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Assessment of Lung and Peripheral Hemodynamics through Time Domain Diffuse Optical Spectroscopy During Forced Breathing

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Abstract: In a pioneering attempt at probing lungs *in-vivo* with time-resolved diffuse optics, we investigated how deep breathing causes synchronous blood volume-related absorption oscillations locally (lungs) and in peripheral circulation (forearm).

1 Introduction

In Europe in 2021, lung diseases were responsible for 6.1% of all deaths [1], underscoring the need for prevention and early diagnosis [2]. Effective diagnostic tools play a crucial role in this regard, and we are investigating the potential of Time Domain Diffuse Optical Spectroscopy (TD-DOS) to assess lung health status quickly, non-invasively, quantitatively, and cost-effectively.

In order to explore the feasibility of probing the deep lung tissue *in-vivo* with TD-DOS, we exploited a forced breathing protocol: the subjects performed forced inhalations and exhalations inducing physiological changes in the lungs in terms of tissue density and blood perfusion that affect the retrieved light signal. Previously, we investigated the effects of this respiration protocol at various wavelengths [3]. Changes in the collected signal were synchronous with respiration, suggesting effective probing of the lung. However, they were affected by significant inter-subject variability, possibly due to several effects (*e.g.*, changes in lung volume and tissue density; mechanical and hemodynamic effects; interplay among sympathetic nervous, respiratory and circulatory systems) with opposing influences on the retrieved counts that may lead to different net outcomes in different subjects.

In this work, we start to investigate the variation in blood volume as one of the possible physiological effects occurring with forced breathing. Given the impact of hemodynamic parameters on circulation, our tests include local (lung) and peripheral (forearm) assessments to help the interpretation based on known physiology. Measurements were performed at 800 nm, where tissue absorption is dominated by blood, and close to the isosbestic point of oxy- and deoxy-hemoglobin absorption, thus providing information on total blood volume.

The description and interpretation of the overall picture is challenging, because of the impossibility to decouple (with the homogenous tissue model used so far) the potential artifacts from the superficial chest layers and the contributions of the different physiological effects. This notwithstanding, a general promising scenario emerges, with encouraging correlations between optical data and breathing protocol, consistent with literature findings.

2 Materials and Methods

2.1 Experimental setup

Light at 800 nm, selected with a Pellin-Broca prism from the beam of a supercontinuum pulsed laser, is injected and collected from tissue through optical fibers in reflectance geometry with a source-detector distance of 4 cm. The re-emitted photons are detected with a hybrid photomultiplier tube and the temporal shape of the output pulse is reconstructed using an electronic board for time-correlated single photon counting. The single wavelength selection grants fast acquisition at 10 Hz.

2.2 Measurement and respiration protocol

Healthy volunteers lie supine on the clinical bed in a semi-reclined position. For lung measurements, the optical probe is placed on the right side of the chest, 2 cm above the nipple, orthogonal to the ribs. For peripheral measurements, the probe is placed sagittally on the right anterior forearm, just below the elbow joint.

During the forced breathing protocol, the subject is asked to perform a deep, thoracic inhalation reaching the maximum lung capacity in 3 seconds, and then to hold breath for 7 seconds. Then, symmetrically, the subject performs a deep exhalation to empty the lungs as much as possible in 3 seconds, followed by an apnea of 7 seconds. This sequence is repeated 5 times. The start and end of the protocol are respectively anticipated and followed by 20

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seconds of baseline acquisition (i.e., regular breathing). A full baseline measurement lasting 20x7 seconds = 140 seconds is also carried out.

Five subjects signed the written informed consent and were enrolled in the study, approved by the Ethical Committee of Politecnico di Milano.

2.3 Data analysis

The photon counts of the detected pulses are integrated over their duration from the peak to 1% of the peak intensity on the trailing edge. Integrated counts are then plotted as a function of the task time and a low pass filter is applied to remove noise fluctuations.

