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Reproducibility of NIRS assessment of muscle oxidative capacity in smokers with and without COPD

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ABSTRACT

Low muscle oxidative capacity contributes to exercise intolerance in chronic obstructive pulmonary disease (COPD). Near-infrared spectroscopy (NIRS) allows non-invasive determination of the muscle oxygen consumption ($m\dot{V}O_2$) recovery rate constant (k), which is proportional to oxidative capacity assuming two conditions are met: 1) exercise intensity is sufficient to fully-activate mitochondrial oxidative enzymes; 2) sufficient O_2 availability. We aimed to determine reproducibility (coefficient of variation, CV; intraclass correlation coefficient, ICC) of NIRS k assessment in the *gastrocnemius* of 64 participants with (FEV_1 64 ± 23%predicted) or without COPD (FEV_1 98 ± 14%predicted). 10–15 s dynamic contractions preceded 6 min of intermittent arterial occlusions (5–10 s each, ~250 mmHg) for k measurement. k was lower ($P < 0.05$) in COPD (1.43 ± 0.4 min^{-1}; CV = 9.8 ± 5.9%, ICC = 0.88) than controls (1.74 ± 0.69 min^{-1}; CV = 9.9 ± 8.4%; ICC = 0.93). Poor k reproducibility was more common when post-contraction $m\dot{V}O_2$ and deoxygenation were low, suggesting insufficient exercise intensity for mitochondrial activation and/or the NIRS signal contained little light reflected from active muscle. The NIRS assessment was well tolerated and reproducible for muscle dysfunction evaluation in COPD.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by dyspnea on exertion, with subsequent reduced exercise tolerance and quality of life. Skeletal muscle dysfunction is a systemic consequence of COPD that also contributes to increased morbidity and mortality in this population (Agustí et al., 2003; Casaburi, 2001; Decramer et al., 2008; Maltais et al., 2000, 2014; Nici, 2000; Vogiatzis and Zakynthinos, 2012; Wouters, 2002). Morphological and structural skeletal muscle alterations in COPD are especially prevalent in the locomotor muscles, and include atrophy and weakness, loss of type I fibers, loss of muscle oxidative capacity and mitochondrial dysfunction, among others (Allaire et al., 2004; Coronell et al., 2004; Couillard and Prefaut, 2005; Engelen et al., 2000; Gosker et al., 2002, 2007; Maltais et al., 2014; Picard et al., 2008; Whittom et al., 1998). Amelioration of these muscular alterations contributes to the substantial benefits of pulmonary rehabilitation in COPD patients (Maltais et al., 2014).

The prevalence and progression of the loss of muscle oxidative phenotype in relation to disease severity is still unclear, and this is partly because measurement of muscle oxidative capacity requires an invasive biopsy or complex ^{31}P magnetic resonance spectroscopy assessments. In review, Meyer et al. (2013) showed that low muscle oxidative capacity and increased reactive oxygen species production was evident in skeletal muscle across all spirometric stages of COPD disease severity. Furthermore, Natanek et al. (2013) showed wide heterogeneity in quadriceps type I fiber expression in 114 COPD patients evenly distributed across GOLD stages 2–4. These findings demonstrate that muscle oxidative capacity appears to be highly variable across disease severity, which underscores the need for simple methods to assess changes in muscle oxidative capacity in COPD patients independent from systemic effects of the disease.

We aimed to address this using a non-invasive method based on near-infrared spectroscopy (NIRS; Motobe et al., 2004; Ryan et al., 2012). This technique provides measurement of the recovery rate constant (k) of muscle oxygen consumption ($m\dot{V}O_2$), isolated from influences of circulatory or pulmonary function, and which is directly related to muscle oxidative capacity in single muscle fibers ($r^2 = 0.77$; Wüst et al., 2013). Muscle k can be assessed by NIRS during ~6 min of recovery from brief contractions, using a series of

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intermittent arterial occlusions (5–10 s each); during occlusions, the rate of decline in the muscle tissue saturation index (TSI) is directly proportional to $m\dot{V}O_2$. This technique has been validated in young healthy subjects against phosphocreatine recovery kinetics and quadriceps muscle biopsy (Ryan et al., 2013, 2014). It has also been used to assess muscle oxidative capacity in spinal cord injury (Erickson et al., 2013), amyotrophic lateral sclerosis (Ryan et al., 2014) and chronic heart failure (Southern et al., 2014), among other conditions. However, to our knowledge, this technique has not been applied in COPD where muscle morphologic adaptations such as fat infiltration, fibrosis, inflammation, increased subcutaneous adipose, loss of type I fibers and mitochondrial density (Maltais et al., 2014) may hamper NIRS measurement of muscle oxidative capacity.

The method relies on two competing assumptions: that exercise is sufficiently intense to maximally activate mitochondrial oxidative enzymes and elicit a sufficient increase in $m\dot{V}O_2$ (Korzeniewski and Rossiter, 2015; Wüst et al., 2011, 2013); that O_2 delivery is not limiting to *k* (Haseler et al., 2004). This latter condition is especially important in COPD where poor systemic O_2 delivery, muscle capillary rarefaction and brief arterial occlusions may combine to reduce TSI below some critical threshold, thereby slowing $m\dot{V}O_2$ recovery kinetics.

