Near infrared spectroscopy for the assessment of peripheral tissue oxygenation in pulmonary arterial hypertension.

Authors

Marios Panagiotou[1], Ioannis Vogiatzis[2], Zafeiris Louvaris[2], Geeshath Jayasekera[1], Alison McKenzie[1], Neil Mcglinchey[1], Julien S. Baker[3], Alistair C. Church[1], Andrew J. Peacock[1], Martin K. Johnson[1].

Affiliations

[1]Scottish Pulmonary Vascular Unit, Golden Jubilee National Hospital, Glasgow, UK; [2]National and Kapodistrian University of Athens, Department of Physical Education and Sports Sciences, Athens, Greece; [3]Institute of Clinical Exercise and Health Science, University of the West of Scotland, Hamilton, UK.

Corresponding author:

Marios Panagiotou: Scottish Pulmonary Vascular Unit, Golden Jubilee National Hospital, Agamemnon Street, Glasgow, G81 4DY, UK; mariopanag@gmail.com; +447478664894.

"take home" message: Near infrared spectroscopy offers a qualitative, noninvasive indication of mixed venous oxygen saturation in PAH.

Pulmonary arterial hypertension (PAH) is characterised by increased pulmonary vascular resistance and results in increased morbidity and mortality due to right heart failure and a progressive decline in cardiac output (CO) [1]. The latter disturbs oxygen delivery to periphery and may lead to pathological changes in tissue oxygenation. The balance between global oxygen supply and demand is reflected in mixed venous oxygen saturation (SvO_2), an index that is generally reduced in patients with PAH [2]. SvO_2 at baseline is one of the strongest predictors of survival in PAH [3-5]; this is also true for changes in SvO_2 during follow-up [4]. Cut-off values of 60% [6] and 65% [4] have been used to distinguish between prognostic groups suggesting that these may be suitable treatment goals. SvO_2 is measured invasively in the pulmonary artery, where venous blood mixes after circulating through the superior and inferior vena cava, coronary sinuses and the right-heart chambers.

Spatially resolved near infrared spectroscopy (NIRS) offers a noninvasive, rapidly responsive method for measuring skeletal muscle oxygenation by examining absorption differences in the near infrared spectrum of light between oxy- and deoxy- haemoglobin and myoglobin molecules in the microvasculature. The *tissue oxygenation index* (StO_2) is commonly adopted as an index of the dynamic balance between local tissue oxygen supply (availability) and utilization (extraction) in both health and disease [7, 8]. Because the contribution of the myoglobin to the NIRS signal is not critical, StO_2 is largely considered as the ratio of oxygenated to total tissue hemoglobin concentration expressed as [oxyhemoglobin/ (oxyhemoglobin + deoxyhemoglobin)] × 100 (%). To evaluate NIRS in PAH, we correlated measurement of vastus lateralis StO_2 with SvO_2 and venous oxygen saturation in the inferior vena cava ($SivcO_2$) during right heart catheterisation.

To measure StO_2, one transcutaneous sensor (S-Type Probe; NIRO-200NX spatially resolved spectrophotometer, Hamamatsu Photonics KK, Japan) was placed over each vastus lateralis muscle, 10-12 cm above the lateral epicondyle. StO_2 values shown are the average values obtained from *both* legs at the time of SvO_2 and $SicvO_2$ single-point measurements. SvO_2 was measured from the distal port of the Swan–Ganz catheter. Resting SivcO2 was measured with a pigtail catheter advanced through the right internal jugular vein sheath to the level of S1 vertebra.

Concurrent, single-point measurements of SvO_2 and StO_2 were repeated during supine exercise in consecutive patients who consented to this task. One patient performed straight leg raise and nine patients exercised on an electronically braked lower limb cycle ergometer secured to the catheterization table. Subjects cycled at 60 revolutions/min for 6 minutes at a constant workload set at 50% of peak work rate achieved during an upright cycle cardiopulmonary exercise test the previous day. SvO2 and StO_2 were measured during the sixth minute. Supplementary oxygen was provided as required to maintain normoxia.

