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The coupling between peripheral microcirculation and slow breathing

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ABSTRACT

Vasomotion (rhythmic changes in arteriolar diameter) is believed to enhance tissue perfusion at low oxygenation levels. We hypothesized that slow breathing and vasomotion may correlate temporally ("coupling"), especially at low oxygenation levels. We paced down spontaneous breathing to about 5 or 6 breaths/min in 14 healthy subjects using device-guided breathing (DGB), and continuously monitored respiration, transcutaneous oxygen pressure ("oxygenation"), and skin capillary blood flow ("microflow") using a laser Doppler flowmeter. The coupling was expressed by cross-correlation calculated in 1-min time windows. Our main results illustrated that: (1) coupling increased gradually upon slowing breathing down in a subgroup, in which initial oxygenation was lower than a threshold of 30 mmHg (0.3 ± 0.2 vs. 0.07 ± 0.2, $P < 10^{-6}$); (2) during DGB changes in oxygenation elicited opposite (relative) changes in microflow, with 4-fold higher sensitivity for low initial oxygenation relative to high (regression slope $-0.094 \pm 0.010\ \mathrm{mmHg}^{-1}$ vs. $-0.020 \pm 0.002\ \mathrm{mmHg}^{-1}$, $P < 10^{-6}$); (3) at low initial oxygenation, we observed larger coupling and (relative) microflow changes in younger subjects, and greater oxygenation changes in females ($P < 10^{-6}$ for all); (4) pulse pressure changes from before to after DGB were reduced by increased oxygenation changes during DGB (-5.5 ± 7.4 mmHg, $r = -0.73$, $P < 0.001$). In conclusion, the present methodology can provide the variation trend of respiration–vasomotion coupling during DGB that may characterize microcirculation behavior at tissue oxygenation below a measurable threshold. The potential association of these trends and thresholds with pathologies or specific conditions of the cardiopulmonary system, and the possible role played by the neural sympathetic activity in that coupling, deserve further studies.

1. Introduction

Microcirculation is part of the blood circulation and includes a system of small blood vessels (microvessels) having an enormous total length of about 100,000 km. It functions to deliver oxygen and nutrients provided by the arteries to the tissues, and bring carbon dioxide generated in the tissues back to the veins. Furthermore, it controls the distribution of blood supply to different organs to match local metabolic demands [1].

The general aim of the present study is to quantitatively investigate potential coupling between breathing movements and the microcirculatory blood flow and oxygen supply. Microcirculation is a challenging system to study because of its complexity, it being subject to multiple control mechanisms, and play an important role in evaluating various conditions such as vasospasm, ischemia, injury and recovery processes. The ability to monitor non-invasively changes in the skin microcirculation level leads to improvements in both diagnosis and treatment of patients' diseases, particularly in cardiovascular diseases.

Peripheral microcirculation [2]: the following background regarding microvessels and their physiological function may be helpful in understanding the core of the study: arterial blood is delivered to the tissues by arterioles (10–100 μm in diameter). Oxygen and nutrients flow into the tissue and carbon dioxide flows out during the passage of blood through capillaries (5–8 μm in diameter). Blood flows out of the capillaries into the venules (10–200 μm in diameter) and is collected by the veins. Arterioles also control the blood flow locally in the following way: The arteriolar wall is wrapped by smooth muscles that, upon contracting, exert radial forces which constrict the arteriolar lumen, and when relaxed, cause the arteriole to dilate. The resistance of a tube to flow varies as the 4th power of 1/diameter (Poiseuille's law). Therefore, for a

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given arterial pressure, the arteriolar blood flow is determined by arteriolar resistance (Ohm's-like law), which reflects its degree of constriction, as induced by smooth muscle contraction ("vascular tone"). The vascular tone itself is subject to multiple control mechanisms including sympathetic neural activity [3].

The vasomotion phenomenon: arterioles display spontaneous rhythmic diameter oscillation called vasomotion. The accompanying changes in resistance result in capillary blood flow oscillations. Vasomotion was explained as a mechanism for increasing arteriolar flow conductance (=1/resistance), which plays an important role in controlling blood pressure [4], and has been demonstrated to increase oxygen supply to tissue under conditions of low oxygenation (hypoxia) [2]. The rationale is that vessel conductance is proportional to the fourth power of its diameter (Poiseuille's law). As a result, the contribution to the average conductance during the diameter increase phase is greater than during diameter decrease, leading to net conductance increase [4]. Evidence shows that sympathetic neural activity oscillations may control or trigger vasomotion [5]. However, the physiological role and underlying mechanism of vasomotion are not fully understood [5]. Typical vasomotion frequencies observed in human skin capillary blood flow with a laser Doppler flowmeter (LDF) are in the range of 4–8 cycles/min (about 0.07–0.13 Hz) [6]. Impaired vasomotion in the range of 6 cycles/min is associated with peripheral sympathetic neuropathy in diabetes [6].

