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Noninvasive monitoring of peripheral microcirculatory hemodynamics under varying degrees of hypoxia

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ABSTRACT

The effect of hypoxia on skin blood flow was examined in anesthetized rabbits during induction of various levels of hypoxia. Peripheral perfusion and oxygenation were monitoring using a combined system (LPT) composed of a laser Doppler flowmeter (LDF), a photoplatysmograph (PPG), and a transcutaneous oxygen tension monitor (tc-PO_2). Central blood parameters (PaO_2, HCO_3^-, SaO_2, pH, and lactate) were measured concomitantly throughout the experiment. A continuous decline was found in both peripheral and central values, depending on the severity of the hypoxia. The results clearly indicate that monitoring peripheral indices with the LPT system enables monitoring changes of vital blood parameters during hypoxia. The system has clinical potential for sensitive and noninvasive monitoring of vital variables during medical procedures in clinics, as well as for homecare for patients with respiratory diseases. Minimizing the system may be useful in various conditions of exposure to low oxygen levels, such as during mountain climbing.

1. Introduction

One of the main goals of hemodynamic support is preservation of tissue perfusion. Monitoring the microcirculation has long been difficult. Recent technological advances have made monitoring of the microcirculation at the bedside of critically ill patients feasible (Allen, 2007; Backer et al., 2012; Wright et al., 2006). Since hypoxia is a clinical condition that may lead to life-threatening complications, early diagnosis as well as monitoring of clinical measures at different levels of hypoxia are therefore essential. Noninvasive monitoring of blood oxygen levels is currently carried out by pulse-oximetry, which monitors oxygen saturation in the periphery. However, the great success of pulse oximetry masks the fact that it still carries an inherent potential error of 3–4% in measurements carried out on critically ill patients and preterm newborns (Nitzan et al., 2014). In addition, the method was found reliable only up to a level of 80% oxygen saturation (Jubran, 1999; Jubran and Tobin, 2013). Hence, there is still a need for a noninvasive device to monitor oxygen levels during severe hypoxia.

Noninvasive methods for measuring cutaneous perfusion have been based on optical sensors (Boggett et al., 1985; Nilsson et al., 1980; Tenland et al., 1983; Weinman, 1978; Nitzan et al., 2006), as well as devices to measure tissue oxygen pressure (Fagrell, 1995; Franzeck et al., 1984; Pittman, 2013). At the Neufeld Cardiac Research Institute, our group has designed a noninvasive system that combines LDF, PPG and tc-PO_2 devices (hence the name LPT) that measure the flux of RBC, the amount of RBC, and oxygen tension, respectively. Each one of them is in clinical use (Ovadia et al., 1995).

The LPT system was found in our previous studies to be a reliable noninvasive monitor of microcirculatory hemodynamic variables under different clinical conditions. The system was sensitive to changes in peripheral microcirculation variables, which it detected earlier than central measures under various clinical conditions such as hemorrhage and resuscitation fluid infusions. The set of devices was reported to assist the physician in diagnosis and medical management (Ovadia et al., 1995; Ovadia et al., 1997).

The microcirculation of the skin and its regulation have been investigated under normal and pathological conditions, including various respiratory states (Babchenko et al., 1999; Levy et al., 2015), diabetes (Arora et al., 2002; Golster et al., 2005; Hosking et al., 2013; Kasalova et al., 2006; Marik, 2006; Shah et al., 2014; Urbancic-Rovan et al., 2006), vascular diseases (De Graaff et al., 2003; Morales et al., 2005; Otah et al., 2005; Przywara et al., 2004; Salminen et al., 2014), and smoking (Arora et al., 2002; Dalla et al., 2004; Rossi et al., 2014). Our aim here was to test the ability of

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the LPT system to evaluate the peripheral microcirculatory hemodynamic changes during different degrees of hypoxia. Proving its usefulness under such conditions could provide an effective noninvasive diagnostic tool for systemic hypoxia.

2. Methods

2.1. Animal preparation

Ten healthy white New Zealand male rabbits, weighing 3–4 kg, were used in the study performed at the Neufeld Cardiac Research Institute of the Sheba Medical Center. After 7 days of acclimation, the rabbit's back was shaved (24 h before the experiment) for the application of three sensors for assessing microcirculation. The ear artery and vein were cannulated for blood sampling and drug injection during the experiment. The rabbits were anesthetized with 35 mg/kg ketamine I.M. and 1 mg/kg xaylazin I.M. Tracheostomy was performed, and the rabbits were ventilated through 3 or 3.5 mm tubes connected to a pediatric mechanical ventilator for Continuous Positive Airway Pressure (CPAP) ventilation at 16 rpm. The respirator was connected to gas tanks that contained a mixture of nitrogen and one of 4 concentrations of oxygen: 21%, 18%, 13% and 8%.

2.2. Variables measured

2.2.1. Peripheral microcirculatory variables using noninvasive techniques based on the LPT system

RBC flux was measured by LDF using a Periflux model PF3 laser Doppler flowmeter (Perimed, Sweden). This is a relative measurement and the signal is expressed as perfusion units.

