However, in order to determine whether wearable technologies should be used for such medical and research purposes, it is essential to first evaluate their performance in relation to laboratory standard equipment. In fact, only about five percent of consumer-grade wearable technologies have been formally validated [36]. As well, when it comes to tracking physiology in individuals with chronic diseases, there is a paucity of devices that have undergone validity and reliability testing. Thus, in order to get an overview of what currently exists in terms of the wearable technologies on the market, the ones that have been formally validated and the ones that have been tested on patients with COPD, this section of the thesis will summarize the most popular devices in the following three categories: (1) wrist-worn devices; (2) sleeves, patches and portable hardware devices; and (3) smart garments.

FIGURE 1.4. Summary of wearable technologies available for monitoring health/performance and targeted physical measurements [36].

1.2.1 Wrist-worn Devices

Wrist-worn devices consist of different sensors and algorithms to provide users with key metrics regarding their HR, RR, physical activity and sleep [36-38]. For example, the HELO

(Health and Lifestyle Oracle, Burlington, Ontario, Canada) smart watch claims to monitor electrocardiogram (ECG), HR, RR, blood pressure as well as oxygen saturation, and display the data in real-time [36]. However, this, among several devices of the sort, has yet to undergo validity and reliability testing [36]. In fact, most of the validated wrist-worn devices exist as activity trackers that make use of accelerometer technology to estimate parameters like steps, distance, time spent in physical activity and energy expenditure [30, 37, 39, 40]. For instance, consumer wearable triaxial accelerometers like Fitbit (Fitbit Inc., San Francisco, CA, USA) and Misfit (Misfit, San Francisco, CA, USA) are being increasingly used in research-settings, since they have been validated against research-grade devices for counting steps [37, 41, 42]. However, studies have still not shown that Fitbit and Misfit devices accurately measure distance, time spent in physical activity or energy expenditure [30, 37, 41, 43]. As well, they have not yet been validated in COPD patients. However, other wrist-worn devices like the triaxial DynaPort MiniMod (McRoberts BV, The Hague, The Netherlands) accelerometer and the biaxial StepWatch (Orthocare Innovations, Mountlake Terrace, WA, USA) accelerometer have both been found to accurately measure steps in COPD [39]. Additionally, DynaPort MiniMod has been found to accurately provide information on body position and distinguish between periods of physical activity and sedentary behaviours [44]. While these wearables seem to be promising for tracking physical activity in COPD patients, researchers have recently identified that activity monitors of the sort still need to improve their accuracy as they tend to be insensitive to low walking speeds (which are characteristic of people with COPD [45]) and that readings become altered when the devices are shaken [46]. Moreover, wrist-worn devices based on actigraphy, like the Actiwatch Spectrum Pro (Philips Respironics, Murrysville, PA, USA), have been widely used for the study of sleep medicine over the last 20 years, as they have been validated against gold-standard

polysomnography [38, 47]. Additionally, smart watch activity trackers like UP (Jawbone, San Francisco, CA, USA) and Fitbit Charge2 (Fitbit Inc., San Francisco, CA, USA) have been validated for detecting sleep as well as measuring total sleep time and the time-point of wake after sleep onset [36, 38, 48-50]. However, these results are only true for healthy individuals, as actigraphy was found to overestimate sleep time and sleep efficiency, as well as underestimate the time-point of wake after sleep onset in individuals with chronic diseases, like COPD [36, 38, 48-52].

In sum, despite the abundance of wrist-worn devices currently available on the market, very few have been validated for the parameters they claim to measure and even fewer have been evaluated for their responsiveness to detect change in physiological parameters over time within individuals. Furthermore, among the wrist-worn devices that have been validated, none are capable of tracking V_T, which when combined with RR, provides information on V'_E, which is the major stimulus to breathlessness in COPD. As well, none of these devices can track the behaviour of dynamic operating lung volumes (i.e., IC and IRV), which are key parameters of interest for physiological monitoring in COPD, particularly as it relates to understanding the pathophysiological mechanisms of exertional symptoms (notably breathlessness) as well as evaluating interventional efficacy (or lack thereof) in people with COPD.

1.2.2 Sleeves, Patches and Portable Hardware Devices

Sleeves, patches and portable hardware devices can be used to measure a range of health parameters, including muscle oxygenation, HR and RR [36]. For example, Moxy (Fortiori Design, LLC, Hutchinson, MN, USA) and PortaMon (Artinis Medical System, Einsteinweg, The Netherlands) are both small portable hardware devices that can be manually attached to any muscle group, and have been validated against phosphorus magnetic resonance spectroscopy for

measuring muscle oxygenation [36, 53-55]. Additionally, the BSX Insight (SX Athletics, Austin, TX, USA) wearable sleeve was designed for placement at the calf, and has been validated against a fiber-based frequency-domain near-infrared spectroscopy system and blood lactate measurements for measuring muscle oxygenation as well as lactate levels, respectively [36, 56]. Of these validated technologies for monitoring metabolism non-invasively, only PortaMon has been evaluated in COPD patients [57]. In fact, the device was found to be a valid and reliable method for assessing COPD-related loss of muscle oxidative capacity [57]. Furthermore, TeleOx (SRETT, Boulogne-Billancourt, France), an oxygen flowrate remote monitoring device, was found to accurately measure RR in COPD patients compared to a polygraph [58]. While this portable hardware device is not necessarily a wearable technology, it is the only validated device of the sort that allows for automatic remote transmission of RR data, in this patient population, and was therefore relevant to mention.

Moreover, with respect to ambulatory cardiac monitoring, several ECG patches have been put on the market to provide patients with the option of having their data recorded with increased comfort compared to traditional Holter monitors [59]. Of these devices, the Zio XT Patch (iRhythm Technologies, San Francisco, CA, USA) has been extensively evaluated in both health and disease, and has been approved for use by the United States Food and Drug Administration [59-61]. It is a water-proof, wireless, single-use, 1-lead adhesive chest wall device that continuously monitors cardiac rhythm for up to 14 days [59]. Validation studies in patients being evaluated for cardiac arrhythmias have shown that the Zio XT Patch has a very high concordance in detecting atrial fibrillation compared with the Holter monitor and even detects more significant clinical events than the conventional Holter monitor [62, 63]. However, the main disadvantage of this technology is that it does not provide users with real-time feedback, as the device has to be

mailed to the healthcare provider for analysis [59]. On the other hand, wearable devices like the Lief patch (Lief Therapeutics, San Francisco, CA, USA) and the Zephyr strap (Medtronic, Dublin, Ireland) are capable of providing users with immediate feedback regarding cardiopulmonary parameters like HR and RR [36]. However, these devices have not (yet) undergone validity and reliability testing [36].

Ultimately, similar to the wrist-worn devices, the sleeves, patches and portable hardware devices on the market seem to serve as promising tools for monitoring the parameters that they have been validated for. However, they have not been evaluated for aspects related to responsiveness, nor do they offer COPD patients and their healthcare providers with the possibility to track V_T expansion (and with the combination of RR, V'_E) or operating lung volumes (i.e., IC and IRV).

1.2.3 Smart Garments

Smart garments are the most promising wearable devices for potential use in the medical and research fields, because they consist of integrated biosensor technology to allow for comprehensive ambulatory physiological monitoring [36, 59]. Examples of such garments include: DynaFeed (Far Eastern New Century Corporation, San Jose, CA, USA), Sensoria (Sensoria, San Francisco, CA, USA), Athos (Mad Apparel Inc., Redwood City, CA, USA) and Hexoskin (Carré Technologies Inc., Montreal, QC, Canada) [36]. While

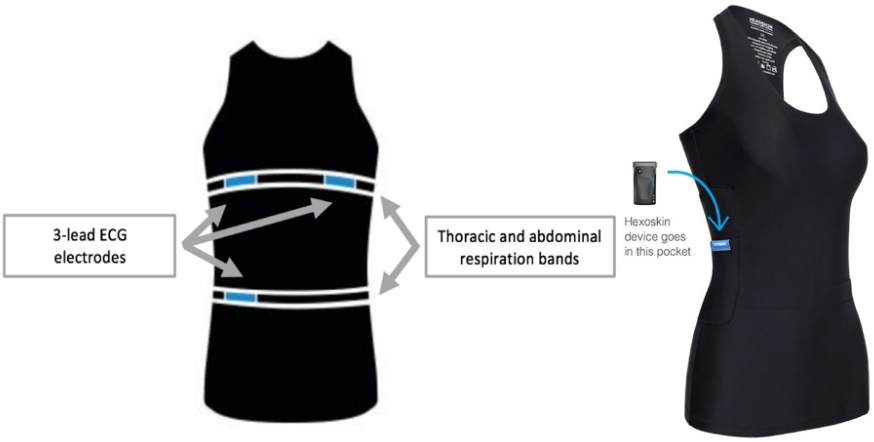


FIGURE 1.5. Hexoskin device and cardiopulmonary sensors.

wearables of this sort tend to perform similar functions and measure similar parameters, Hexoskin has been increasingly gaining the most attention, and is the only one to have been independently validated by several research groups [36, 38, 59, 64-66].

The Hexoskin technology involves a biometric smart shirt as well as the Hexoskin device itself, which attaches to the shirt to record and collect data (Figure 1.5). The shirt contains a hip tri-axial accelerometer, two respiration bands (thoracic and abdominal) and three-lead ECG electrodes (two on the thoracic band, and one on the right side of the abdominal band) (Figure 1.5) [64, 65]. Cardiac, ventilatory and hip motion intensity signals are detected by the embedded sensors on the smart shirt, recorded by the Hexoskin device and, through Bluetooth or a USB connection, the data gets transmitted to a smartphone or computer where the user can view the recorded data on either the Hexoskin App or the Hexoskin web dashboard [35, 64]. Ultimately, this wearable technology provides users with real-time feedback on HR, HR variability, RR, V_T, V'_E, steps and cadence [36]. Additionally, through wearable sensor analysis platforms, the data recorded by the Hexoskin respiration bands have the potential to monitor the behaviour dynamic of operating lung volumes, specifically EELV (or IC assuming that TLC remains unchanged) and EILV (or IRV, which is calculated as the difference between IC and V_T). Thus, due to the potential of the Hexoskin biometric smart shirt to measure relevant cardiopulmonary physiology in COPD, namely breathing pattern (V_T, RR) and operating lung volumes (IC, IRV), it was selected as the focus of the research project described below.

1.3 Research Objectives

Overall, the objective of this M.Sc. thesis project was to fill in a gap in the literature as there is a paucity of wearable technologies currently available for continuously tracking

physiology, particularly breathing pattern and operating lung volumes, in COPD. Specifically, the purpose of this project was two-fold: (1) to evaluate the validity of the Hexoskin biometric smart shirt for measuring cardiopulmonary parameters at rest and during laboratory-based CPET in adults with COPD; and (2) to evaluate the responsiveness of the Hexoskin biometric smart shirt to the stimulus of exercise and its ability to detect changes in V'_E, V_T, RR, HR, IC and IRV following completion of a 7-8 week pulmonary rehabilitation (PR) program, which included thrice weekly rehabilitative exercise training (ExT).

CHAPTER 2. Validation and Responsiveness of Wearable Biometric Technology to Monitor Cardiac and Ventilatory Parameters at Rest and During Exercise in COPD

2.1 Abstract

We evaluated the validity of the Hexoskin biometric smart shirt (n=34) as well as its responsiveness to detect rehabilitative exercise training-induced (n=7) changes in cardiac and ventilatory parameters, in adults with mild-to-very-severe COPD (mean ± SD FEV_1 = 69 ± 26% predicted [range: 20-105% predicted]). Temporal patterns recorded by Hexoskin and the SensorMedics Vmax 229d metabolic cart were very similar throughout symptom-limited incremental and constant workload cardiopulmonary cycle exercise tests (CPET) for the parameters measured. Strong correlations were found between the two devices for measuring V'_E (R^2=0.80-1.00), V_T (R^2=0.48-1.00), RR (R^2=0.69-1.00), HR (R^2=0.71-1.00), IC (R^2=0.62-1.00) and IRV (R^2=0.58-1.00) throughout CPET as well as their magnitudes of change from rest to peak exercise (R^2=0.69-0.90). Furthermore, individual subject pre- to post-PR changes in each of the cardiopulmonary parameters were also highly correlated between the two devices (R^2=0.54-0.97). In conclusion, Hexoskin is a valid and responsive tool for measuring cardiac and ventilatory parameters at rest and during exercise in people with COPD.

2.2 Introduction

The growing commercial market for ambulatory physiological monitoring has led to the development of a wide range of devices that can continuously track parameters like heart rate (HR), respiratory rate (RR), movement patterns, tissue oxygenation and sleep [30, 36]. However, despite their rapidly increasing popularity, very few (~5%) of these devices have been formally validated in healthy individuals, let alone in individuals with chronic diseases like chronic obstructive pulmonary disease (COPD) [36]. As well, most of the existing wearable technologies (e.g., smart watches, straps and patches) for health monitoring are only capable of measuring few physiological parameters. This explains why they have only been validated for single (or very few) parameters and, therefore, do not provide a holistic view of an individual's integrative cardiopulmonary physiology [30, 36, 38]. Fortunately, wearable smart garments have overcome this limitation by integrating multiple biosensors [36, 59]. Of these garments, the Hexoskin biometric smart shirt has been the only one to be independently validated by several research groups [36, 38, 59, 64-66]. Specifically, researchers found that during lying, sitting, standing and walking activities in healthy adults, Hexoskin accurately and consistently tracked HR, RR, hip motion intensity, tidal volume (V_T) and minute ventilation (V'_E) compared to laboratory standard devices [64]. As well, in elite cyclists, during a progressive cycle exercise test to exhaustion, Hexoskin was found to be valid and reliable for measuring HR and RR compared to the MetaMax 3B metabolic cart [66]. However, validation research has yet to explore Hexoskin's accuracy for measuring cardiopulmonary physiology in individuals with COPD during cardiopulmonary exercise testing (CPET). As well, Hexoskin's potentially unique ability to track the behaviour of dynamic operating lung volumes during CPET (i.e., end-expiratory [EELV] and end-inspiratory lung volumes [EILV]) has not been assessed, nor has the responsiveness of the device to detect

changes in physiological parameters during CPET been evaluated. This is important since very few integrated wearable technologies exist to monitor cardiopulmonary physiology in COPD, and even fewer of these devices have been validated or evaluated for aspects related to responsiveness. In people with COPD, the ability to track breathing pattern (V_T, RR), V'_E, and the behaviour of operating lung volumes would be particularly meaningful, since changes in these parameters are mechanistically linked to breathlessness and physical activity-limitation/avoidance [25, 67, 68] and are known to contribute to exacerbations (with attendant acceleration of disease progression) [60, 69] and premature death [12, 16, 24, 27]. As well, the ability to continuously track said variables may allow researchers and health care providers to monitor their patient's response to therapeutic interventions (e.g., bronchodilator therapy) and perhaps also predict the occurrence of adverse health outcomes (e.g., exacerbation).

The primary aim of this study was to assess the validity of Hexoskin's biometric smart shirt for measuring cardiac and ventilatory responses to symptom-limited CPET in adults with COPD. The secondary aim of this study was to evaluate the responsiveness of Hexoskin's biometric smart shirt to detect changes in cardiac and ventilatory responses to symptom-limited CPET in adults with COPD following 7-8 weeks of rehabilitative exercise training.

2.3 Methods

2.3.1 Study Design

A multicenter study took place from November 2015 to March 2017, wherein thirty-seven adults with COPD (22 men, 15 women) participated in a 7-8 week outpatient (hospital-based) pulmonary rehabilitation (PR) program at the Montreal Chest Institute (MCI; n=26) or the Mount Sinai Hospital of Montreal (MSH; n=11). Participants were excluded if they (1) exacerbated or changed medication dose/frequency in the previous 6 weeks; (2) had clinical evidence of asthma; (3) had cardiovascular and/or neuromuscular disease that may contribute to exercise limitation; or (4) had any other contraindication to exercise training/testing. The overall design of this study as well as the evaluative procedures performed are shown in Figure 2.1.