Twenty-five subjects with PAH were studied at rest, 10 of whom also exercised.
The main clinical and physiological characteristics are presented in figure 1. Combining all the resting and exercise data points (n=35), StO_2 showed a good correlation with SvO2 ($r=.703$, $p<.001$). This level of correlation persisted when looking separately at rest ($r=.701$, $p<.001$) and exercise data ($r=.863$, $p=.001$) (figure 1) but also for the change from rest to exercise in StO_2 and S_vO_2 ($r=.669$, $p=.034$). A significant reduction ($p<.001$) was observed in StO_2 during exercise. Resting values of StO_2 exhibited similar level of

correlation with $SivcO_2$ (r=.655, p=.001). A good correlation (r=.703, p<.001) was observed between $SivcO_2$ and SvO_2, whereas the resting correlations of StO_2 with S_vO_2 and $SivcO_2$ were not statistically different (Z=0.3, p =.76).

Resting StO_2 correlated with age (r=-.416, p= .038) but also with indices of disease severity including the six-minute walk distance (r=.528, p=.008), N-terminal pro-brain natriuretic peptide (r=-.395, p=.05), diffusing lung capacity for carbon monoxide percent predicted (r=.398, p=.049).

To our knowledge, this is the first study to report on the association between StO_2 and SvO_2. Good correlation between vastus lateralis StO_2 and femoral venous oxygen saturation has also been reported in healthy trained subjects [9] albeit earlier studies did not confirm such correlation [10, 11]. However, comparisons should be made with caution as responses of StO_2 depend highly on the mode, intensity and duration of exercise and neither of those studies is matched in design to our resting and steady-state exercise protocol. Instead, they report on measurements either during incremental exercise [9] or over time during constant load exercise [10, 11].

Nonetheless, the correlation between StO_2 and SvO_2 or $SivcO_2$ is not absolute and results of relating StO_2 to venous blood oxygenation should not be interpreted in a quantitative sense. This may be because the specific tissue volume investigated by NIRS is not fully representative of the oxygen status of the body segment (lower limb) or global tissue oxygenation as measured by $SivcO_2$ and SvO_2, respectively [7]. It is not surprising that

the highest correlations between StO_2 and venous oxygen saturation were shown when the sampled venous effluent was specific for the interrogated tissue volume such as that obtained from a deep forearm vein that drained the exercising muscle (r=.92) [8] or from a vein that drained only the electrically simulated muscle of dogs (r=.97) [12]. Accordingly, $SivcO_2$ would be expected to exhibit a higher correlation with StO_2 than SvO_2. However, we observed similar correlation between StO_2 and SvO_2. This seeming paradox may be due to venous return from the lower limbs being the major determinant of SvO_2 in the supine leg exercise.

The design of the present study does not allow for reliable conclusions on the tissue oxygen status *per se*; the presented measurements should be interpreted within the context of oxygen supplementation to maintain resting normoxia and the absence of a matched control group. However, our findings provide support for the use of NIRS in the investigation of the pathophysiological abnormalities in PAH. Also, taken together, findings cannot exclude a role of the periphery in the pathophysiology of PAH since skeletal muscle tissue microenvironment, which is an important factor of the local oxygen status, is disturbed in PAH [13]. Perhaps, combination of NIRS with other techniques such as vascular occlusion, sidestream dark field imaging and histological examination could enable further exploration.

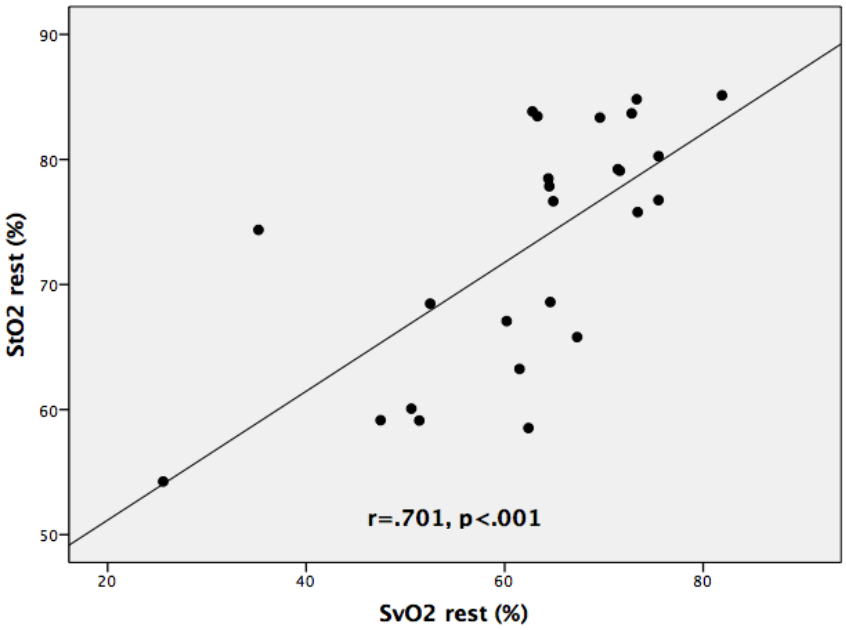
Limited experience from application of NIRS in PAH showed significantly lower resting thenar muscle oxygen saturation in PAH patients compared with matched healthy subjects and patients with CHF [14]. Also, study of the kinetics of the vastus lateralis fractional oxygen extraction (% Δ deoxyhemoglobin/myoglobin) relative to oxygen

