



Impact of shear rate pattern on post-occlusive near-infrared spectroscopy microvascular reactivity

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ABSTRACT

The primary aim of the present study was to determine the impact of acute changes in shear rate patterns, in particular retrograde shear rate, on microvascular function in 15 healthy, young men and women as determined via the post-occlusive near-infrared spectroscopy (NIRS) microvascular reactivity response. Microvascular reactivity, via NIRS-derived measurements of post-occlusion tissue saturation index (TSI%) and total microvascular hemoglobin + myoglobin concentration ($[Hb]_{total}$), were assessed in each participant before and immediately after exposure to a 30 min retrograde shear treatment. Retrograde shear was achieved via a blood pressure cuff placed below the knee inflated to 75 mm Hg. One leg was exposed to the retrograde shear (Treatment leg) and the contralateral leg served as a non-treatment control. In the Treatment leg, significant increases in retrograde shear rate occurred during the retrograde intervention. Following the intervention, the area under the TSI% post-occlusion response curve, which represents the total microvascular reactivity response, and the absolute peak TSI% response were significantly increased compared to pre-intervention in the Treatment leg, but not the Control leg. The absolute peak $[Hb]_{total}$ response was significantly increased post-intervention in both legs. These results are in contrast to our hypothesis that 75 mm Hg cuff inflation, designed to increase retrograde shear rate in the femoral artery would negatively affect post-occlusive microvascular reactivity. These data suggest that the current method of increasing retrograde shear rate in the intact human does not adversely impact NIRS derived measurements of microvascular reactivity.

1. Introduction

Endothelial cells within the peripheral vasculature are highly sensitive to changes in hemodynamic shear rate, such that periods of increased oscillatory and retrograde shear acutely decrease endothelial function and promote a proatherogenic endothelial cell phenotype (Laughlin et al., 2008). Human umbilical veins exposed to oscillatory shear rates, which consisted of a large retrograde shear component, experienced an increased leukocyte expression due, in part, to changes in oxidative stress (Chappell et al., 1998). Similarly, bovine and murine aortic endothelial cells exposed to increased oscillatory shear rate have an amplified production of endothelial cell superoxide ($O_2^{\cdot -}$), which contributes to overall endothelial dysfunction (Hwang et al., 2003; McNally et al., 2003; Ziegler et al., 1998). Recently, studies in the intact human have provided further insight into the adverse effects of increased oscillatory and retrograde shear rate patterns on endothelial function in the large brachial and femoral arteries. Thijssen et al.

(2009) demonstrated, in young men that exposing the brachial artery to a 30 min increase in retrograde shear rate significantly decreased brachial artery endothelial-dependent flow mediated dilation (Thijssen et al., 2009). Additionally, Totosty de Zepetnek et al. (2015) recently altered shear rate patterns with significant increases in retrograde shear rate in the femoral artery of spinal cord injury patients and observed decreases in flow mediated dilation. In each of these studies, the increased retrograde shear was achieved via mild inflation of a blood pressure cuff on the experimental limb, which significantly increases retrograde shear rate, as measured via vascular Doppler ultrasound, in the larger vessels. However, to our knowledge, no studies have investigated the effect of this cuffing method to increase retrograde shear rate on non-invasive measurements of microvascular function.

Near Infrared Spectroscopy (NIRS) provides a non-invasive method of evaluating changes in the redox state of hemoglobin and myoglobin within the muscle microvascular network and has previously been used to evaluate post-occlusive microvascular reactivity in various disease