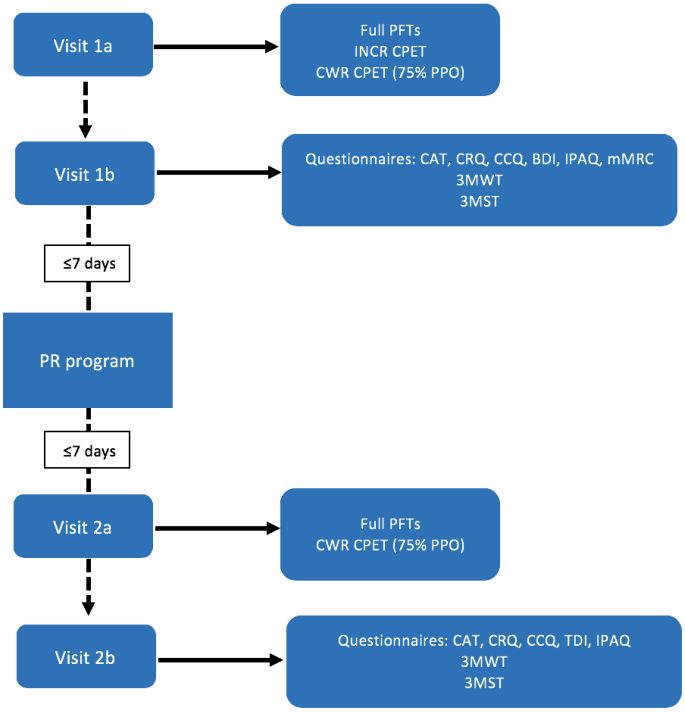


FIGURE 2.1. Experimental design and evaluative procedures. Abbreviations: PFT = pulmonary function test; INCR = incremental; CWR = constant workload; CPET = cardiopulmonary cycle exercise test; PPO = peak power output; CAT = COPD Assessment Test; CRQ = Chronic Respiratory Disease Questionnaire; CCQ = Clinical COPD Questionnaire; BDI = Baseline Dyspnea Index; TDI = Transition Dyspnea Index; mMRC = Modified Medical Research Council Dyspnea Scale; IPAQ = International Physical Activity Questionnaire; PR = pulmonary rehabilitation.

2.3.1.1 Pulmonary rehabilitation program.

The standard procedures of each site's PR program are described below in Table 2.1. At both the MCI and the MSH, PR involved 3 ExT sessions/week but with differing durations depending on the site: 7 weeks at the MCI; and 8 weeks at the MSH. As well, the target intensity for ExT differed depending on the PR site: 70% of the maximal HR achieved during the symptom-limited incremental (INCR) CPET performed at Visit 1a at the MCI; and dyspnea intensity ratings of 4-6 on Borg's modified 0-10 category ratio scale [70] at the MSH. Despite differences in the duration and structure of each site's PR program, the ExT and evaluative procedures were virtually identical and included: 30 minutes of aerobic training (treadmill or cycling exercise); 30 minutes of strength training (resistance exercises targeting the upper and lower limb muscles); stretching; and breathing exercises. In addition, each site's PR program included 6-24 standardized educational sessions, each lasting 1-2 hours.

TABLE 2.1. Summary of PR Programs.

Standard PRP procedures	Site	
	Montreal Chest Institute (MCI)	**Mount Sinai Hospital (MSH)**
Patient recruitment (n=)	8	11
Program duration (weeks): frequency (sessions/week): exercise time (min)	7 : 3 : 90	8 : 3 : 60
Exercise training (duration/intensity)	Aerobic training: - 30 minutes - 70% HR_{max} Strength training: - 30 minutes - 8-12 repetitions - 1-2 sets - Free weights - Functional exercises - Machines	Aerobic training - 30 minutes - 4-6 DBS Strength training: - 30 minutes - 10 repetitions - 1-2 sets - Free weights - Functional exercises
Training modality	Stationary bicycle or treadmill walking	Stationary bicycle or treadmill walking
Other exercises	Diaphragm deep breathing (DDB)	Diaphragm deep breathing (DDB)
Progression, monitoring & supervision	DBS 4-6 RPE 4-6 Pulse oximetry	DBS 4-6 RPE 4-6 Pulse oximetry
Educational counseling (number:duration (min))	6 (4 optional) : 60 minutes - Living Well with COPD	24 : 60 minutes - Living Well with COPD

HR = heart rate; DBS = dyspnea Borg scale; RPE = rating of perceived exertion

2.3.1.2 Evaluative procedures performed during patient visits.

After providing written informed consent, each participant completed four visits to the research laboratory: two pre-PR visits (Visits 1a and 1b) and two post-PR visits (Visits 2a and 2b) (Figure 2.1). The pre-PR visits were completed within 1 week prior to commencing the PR program, while post-PR visits were completed within 1 week following the PR program. Visit 1a consisted of a symptom-limited INCR CPET to determine peak power output (PPO), which was defined as the highest power output that the patient could maintain for at least 30-sec. INCR CPETs included a steady-state resting period of at least 3-min, a 1-min warm-up of unloaded pedaling,

followed by 10 watt/min increases in power output (starting at 10 watts) to symptom-limitation. Moreover, both Visits 1a and 2a involved post-bronchodilator (400 mg salbutamol) pulmonary function testing (PFT) and a constant workload (CWR) CPET at 75% of PPO (CWR1 and CWR2, respectively). PFTs, which included spirometry, constant-volume body plethysmography and single-breath diffusing capacity for carbon monoxide, were performed according to recommended techniques with patients seated upright [71-74]. CWR CPETs included a steady-state resting period of at least 3-min, a 1-min warm-up of unloaded pedalling, followed by an immediate step increase in power output to 75% PPO (rounded up to the nearest 5 watts), which was maintained until symptom-limitation. On Visit 1a, INCR and CWR1 CPETs were separated by a rest period of at least 45-min.

Visits 1b and 2b each included a 3-minute constant-rate shuttle walk test (3MWT) and 3-minute constant-rate stair stepping test (3MST), interspersed by at least 30 minutes of rest, following the completion of various questionnaires: activity-related dyspnea and health-related quality of life were assessed using the COPD Assessment Test (CAT), the Chronic Respiratory Disease Questionnaire (CRQ), the Clinical COPD Questionnaire (CCQ), the Baseline Dyspnea Index (BDI, Visit 1b only), the Transition Dyspnea Index (TDI, Visit 2b only), and the Modified Medical Research Council Dyspnea Scale (mMRC), while self-reported daytime physical activity levels were assessed using the International Physical Activity Questionnaire (IPAQ). However, it should be noted that these two patient visits are tangential to the aims of this particular study since they did not include measurements made by the Hexoskin biometric smart shirt or the SensorMedics Vmax 229d metabolic cart. In fact, only Visits 1a and 2a are relevant for the purpose of this project since they, unlike Visits 1b and 2b, involved simultaneous measurements, collected

breath-by-breath, from the two devices. Thus, it is ultimately the data obtained from Visits 1a and 2a that allow for the evaluation of the validity and responsiveness of the Hexoskin technology.

2.3.2 Participants

As shown in Figure 2.2, of the 37 subjects who participated in the PR study, fourteen adults (10 men, 4 women) aged 71.6 ± 8.9 years with mild-to-very severe COPD (mean ± SD Forced expiratory volume in 1-sec [FEV_1] = 69 ± 26% predicted [range: 20-105% predicted]) wore the Hexoskin biometric smart shirt during INCR and CWR CPETs. From these fourteen patients, a total of thirty-four measurements were used to assess the validity of the Hexoskin biometric technology as well as its responsiveness to an exercise stimulus, while a total of seven measurements were used to evaluate its responsiveness to PR (Figure 2.2).

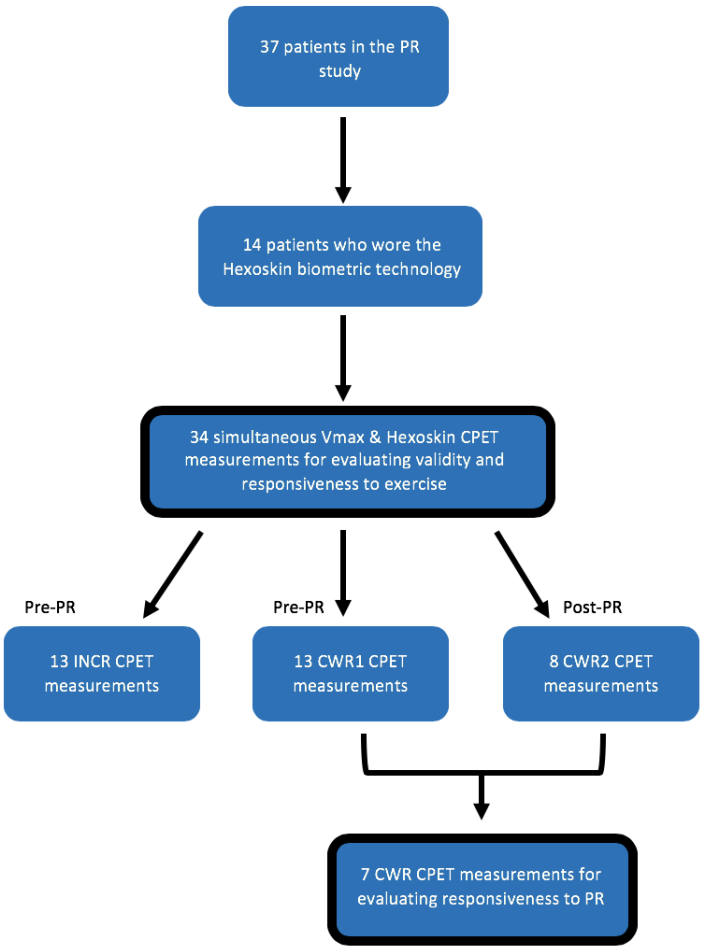


FIGURE 2.2. Samples used for evaluating Hexoskin's validity and responsiveness. Abbreviations: CPET = cardiopulmonary cycle exercise test; INCR = incremental; CWR = constant workload; PR = pulmonary rehabilitation.

2.3.3 Simultaneous Data Collection by Hexoskin and Vmax

INCR and CWR CPETs were performed on an electronically-braked cycle ergometer in accordance with clinical exercise testing guidelines [75], where patients wore the Hexoskin

biometric smart shirt as well as attachments to the SensorMedics Vmax 229d metabolic cart. Vmax collects measurements as patients breathe through a mouthpiece and a low resistance flow transducer with nasal passages occluded by a nose clip. Specifically, these measurements included: standard cardiorespiratory and breathing pattern parameters collected breath-by-breath; HR by 12-lead ECG; and dynamic operating lung volumes derived from serial IC maneuvers performed at rest, within the last 30-sec of each 2-min interval during exercise, and at end-exercise [20].

Moreover, Hexoskin measures HR (in beats/min) by incorporating three-lead ECG electrodes into a single ECG signal sampled at 256 Hz [64, 65]. As well, the garment's two strain gauge bands (thoracic and abdominal) allow it to evaluate respiration *via* inductance plethysmography, a well-established technique in breathing surveillance for wearable measurement systems [76, 77], at 128 Hz [64, 65]. This signal provides users with RR (in breaths/min), V_T (in arbitrary units) and V'_E (in arbitrary units/min), on a breath-by-breath basis [64, 65].

2.3.4 Data Extraction

Hexoskin raw ECG and respiration (thoracic) channel files were downloaded directly from the Hexoskin dashboard and imported into a wearable sensor analysis platform called VivoSense (Vivonoetics Inc., San Diego, CA, USA) for analysis at sampling rates of 256 Hz and 128 Hz, respectively. The Hexoskin and Vmax data were time-aligned using timestamps recorded on the Hexoskin device during CPETs. Both sets of data were averaged for V'_E, V_T, RR and HR at the following time points: (1) the last 60-sec of the steady-state resting period prior to the start of exercise; (2) every 2-min during exercise and; (3) the last 30-sec of loaded pedaling. As well, since IC maneuvers were performed at all of these intervals, IC and IRV data was obtained for each device at the specified measurement time points. More specifically, the directly measured V'_E

(L/min), V_T (L), RR (breaths/min), HR (beats/min), and IC (L), from the Vmax CPET system, were averaged for the aforementioned intervals of interest, while the IRV (L) was calculated as the difference between the IC and the contemporaneous average V_T of each interval. For the Hexoskin data imported into VivoSense, HR (beats/min) and RR (breaths/min) were directly exported and averaged for the intervals of interest, whereas V_T was manually determined, breath-by-breath, by identifying the difference in volume between EELV and EILV on the respiration (thoracic) channel trace (Figure 2.3). More specifically, V_T (arbitrary units) was calculated as the difference between the average EELV and average EILV of each selected interval. Similarly, V'_E (arbitrary units/min) was determined by multiplying each interval's V_T and RR, while IC (arbitrary units) was determined by taking the difference between the maximum EILV and the average of the five EELVs prior to the manoeuvre. IRV (arbitrary units) was subsequently determined by taking the difference between each interval's IC and average V_T. Furthermore, when it comes to evaluating a device's ability to record operating lung volumes (IC, IRV), it was essential to first ensure that the device records an unchanging TLC, as this is fundamental to the analysis of said volumes. Thus, the peak EILV (the largest EILV value obtained) during each IC maneuver (representing TLC) was determined in order to assess for consistency in maximal voluntary ribcage expansion recorded by Hexoskin (Figure 2.3).

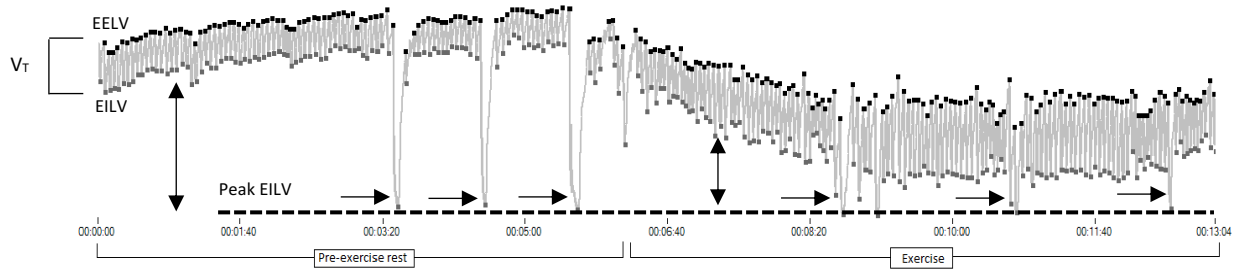


FIGURE 2.3. Hexoskin respiration (thoracic) trace for subject X throughout CPET. Resting lung volumes as well as the exercise-induced dynamic rise in EELV and EILV (fall in IC and IRV from rest) are shown. Single-headed arrows indicate IC maneuvres; double-headed arrows indicate IRV. Abbreviations: V_T = tidal volume; EELV = end expiratory lung volume; EILV = end inspiratory lung volume.

2.3.5 Data Analysis

2.3.5.1 Intervals used for CPET analysis.

The time points used for data analysis were: (1) baseline, the last 60-sec of the steady-state resting period; (2) highest equivalent time (HET), the last 30-sec of the highest equivalent submaximal time (rounded down to the nearest whole minute) achieved by all patients during INCR and CWR CPETs; (3) isotime (ISO), the last 30-sec of the highest equivalent submaximal time (rounded down to the nearest whole minute) achieved by a given patient during both pre- and post-PR CWR CPETs (i.e., CWR1 and CWR2, respectively) and; (4) peak, the last 30-sec of loaded pedalling.

2.3.5.2 Coefficients of variation.

To determine the degree of variation between the peak EILV values recorded by the Hexoskin device during serial IC maneuvers performed by a given subject within a given CPET trial, the coefficient of variation (CV) was first calculated for each of the thirty-four CPETs performed. Specifically, the CV was determined by taking the ratio of the standard deviation to the mean for the peak EILV values of an individual subject's CPET. To express the CV as a percentage, this was then multiplied by 100. Group mean CVs for the INCR, CWR1 and CWR2 trials were then obtained by taking the average CV for each respective CPET trial.

2.3.5.3 Correlations.

To determine the strength of the correlation (R^2) between Hexoskin and Vmax for measuring V'_E, V_T, RR, HR, IC and IRV throughout CPET, the data obtained from the two devices at baseline, every 2-min during exercise and peak were entered into a single correlation for each parameter. Specifically, x-y plots were constructed for the paired CPET measurements. For each x-y plot, a trendline was added from which an R^2 value was obtained. The overall strength of the

correlation was then determined by taking the average of the individual subject R^2 values. We followed this same process for evaluating the strength of the correlation between Hexoskin and Vmax for measuring the magnitude of change from rest-to-peak exercise as well as the pre- to post-PR changes in the aforementioned cardiac and ventilatory parameters.

2.3.5.4 Statistical methods.

Through the SPSS statistical analysis software, we used the analysis of variance (ANOVA) and the paired-samples t-test to determine whether there were significant differences between group means. Specifically, repeated measures ANOVAs were conducted in order to directly compare Hexoskin and Vmax for measuring RR and HR as well as to evaluate the devices for aspects related to responsiveness, and a paired-samples t-test was used to evaluate CWR cycle exercise endurance time pre- to post-PR.

