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ORIGINAL ARTICLE

Measurement of Regional Tissue Bed Venous Weighted Oximetric Trends During Exercise by Near Infrared Spectroscopy

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Abstract
Background Cardiopulmonary exercise testing (CPET) is limited to children able to tolerate the equipment. Modification of instrumentation to reduce invasiveness will open CPET to a wider population. Near Infrared Spectroscopy (NIRS) devices measure regional oxyhemoglobin saturation (rSO2). We aim to predict anaerobic threshold (AT) during CPET using multiorgan NIRS monitoring.
Methods and Results Nineteen subjects were recruited. NIRS probes were placed on the forehead, para vertebral space, vastus lateralis, and deltoid muscle (rSO2 C, rSO2 R, rSO2 L and rSO2 A). rSO2 was recorded at six second intervals at rest, exercise, and through a five minute recovery period. The AT was computed using the v-slope method. AT was also predicted using NIRS data by identifying the inflection point of the rSO2 trends for all the four sites. AT can be estimated by the point of slope change of rSO2 R, rSO2 C and the four-site composite measure.
Conclusions Multisite NIRS monitoring of visceral organs is a potential predictor of AT. This allows for monitoring in all forms of exercise over a wide age range.

Keywords NIRS · Exercise · Pediatrics

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Introduction

Cardiopulmonary exercise testing (CPET) provides assessment of the integrative responses involving the pulmonary, cardiovascular and skeletal muscle systems, which are not adequately assessed through the measurement of global or individual organ system function during resting conditions. It is based on the principle that failure typically occurs while the system (e.g., muscular, cardiovascular or pulmonary) is under stress [10, 22]. However, the application of exercise testing remains limited to children who are able to understand and cooperate with the exercise protocol, and who can tolerate the necessary equipment for measurement of cardiopulmonary responses. Modification of CPET instrumentation to reduce invasiveness would open this method of assessment to a wider range of subjects, particularly younger children, thereby conferring significant advantage.

Near-infrared spectroscopy (NIRS) provides a noninvasive, continuous method to monitor regional tissue oxygenation (rSO2) [15, 29]. NIRS techniques rely on applications of the Beer-Lambert law for measurement of

the concentration of a substance according to its absorption of light [21]. As in pulse oximetry, the oxygen saturation of hemoglobin is approximated by the differential absorption of two or more wavelengths of light [21]. NIRS devices measure the venous weighted oxyhemoglobin saturation in a field of tissue, rather than in arteries, and thus the rSO2 parameter provides a window into regional oxygen supply-demand relations. The use of multisite NIRS monitoring during CPET for the purpose of studying global cardiac output distribution trends through the patterning of visceral, muscular and cerebral saturations data in combination with oxygen consumption data has not been reported to date.

Since blood flow distribution during exercise depends on the interaction of regional, autonomic, and humoral mechanisms affecting vascular resistance, regional blood flow-metabolism relations should change during activation of autonomic and behavioral responses to progressively intense exercise. We hypothesize that multisite NIRS monitoring will show differential desaturation patterns in the exercising muscle, brain, somatic muscle, and renal vascular beds during CPET, and that these patterns underlie the systemic oxygen consumption to flow-coupling dynamics observed during increasing levels of exercise. Our specific aim is to predict anaerobic threshold (AT) during CPET noninvasively using multisite organ NIRS monitoring. Achievement of a practical noninvasive technology for estimating AT will increase the compatibility of CPET for the pediatric population.

Methods

This pilot study was initiated with funding assistance from the Children's Research Institute, a division of Children's Hospital and Health System and the Medical College of Wisconsin, Milwaukee, WI, with institutional review board approval. Patients without structural or acquired heart disease were eligible for inclusion if they were ordered to undergo CPET by a cardiologist at the Herma Heart Center's Exercise Physiology Laboratory for evaluation of nonlife-threatening symptoms. The patients underwent a routine physical exam before initiation of the exercise assessment. Consent from parent and assent from subject was obtained before enrollment.