uptake at the beginning of heavy-intensity exercise, suggests that patients with PAH have greater microvascular oxygen delivery-to-utilization inequalities compared to healthy control, which contribute to slow adaptation rate of aerobic metabolism [15].

In summary, skeletal muscle StO_2 in PAH subjects correlated significantly with SvO_2 under both resting and exercise conditions. Also, StO_2 correlated significantly, albeit weakly, with indices of disease severity. These novel findings suggest that StO_2 may serve as a clinically useful research tool for the qualitative, noninvasive assessment of the dynamic balance between oxygen supply and utilization in PAH. Further studies are warranted to explore the value of NIRS in the assessment and prognosis of PAH.

Figure legends

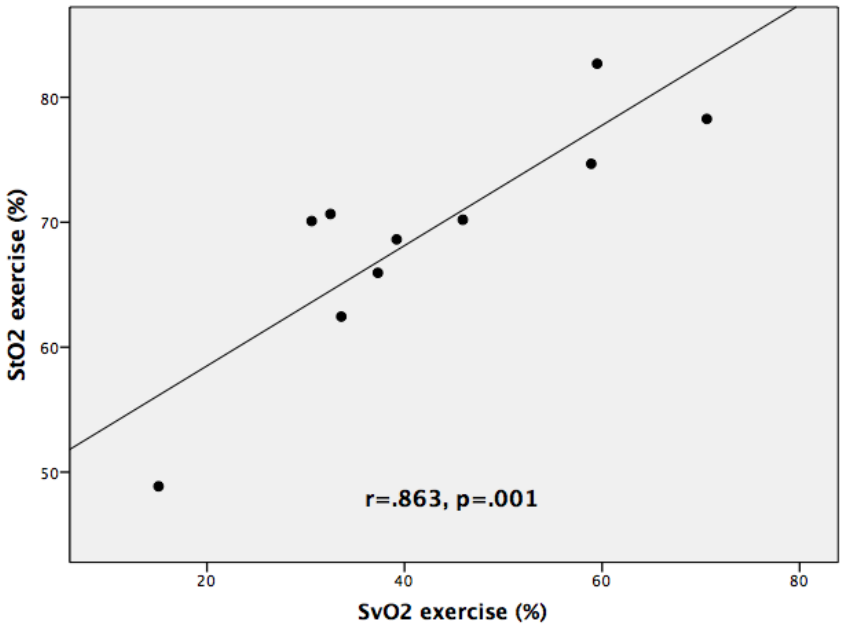
Figure 1: Patient characteristics and correlations between StO_2 and SvO_2 at rest (A) and during exercise (B).



Patient characteristic	**Rest (n=25)**	**Exercise (n=10; rest/exercise)**
Age, y	61.9 ± 11.6	55.6 ± 8.4
Sex, males: females	11: 14	4: 6

IPAH; FPAH; C TD; CHD; PoPH	13;1;7;1;3	4;1;3;1;1
6MWT, m	256 ± 134	344 ± 144
NTproBNP, pg/ml	1101 (153, 2928)	263 (42, 1461)
mean PAP, mm Hg	43 ± 11	40.7 ± 10.2/66.1 ± 13.8*
CO, L/min	4.6 ± 1.7	5.5 ± 1.96/8.6 ± 3.3*
PVR, Wood units	9.5 ± 5.9	7.3 ± 4.3/7.9 ± 4.5
SvO2, %	62.5 ± 12.9	70.3 ± 8.6/42.3 ± 16.6*
SivcO2, %	64.2 ± 14.3	N/A
StO2, %	73.1 ± 9.8	77.62 ± 6.9/69.2 ± 9.2*

C.