2.3.5.5 Samples used for analysis.

To explore Hexoskin for aspects related to validity we: (1) evaluated the smart shirt for consistency in maximal voluntary ribcage expansion during serial IC maneuvers; (2) compared the temporal patterns recorded by Hexoskin for V'_E, V_T, RR, HR, IC and IRV during the INCR and CWR CPETs to those recorded by the SensorMedics Vmax 229d metabolic cart and examined whether there were significant differences between the RR and HR measurements made by the two devices

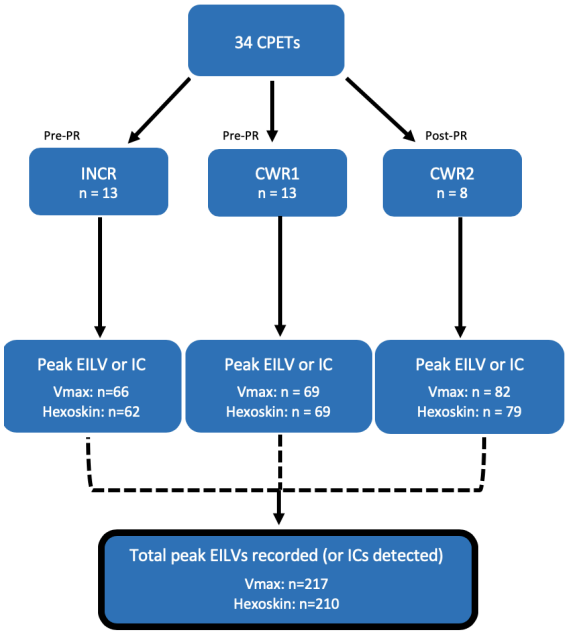


FIGURE 2.4. Samples used for evaluating the consistency in maximal voluntary ribcage expansion during serial inspiratory capacity (IC) maneuvers on the Hexoskin device. Abbreviations: CPET = cardiopulmonary cycle exercise test; INCR = incremental; CWR = constant workload; PR = pulmonary rehabilitation; EILV = end inspiratory lung volume.

and; (3) assessed the correlations between the two devices for measuring the aforementioned cardiopulmonary parameters as well as their magnitudes of change from rest to peak exercise during the INCR and CWR CPETs. A total of 210 peak EILVs from thirty-four CPETs were used to evaluate Hexoskin for consistency in maximal voluntary ribcage expansion throughout the INCR (n=13), CWR1 (n=13) and CWR2 (n=8) CPETs (Figure 2.4). Temporal patterns recorded by Hexoskin and Vmax for V'_E, V_T, RR, HR, IC and IRV were examined in thirteen INCR (except for HR where n=11), seven CWR1 and seven CWR2 measurements (except for IC and IRV where n=5) (Figure 2.5). Direct comparisons were made between the two devices for their RR and HR measurements throughout CPET in thirteen INCR (except for HR where n=11), seven CWR1 and seven CWR2 measurements (Figure 2.5).

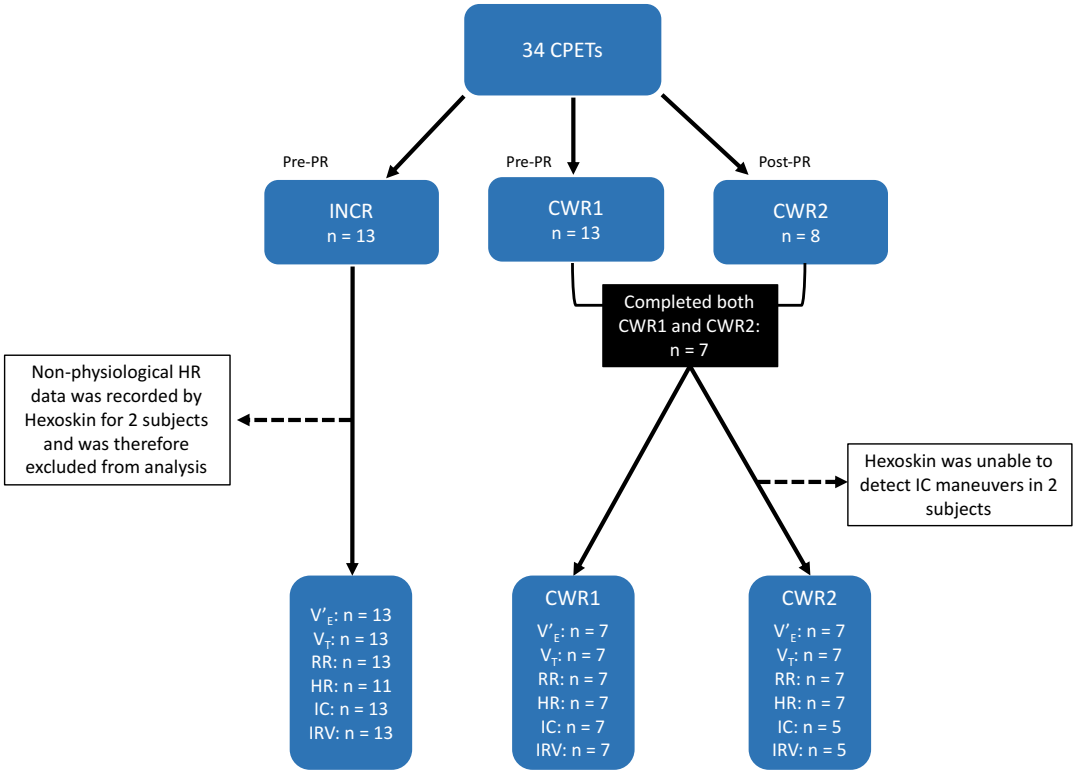


FIGURE 2.5. Samples used to compare the temporal patterns recorded by Hexoskin and Vmax, evaluate their responsiveness to exercise and assess mean pre- to post-PR changes. Abbreviations: CPET = cardiopulmonary cycle exercise test; INCR = incremental; CWR = constant workload; PR = pulmonary rehabilitation; V'_E = minute ventilation; V_T = tidal volume; RR = respiratory rate; HR = heart rate; IC = inspiratory capacity; IRV = inspiratory reserve volume.

To determine the correlation between Hexoskin and Vmax for measuring V'_E, V_T, RR, HR, IC and IRV throughout CPET, a sample of thirteen INCR (except for HR where n=11), thirteen CWR1 (except for HR where n=11) and eight CWR2 measurements was used (Figure 2.6). As well, we assessed the correlation between the two devices for measuring the magnitude of change from rest to peak exercise in each of these parameters in a sample of thirteen INCR (except for HR where n=11, as well as IC and IRV where n=12), thirteen CWR1 (except for HR, where n=11) and eight CWR2 (except for IC and IRV where n=7) measurements (Figure 2.6).

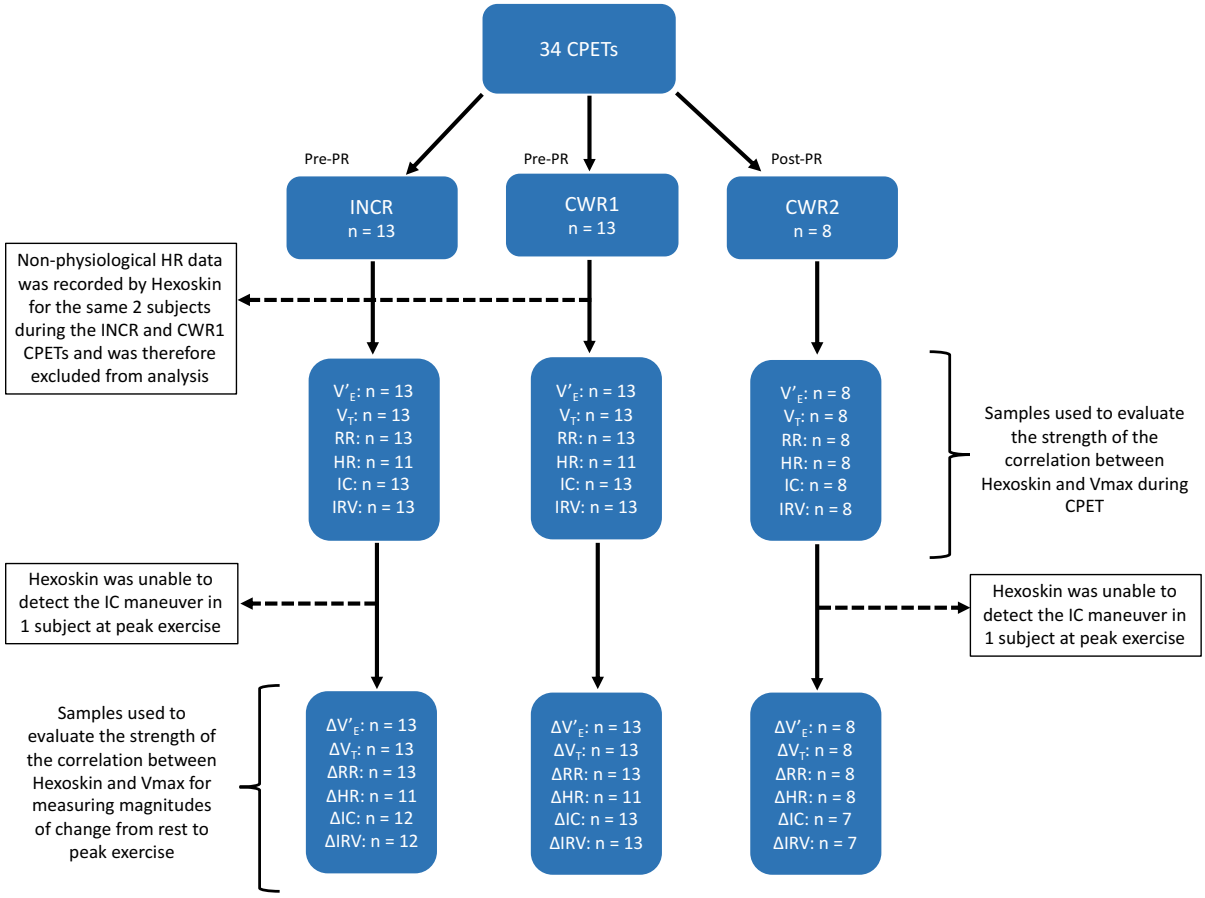


FIGURE 2.6. Samples used to evaluate the strength of the correlation between Hexoskin and Vmax for measuring cardiac and ventilatory parameters as well as their magnitudes of change from rest to peak exercise. Abbreviations: CPET = cardiopulmonary cycle exercise test; INCR = incremental; CWR = constant workload; PR = pulmonary rehabilitation; V'_E = minute ventilation; V_T = tidal volume; RR = respiratory rate; HR = heart rate; IC = inspiratory capacity; IRV = inspiratory reserve volume.

Furthermore, to explore the smart shirt for aspects related to responsiveness we: (1) determined its responsiveness to the stimulus of exercise; (2) assessed its responsiveness to detect changes in physiological parameters at standardized time points during CPET from pre- to post-PR; (3) evaluated its responsiveness to detect individual subject pre- to post-PR changes in physiological parameters. Responsiveness to an exercise stimulus was examined in thirteen INCR (except for HR where n=11), seven CWR1 and seven CWR2 measurements (except for IC and IRV where n=5) (Figure 2.5). With the exception of IC and IRV, where n=5 as a result of two subjects having unidentifiable ICs during the CWR2 trial on the Hexoskin device, mean pre- to post-PR changes were assessed in seven paired CWR CPET measurements (Figure 2.5). Lastly, individual subject pre- to post-PR improvements and deteriorations were evaluated in a sample of seven patients (except for IC and IRV at baseline and HET where n=6, as well as IC and IRV at ISO where n=5) (Figure 2.7).

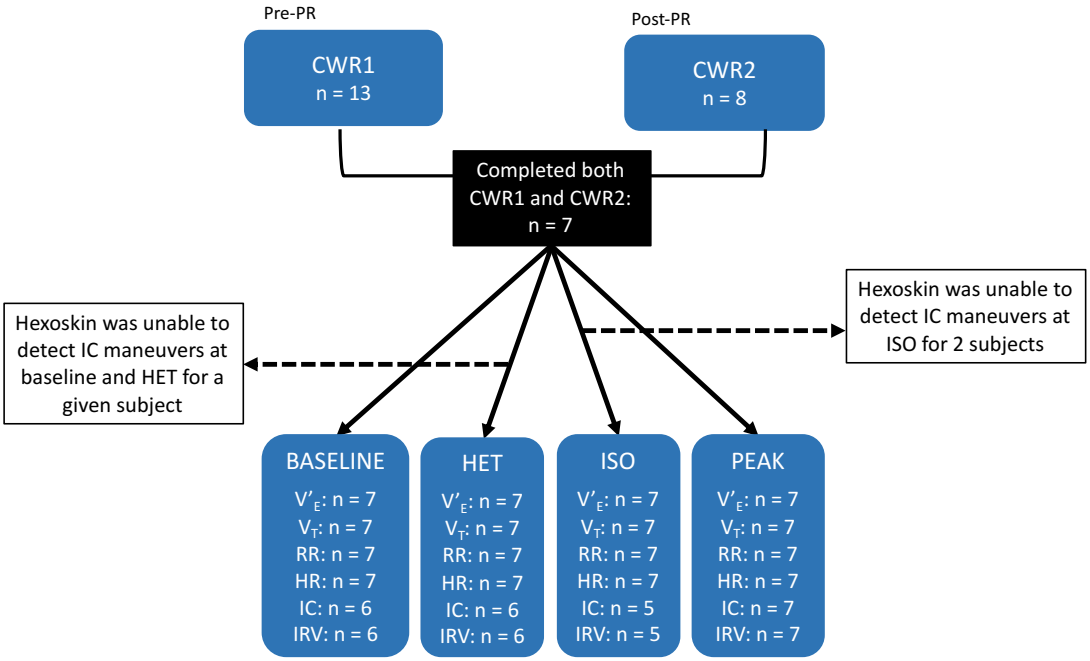


FIGURE 2.7. Samples used to evaluate individual subject pre- to post-PR improvements and deteriorations. Abbreviations: CWR = constant workload; PR = pulmonary rehabilitation; HET = highest equivalent time; ISO = isotime; V'_E = minute ventilation; V_T = tidal volume; RR = respiratory rate; HR = heart rate; IC = inspiratory capacity; IRV = inspiratory reserve volume.

2.4 Results

2.4.1. Validity of the Hexoskin Biometric Smart Shirt

2.4.1.1 Ribcage expansion.

The Hexoskin biometric smart shirt recorded consistent maximal voluntary ribcage expansion during serial IC maneuvers as evidenced by the negligible CVs and the non-significant effects of measurement time on the peak EILVs (representing TLC) recorded by Hexoskin during INCR (p=0.110), CWR1 (p=0.057) and CWR2 (p=0.548) CPETs (Figure 2.8; Table 2.2). This is also shown above by subject X's respiration (thoracic) trace on Figure 2.3, where the peak EILV remained virtually identical throughout the CPET trial.

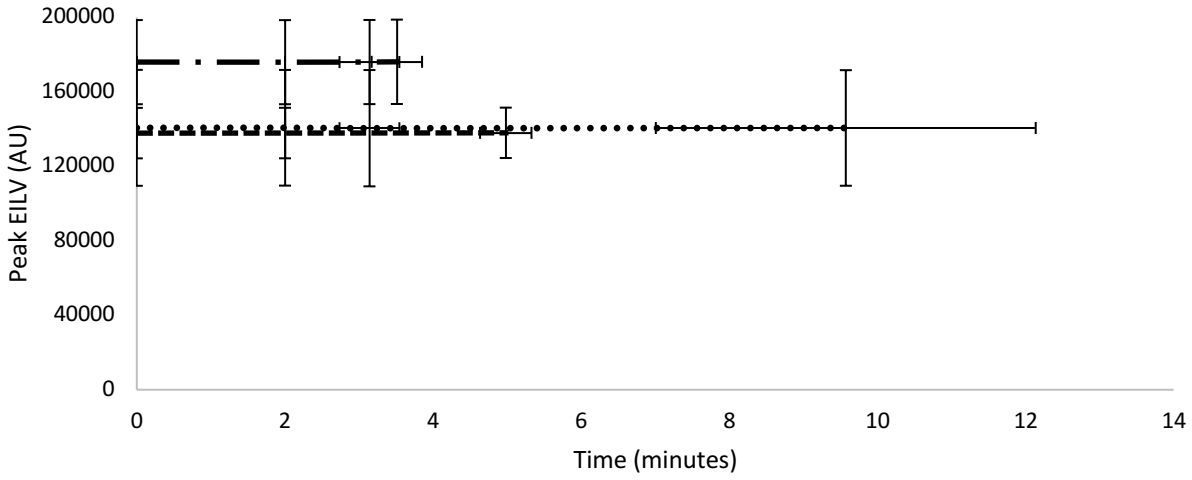


FIGURE 2.8. Peak EILV recorded by Hexoskin during INCR (■), CWR1 (— ▪) and CWR2 (●).