The CPET protocol began with application of 12-lead electrocardiogram leads, an automated oscillometric blood pressure cuff on the left arm, and a pulse oximeter on the right index finger (GE- Marquette, Waukesha, WI). Four NIRS probes with 4 cm source-detector spacing and shallow-field rejection (Adult Somasensor, INVOS 5100C, Somanetics Corporation, Troy, MI) were placed on the midline forehead, below the 12th rib in the left para vertebral space, on the vastus lateralis, and on the deltoid muscle (rSO2 C, rSO2 R, rSO2 L and rSO2 A), respectively. Regional rSO2 was computed and recorded continuously at six second intervals at rest, during exercise, and through a five minute recovery period. Baseline spirometry using a forced expiratory maneuver was performed following the standards of the American Thoracic Society. Patients were introduced to the treadmill and given specific instructions as to what to expect during the exercise portion of the study. Immediately before the initiation of exercise, a snorkel-style mouthpiece was placed in the child's mouth for the measurement of breath-by-breath oxygen consumption (VO2), carbon dioxide production (VCO2), and instantaneous respiratory quotient (RQ). After one minute of baseline data collection, a ramping treadmill protocol was initiated. At set intervals throughout the test, the workload was progressively increased. The progression was terminated when the child reached voluntary or symptom-limited exhaustion (quitting time (QT)). Throughout the exercise portion of the test a 12-lead ECG, blood pressure, and O2 saturation was recorded on a minute-by-minute basis in addition to breath-by-breath ventilatory measures. Immediately postexercise the child was allowed to cool down for 3 minutes by walking slowly, with the remainder of the 5-minute recovery being performed in a seated position. All SpO2, heart rate, blood pressure, VO2, VCO2, RQ, and NIRS data were synchronously aggregated. Subjects who completed the CPET protocol to the satisfaction of the exercise physiologist had data included in this analysis. Subjects who were unable to complete the CPET protocol or those with incomplete metabolic cart data acquisition were excluded.

The whole-body anaerobic threshold (VAT) was computed on VCO2 and RQ post-hoc using the v-slope method [25]. Absolute NIRS data and the change from resting baseline were analyzed using time-series and local polynomial regression techniques. For each subject, VAT and QT were used to align the NIRS time series, and the slope ΔrSO2/minute was computed for each region for the respective aerobic, anaerobic, and recovery periods. Piecewise linear regression and smooth splines were used to identify the inflection point of the regional rSO2 time series, which were identified as the noninvasive regional NIRS anaerobic threshold (NAT) for each of the four monitored regions individually (NAT- rSO2-C, NAT-rSO2-R, NAT- rSO2-A, NAT-rSO2-L); a composite four site measure (NAT-4) was defined by the average of regional NAT measures. Agreement between the VAT and regional NAT was assessed by the Lin's concordance correlation coefficient, and limits of agreement by the methods of Bland and Altman. The kappa statistic was used to denote agreement with an arbitrary cutoff criterion of two minutes. All statistics were obtained using standard

techniques (Stata Version 10, Stata Corporation, College Station, TX; SAS Version X, SAS Institute, Cary, NC).

Results

Data from nineteen subjects, average age 16 years (9–20 yrs), 9 male, were used for analysis (Table 1). Average exercise time was 13.3 ± 2.7 minutes, with the VAT at 10.0 ± 2.7 minutes. Data for rSO2-C in subject 2 and rSO2-A in subject 6 were not available due to problems with the probe-skin adhesion. There were no other data dropouts during the study.