References

1. Authors/Task Force M, Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, et al: **2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT).** *Eur Heart J* 2015.
2. Kielstein JT, Bode-Boger SM, Hesse G, Martens-Lobenhoffer J, Takacs A, Fliser D, Hoeper MM: **Asymmetrical dimethylarginine in idiopathic pulmonary arterial hypertension.** *Arterioscler Thromb Vasc Biol* 2005, **25:**1414-1418.
3. Sandoval J, Bauerle O, Palomar A, Gomez A, Martinez-Guerra ML, Beltran M, Guerrero ML: **Survival in primary pulmonary hypertension. Validation of a prognostic equation.** *Circulation* 1994, **89:**1733-1744.
4. Nickel N, Golpon H, Greer M, Knudsen L, Olsson K, Westerkamp V, Welte T, Hoeper MM: **The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension.** *Eur Respir J* 2012, **39:**589-596.
5. Wensel R, Opitz CF, Anker SD, Winkler J, Hoffken G, Kleber FX, Sharma R, Hummel M, Hetzer R, Ewert R: **Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing.** *Circulation* 2002, **106:**319-324.
6. Higenbottam T, Butt AY, McMahon A, Westerbeck R, Sharples L: **Long-term intravenous prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension.** *Heart* 1998, **80:**151-155.
7. Boushel R, Langberg H, Olesen J, Gonzales-Alonzo J, Bulow J, Kjaer M: **Monitoring tissue oxygen availability with near infrared spectroscopy (NIRS) in health and disease.** *Scand J Med Sci Sports* 2001, **11:**213-222.
8. Mancini DM, Bolinger L, Li H, Kendrick K, Chance B, Wilson JR: **Validation of near-infrared spectroscopy in humans.** *J Appl Physiol (1985)* 1994, **77:**2740-2747.
9. Vogiatzis I, Habazettl H, Louvaris Z, Andrianopoulos V, Wagner H, Zakynthinos S, Wagner PD: **A method for assessing heterogeneity of blood flow and metabolism in exercising normal human muscle by near-infrared spectroscopy.** *J Appl Physiol (1985)* 2015, **118:**783-793.
10. Costes F, Barthelemy JC, Feasson L, Busso T, Geyssant A, Denis C: **Comparison of muscle near-infrared spectroscopy and femoral blood gases during steady-state exercise in humans.** *J Appl Physiol (1985)* 1996, **80:**1345-1350.

11. MacDonald MJ, Tarnopolsky MA, Green HJ, Hughson RL: **Comparison of femoral blood gases and muscle near-infrared spectroscopy at exercise onset in humans.** *J Appl Physiol (1985)* 1999, **86:**687-693.
12. Wilson JR, Mancini DM, McCully K, Ferraro N, Lanoce V, Chance B: **Noninvasive detection of skeletal muscle underperfusion with near-infrared spectroscopy in patients with heart failure.** *Circulation* 1989, **80:**1668-1674.
13. Panagiotou M, Peacock AJ, Johnson MK: **Respiratory and limb muscle dysfunction in pulmonary arterial hypertension: a role for exercise training?** *Pulm Circ* 2015, **5:**424-434.
14. Dimopoulos S, Tzanis G, Manetos C, Tasoulis A, Mpouchla A, Tseliou E, Vasileiadis I, Diakos N, Terrovitis J, Nanas S: **Peripheral muscle microcirculatory alterations in patients with pulmonary arterial hypertension: a pilot study.** *Respir Care* 2013, **58:**2134-2141.
15. Barbosa PB, Ferreira EM, Arakaki JS, Takara LS, Moura J, Nascimento RB, Nery LE, Neder JA: **Kinetics of skeletal muscle O2 delivery and utilization at the onset of heavy-intensity exercise in pulmonary arterial hypertension.** *Eur J Appl Physiol* 2011, **111:**1851-1861.