TABLE 2.2. Coefficient of variation for the peak EILVs recorded by Hexoskin during each CPET trial.

CPET trial	Coefficient of variation (%)
INCR (n=13)	0.09 ± 0.09 [0.02-0.35]
CWR1 (n=13)	0.07 ± 0.05 [0.02-0.20]
CWR2 (n=8)	0.24 ± 0.47 [0.05-1.40]

Coefficients of variation reported as: mean CV ± SD [min – max])

2.4.1.2 Temporal patterns during CPET.

Despite recording the data in different units, Hexoskin and Vmax tracked similar temporal patterns for V'_E, V_T, IC and IRV throughout the INCR, CWR1 and CWR2 CPETs (Figures 2.9-2.11). As well, throughout all three CPET trials, RR and HR trends were virtually identical between the two devices (Figures 2.9-2.11); that is, while there was an anticipated main effect of measurement time for both RR and HR during INCR (p=0.001), CWR1 (p=0.001) and CWR2 trials (p=0.001), there was no statistically significant device main effect or device*time interaction for the RR and HR measurements made during the INCR, CWR1 or CWR2 trials (p=0.052-0.844).

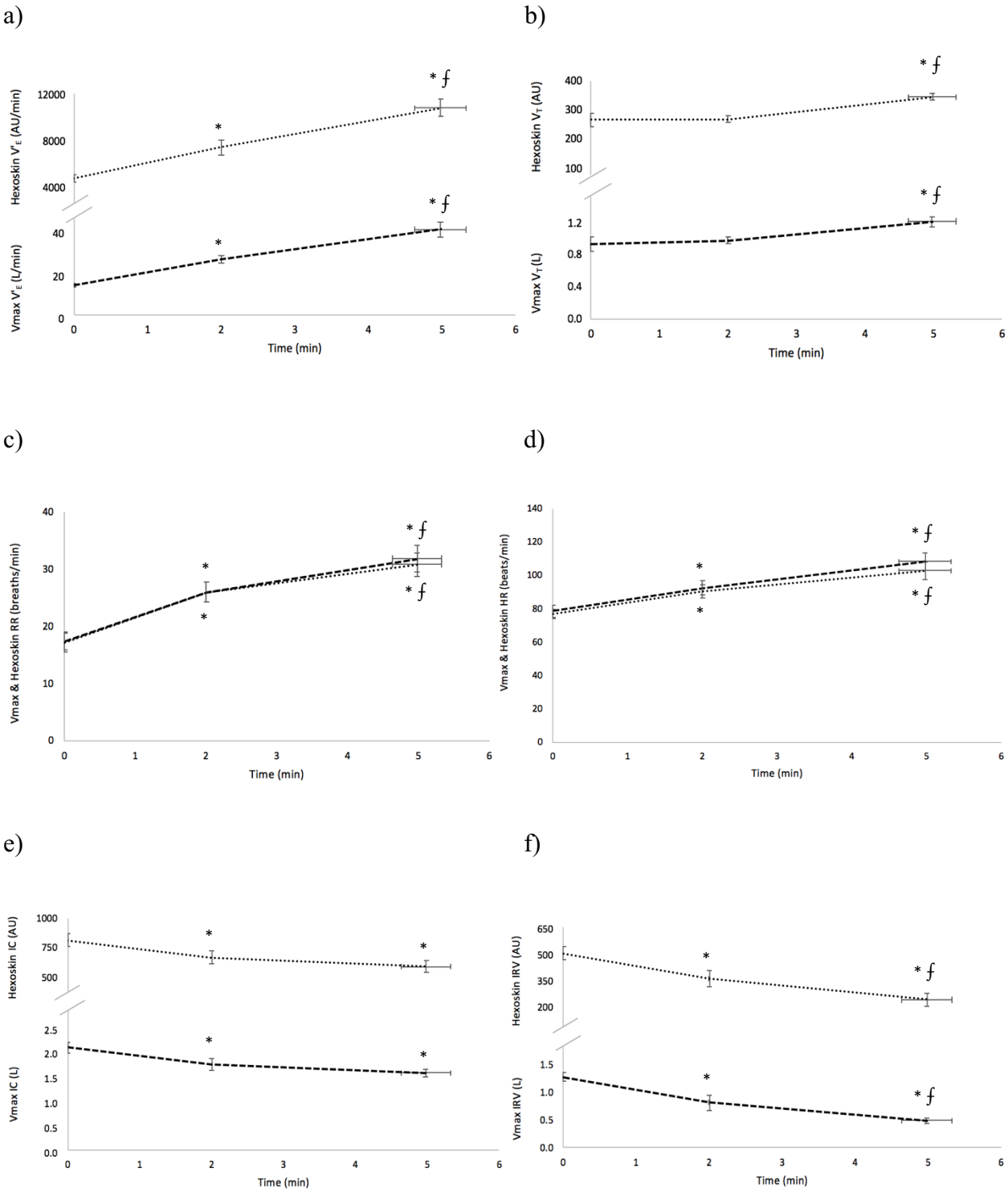


FIGURE 2.9. Temporal patterns recorded by Vmax (■) and Hexoskin (●) at baseline, the highest equivalent exercise time (HET) and at peak exercise for: a) minute ventilation (V'_E); b) tidal volume (V_T); c) respiratory rate (RR); d) heart rate (HR); e) inspiratory capacity (IC) and; f) inspiratory reserve volume (IRV) during the INCR CPET. *: $p<0.05$ vs baseline; and ƒ: $p<0.05$ vs HET.

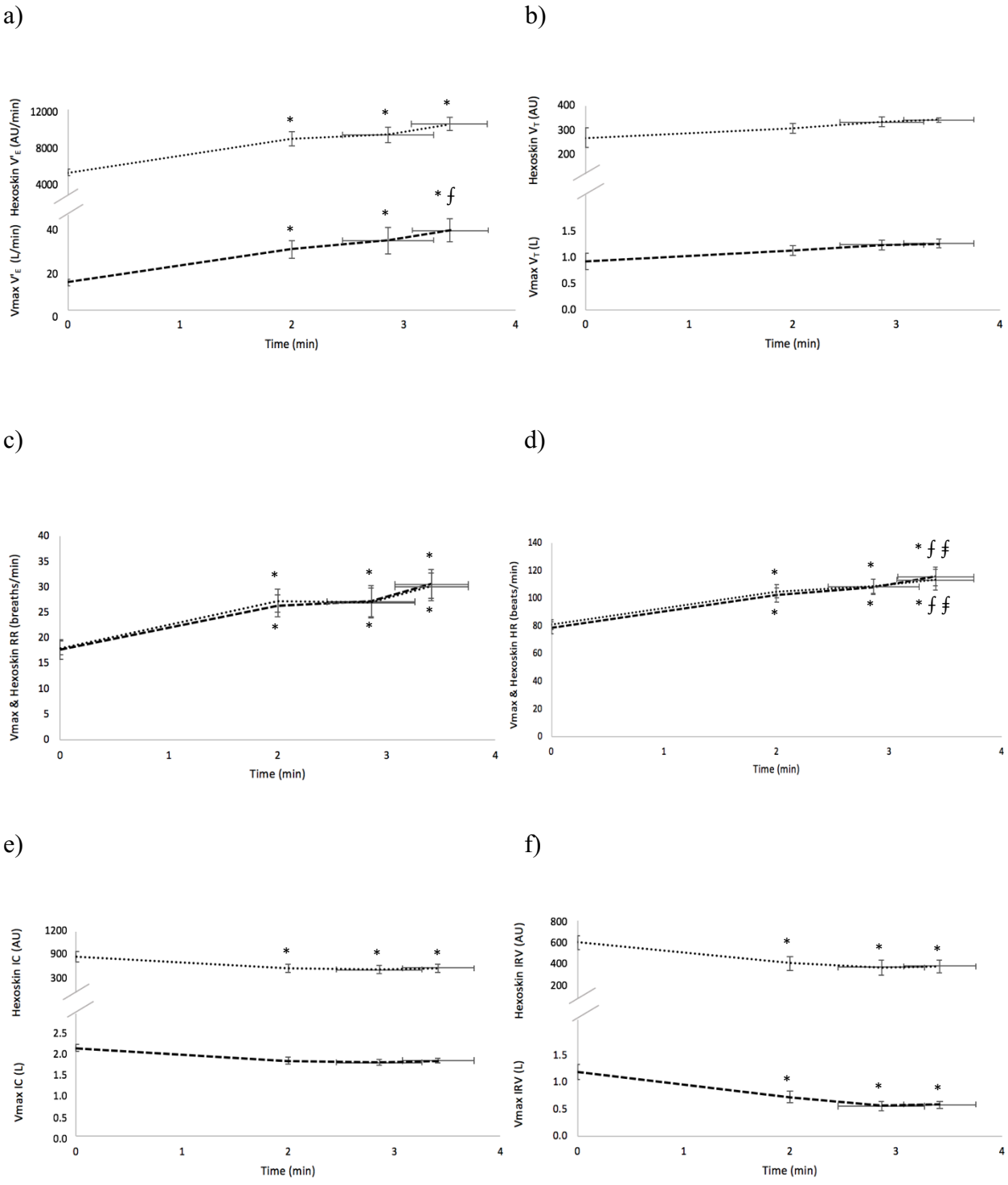


FIGURE 2.10. Temporal patterns recorded by Vmax (■) and Hexoskin (●) at baseline, the highest equivalent exercise time (HET), isotime (ISO) and peak exercise for: a) minute ventilation (V'_E); b) tidal volume (V_T); c) respiratory rate (RR); d) heart rate (HR); e) inspiratory capacity (IC) and; f) inspiratory reserve volume (IRV) during the CWR1 CPET. *: $p<0.05$ vs baseline; ƒ: $p<0.05$ vs HET and; ƒ: $p<0.05$ vs ISO.

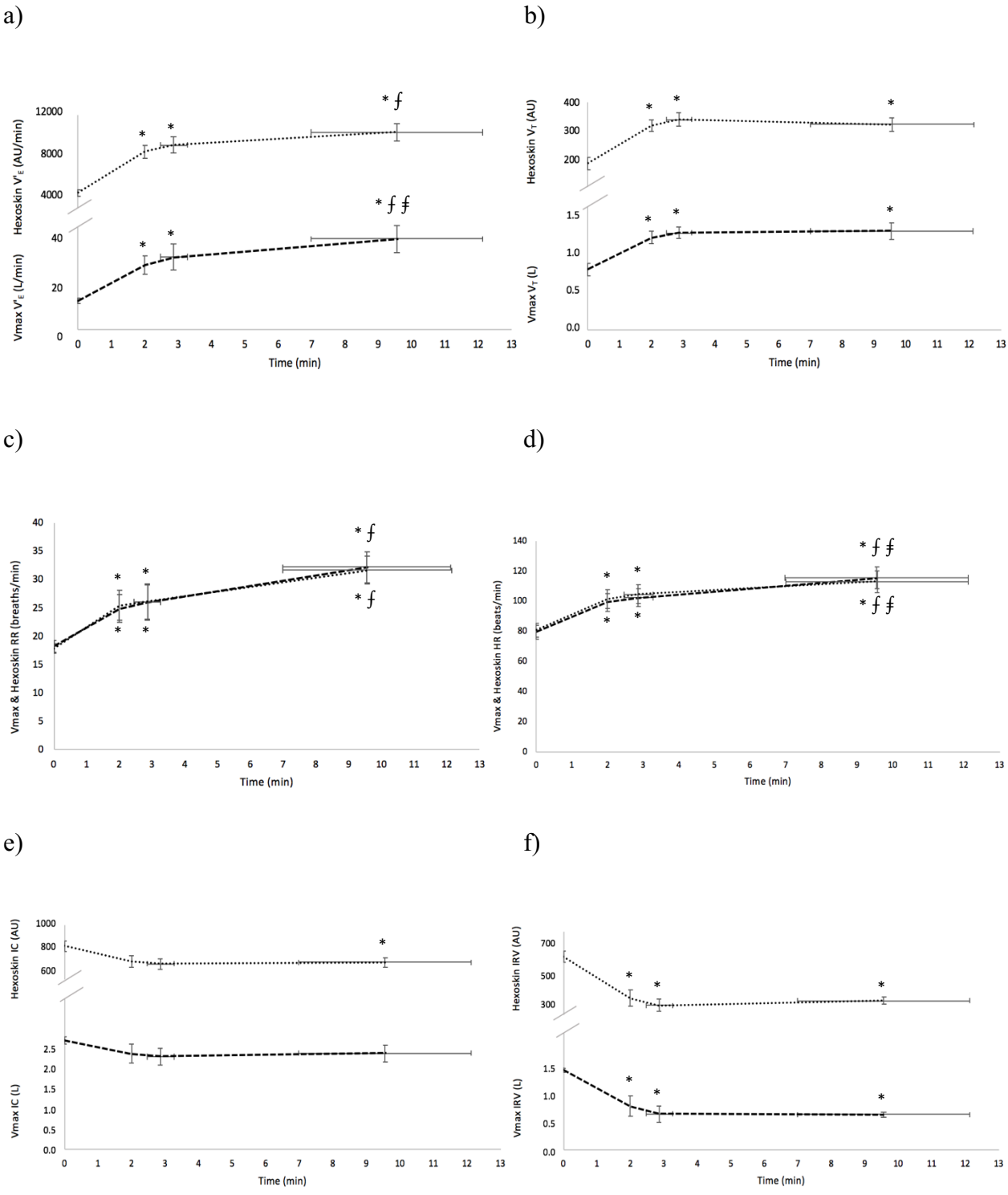


FIGURE 2.11. Temporal patterns recorded by Vmax (■) and Hexoskin (●) at baseline, the highest equivalent exercise time (HET), isotime (ISO) and peak exercise for: a) minute ventilation (V'_E); b) tidal volume (V_T); c) respiratory rate (RR); d) heart rate (HR); e) inspiratory capacity (IC) and; f) inspiratory reserve volume (IRV) during the CWR2 CPET. *: $p<0.05$ vs baseline; ƒ: $p<0.05$ vs HET and; ƒƒ: $p<0.05$ vs ISO.

2.4.1.3 Correlations between Hexoskin and Vmax.

Hexoskin and Vmax were highly correlated for measuring exercise-induced changes in V'_E, V_T, RR, HR, IC and IRV (Table 2.3) as well as their magnitudes of change from rest to peak exercise (Figure 2.12). This was also the case when the correlations between the two devices were analyzed within each individual CPET trial (Appendix A).

TABLE 2.3. Correlation between Vmax and Hexoskin for measuring cardiopulmonary parameters throughout CPET.

Cardiopulmonary parameters	Mean R^2 ± SD [min – max]
V'_E	0.95 ± 0.05 [0.80-1.00]
V_T	0.89 ± 0.13 [0.48-1.00]
RR	0.94 ± 0.07 [0.69-1.00]
HR	0.97 ± 0.06 [0.71-1.00]
IC	0.89 ± 0.10 [0.62-1.00]
IRV	0.93 ± 0.09 [0.58-1.00]

V'_E = minute ventilation; V_T = tidal volume; RR = respiratory rate; HR = heart rate; IC = inspiratory capacity; IRV = inspiratory reserve volume.