The trends in aggregate regional rSO2 for all the subjects during the course of exercise are shown in Fig. 1. Oxygenation in exercising muscle tended to increase early in aerobic exercise and to decrease below baseline at the anaerobic threshold, with hyperemia during recovery. The regional oxygenation trends in nonexercising somatic sites showed progressive desaturation with an accelerated slope during the anaerobic phase, followed by rapid recovery and more variable hyperemia. The slope of rSO2/time during progressive exercise accelerated near the VAT; aggregated data for piecewise regression of rSO2-R vs time is shown in Fig. 2. The slope rSO2-R/min changed from −0.8 +/−0.2 to −3.2 +/−0.8 ($p < 0.01$) at the anaerobic transition and further renal desaturation occurred until exhaustion followed by rapid recovery. The cerebral saturation trends were unique; compared with other beds, rSO2-C was unchanged during aerobic exercise. Cerebral desaturation occurred slightly after the VAT and other regional beds. (Fig. 3). The lowest rSO2-C corresponded with peak exhaustion and voluntary exercise termination in all cases, and return to baseline lagged other beds. Resting rSO2 C

Table 1 Group exercise data

Variable	Time point		
	Pre-exercise	VAT	Peak-exercise
HR (beats/minute)	75.8 ± 10.3	148.2 ± 9.3	198.2 ± 10.2
% Predicted max	37.3 ± 5.1	74.3 ± 13.4	98.7 ± 19.5
VO_2 (liters/minute)	0.3 ± 0.1	1.9 ± 0.7	2.7 ± 0.9
VO_2 (ml/kg/minute)	5.5 ± 1.5	26.6 ± 12.3	42.9 ± 9.2
% Predicted	–		107.5 ± 25.5
VAT (% of peak VO_2)	–	–	69.2 ± 19.4
Respiratory quotient	0.81 ± 0.10	1.0 ± 0.04	1.11 ± 0.08
Time (minutes)	–	10.0 ± 2.7	13.3 ± 2.7
Blood pressure			
Systolic (mmHg)	112.2 ± 7.7	–	140.2 ± 27.4
Diastolic (mmHg)	68.1 ± 8.4	–	61.8 ± 14.3

HR Heart rate, *VO_2* Oxygen consumption, *%* Percentage, *VAT* Ventilatory anaerobic threshold

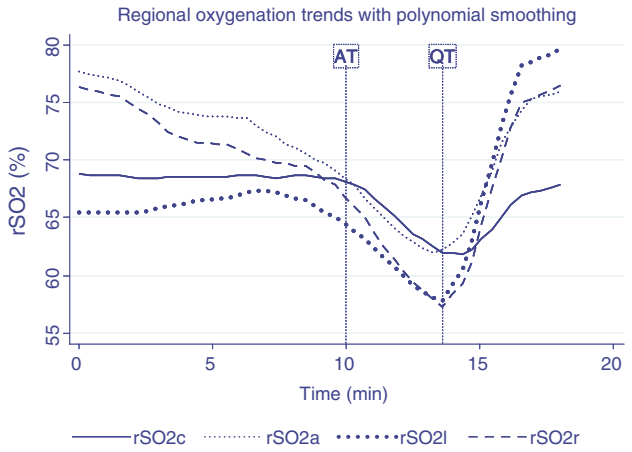

Fig. 1 Aggregate regional rSO2 vs time. Distinct patterns are evident for exercising muscle (rSO2-L), nonexercising somatic (rSO2-A and rSO2-R), and cerebral (rSO2-C) beds. Peak desaturation occurred in all somatic beds before peak cerebral desaturation. The lowest rSO2-C corresponded with peak exhaustion and voluntary exercise termination

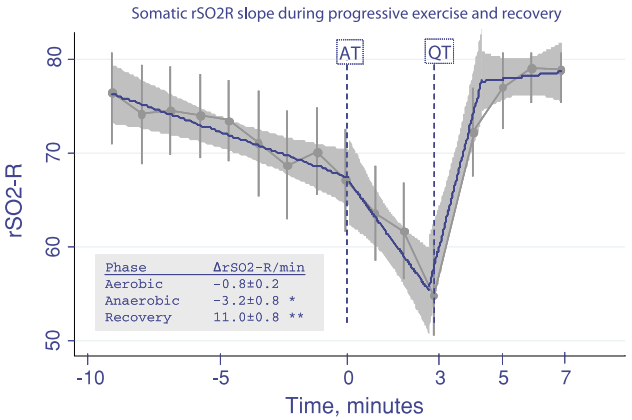

Fig. 2 Regression slopes of rSO2-R during aerobic, anaerobic, and recovery periods