3 Results and Discussion

3.1 Measurements on the thorax

Fig. 1 presents the results for one of the subjects enrolled in the study, during the full baseline acquisition (blue) and the forced breathing protocol (black). Vertical, dashed red lines indicate the end of inhalation (green background) or exhalation (yellow background) phase, coinciding with the beginning of the apnea. During the forced breathing protocol, oscillations in the integrated counts are clearly visible and correctly aligned with the mentioned time references. In particular, counts increase noticeably during inhalation, remain constant or increase slowly while the subject is in apnea with filled lungs, then decrease noticeably during exhalation, and continue to decrease with a lower slope during apnea with empty lungs. The same trend characterizes all other subjects enrolled in the study. These oscillations indicate a decrease in total hemoglobin (*i.e.*, blood volume) during inhalation and the following apnea, and an increase during exhalation.

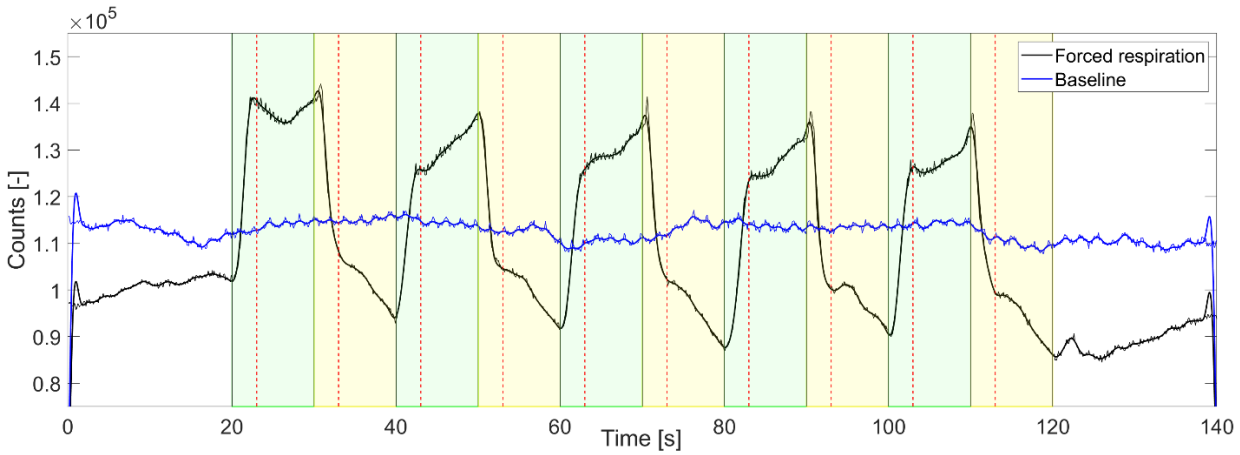

Fig. 1 Integrated photon counts measured on the chest during a baseline measurement (blue) and forced breathing protocol (black). Green regions correspond to inhalation, yellow regions to exhalation. Red dashed lines indicate the end of inhalation/exhalation and start of apnea.

Assuming that changes in blood volume are mainly happening in the lung tissue and not in the overlying chest layer, a possible explanation for these oscillations can be found in the variation of total pulmonary vascular resistance. When lung volume expands (*i.e.*, inhalation), alveolar vessels are compressed and their resistance to blood flow increases, whereas extra-alveolar vessels are stretched, with the opposite effect. At total lung capacitance, which is the "filled lung" condition reached during our breathing protocol, the contribution of the alveolar component is dominant, thus inducing a growth in the net pulmonary vascular resistance [4], with the consequent reduction in blood flow, and eventually the increase in output counts that we observe.

3.2 Measurements on the forearm

Results from the peripheral measurements on the forearm are reported in Fig. 2 for the same subject as in Fig. 1. Oscillations in total counts are again synchronous with the forced breathing, and the same happens for all the other subjects. Oscillations indicate an increase in peripheral blood volume during inhalation, and a decrease during exhalation, opposite with respect to the thoracic ones.