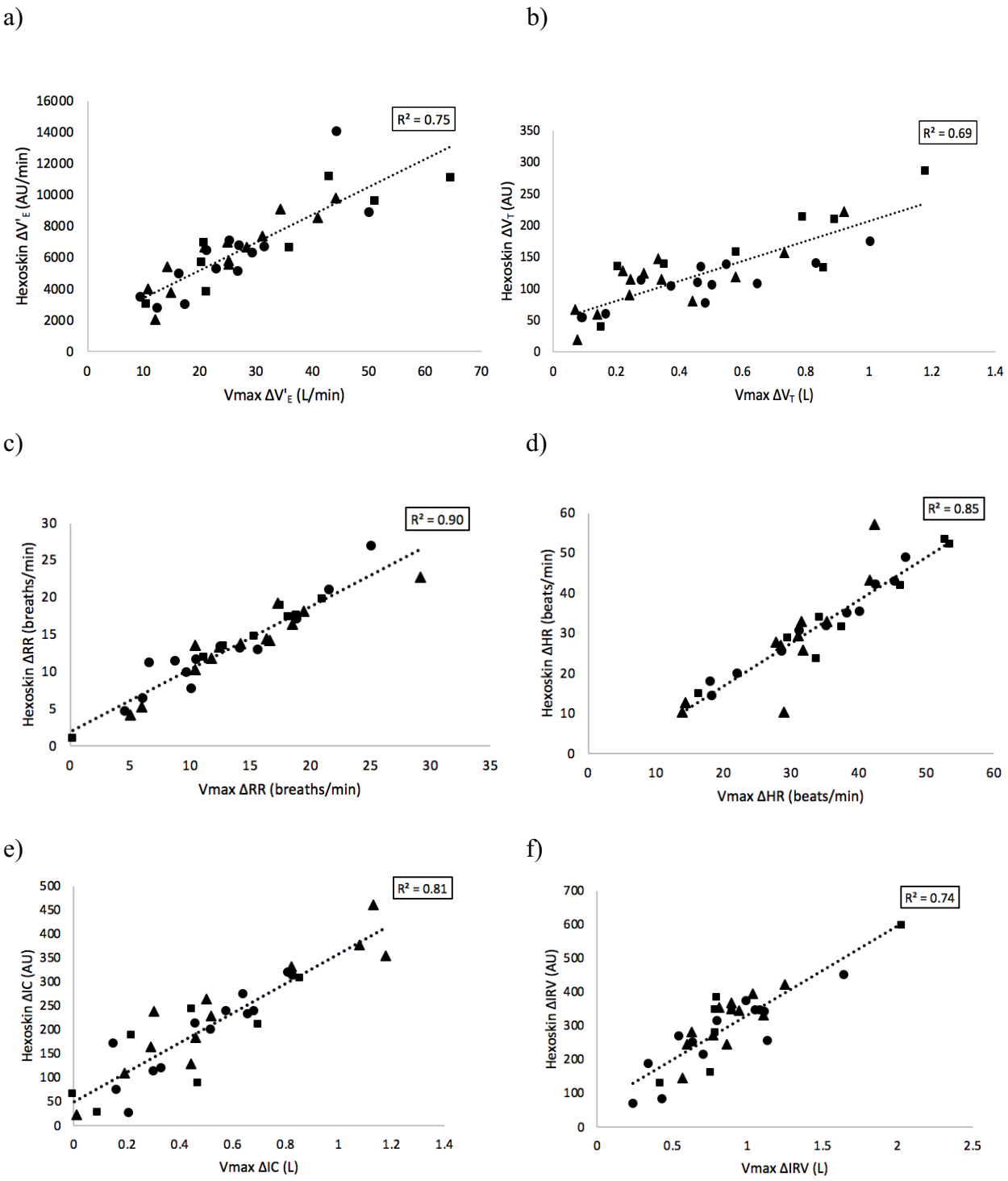


FIGURE 2.12. Correlation between Vmax and Hexoskin for measuring the magnitude of change (Δ) from rest-to-peak exercise in: a) minute ventilation (V'_E); b) tidal volume (V_T); c) respiratory rate (RR); d) heart rate (HR); e) inspiratory capacity (IC) and; f) inspiratory reserve volume (IRV) throughout INCR (▲), CWR1 (●) and CWR2 (■) cardiopulmonary cycle exercise tests.

2.4.2 Evaluation of the Hexoskin Biometric Smart Shirt's Responsiveness

2.4.2.1 Responsiveness to exercise.

With the exception of V_T during the CWR1 trial, where no significant main effects of time were found in the Hexoskin or Vmax measurements, and IC during the CWR1 and CWR2 trials, where no significant main effects of time were found in the Vmax measurements alone, the Hexoskin and Vmax devices were both found to be responsive to the stimulus of exercise. Specifically, they were responsive for detecting increases in V'_E, V_T, RR and HR as well as deteriorations in IC and IRV, from rest-to-peak exercise (Figures 2.9-2.11). This is supported by the results of 1-way repeated measures ANOVAs that evaluated whether there were main effects of time for the measurements made during the INCR, CWR1 and CWR2 CPETs:

INCR: V'_E (Hexoskin: p=0.001; Vmax: p=0.001), V_T (Hexoskin: p=0.003; Vmax: p=0.002), RR (Hexoskin: p=0.001; Vmax: p=0.001), HR (Hexoskin: p=0.001; Vmax: p=0.001), IC (Hexoskin: p=0.001; Vmax: p=0.001) and IRV (Hexoskin: p=0.001; Vmax: p=0.001);

CWR1: V'_E (Hexoskin: p=0.001; Vmax: p=0.001), V_T (Hexoskin: p=0.106; Vmax: p=0.097), RR (Hexoskin: p=0.001; Vmax: p=0.001), HR (Hexoskin: p=0.001; Vmax: p=0.001), IC (Hexoskin: p=0.027; Vmax: p=0.053) and IRV (Hexoskin: p=0.001; Vmax: p=0.001);

CWR2: V'_E (Hexoskin: p=0.001; Vmax: p=0.001), V_T (Hexoskin: p=0.001; Vmax: p=0.001), RR (Hexoskin: p=0.001; Vmax: p=0.001), HR (Hexoskin: p=0.001; Vmax: p=0.001), IC (Hexoskin: p=0.020; Vmax: p=0.133) and IRV (Hexoskin: p=0.001; Vmax: p=0.005).

2.4.2.2 Responsiveness to pulmonary rehabilitation.

No mean physiological change was detected pre- to post-PR, other than a marked improvement in CWR exercise endurance time (from 3.7 ± 1.3 to 8.1 ± 6.4 minutes, p=0.036 by paired t-test) (Figure 2.13). This is also evidenced by non-significant main effects of trial whether

measured by Hexoskin or Vmax: V'_E (Hexoskin: p=0.176, Vmax: p=0.899), V_T (Hexoskin: p=0.164, Vmax: p=0.798), RR (Hexoskin: p=0.799, Vmax: p=0.950) HR (Hexoskin: p=0.383, Vmax: p=0.373), IC (Hexoskin: p=0.614, Vmax: p=0.559) and IRV (Hexoskin: p=0.069, Vmax: p=0.506). However, when the data was analyzed for each individual subject, Hexoskin was found to accurately detect pre- to post-PR improvements and deteriorations. This is depicted in Appendix B-E and is supported by strong correlations between Hexoskin and Vmax for measuring individual subject pre- to post-PR changes at baseline, HET, ISO and peak (Table 2.4).

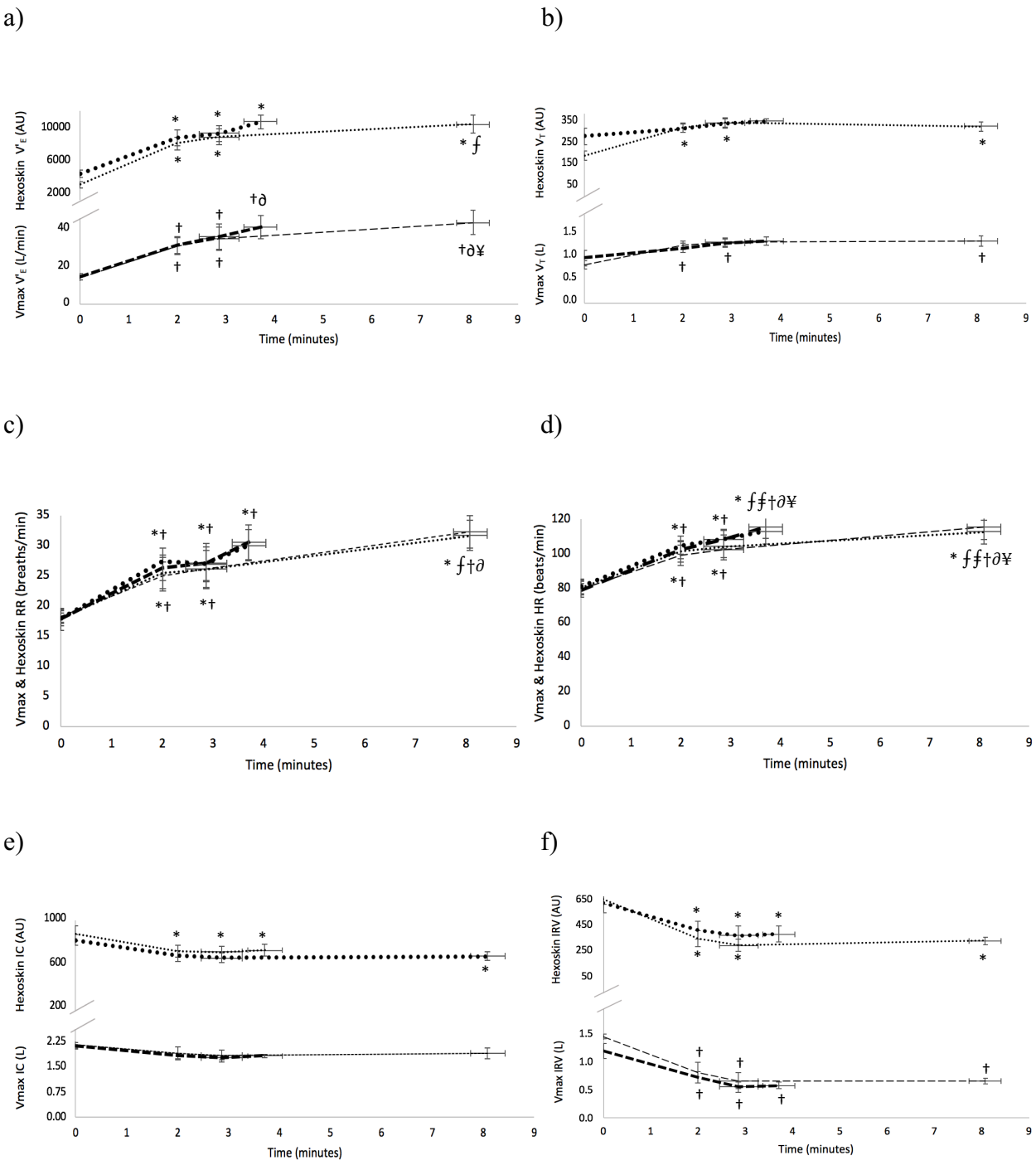


FIGURE 2.13. Temporal patterns recorded pre- and post-PR by Vmax and Hexoskin for: a) minute ventilation (V'_E); b) tidal volume (V_T); c) respiratory rate (RR); d) heart rate (HR); e) inspiratory capacity (IC) and; f) inspiratory reserve volume (IRV). ■: Vmax CWR1; − Vmax CWR2; ●: Hexoskin CWR1 and; ⋆ : Hexoskin CWR2. *: $p<0.05$ vs baseline for Hexoskin; ƒ: $p<0.05$ vs the highest equivalent exercise time (HET) for Hexoskin; ƒ: $p<0.05$ vs isotime (ISO) for Hexoskin; †: $p<0.005$ vs baseline for Vmax; ∂: $p<0.005$ vs HET for Vmax and; ¥: $p<0.005$ vs ISO for Vmax.

TABLE 2.4. Correlation between Vmax and Hexoskin for measuring individual subject pre- to post-PR changes (Δ) in cardiopulmonary parameters at baseline, highest equivalent exercise time (HET), isotime (ISO) and peak exercise.

Cardiopulmonary parameters	Measurement Time			
	Baseline	HET	ISO	Peak
$\Delta V'_E$	0.54	0.87	0.64	0.97
ΔV_T	0.89	0.74	0.97	0.91
ΔRR	0.83	0.87	0.93	0.72
ΔHR	0.73	0.90	0.88	0.97
ΔIC	0.65	0.80	0.88	0.85
ΔIRV	0.73	0.91	0.96	0.63

Correlations reported as: R^2

V'_E = minute ventilation; V_T = tidal volume; RR = respiratory rate; HR = heart rate; IC = inspiratory capacity; IRV = inspiratory reserve volume.

2.5 Discussion

This study is the first to demonstrate that the Hexoskin biometric smart shirt is both a valid and responsive tool for measuring changes in cardiac and ventilatory parameters (including dynamic operating lung volumes) during symptom-limited CPET in people with COPD.

2.5.1 Validity of the Hexoskin Biometric Smart Shirt

To evaluate the validity of the Hexoskin biometric smart shirt, we (i) compared the temporal patterns of change in cardiac and respiratory parameters recorded by Hexoskin and Vmax during CPET and (ii) examined the strength of the correlation between Hexoskin and Vmax for measuring exercise-induced changes in cardiac and respiratory parameters.

In all CPET trials, the temporal patterns of change in V'_E, V_T, RR and HR from rest to peak exercise were very similar when recorded using Hexoskin's biometric smart compared with Vmax: qualitatively similar for V'_E and V_T; and quantitatively similar for RR and HR (Figures 2.9-2.11). Furthermore, Hexoskin and Vmax were highly correlated for measuring exercise-induced changes in V'_E, V_T, RR and HR (Table 2.2; Figure 2.12; Appendix A). Altogether, these findings support the validity of Hexoskin's biometric smart shirt for measuring V'_E, V_T, RR and HR during physical activity, and confirm earlier work that evaluated Hexoskin's ability to track these parameters in health [64, 66]. Specifically, in healthy adults, Hexoskin was found to be a valid and consistent tool for monitoring activities typical of daily living such as different body positions (lying, sitting and standing) and various walking speeds [64]. As well, in elite cyclists, Hexoskin was found to be both valid and reliable for measuring HR and RR during an incremental cycling test to exhaustion [66]. However, unique to this study is that it extends these observations to people with COPD during INCR and CWR CPET, which are both commonly used in clinical and research

settings to assess for cardiorespiratory fitness, mechanisms of unexplained symptoms (e.g., dyspnea) and efficacy of therapeutic interventions (e.g., bronchodilation) [24, 78].

This study is the first, in health or disease, to evaluate the ability of Hexoskin's biometric smart shirt to track the behavior of dynamic operating lung volumes (namely IC and IRV) during exercise. To ensure that the Hexoskin device was recording exercise-induced changes in operating lung volumes and not variation in peak EILV (or maximal voluntary rib cage expansion), we calculated the CVs for the peak EILV values (representing TLC) recorded by the smart shirt during each maximal voluntary IC maneuver performed at rest and throughout each CPET trial. Ultimately, there was no mean CV greater than 0.24%, and no individual subject had a CV greater than 1.4% for the peak EILV values recorded during any CPET trial (Figure 2.8; Table 2.1). Additionally, we did not find any significant effects of measurement time on the peak EILVs during IC maneuvers from rest-to-peak exercise within either CPET trial. In light of these observations, we were confident that any exercise-induced changes in IC and IRV recorded by Hexoskin reflected 'true' physiological (or pathophysiological) changes in the behavior of dynamic EELV and EILV, respectively, and not variation in the peak EILV due to variation in voluntary effort during serial IC maneuvers. Furthermore, like V'_E, V_T, RR and HR, the temporal patterns of change in IC and IRV from rest to peak exercise were very similar when recorded using Hexoskin's biometric smart shirt compared with Vmax (Figures 2.9-2.11). Specifically, IC and IRV measurements made with both Hexoskin and Vmax illustrated the presence of dynamic lung hyperinflation (i.e., decrease in dynamic IC from rest-to-peak exercise) with attendant severe restrictive constraints on V_T expansion near the limits of exercise tolerance (i.e., progressive decline in IRV from rest to peak exercise), which are pathophysiological hallmarks of the respiratory mechanical response to exercise in people with COPD [22] and also mechanistically

linked to the burden of exertional breathlessness in this patient population. In addition, Hexoskin and Vmax were highly correlated for measuring exercise-induced changes in IC and IRV (Table 2.2; Figure 2.12; Appendix A Table A.1 and Table A.2).

2.5.2 Responsiveness of the Hexoskin Biometric Smart Shirt

In terms of the responsiveness of Hexoskin's biometric smart shirt to PR, we analyzed both our mean and individual subject data to get a comprehensive understanding of the pre- to post-PR changes in cardiac and ventilatory parameters during exercise. Despite a 2.5-fold increase in constant-load cycle exercise endurance time following 7-8 weeks of PR (from 3.7 to 8.1 minutes), there were no demonstrable mean changes in V'_E, V_T, RR, HR, IC and IRV at any time point during CWR CPETs performed pre- vs. post-PR, regardless of whether measurements were performed using Hexoskin or Vmax (Figure 2.13). While it would have been ideal to identify a submaximal change pre- to post-PR, this still does not invalidate the responsiveness of the Hexoskin device. Rather, it simply sheds light on the fact that, despite a ~2 fold improvement in CWR exercise endurance time, the exercise training stimulus (intensity and/or volume) applied to our volunteers during their participation in a 7-8 week hospital-based (outpatient) PR program was not sufficient to improve physiological responses during submaximal exercise, which is in keeping with the results of an earlier study by Wadell al. [79]. Ultimately, since submaximal exercise responses were not different pre- to post-PR, we relied on the correlations between Hexoskin and Vmax for measuring the magnitude of individual subject pre- to post-PR changes in cardiac and respiratory parameters during CWR CPET, in order to evaluate the responsiveness of the smart shirt to an established clinical (therapeutic) intervention. As summarized in Table 2.4 and Appendices B-E, strong correlations were found between the two devices at each measurement time (i.e., rest, HET, ISO and peak), as evidenced by R^2 values ranging from 0.54 to 0.97 (Table

2.4; Appendix B-E). Altogether, these findings support the responsiveness of the Hexoskin biometric smart shirt to detect both exercise-induced (see *Section 2.5.1*) and PR-induced changes in V'_E, V_T, RR, HR, IC and IRV during CPET.