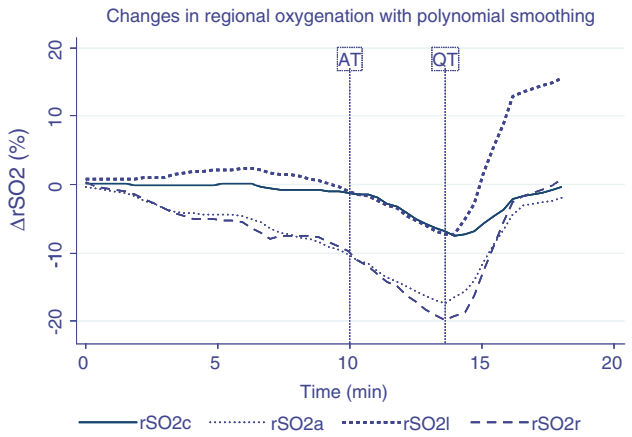

Fig. 3 Changes in rSO2 versus time

was 69.4 ± 6.8. Exhaustion occurred at mean rSO2 C of 60 ± 6.50, beyond VAT, at an average PetCO2 of 37.5 ± 2 torr.

Average VAT and NAT values are summarized in Table 2. The VAT measured 10 ± 2.8 minutes. The linear and concordance correlations, and limits of agreement between regional NAT and VAT, are shown in Table 3. The VAT correlated with the NAT-rSO2-R, at 9.7 +/− 2.2 minutes. A combined four site average of NAT had the closest agreement with VAT by concordance analysis (Table 3 and Fig. 4).

Using an agreement criterion of 2 minutes, the VAT was best estimated by the 4 site average NAT, with agreement in 17/19 subjects. In 16 of 19 subjects, the NAT predicted by renal NIRS monitoring was within 2 minutes of the VAT. The rSO2 C NAT predicted VAT in 16 of 18

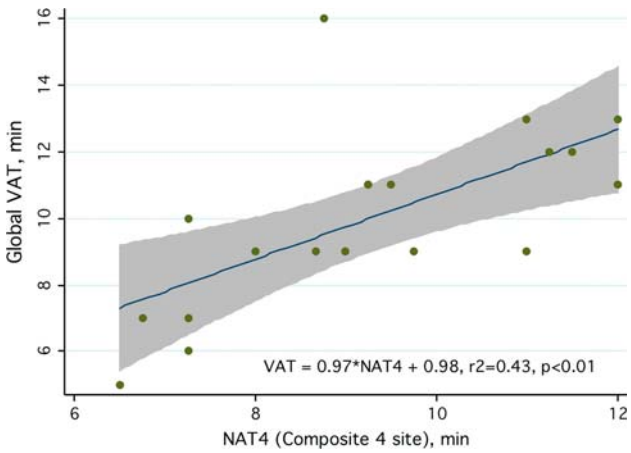

Fig. 4 Relation between VAT and NAT-4 expressed as linear correlation

Table 2 Anaerobic thresholds (in minutes) by NIRS and metabolic cart

Patient	NAT-rSO2-C	NAT-rSO2-R	NAT-rSO2-L	NAT-RSO2-A	VAT
1	11	11	6	10	11
2		12	12	12	13
3	6	7	5	8	5
4	9	11	6	10	9
5	11	9	9	8	11
6	9	8		9	9
7	8	6	7	6	7
8	9	7	8	8	9
9	6	10	8	11	16
10	12	11	9	12	13
11	12	11	11	12	12
12	8	8	5	8	7
13	13	12	12	7	9
14	12	5	5	7	10
15	6	8	8	7	6
16	9	9	10	11	9
17	12	12	12	12	11
18	10	9	12	6	11
19	11	11	11	12	12
Average	9.7 +/−2.2	9.3 +/−2.1	8.6 +/−2.6	9.3 +/−2.2	10 +/−2.7