The amount of RBC was measured by PPG, using an EC-5R plethysmograph (D.E. Hokanson Inc.), set at AC current, 2 kHz/cm. This is a relative measurement expressed in volts.

Tissue oxygen tension was measured by tc-PO_2, model TCM3 (Radiometer, Copenhagen, Denmark). The measurement is quantitative and is expressed in mmHg units.

2.2.2. Central variables based on arterial blood samples

Arterial blood samples (1 ml each) were drawn throughout the study to track changes in oxygen pressure (PaO_2), bicarbonate (HCO_3^-), oxygen saturation (SaO_2), lactate and pH.

2.3. The protocol

The stages of the experiment were as follows:

1. Induction of anesthesia and connection to the CPAP.
2. Ventilation with 21% O_2 for 15 min. A sample of arterial blood was taken at the end of this stage.
3. Ventilation with 18% O_2 for 15 min. Samples of arterial blood were taken every 5 min.
4. Ventilation with 13% O_2 for 15 min. Samples of arterial blood were taken every 5 min.
5. Ventilation with 8% O_2 for 15 min. Samples of arterial blood were taken every 5 min.
6. Sacrificing the rabbit.

In accordance with legal requirements, the study was approved by the Institutional Animal Ethics Committee of Tel Aviv University, based on the guide for the care and use of laboratory animals of the US National Institutes of Health (NIH).

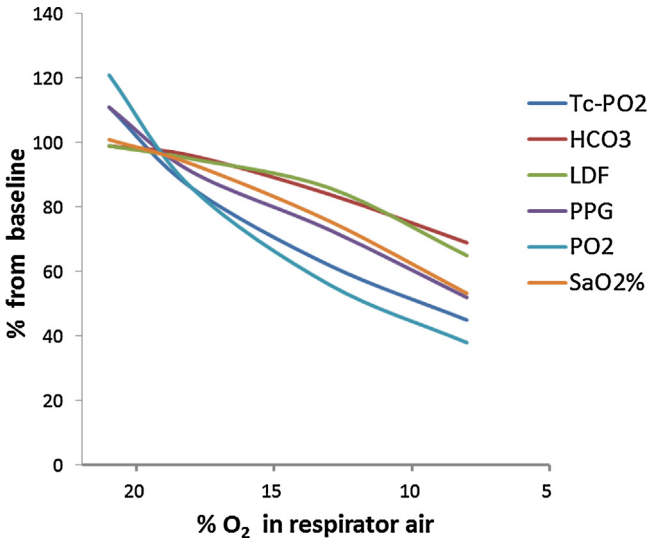

Fig. 1. Central and microcirculation variables vs. $\%O_2$: The changes in peripheral microcirculation and central variables during hypoxia.

2.4. Data analysis and statistics

Data are expressed as percentages of the baseline values. First order polynomials were fitted for characterizing the changes of different variables throughout the experiment. Regression analysis was used to find the best linear fit (in terms of mean square error) between the peripheral variables and the central variables. ANOVA and the *t*-test were used to demonstrate the significance of the obtained results. Statistical significance was defined as $p < 0.01$.

3. Results

The changes in the peripheral microcirculatory and the central variables during various degrees of hypoxia are presented in Fig. 1. The *X*-axis depicts the percentage of oxygen in the respirator air and the *Y*-axis depicts the measured values as percentages of their baseline value. These graphs represent the average measurements of ten rabbits collected at the end of each stage. The peripheral microcirculatory and central values also presented in Tables 1 and 2,

Table 1
Microcirculation variables at the end of each stage of the experiments.

Stage	Time [min]	tc-PO_2%	LDF%	PPG%
21% O_2	15	111 ± 5	99 ± 5	111 ± 7
18% O_2	15	86 ± 5	95 ± 5	91 ± 4
13% O_2	15	62 ± 4	86 ± 7	73 ± 6
8% O_2	15	45 ± 3	65 ± 4	52 ± 4
p-Value		<0.01	<0.01	<0.01

Note: All values were calculated as a percentage of baseline values and expressed as means ± SD. $N = 10$. $p < 0.01$ indicates significantly different from the previous step throughout the experiment.

Table 2
Central variables at the end of each stage of the experiments.

Stage	Time [min]	PO_2%	SaO_2%	HCO_3^-%	PH%	Lactate%
21% O_2	15	121 ± 7	101 ± 4	99 ± 7	100 ± 2	95 ± 10
18% O_2	15	86 ± 5	93 ± 3	96 ± 7	100 ± 2	119 ± 11
13% O_2	15	56 ± 3	76 ± 4	84 ± 4	101 ± 2	159 ± 11
8% O_2	15	38 ± 3	53 ± 2	69 ± 5	101 ± 2	127 ± 10
p-Value		<0.01	<0.01	<0.01	NS	NS

Note: All values were calculated as a percentage of baseline values and expressed as means ± SD. $N = 10$. $p < 0.01$ indicates significantly different from the previous step throughout all the experiment.