Slow breathing effect on sympathetic neural activity (SNA): during slow breathing, typically 6 breaths/min (0.1 Hz), but not during spontaneous breathing, typically 12–20 breaths/min (0.2–0.3 Hz), the SNA generated centrally by the brain is inhibited during exhalation only [7]. Thus, breathing movements induce SNA oscillations that are enhanced at a slow breathing rate and especially with prolonged exhalation. Therefore, SNA oscillations may be an input that drives vasomotion, but also an output of respiration. In this paper, we will use the terms "respiration" and "breathing" interchangeably.

With this background, we hypothesize that when respiration rate is reduced, in a way that it overlays the vasomotion frequency range, we may expect to see some synchronicity, or more precisely, enhanced temporal correlation ("coupling") between respiration and vasomotion. We evaluated this hypothesis quantitatively by simultaneous monitoring of skin capillary blood flow ("microflow") and transcutaneous tissue oxygenation ("oxygenation") in peripheral microcirculation and respiration, while pacing down breathing to slow rates, using an experimental setup already applied successfully for measurements of peripheral microcirculation response to hemorrhage [8], vasoactive drugs [9], hypoxia [7] and myocardial ischemia [10].

2. Methods

2.1. Subjects

Fourteen subjects, self-declared as healthy, including 50% females in two age ranges: 23–30 years and 31–49 years, were recruited at Afeka, Tel Aviv Academic College of Engineering. All subjects signed a written informed consent. The study was approved by the Helsinki Committee of the Sheba Medical Center, Tel Hashomer, Israel (ID 0233-13-SMC).

2.2. Experimental setup

Breathing pacing from spontaneous to low rates was done using the RESPeRATE™ device (RESPeRATE Inc., USA). The device monitors respiration with a belt-type sensor placed on the upper abdomen or chest; analyzes inspiration and expiration durations in real time, and composes musical tones in real time with durations

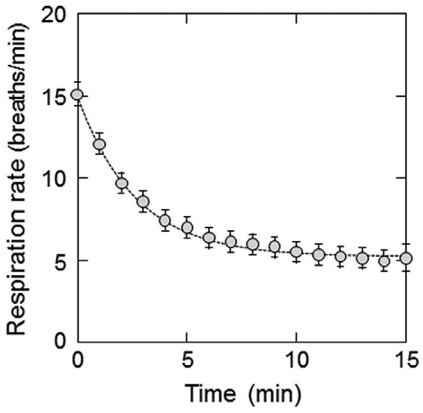

Fig. 1. Variation of the respiration rate during 15-min device-guided breathing (DGB) exercise. The circles represent mean respiration rate calculated in one-minute intervals. Standard error bars are marked. The dashed line represents exponential decay curve best-fitted to the mean values using nonlinear regression procedure (r = 0.998).

that correspond to the monitored inhale and exhale movements but with slightly longer durations, according to proprietary algorithms. The "breathing guiding" function is achieved when the user synchronizes breathing movements with these tones. This closed-loop operation, hereafter called "device-guided breathing" (DGB), guides the user to slow breathing gradually from a spontaneous breathing rate to about 5–6 breaths/min without conscious effort (Fig. 1), where during the guiding, expiration-to-inspiration duration ratio increases in an individualized way [11]. The intervention is initialized by measuring the spontaneous breathing pattern while playing non-rhythmic music. The device displays respiration rate calculated using the last three breaths that pass propriety acceptability tests which eliminate motion artifacts and sudden changes in breathing behavior, *e.g.*, yawning, and shuts off automatically after a predetermined duration of the breathing guiding phase.

The peripheral microcirculation measures were acquired using an experimental setup that has been shown to be successful for measurements of peripheral microcirculation response to hemorrhage [8], vasoactive drugs [9], hypoxia [7] and myocardial ischemia [10]. The setup included measurement of transcutaneous oxygen pressure ($tcpO_2$, in mmHg) to quantify skin blood oxygenation [12,13]. Skin capillary blood flow was measured by LDF, in "Perfusion Units")PU) [14]. Both $tcpO_2$ and LDF signals were acquired using PeriFlux system (PERIMED™, Sweden).

Respiration rate was measured using a respiration belt transducer that detects variations in the abdomen/chest circumference, which were converted to voltage using a BIOPAC™ system (BIOPAC Systems, Inc., USA). The BIOPAC system also acquired electrocardiography (ECG) in order to verify that no major changes occurred in heart activity during the experiment. The simultaneousness recording of all the signals obtained from the PERIMED and BIOPAC systems with the same time base was achieved by displaying the signals on a split screen and using marking of common events. In addition, readings of brachial blood pressure (BP) and heart rate (HR) were taken before and immediately after each session, using a standard digital blood pressure monitor (OMRON IC, IntelliSense™, Japan).

2.3. Protocol

All measurements were performed during a single session. The subjects were requested to refrain from eating, smoking and any sport activity for at least 2 h prior to their arrival at the measurement session. The subjects were seated near a table with forearm and hand comfortably supported. The LDF and $tcpO_2$ sensors