Table 3 Correlation and concordance of timing of regional NAT and global VAT

Site	Linear correlation	Concordance correlation	Mean difference	95% Limits of agreement
NAT-rSO2-C	0.39	0.39	0.2 +/−2.8	−5.2 ... +5.5
NAT-rSO2-R	0.56	0.53	0.7 +/−2.3	−3.8 ... +5.2
NAT-rSO2-A	0.46	0.40	1.4 +/−2.8	−4.1 ... +6.9
NAT-rSO2-L	0.63	0.59	0.7 +/−2.2	−3.5 ... +5.0
NAT-4 (4 sites)	0.65	0.65	0.7 +/−2.0	−3.2 ... +4.7

NAT-4 was computed as the average inflection time of the individual regional piecewise regression slopes from 4 sites. The best agreement with global VAT was with the combined 4 site regional NAT measure

Table 4 Agreement between VAT and regional NAT using a criterion of 2 min. The best agreement was achieved by using the composite 4 site NAT

	NAT-rSO2-C	NAT-rSO2-R	NAT-rSO2-A	NAT-rSO2-L	NAT-4
Agree	16	16	12	14	17
Disagree	2	3	6	5	2
Total	18	19	18	19	19

subjects within 2 minutes. The agreement for arm and le.g.,sites was not good. See Table 4 for details.

Discussion

CPET is used increasingly in a wide spectrum of clinical applications for evaluation of undiagnosed exercise intolerance and for objective determination of functional capacity and impairment [1]. Anaerobic threshold (AT) has been defined as an intensity of exercise above which an uncoupling of oxygen delivery to consumption relation is associated with lactate accumulation in the blood, elevated carbon dioxide output, and increased ventilatory rate [17, 25]. Various methods of determining AT have previously been used. The simplest and the most common method used is the V-slope method which is based on the determination of the nonlinear point of increase in slope of carbon dioxide production (VCO_2) versus oxygen uptake (VO_2) during incremental exercise [2].

To date, the majority of the studies evaluating tissue oxygenation by NIRS have measured regional oximetry in muscles, particularly the vastus lateralis [7, 8]. Initial studies of muscular oxygenation measured by NIRS with incremental exercise on a bicycle ergometer described an accelerated desaturation during anaerobic exercise [3]. Prediction of AT by NIRS monitoring of vastus lateralis has been described during exercise on bicycle ergometer. This study correlated AT with the decrease in muscle oxygenation measured by NIRS below baseline [5]. This finding has been replicated in our study, with rSO2-L reaching baseline almost at the AT (Fig. 3). Respiratory muscles deoxygenation during incremental exercise by bicycle ergometry in children has also been described. This investigation validated the use of NIRS as an additional tool for the determination of AT [16]. Cerebral oxygenation during exercise has been investigated with NIRS monitoring [6].

The concept of multisite NIRS monitoring to characterize changes in integrative circulatory physiology has been previously described, and has been extensively evaluated in the cerebral [13, 14, 20, 27, 29, 30] and splanchnic [11, 23] and quasi-global circulations [18, 24, 28]. Hoffman et al. used frontal cerebral (rSO2-C) and dorsolateral T10-L2 (rSO2-R) renal probe sites to reflect changes in regional oxygenation in circulations presumably under different physiologic control, and found distinct changes in cerebral and somatic oxygenation during different phases of operation with full flow bypass and selective cerebral perfusion, thus demonstrating the regional nature of rSO2 measures. NIRS can be used to monitor cerebral and somatic oxygenation in various clinical situations including during cardiopulmonary bypass, deep hypothermic circulatory arrest [14, 19] and in other high-risk newborns [4, 11, 26, 28, 29], and has been found to be helpful in predicting cerebrovascular dysfunction [20, 26] and splanchnic ischemia [11].