Test-retest reliability (intraclass correlation coefficient, ICC) of *k* in healthy subjects ranges from 0.26 to 0.68 (Ryan et al., 2012; Southern et al., 2014), and whether reliable measurements are possible in COPD is currently unknown. This is particularly important in relation to the expected effect magnitude of oxidative capacity loss in COPD (~10–50%; Meyer et al., 2013). Therefore, we aimed to determine the reliability of NIRS assessment of *gastrocnemius* muscle oxidative capacity in smokers with and without COPD. We hypothesized that test-retest variability in *k* would be sufficiently low to allow NIRS estimates of oxidative capacity to be a useful method to detect COPD-related loss. Secondly, we aimed to identify correlates of high variability in repeated *k* measurement, if it occurred. These correlates may provide a basis for quality control of the NIRS muscle assessment.

2. Materials and methods

2.1. Participants

Both smoking (Montes de Oca et al., 2008) and COPD (Maltais et al., 2014) have each been implicated in COPD-associated muscle dysfunction. Therefore, to account for the independent influence of smoking history, we sought current and former smokers with at least 10 pack-year smoking history to volunteer: 32 COPD patients (GOLD stage 1–4, defined by the criteria for the Global initiative for Chronic Obstructive Lung Disease) and 28 participants with normal spirometry (CON) (Table 1). This was an ancillary study of COPDGene (ClinicalsTrials.gov Identifier NCT00608764), for which a complete list of inclusion and exclusion criteria is given in Regan et al. (2010). Participants were informed about the procedures and risks associated with the study, and gave written informed consent. The study was approved by the Institutional Review Board of Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, in accordance with the Declaration of Helsinki.

2.2. Protocol

Each participant visited the laboratory once, during which NIRS muscle oxidative capacity and spirometry tests were performed.

2.2.1. NIRS muscle oxidative capacity test

A wireless, portable, continuous-wave, spatially-resolved spectroscopy (SRS) NIRS device (PortaMon, Artinis, The Netherlands) was used to measure relative concentrations of *deoxy*-hemoglobin and *deoxy*-myoglobin (here termed HHb for simplicity) and *oxy*-hemoglobin and *oxy*-myoglobin (HbO_2) in the tissues ~1.5 cm beneath the probe (interoptode distance was 3 cm). From these measurements relative changes in total hemoglobin and myoglobin ($THb = HHb + HbO_2$) and the Hb difference ($Hb_{diff} = HbO_2$-HHb) were calculated. In addition, the tissue saturation index (TSI, %) was measured using the SRS approach (using interoptode distances of 2–3 cm) (Ferrari et al., 2004).

A modified NIRS protocol based on Ryan et al. (2012) was used. The participant lay supine and the NIRS probe was wrapped in plastic film, placed longitudinally on the belly of the right medial *gastrocnemius*, and secured with an elastic bandage. A 13 × 85 cm rapid-inflation pressure-cuff (SC12D, Hokanson, USA) was placed on the proximal thigh of the same leg and attached to an electronically-controlled rapid cuff-inflator (E20, Hokanson, USA). A pad was placed under the ankle such that the lower leg and NIRS probe was suspended above the bed. During the ~30 min assessment, the participant was asked to relax and refrain from moving the leg except when instructed.

Initially, the participant was familiarized with the execution of cyclical plantar-flexion/relaxation exercise at ~1 Hz, to activate the medial *gastrocnemius* against a manually applied resistance, and with the rapid-cuff inflation procedures. Repeated cuff inflations from low (~50 mmHg) to high (~250 mmHg) pressures were performed during this familiarization phase. Arterial occlusion was determined from a tolerated cuff-pressure within the range of 230–300 mmHg (236 ± 17 mmHg) that resulted in HHb rise, HbO_2 fall and approximately constant THb over ~15–20 s.

The measurement protocol began after 2–3 min of rest, where baseline TSI and SpO_2 at a fingertip (Rad-5 Pulse Oximeter MasimoSET®, Masimo Co., Irvine, CA) were measured over 2 min. Subsequently, after having removed the pulse oximeter, the participant was instructed to execute 10–12 cycles of plantar-flexion exercise, followed immediately by arterial occlusion until a steady-state in TSI was reached (mean duration ~90 s; Fig. 1). The cuff was then instantly deflated and muscle reoxygenation was recorded until a steady-state was reached (typically ~3 min). This procedure (the physiologic normalization, PN) identified the functional range of TSI under resting conditions from TSI*min* at the end of the sustained arterial occlusion to TSI*max* at the peak of the reactive

Table 1
Participant characteristics.

	COPD	CON
Characteristics		
N.	28	28
Age (yrs)	65 (±8)	60 (±7)*
Weight (kg)	76 (±15)	79 (±17)
Height (cm)	171 (±11)	170 (±8)
BMI (kg/m^2)	26 (±5)	27 (±5)
Gender (M/F)	17/11	16/12
Race (AA/NHW)	5/23	15/13
FVC (L)	3.3 (±0.9)	3.5 (±0.8)
FEV_1 (L)	1.8 (±0.7)	2.8 (±0.6)*
FEV_1%pred	63.9 (±23.4)	97.9 (±13.6)*
SpO_2 (%)	97 (±1.6)	98 (±1.1)
GOLD stage N. (1/2/3/4)	7/13/5/3	
Resting Muscle Characteristics		
Saturation (TSI) (%)	66 (±6)	68 (±5)
ATT (mm)	2.3 (±1.9)¶	2.8 (±1.9)♯

Data are mean (±SD). CON = controls; BMI = body mass index; M = male; F = female; AA = African American; NHW = Non Hispanic White; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; SpO_2 = arterial oxygen saturation; TSI = tissue saturation index; ATT = adipose tissue thickness.
* $P \leq 0.01$ *vs.* COPD patients.
¶ COPD n = 21.
♯ CON n = 18.

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