Many studies were conducted on the interplay between respiration and peripheral hemodynamics [5]. The major role in mediating these effects is ascribed to the sympathetic nervous system, which drives regional vascular distensibility and arterial blood pressure. Sympathetic activity is at maximum during exhalation and drops during

inhalation, leading to reduced peripheral vasoconstriction and increased blood volume. This justifies the out-of-phase behavior of lung and peripheral oscillations at 800 nm. In light of the relation between the respiratory, the hemodynamic and the sympathetic systems, peripheral measurements of blood volume during specific breathing exercises might represent a proof of consistency with physiology and open the possibility to extend our research to the investigation of the autonomic nervous system for the identification and diagnosis of its pathologies, such as diabetic neuropathy. It is worth noting that while this effect seems robust at 800 nm, it might not be as consistent for other wavelengths, where blood is not the dominant absorber and other contributions may prevail, thus explaining the inter-subject and intra-subject variability in oscillations sign we observed with previous measurements.

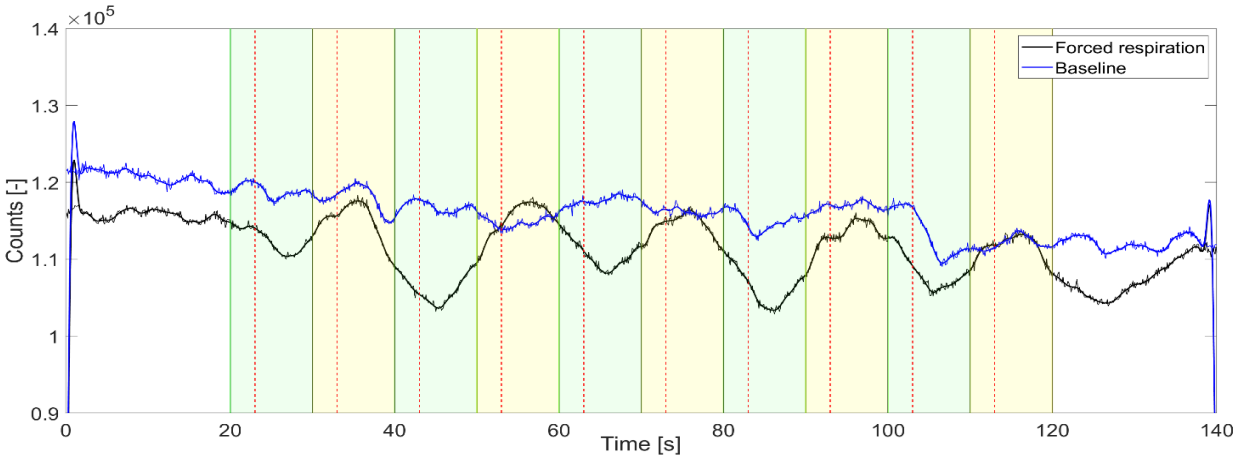

Fig. 2 Integrated photon counts measured on the forearm during a baseline measurement (blue) and forced breathing protocol (black). Green regions correspond to inhalation, yellow regions to exhalation. Red dashed lines indicate the end of inhalation/exhalation and start of apnea.

4 Conclusions

TD-DOS has relevant potential for the non-invasive, quantitative and cost-effective assessment of lung health. However, this application is challenging, mostly due to the heterogeneity of lung tissue and its depth in the thorax. At this stage of research, we are exploring the possible physiological effects influencing and influenced by variations in lungs composition and volume during a deep breathing protocol. In this work, we focused on blood-volume-related contrasts in the lungs and on the forearm through peripheral circulation using light at 800 nm acquiring at 10 Hz for fast tracking. Although challenging, the correlation between optical data, breathing protocol and literature findings highlights the potential of this application.

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