This is the first study that explores the use of multisite NIRS technology in CPET. Brain and kidney monitoring sites were chosen for prediction of AT as they represent two poles of circulatory hierarchies and are not directly affected by exercise modality or location of exercising muscle. The trends in the somatic regional oxygen saturations showed progressive desaturation with an accelerated slope after anaerobic threshold till exhaustion followed by rapid recovery. AT prediction by NIRS monitoring described by Bhambhani et al [5] used bicycle ergometry for the testing modality. They measured rSO2 in vastus lateralis while performing CPET on a bicycle on healthy volunteers and found correlation of point of measured AT with the point of decrease of the rSO2 in the muscle below baseline rSO2. Applying Bhambhani et al's criteria on our cohort; we could predict AT in only 6 of 19 patients. This inability to duplicate findings could be a result of differing patterns of muscular group deployment while running on a treadmill as opposed riding a bicycle. By using the data from multiple somatic and visceral organs that have been tested in clinical practice, we have described a method of monitoring that should be broadly applicable to different types of exercise. AT can be estimated the point of slope change of rSO2-R and rSO2-C, and the four-site composite measure, during CPET.

Recent study [30] documented that during cycle exercise at 360 W performed to exhaustion, the left and right cerebral artery mean flow and velocity measured by doppler ultrasound decreased continuously from the onset of exercise. However, cardiac output and mean arterial pressure demonstrated an increase at the onset of exercise reaching a peak value after approximately 3–5 min, and then decreased slightly before exhaustion [12]. It has been theorized that

acute appearance of metabolic acidosis with anaerobic work induces a respiratory alkalosis which acutely elevates brain pH and cerebrovascular resistance, with a resulting reduction in cerebral blood flow [6]. The findings by Bhambhani et al suggested that the decreases in cerebral oxygenation and cerebral blood volume that were evident just beyond the AT were associated with a significant reduction in PETCO2 (an indirect estimate of PaCO2) that occurred at this threshold [6]. Our observation of a change in the slope of the rSO2-C at anaerobic threshold is explained by this phenomenon. The rSO2C also shows a slower recovery trend after exercise termination compared with other tissue beds. This may be a result of ongoing hyperventilation that continues even after the termination of exercise. This pattern is different from the postulated mechanism of change of the rSO2 R; the accelerated regional desaturation the renal bed in anaerobic exercise is related to sympathetically-mediated redistribution of blood flow away from nonexercising somatic beds, which begins at the onset of exercise and accelerates at the AT. Thus, at exercise termination, a reduction in sympathetic tone can immediately reduce renal and somatic resistance with quick recovery of rSO2 R. This highlights the distinct advantage of monitoring multiple organ tissue beds under different physiologic control in CPET as it provided real time data of flow to demand coupling dynamics in different vascular beds with differing physiologic control mechanisms. Although progressive sympathetic nervous system activation during exercise serves to match cardiac output to exercising muscle, the hierarchical redistribution of flow is known to be affected by individual differences, drug effects, and disease states. Individual variations in regional patterns of blood flow are likely to emerge under different pathologic and physiologic conditions.

Application of exercise testing remains limited to children that are able to cooperate with the examiner and to tolerate the equipment necessary for measurement of cardiopulmonary responses. Peak performance is more dependent on the subjects' motivation, especially in children [9, 22].

Ability of multisite NIRS monitoring to detect AT will resolve this problem and make CPET compatible with a wide range of pediatric age groups, perhaps even obviating the need for mouthpieces, masks and a metabolic cart. Prediction of AT with NIRS will bring this testing to more diverse pediatric age groups. Using multisite NIRS monitoring in CPET will prove to be tool for researching the physiology of exercise and its value in understanding pathology. This type of technology is currently unavailable to children with heart disease and potentially could change the management and follow-up strategies for patients with every form of congenital heart disease. This would create a benchmark for performance of CPET.

The limitation of the study is the few number of patients tested. However, this was a pilot study and a larger prospective study is presently underway with plans of recruiting 100 subjects per year. Normal subjects will be studied initially following which subjects with heart disease will be studied once normative data are established.

Conclusions

Multisite NIRS monitoring of visceral organs is a potential predictor of AT. During exercise, AT is associated with rapid desaturation in nonexercising organs. This allows for monitoring in all forms of exercise over a wide age range. Adjunctive monitoring with NIRS during CPET is a potential tool that will increase its clinical utility and compatibility and also has potential applications in future of research in the field of exercise physiology.

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