2.5.3 Data Loss

From all the cardiac and ventilatory parameters measured in this study, data loss only occurred with respect to HR and IC (and in turn, IRV). Non-physiological HR data was recorded by Hexoskin for two individuals during both their INCR and CWR1 CPETs. Since the INCR and CWR1 trials took place on the same day and the patients did not remove the smart shirt in between the trials, it is unlikely that this was random data loss. Rather, it is possible that the garment did not fit snug enough on these patients or that the ECG electrodes from Vmax were placed in a manner that overlapped with the regions of the 3-lead ECG electrodes embedded within the smart shirt, such that Hexoskin could not properly detect cardiac activity. For IC and IRV, data loss was more random. Hexoskin was unable to detect a total of seven IC maneuvers (from five individuals) throughout the different CPET trials (Figure 2.4). While these unidentified ICs occurred at different measurement time-points, most ICs went undetected when the patients were cycling: one IC was undetected at baseline, five ICs were undetected throughout exercise and one IC was undetected at peak exercise. This makes sense considering the greater movement artifact that occurs with cycling compared to simply remaining seated. However, despite this data loss, it is important to note that since it only represents 3% of the data, it is quite negligible.

2.5.4 Methodological Considerations

Despite the fact that the Hexoskin biometric smart shirt consists of both an abdominal and thoracic (rib cage) respiration band, we excluded the abdominal band and solely relied on the thoracic band for evaluating ventilatory parameters in this study. This was mainly because we were

able to reliably identify only 47% of the IC maneuvers performed (n=102 of 217) when both the abdominal and thoracic bands were used, as the two respiration channels often cancelled each other out. However, when we used the thoracic respiration band alone, the amount of detectable IC maneuvers increased to 97% (n=210 of 217) (Figure 2.4). Excluding the abdominal respiration band from analysis forced us to abandon the idea of calibrating the respired volume signal recorded using Hexoskin and quantifying V_T expansion and V'_E in L and L/min, respectively. While this may be perceived as a limitation, it actually enabled us to assess the validity and responsiveness of the Hexoskin biometric smart shirt in the way that it would most likely be used in the 'real world', because practically speaking, it is highly unlikely that end-users would have the ability to do a volumetric calibration of Hexoskin's biometric smart shirt to that of a calibrated pneumotachograph. Additionally, by excluding the abdominal respiration band, we were able to avoid making assumptions about thoracic and abdominal contributions to tidal breathing, which differ depending on factors like an individual's body size or posture [80-85]. Lastly, studies making use of optoelectronic plethysmography to assess the degree of lung hyperinflation during exercise in COPD tend to mainly report on ribcage hyperinflation [86], which further supports our decision to rely on the thoracic (rib cage) band to evaluate exercise- and PR-induced changes in breathing pattern and operating lung volume. Moreover, as described in section 2.3.4 of the thesis, the Hexoskin V'_E, V_T, IC and IRV data were obtained from the respiration (thoracic) channel trace imported into the VivoSense wearable sensor analysis platform, where the resulting voltage units were considered arbitrary. This limited the types of analyses that could be performed to evaluate the ability of the Hexoskin device to accurately measure the aforementioned parameters since its units differed from those of the Vmax metabolic cart. Thus, instead of making direct comparisons between the two devices, we relied on temporal patterns and correlations. While this may be

perceived as a limitation, it actually allowed us to avoid using any calibrations that may have altered the original data recorded by the Hexoskin device and it enabled us to assess the validity and responsiveness of the Hexoskin biometric smart shirt in the way that it would most likely be used in the 'real world', because, again, practically speaking, end-users would not necessarily be able to run a calibration to convert the arbitrary voltage units into a volume.

In the absence of mean differences in cardiac and respiratory responses to CWR exercise from pre- to post-PR, we relied on the strength of the correlations between Hexoskin and Vmax for measuring the magnitude of individual subject pre- to post-PR changes in cardiac and respiratory parameters during CWR CPET, which we must concede is not ideal to confirm responsiveness of the Hexoskin biometric smart shirt. To further assess Hexoskin's responsiveness to detect within-subject changes in cardiac and respiratory responses to exercise, future studies should consider the implementation of interventions other than rehabilitative exercise training that are likely to yield consistent mean differences pre- to post-intervention. For example, we observed exercise-induced declines in IC and IRV; the corollary of these findings is that the Hexoskin biometric smart shirt should be able to detect improvements in IC and IRV at rest and during exercise in COPD following pharmacologic (bronchodilator) therapy or surgical lung volume reduction. However, a prospective study is needed to confirm this postulate and extend the potential use of the Hexoskin device to assess interventional efficacy on operating lung volumes. Furthermore, while our results confirm those of earlier studies in health [64, 66] and are the first to report on IC and IRV as well as responses in COPD, we can only assume that they would be transferable to other patient population (e.g., asthma, interstitial lung disease, heart failure) as future research would be required in this regard.

Finally, the results of this study should be interpreted as preliminary evidence in support of Hexoskin's biometric smart shirt for monitoring cardiac and ventilatory parameters in COPD, since the device was only evaluated in a relatively small and homogeneous sample of patients, and no reliability data was collected. As well, the results may only apply to cycle exercise testing, and should be confirmed during weight-bearing exercises such as walking and/or running (which are more commonly performed during ADLs than cycling) where validity and responsiveness of the Hexoskin biometric smart shirt to detect exercise- and PR-induced changes in cardiac and ventilatory parameters may be compromised because of greater movement-related artefacts. Furthermore, due to the controlled laboratory-based nature of the study, we could not report on how the smart shirt would perform in the 'real world' when variables like posture and/or the intensity of physical activity are poorly controlled. We also did not ask our participants to describe their level of interest and/or proficiency interacting with the web-based data acquisition platform, the comfort of the shirt, the real or anticipated ease of taking it on/off or the likelihood that they would wear the shirt daily and for how long. Therefore, in addition to assessing the reliability of the device and its performance in a larger sample of COPD patients, future research should evaluate the device for its application to real life, aspects related to feasibility as well as acceptability by the patient in order to uncover the full potential of the smart shirt for tracking cardiopulmonary physiology in this patient population.

2.5.5 Clinical Implications and Applications

Given the paucity of wearable technologies currently available for ambulatory physiological monitoring in COPD, this study represents an obligatory first step in providing evidence in support of the Hexoskin biometric smart shirt as a valid and responsive clinical tool in this patient population. As mentioned in section 1.1 above, the Hexoskin device has the potential

to be used for purposes such as better understanding the pathophysiological mechanisms of patient-reported symptoms in daily life or evaluating the efficacy of therapeutic interventions on sensory-mechanical relationships during ADLs. However, since Hexoskin can measure physical activity, sleep parameters and heart rate variability (HRV) in addition to the cardiac and ventilatory parameters measured in this study, it could also be used alongside computer/machine learning technologies to identify physiological markers of clinical deterioration resulting in adverse health outcomes, including acute exacerbations of COPD (AECOPD), hospitalization and perhaps also premature death. Specifically, physical activity levels decrease early during AECOPD [87, 88] and physical inactivity is independently associated with the number of hospitalizations for AECOPD [89]. Furthermore, AECOPD is associated with decreased total sleep time and poor sleep efficiency [90] and patient-reported sleep quality is inversely related to the rate of AECOPD and time to first AECOPD [91]. As well, AECOPD is associated with increased parasympathetic modulation of heart rate (as evidenced by increased HRV) [92], increased RR [60, 93-96] and worsening airflow obstruction and lung hyperinflation (as evidenced by decreased IC) [97]. Therefore, the continuous monitoring of these parameters (physical activity, sleep, HRV, RR and IC) with valid and responsive wearable technology like Hexoskin's biometric smart shirt may allow for the early identification (prediction) of adverse health outcomes in COPD, notably AECOPD. This would be particularly meaningful considering that early detection (and treatment) of AECOPD has the potential to prevent the accelerated decline in lung function, hospitalization, diminished quality of life and higher mortality typically associated with AECOPD [98].

2.5.6 Conclusion

The results of this study provide evidence that Hexoskin is a valid and responsive wearable technology for ambulatory monitoring of cardiopulmonary parameters in COPD. Specifically, we found the device to be (i) valid for measuring V'_E, V_T, RR, HR, IC and IRV throughout INCR and CWR CPET, and (ii) responsive for detecting PR-induced changes in these parameters during CPET in adults with COPD. Ultimately, this research represents an important first step towards uncovering the potential of the Hexoskin biometric smart shirt to be used as a clinical tool in this patient population, as it may offer healthcare providers and clinical researchers with unique opportunities to optimize medical management of their patients by bettering their understanding of sensory-mechanical relationships in daily life and by predicting (and promptly treating) COPD exacerbations and its associated adverse health outcomes.

REFERENCES

1. *Life and Breath: Respiratory Disease in Canada*. 2007: Public Health Agency of Canada.
2. O'donnell, D.E., et al., *Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease–2007 update.* Canadian Respiratory Journal, 2007. **14**(Suppl B): p. 5B-32B.
3. Buist, A.S., et al., *International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study.* The Lancet, 2007. **370**(9589): p. 741-750.
4. Hodder, R., *COPD a social disease: Inappropriateness and pharmaco-economics. The situation in North America: The view from Canada.* Multidisciplinary Respiratory Medicine, 2010. **5**: p. 119-21.
5. Chapman, K.R., J. Bourbeau, and L. Rance, *The burden of COPD in Canada: results from the confronting COPD survey.* Respiratory Medicine, 2003. **97**: p. S23-S31.
6. *Chronic obstructive pulmonary disease (COPD): A national report card*. 2005: Canadian Lung Association.
7. Murray, C.J. and A.D. Lopez, *Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study.* The Lancet, 1997. **349**(9064): p. 1498-1504.
8. Pauwels, R.A., et al., *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease.* 2001. **163**(5): p. 1256-1276.
9. Vogelmeier, C.F., et al., *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary.* American Journal of Respiratory and Critical Care Medicine, 2017. **195**(5): p. 557-582.
10. Mannino, D.M. and A.S. Buist, *Global burden of COPD: risk factors, prevalence, and future trends.* The Lancet, 2007. **370**(9589): p. 765-773.

11. Vogiatzis, I. and S. Zakynthinos, *Factors limiting exercise tolerance in chronic lung diseases.* Comprehensive Physiology, 2012. **2**(3): p. 1779-1817.

12. Waschki, B., et al., *Physical Activity Is the Strongest Predictor of All-Cause Mortality in Patients With COPD.* 2011. **140**(2): p. 331-342.

13. Kim, V. and G.J. Criner, *Chronic Bronchitis and Chronic Obstructive Pulmonary Disease.* American Journal of Respiratory and Critical Care Medicine, 2013. **187**(3): p. 228-237.

14. Gagnon, P., et al., *Pathogenesis of hyperinflation in chronic obstructive pulmonary disease.* International Journal of Chronic Obstructive Pulmonary Disease, 2014: p. 187.

15. O'donnell, D. and P. Laveneziana, *Physiology and consequences of lung hyperinflation in COPD.* European Respiratory Review, 2006. **15**(100): p. 61-67.

16. Oga, T., et al., *Analysis of the Factors Related to Mortality in Chronic Obstructive Pulmonary Disease.* American Journal of Respiratory and Critical Care Medicine, 2003. **167**(4): p. 544-549.

17. Deesomchok, A., et al., *Lung Hyperinflation and Its Reversibility in Patients with Airway Obstruction of Varying Severity.* 2010. **7**(6): p. 428-437.

18. O'Donnell, D.E., et al., *Pathophysiology of Dyspnea in Chronic Obstructive Pulmonary Disease: A Roundtable.* American Thoracic Society, 2007. **4**(2): p. 145-168.

19. Ferguson, G.T., *Why Does the Lung Hyperinflate?* American Thoracic Society, 2006. **3**(2): p. 176-179.

20. O'Donnell, D.E., S.M. Revill, and K.A. Webb, *Dynamic Hyperinflation and Exercise Intolerance in Chronic Obstructive Pulmonary Disease.* American Journal of Respiratory and Critical Care Medicine, 2001. **164**(5): p. 770-777.

21. Dubé, B.-P., et al., *The clinical relevance of the emphysema-hyperinflated phenotype in COPD.* COPD Research and Practice, 2015. **2**(1).

22. O'Donnell, D.E., et al., *The Link between Reduced Inspiratory Capacity and Exercise Intolerance in Chronic Obstructive Pulmonary Disease.* Annals of the American Thoracic Society, 2017. **14**(Supplement_1): p. S30-S39.

23. Jensen, D., M.R. Schaeffer, and J.A. Guenette, *Pathophysiological mechanisms of exertional breathlessness in chronic obstructive pulmonary disease and interstitial lung disease.* Current Opinion in Supportive and Palliative Care, 2018. **12**(3): p. 237-245.

24. O'Donnell, D.E., et al., *Exertional dyspnoea in COPD: the clinical utility of cardiopulmonary exercise testing.* European Respiratory Review, 2016. **25**(141): p. 333-347.

25. Ramon, M.A., et al., *The dyspnoea–inactivity vicious circle in COPD: development and external validation of a conceptual model.* European Respiratory Journal, 2018. **52**(3): p. 1800079.

26. O'Donnell, D.E., *Hyperinflation, Dyspnea, and Exercise Intolerance in Chronic Obstructive Pulmonary Disease.* Proceedings of the American Thoracic Society, 2006. **3**(2): p. 180-184.

27. Nishimura, K., et al., *Dyspnea Is a Better Predictor of 5-Year Survival Than Airway Obstruction in Patients With COPD.* Chest, 2002. **121**(5): p. 1434-1440.

28. Thompson, W.R., *Worldwide survey of fitness trends for 2018: the CREP edition.* ACSM's Health & Fitness Journal, 2017. **21**(6): p. 10-29.

29. Boudreaux, B.D., et al., *Validity of Wearable Activity Monitors during Cycling and Resistance Exercise.* Med Sci Sports Exerc, 2018. **50**(3): p. 624-633.

30. Evenson, K.R., M.M. Goto, and R.D. Furberg, *Systematic review of the validity and reliability of consumer-wearable activity trackers.* International Journal of Behavioral Nutrition and Physical Activity, 2015. **12**(1).

31. Izmailova, E.S., J.A. Wagner, and E.D. Perakslis, *Wearable Devices in Clinical Trials: Hype and Hypothesis.* Clinical Pharmacology & Therapeutics, 2018. **104**(1): p. 42-52.

32. Deshmukh, S.D. and S.N. Shilaskar. *Wearable sensors and patient monitoring system: A Review*. IEEE.

33. Andreu-Perez, J., et al., *From Wearable Sensors to Smart Implants-–Toward Pervasive and Personalized Healthcare.* 2015. **62**(12): p. 2750-2762.

34. Jill Doty, T., et al., *The Wearable Multimodal Monitoring System: A platform to study falls and near-falls in the real-world*. 2015.

35. Aliverti, A., *Wearable technology: role in respiratory health and disease.* Breathe (Sheffield, England), 2017. **13**(2): p. e27-e36.

36. Peake, J.M., G. Kerr, and J.P. Sullivan, *A Critical Review of Consumer Wearables, Mobile Applications, and Equipment for Providing Biofeedback, Monitoring Stress, and Sleep in Physically Active Populations.* Frontiers in Physiology, 2018. **9**.

37. Henriksen, A., et al., *Using Fitness Trackers and Smartwatches to Measure Physical Activity in Research: Analysis of Consumer Wrist-Worn Wearables.* Journal of medical Internet research, 2018. **20**(3): p. e110-e110.

38. Düking, P., et al., *Comparison of Non-Invasive Individual Monitoring of the Training and Health of Athletes with Commercially Available Wearable Technologies.* 2016. **7**.

39. Gore, S., et al., *Validity and Reliability of Accelerometers in Patients With COPD A SYSTEMATIC REVIEW.* Journal of Cardiopulmonary Rehabilitation and Prevention, 2017: p. 1.

40. Van Remoortel, H., et al., *Validity of activity monitors in health and chronic disease: a systematic review.* International Journal of Behavioral Nutrition and Physical Activity, 2012. **9**(1): p. 84.

41. Ferguson, T., et al., *The validity of consumer-level, activity monitors in healthy adults worn in free-living conditions: a cross-sectional study.* International Journal of Behavioral Nutrition and Physical Activity, 2015. **12**(1).

42. Straiton, N., et al., *The validity and reliability of consumer-grade activity trackers in older, community-dwelling adults: A systematic review.* Maturitas, 2018. **112**: p. 85-93.

