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

### **Authors**

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

### **Affiliations**

<sup>1</sup>Scottish Pulmonary Vascular Unit, Golden Jubilee National Hospital, Glasgow, UK;

<sup>2</sup>National and Kapodistrian University of Athens, Department of Physical Education and Sports Sciences, Athens, Greece; <sup>3</sup>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](mailto: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<sub>2</sub>), an index that is generally reduced in patients with PAH [2]. SvO<sub>2</sub> at baseline is one of the strongest predictors of survival in PAH [3-5]; this is also true for changes in SvO<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub>) 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<sub>2</sub> is largely considered as the ratio of oxygenated to total tissue hemoglobin concentration expressed as  $[\text{oxyhemoglobin} / (\text{oxyhemoglobin} + \text{deoxyhemoglobin})] \times 100 (\%)$ . To evaluate NIRS in PAH, we correlated measurement of vastus lateralis StO<sub>2</sub> with SvO<sub>2</sub> and venous oxygen saturation in the inferior vena cava (SivcO<sub>2</sub>) during right heart catheterisation.

To measure StO<sub>2</sub>, 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<sub>2</sub> values shown are the average values obtained from *both* legs at the time of SvO<sub>2</sub> and SicvO<sub>2</sub> single-point measurements. SvO<sub>2</sub> was measured from the distal port of the Swan–Ganz catheter. Resting SicvO<sub>2</sub> 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<sub>2</sub> and StO<sub>2</sub> 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. SvO<sub>2</sub> and StO<sub>2</sub> 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<sub>2</sub> showed a good correlation with SvO<sub>2</sub> (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<sub>2</sub> and SvO<sub>2</sub> (r=.669, p=.034). A significant reduction (p<.001) was observed in StO<sub>2</sub> during exercise. Resting values of StO<sub>2</sub> 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  $SvO_2$  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<sub>2</sub> 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, S<sub>ivc</sub>O<sub>2</sub> would be expected to exhibit a higher correlation with StO<sub>2</sub> than SvO<sub>2</sub>. However, we observed similar correlation between StO<sub>2</sub> and SvO<sub>2</sub>. This seeming paradox may be due to venous return from the lower limbs being the major determinant of SvO<sub>2</sub> 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 (%  $\Delta$  deoxyhemoglobin/myoglobin) relative to oxygen

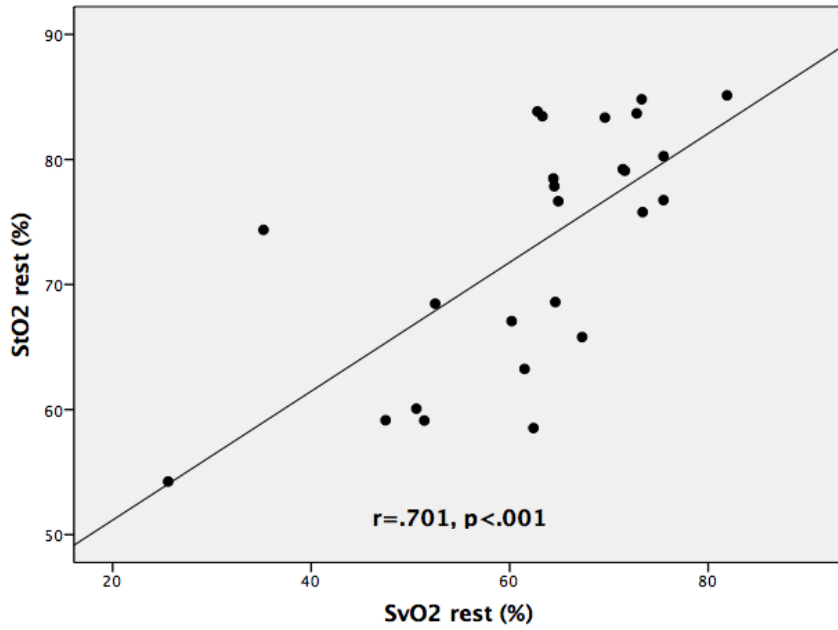
uptake at the beginning of heavy-intensity exercise, suggests that patients with PAH have greater microvascular oxygen delivery-to-utilization inequalities compared to healthy control, which contribute to slow adaptation rate of aerobic metabolism [15].

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

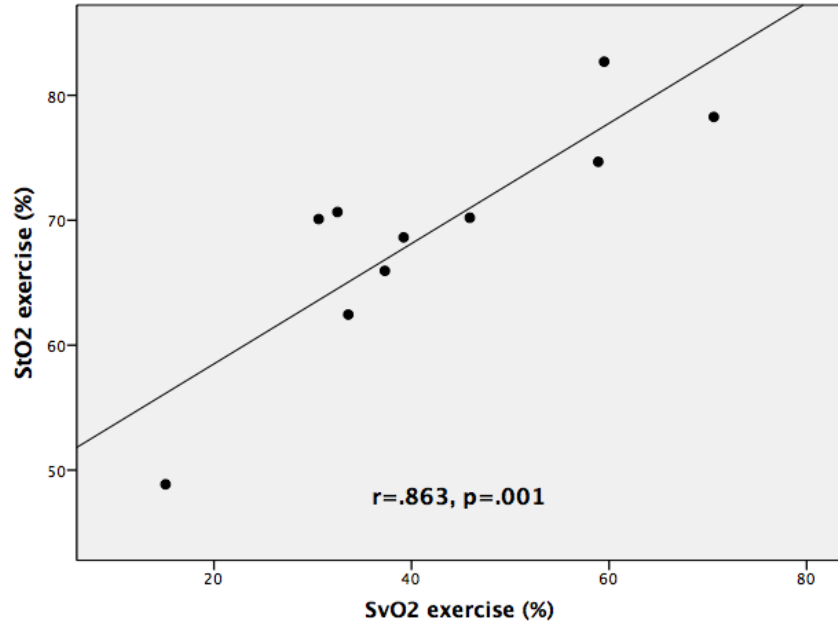
**Figure 1:** Patient characteristics and correlations between StO<sub>2</sub> and SvO<sub>2</sub> at rest (A) and during exercise (B).



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

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

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