43. Feehan, L.M., et al., *Accuracy of Fitbit Devices: Systematic Review and Narrative Syntheses of Quantitative Data.* JMIR mHealth and uHealth, 2018. **6**(8): p. e10527-e10527.

44. Andersson, M., C. Janson, and M. Emtner, *Accuracy of Three Activity Monitors in Patients with Chronic Obstructive Pulmonary Disease: A Comparison with Video Recordings.* 2014. **11**(5): p. 560-567.

45. Nolan, C.M., et al., *Gait speed and pedestrian crossings in COPD.* Thorax, 2018. **73**(2): p. 191-192.

46. Pericleous, P. and T.P. Van Staa, *The use of wearable technology to monitor physical activity in patients with COPD: a literature review.* International Journal of Chronic Obstructive Pulmonary Disease, 2019. **Volume 14**: p. 1317-1322.

47. Marino, M., et al., *Measuring Sleep: Accuracy, Sensitivity, and Specificity of Wrist Actigraphy Compared to Polysomnography.* Sleep, 2013. **36**(11): p. 1747-1755.

48. De Zambotti, M., et al., *The Sleep of the Ring: Comparison of the ŌURA Sleep Tracker Against Polysomnography.* Behavioral Sleep Medicine, 2019. **17**(2): p. 124-136.

49. De Zambotti, M., et al., *A validation study of Fitbit Charge 2™ compared with polysomnography in adults.* Chronobiology International, 2018. **35**(4): p. 465-476.

50. De Zambotti, M., et al., *Evaluation of a consumer fitness-tracking device to assess sleep in adults.* 2015. **32**(7): p. 1024-1028.

51. Kapella, M.C., et al., *Actigraphy scoring for sleep outcome measures in chronic obstructive pulmonary disease.* Sleep Medicine, 2017. **37**: p. 124-129.

52. Conley, S., et al., *Agreement between actigraphic and polysomnographic measures of sleep in adults with and without chronic conditions: A systematic review and meta-analysis.* Sleep Medicine Reviews, 2019.

53. Ryan, T.E., et al., *A cross-validation of near-infrared spectroscopy measurements of skeletal muscle oxidative capacity with phosphorus magnetic resonance spectroscopy.* J Appl Physiol (1985), 2013. **115**(12): p. 1757-66.

54. Farzam, P., Z. Starkweather, and M.A. Franceschini, *Validation of a novel wearable, wireless technology to estimate oxygen levels and lactate threshold power in the exercising muscle.* Physiological Reports, 2018. **6**(7): p. e13664.

55. McManus, C.J., J. Collison, and C.E. Cooper, *Performance comparison of the MOXY and PortaMon near-infrared spectroscopy muscle oximeters at rest and during exercise.* Journal of Biomedical Optics, 2018. **23**(01): p. 1.

56. Borges, N.R. and M.W. Driller, *Wearable Lactate Threshold Predicting Device is Valid and Reliable in Runners.* J Strength Cond Res, 2016. **30**(8): p. 2212-8.

57. Adami, A., et al., *Reproducibility of NIRS assessment of muscle oxidative capacity in smokers with and without COPD.* 2017. **235**: p. 18-26.

58. Soler, J., et al., *Validation of respiratory rate measurements from remote monitoring device in COPD patients.* Respir Med Res, 2019. **76**: p. 1-3.

59. Walsh, J.A., E.J. Topol, and S.R. Steinhubl, *Novel Wireless Devices for Cardiac Monitoring.* 2014. **130**(7): p. 573-581.

60. Tomasic, I., et al., *Continuous remote monitoring of COPD patients—justification and explanation of the requirements and a survey of the available technologies.* Medical & Biological Engineering & Computing, 2018. **56**(4): p. 547-569.

61. Steinhubl, S.R., et al., *Rationale and design of a home-based trial using wearable sensors to detect asymptomatic atrial fibrillation in a targeted population: The mHealth Screening To Prevent Strokes (mSToPS) trial.* 2016. **175**: p. 77-85.

62. Barrett, P.M., et al., *Comparison of 24-hour Holter Monitoring with 14-day Novel Adhesive Patch Electrocardiographic Monitoring.* 2014. **127**(1): p. 95.e11-95.e17.

63. Rosenberg, M.A., et al., *Use of a Noninvasive Continuous Monitoring Device in the Management of Atrial Fibrillation: A Pilot Study.* 2013. **36**(3): p. 328-333.

64. Villar, R., T. Beltrame, and R.L. Hughson, *Validation of the Hexoskin wearable vest during lying, sitting, standing, and walking activities.* Applied Physiology, Nutrition, and Metabolism, 2015. **40**(10): p. 1019-1024.

65. Beltrame, T., et al., *Extracting aerobic system dynamics during unsupervised activities of daily living using wearable sensor machine learning models.* Journal of Applied Physiology, 2018. **124**(2): p. 473-481.

66. Elliot, C.A., M.J. Hamlin, and C.A. Lizamore, *Validity and Reliability of the Hexoskin Wearable Biometric Vest During Maximal Aerobic Power Testing in Elite Cyclists.* Journal of Strength and Conditioning Research, 2019. **33**(5): p. 1437-1444.

67. Stevenson, N.J., et al., *Lung Mechanics and Dyspnea during Exacerbations of Chronic Obstructive Pulmonary Disease.* 2005. **172**(12): p. 1510-1516.

68. Thomas, M., M. Decramer, and D.E. O'Donnell, *No room to breathe: the importance of lung hyperinflation in COPD.* Primary Care Respiratory Journal, 2013. **22**(1): p. 101-111.

69. Van Geffen, W.H., D.-J. Slebos, and H.A.M. Kerstjens, *Hyperinflation in COPD exacerbations.* 2015. **3**(12): p. e43-e44.

70. Borg, G.A., *Psychophysical bases of perceived exertion.* Med Sci Sports Exerc, 1982. **14**(5): p. 377-81.

71. Miller, M.R., *Standardisation of spirometry.* European Respiratory Journal, 2005. **26**(2): p. 319-338.

72. Miller, M.R., *General considerations for lung function testing.* European Respiratory Journal, 2005. **26**(1): p. 153-161.

73. Macintyre, N., *Standardisation of the single-breath determination of carbon monoxide uptake in the lung.* 2005. **26**(4): p. 720-735.

74. Wanger, J., *Standardisation of the measurement of lung volumes.* 2005. **26**(3): p. 511-522.

75. Ross, R.M., *ATS/ACCP statement on cardiopulmonary exercise testing.* Am J Respir Crit Care Med, 2003. **167**(10): p. 1451; author reply 1451.

76. Elfaramawy, T., et al., *A Wireless Respiratory Monitoring System Using a Wearable Patch Sensor Network.* IEEE Sensors Journal, 2019. **19**(2): p. 650-657.

77. Hart, A., et al. *A contact-free respiration monitor for smart bed and ambulatory monitoring applications*. in *2010 Annual International Conference of the IEEE Engineering in Medicine and Biology*. 2010.

78. Herdy, A.H., et al., *Cardiopulmonary Exercise Test: Fundamentals, Applicability and Interpretation.* Arquivos Brasileiros de Cardiologia, 2016.

79. Wadell, K., et al., *Impact of pulmonary rehabilitation on the major dimensions of dyspnea in COPD.* Copd, 2013. **10**(4): p. 425-35.

80. Konno, K. and J. Mead, *Measurement of the separate volume changes of rib cage and abdomen during breathing.* Journal of Applied Physiology, 1967. **22**(3): p. 407-422.

81. Sharp, J.T., et al., *Relative contributions of rib cage and abdomen to breathing in normal subjects.* J Appl Physiol, 1975. **39**(4): p. 608-18.

82. Vellody, V.P., et al., *Effects of body position change on thoracoabdominal motion.* J Appl Physiol Respir Environ Exerc Physiol, 1978. **45**(4): p. 581-9.

83. Lee, L.J., et al., *Changes in sitting posture induce multiplanar changes in chest wall shape and motion with breathing.* Respir Physiol Neurobiol, 2010. **170**(3): p. 236-45.

84. Romei, M., et al., *Effects of gender and posture on thoraco-abdominal kinematics during quiet breathing in healthy adults.* Respiratory Physiology & Neurobiology, 2010. **172**(3): p. 184-191.

85. Bellemare, F., A. Jeanneret, and J. Couture, *Sex Differences in Thoracic Dimensions and Configuration.* American Journal of Respiratory and Critical Care Medicine, 2003. **168**(3): p. 305-312.

86. Massaroni, C., et al., *Optoelectronic Plethysmography in Clinical Practice and Research: A Review.* Respiration, 2017. **93**(5): p. 339-354.

87. Ehsan, M., et al., *A Longitudinal Study Evaluating the Effect of Exacerbations on Physical Activity in Patients with Chronic Obstructive Pulmonary Disease.* Annals of the American Thoracic Society, 2013. **10**(6): p. 559-564.

88. Alahmari, A.D., et al., *Daily activity during stability and exacerbation of chronic obstructive pulmonary disease.* BMC Pulmonary Medicine, 2014. **14**(1): p. 98.

89. Katajisto, M., et al., *Physical activity in COPD patients decreases short-acting bronchodilator use and the number of exacerbations.* Respiratory Medicine, 2015. **109**(10): p. 1320-1325.

90. Vanaparthy, R., et al., *A longitudinal assessment of sleep variables during exacerbations of chronic obstructive pulmonary disease.* Chronic Respiratory Disease, 2015. **12**(4): p. 299-304.

91. Geiger-Brown, J., et al., *Self-reported sleep quality and acute exacerbations of chronic obstructive pulmonary disease.* International Journal of Chronic Obstructive Pulmonary Disease, 2015: p. 389.

92. Kabbach, E.Z., et al., *Increased parasympathetic cardiac modulation in patients with acute exacerbation of COPD: how should we interpret it?* International Journal of Chronic Obstructive Pulmonary Disease, 2017. **Volume 12**: p. 2221-2230.

93. Shah, S.A., et al., *Exacerbations in Chronic Obstructive Pulmonary Disease: Identification and Prediction Using a Digital Health System.* J Med Internet Res, 2017. **19**(3): p. e69.

94. Ballal, T., et al., *A pilot study of the nocturnal respiration rates in COPD patients in the home environment using a non-contact biomotion sensor.* 2014. **35**(12): p. 2513-2527.

95. Yanez, A.M., et al., *Monitoring breathing rate at home allows early identification of COPD exacerbations.* Chest, 2012. **142**(6): p. 1524-1529.

96. Franciosi, L.G., et al., *Markers of exacerbation severity in chronic obstructive pulmonary disease.* Respiratory Research, 2006. **7**(1).

97. Parker, C.M., et al., *Physiological changes during symptom recovery from moderate exacerbations of COPD.* European Respiratory Journal, 2005. **26**(3): p. 420-428.

98. Wu, R., et al., *Feasibility of Using a Smartwatch to Intensively Monitor Patients With Chronic Obstructive Pulmonary Disease: Prospective Cohort Study.* JMIR Mhealth Uhealth, 2018. **6**(6): p. e10046.

APPENDIX A

Table A.1. Correlation between Vmax and Hexoskin for measuring cardiopulmonary parameters during each individual CPET trial.

Cardiopulmonary parameters	CPET trial		
	INCR	CWR1	CWR2
V'_E	0.93 ± 0.05 [0.80-0.99]	0.99 ± 0.02 [0.95-1.00]	0.94 ± 0.06 [0.82-1.00]
V_T	0.82 ± 0.17 [0.48-0.99]	0.96 ± 0.05 [0.85-1.00]	0.90 ± 0.10 [0.71-1.00]
RR	0.94 ± 0.08 [0.72-1.00]	0.96 ± 0.04 [0.88-1.00]	0.96 ± 0.05 [0.85-0.99]
HR	0.95 ± 0.09 [0.71-1.00]	0.99 ± 0.03 [0.88-1.00]	0.98 ± 0.04 [0.89-1.00]
IC	0.85 ± 0.11 [0.63-0.99]	0.92 ± 0.09 [0.70-1.00]	0.90 ± 0.09 [0.75-1.00]
IRV	0.88 ± 0.13 [0.58-1.00]	0.96 ± 0.04 [0.86-1.00]	0.96 ± 0.06 [0.84-1.00]

Correlations reported as: mean R^2 ± SD [min – max])

Table A.2. Correlation between Vmax and Hexoskin for measuring magnitudes of change from rest-to-peak exercise during each individual CPET trial.

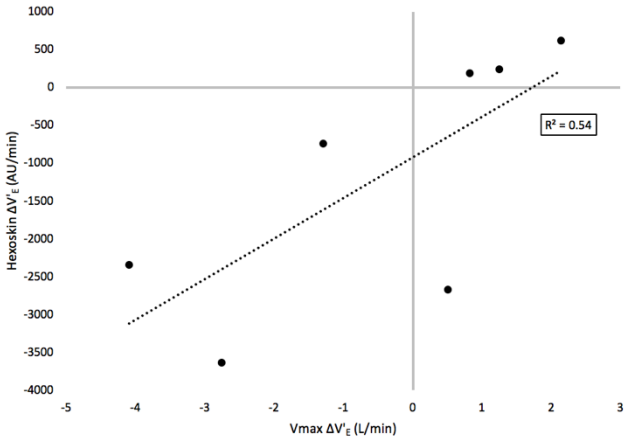
Cardiopulmonary parameters	CPET trial		
	INCR	CWR1	CWR2
$\Delta V'_E$	0.83	0.71	0.80
ΔV_T	0.67	0.75	0.72
ΔRR	0.88	0.90	0.98
ΔHR	0.74	0.97	0.93
ΔIC	0.86	0.82	0.64
ΔIRV	0.66	0.77	0.79

Correlations reported as: R^2

APPENDIX B

Correlation between Vmax and Hexoskin for measuring individual subject pre- to post-PR changes at baseline for: a) minute ventilation (V'_E); b) tidal volume (V_T); c) respiratory rate (RR); d) heart rate (HR); e) inspiratory capacity (IC) and; f) inspiratory reserve volume (IRV).

a)



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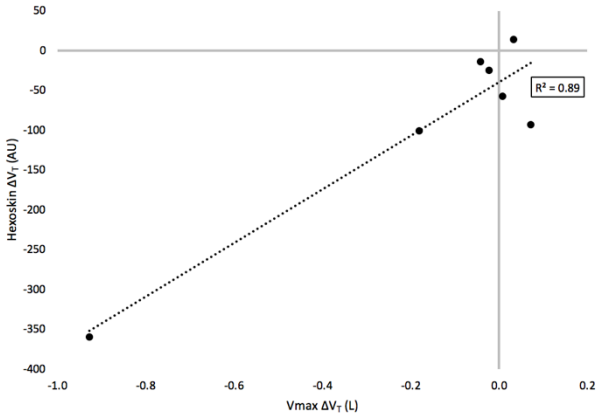

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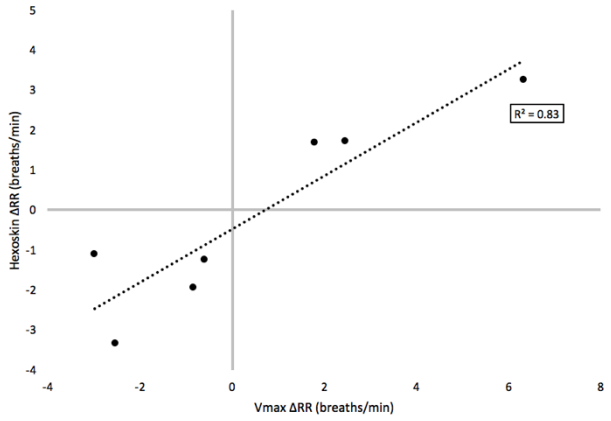

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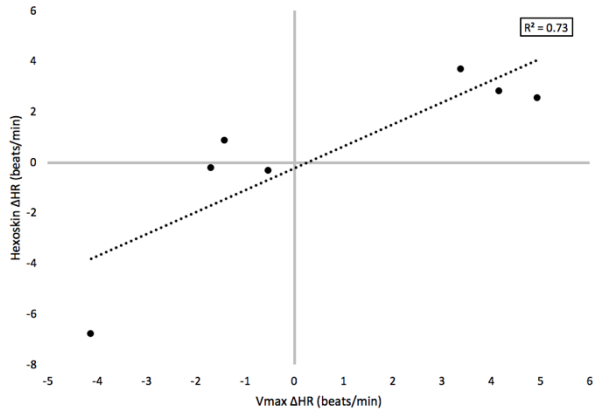

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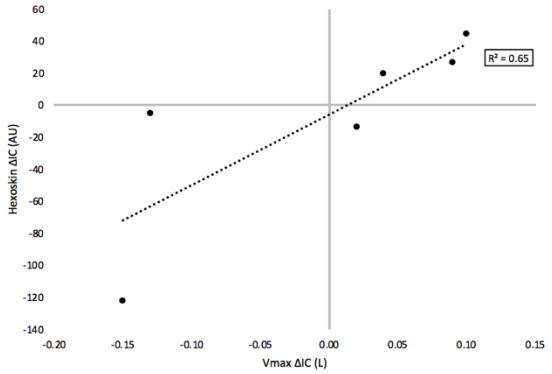

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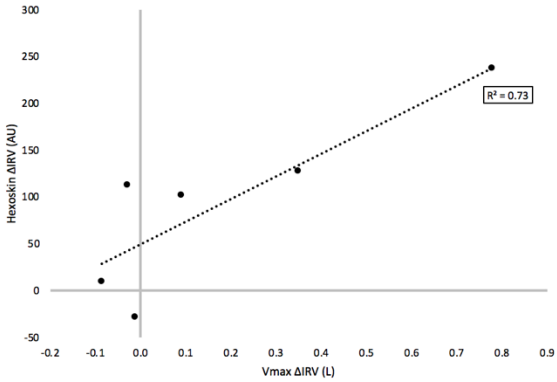
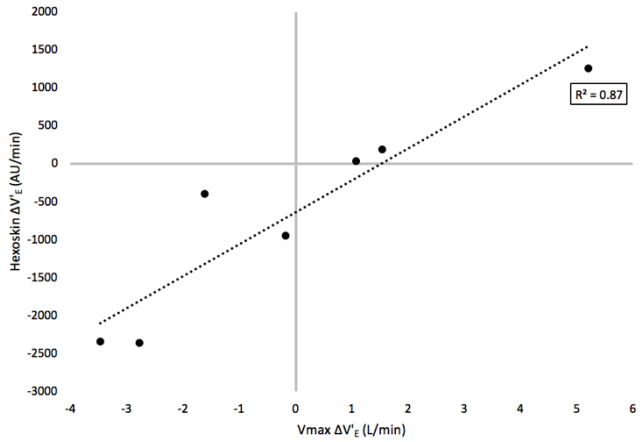


APPENDIX C

Correlation between Vmax and Hexoskin for measuring individual subject pre- to post-PR changes at highest equivalent time (HET) for: a) minute ventilation (V'_E); b) tidal volume (V_T); c) respiratory rate (RR); d) heart rate (HR); e) inspiratory capacity (IC) and; f) inspiratory reserve volume (IRV).

a)



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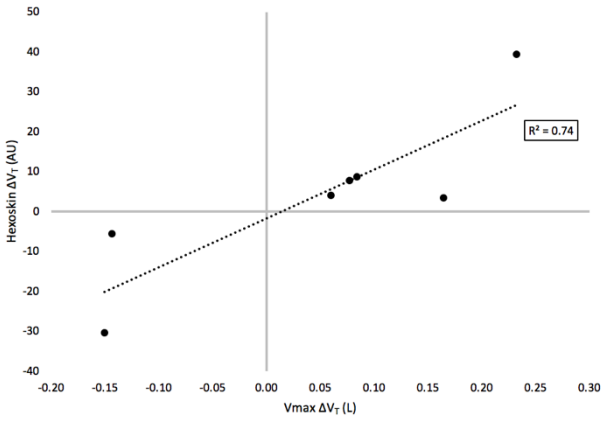

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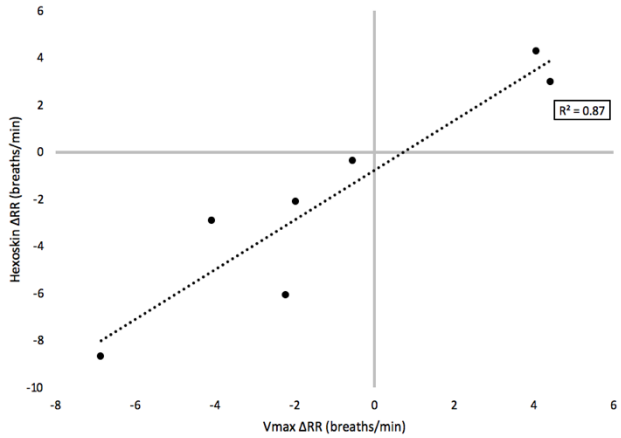

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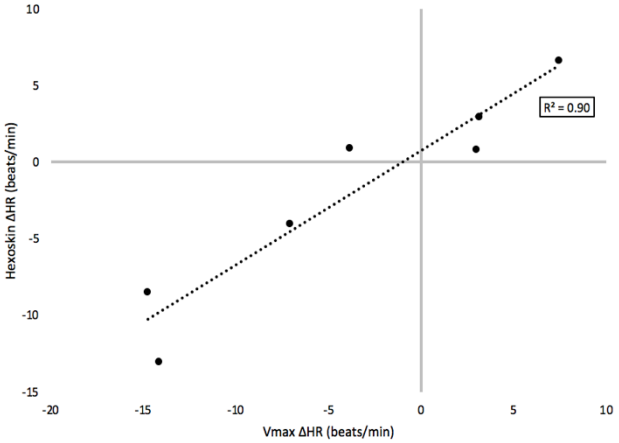

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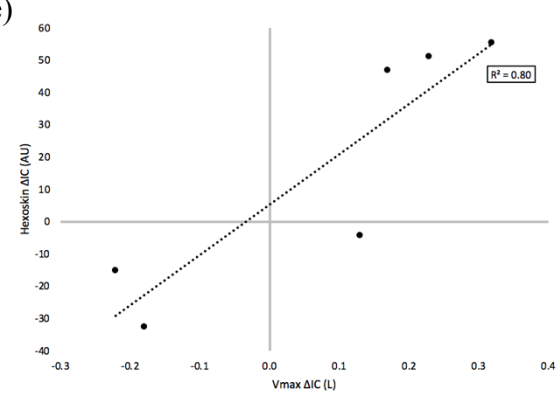

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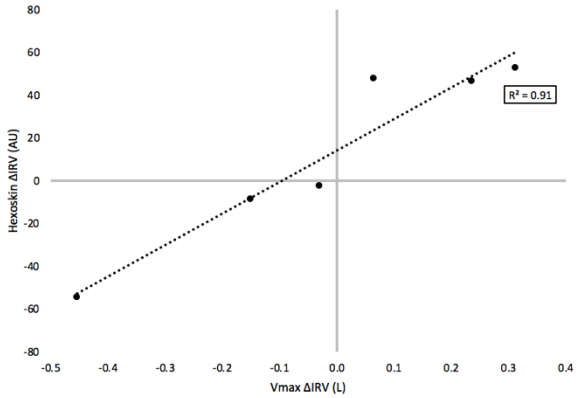
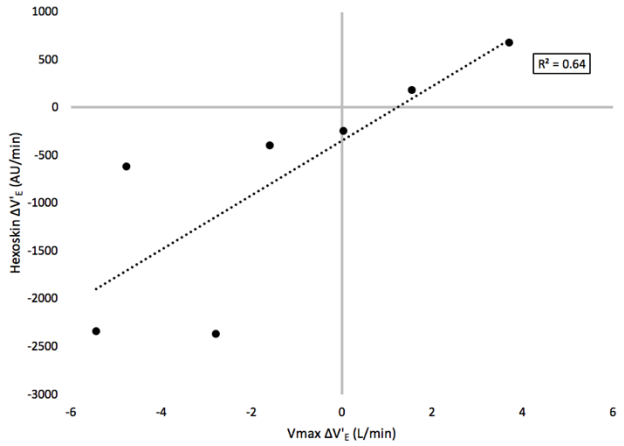


APPENDIX D

Correlation between Vmax and Hexoskin for measuring individual subject pre- to post-PR changes at isotime (ISO) for: a) minute ventilation (V'_E); b) tidal volume (V_T); c) respiratory rate (RR); d) heart rate (HR); e) inspiratory capacity (IC) and; f) inspiratory reserve volume (IRV).

a)



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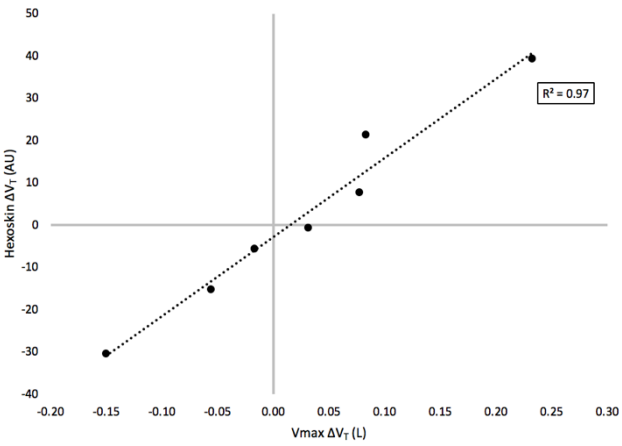

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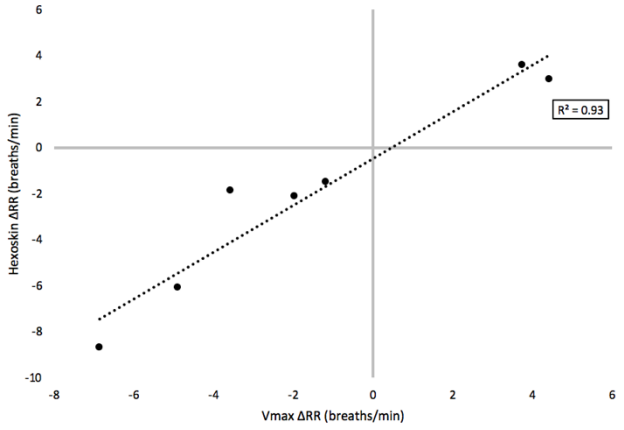

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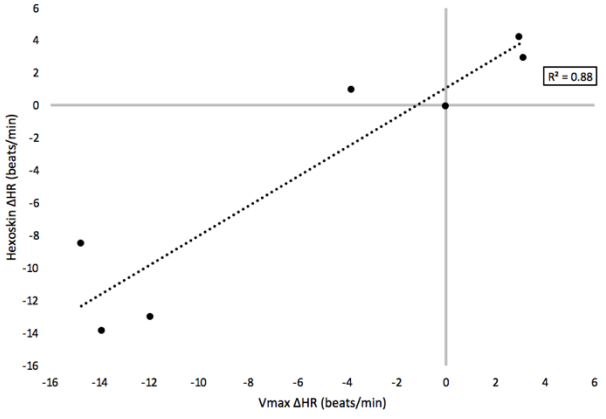

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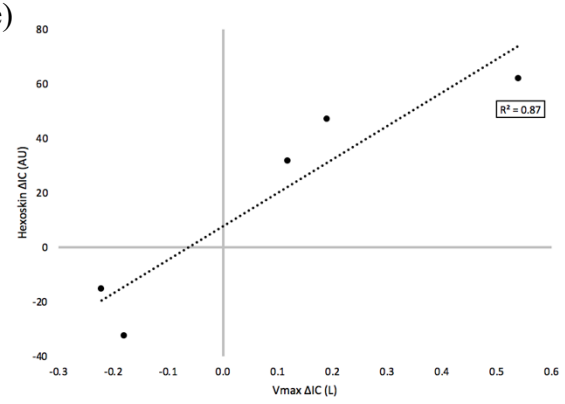

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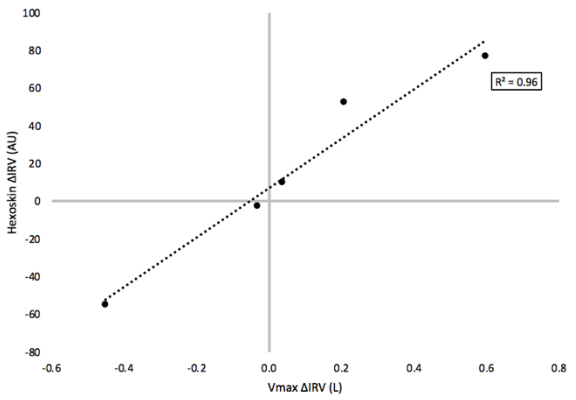
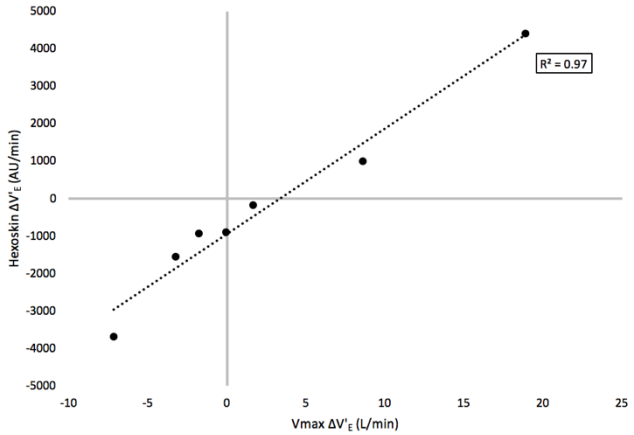


APPENDIX E

Correlation between Vmax and Hexoskin for measuring individual subject pre- to post-PR changes at peak for: a) minute ventilation (V'_E); b) tidal volume (V_T); c) respiratory rate (RR); d) heart rate (HR); e) inspiratory capacity (IC) and; f) inspiratory reserve volume (IRV).

a)



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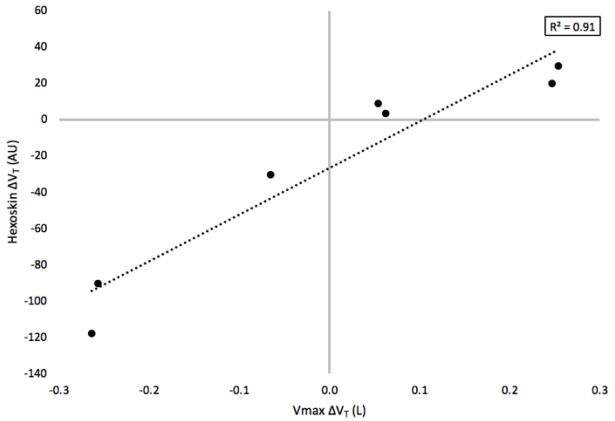

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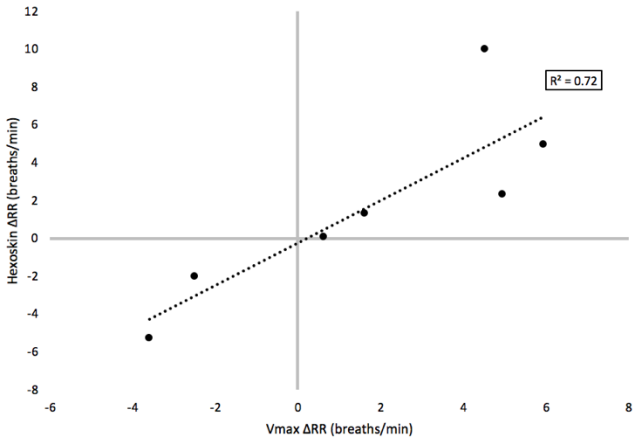

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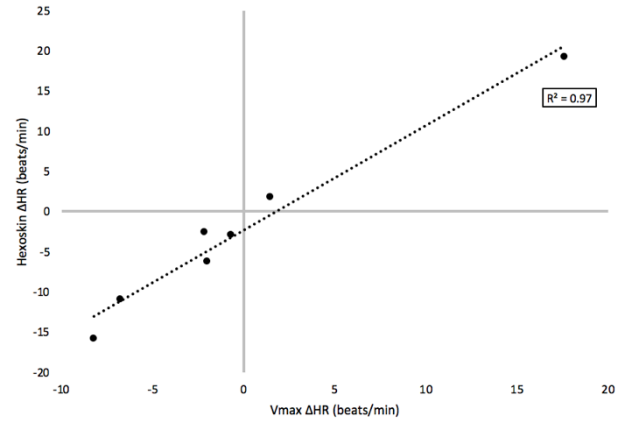

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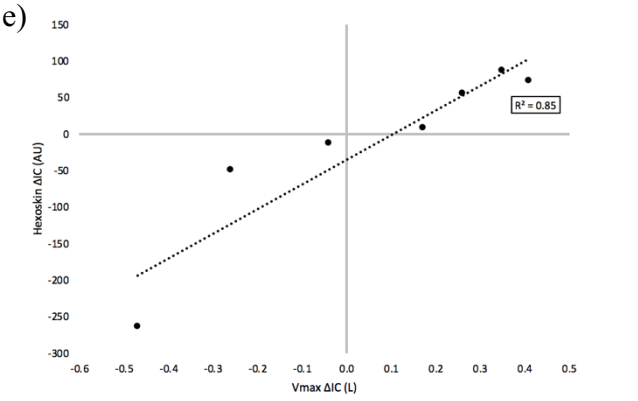

f)