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states (De Blasi et al., 2005; Kragelj et al., 2001). Following a 5 min period of complete vascular occlusion, microvascular reactivity as assessed via the NIRS derived tissue oxygen saturation response is significantly decreased in patients with septic shock compared to healthy controls (De Blasi et al., 2005). Similarly, Kragelj et al. (2001) compared patients with peripheral vascular disease to healthy subjects via NIRS derived measurements of post-occlusive microvascular reactivity and revealed significant decreases in those with disease (Kragelj et al., 2001). This post-occlusive vascular response is thought to occur primarily as the result of endothelial, myogenic, local metabolic factors within the resistance vessels of the occluded limb (Flammer et al., 2012). As such, the responses to arterial ischemia characterized by changes in NIRS parameters or the post-occlusive brachial artery blood flow response can be used as tests of microvascular function (Flammer et al., 2012). Although a transient increase in both brachial artery and microvascular blood flow occurs following the post-occlusive period, only a few studies have directly compared these responses. Dhindsa et al. (2008) reported a significant correlation between brachial artery reactive hyperemic flow and microvascular reactivity in the finger. Similarly, Bopp et al. (2014) demonstrated a strong correlation between the post-occlusive brachial artery blood flow and $[Hb]_{\text{total}}$ response, suggesting that measures of NIRS microvascular reactivity are linked to the macrovascular hyperemic flows traditionally observed with Doppler ultrasound. However, this cannot be said for all comparisons between measurements of macrovascular and microvascular function. To date comparisons between flow-mediated dilation, which is largely nitric oxide mediated (Green et al., 2014), and post-occlusive microvascular reactivity measurements have revealed only modest associations (Dhindsa et al., 2008; McLay et al., 2016). Given this previous work, the evaluation of the altered NIRS derived tissue O_2 saturation characteristics in response to different hemodynamic shear rates may provide valuable insight into microcirculatory consequences of acute increases in retrograde shear. To date, the impact of different shear rate patterns induced by mild cuff inflation, to our knowledge, has not been previously examined in humans at the microcirculatory level. Therefore, the primary aim of the present investigation was to determine, via the post-occlusive NIRS microvascular reactivity response, the impact of a 30 min intervention consisting of cuff inflation to 75 mm Hg (Totossy de Zepetnek et al., 2015) designed to alter conduit artery shear rate patterns, in particular retrograde shear rate, on NIRS derived measurements of microvascular function. It was hypothesized this technique would significantly decrease microvascular reactivity via decreases in the post-occlusive NIRS microvascular reactivity response.

2. Methods

2.1. Subjects

15 healthy individuals (men (9) and women (6), 23 ± 3 yr. (mean $\pm$ SD)) participated in the study. Females were tested during the early follicular phase (i.e., days 1 to 7 of the menstrual cycle). All experimental testing was completed on a single test day and each participant served as their own control. Testing sessions were performed in a thermo-neutral setting ($21\text{--}23^\circ\text{C}$). Time of day was not controlled. All subjects were free from known cardiovascular disease, diabetes, hypertension, and were non-smokers, as determined via health history questionnaire. All subjects were considered sedentary-to-recreationally active (i.e., < 10 h of vigorous physical activity per week). Verbal and written consent were obtained following approval of the study by the Institutional Review Board for Research Involving Human Subjects at the University of Oklahoma, in accordance to the Declaration of Helsinki.

2.2. Experimental design

On the experimental day, participants reported to the laboratory

following a 6 h fast and having refrained from strenuous exercise, alcohol, and caffeine for 12 h. Following a 15 min supine rest, post-occlusive NIRS-derived microvascular reactivity was examined in the m. rectus femoris of both legs, before and 5 min after a 30 min intervention designed to increase femoral artery retrograde shear rate in one randomly selected leg (Treatment leg).

In the randomly selected Treatment leg, acute changes in the shear rate patterns were achieved via mild inflation of a blood pressure cuff placed below the knee. Using a similar method as previously described, the cuff was inflated to a target pressure of 75 mm Hg for a 30 min period (Totossy de Zepetnek et al., 2015). The contralateral leg served as the Control/non-Treatment leg (Control leg). Superficial femoral artery diameter and blood velocity measures were obtained in both legs, via two dimensional and Doppler ultrasound with a linear array transducer operating in duplex mode and an insonation angle of $< 60^\circ$ (Logic S8, GE Medical Systems, Milwaukee, WI) at the beginning, middle, and end of the shear rate treatment. All measurements of arterial diameters and velocities were performed over 10 continuous cardiac cycles. Mean (i.e., across the entire cardiac cycle), antegrade, and retrograde shear rates were calculated using mean, antegrade and retrograde blood velocities, respectively in combination with femoral artery diameter as follows: shear rate = $4 \times \text{doppler velocity} / \text{diameter}$.

2.3. Post-occlusive microvascular reactivity

In the present study oxygenation and haemodynamics of the m. rectus femoris in the Treatment and Control legs were simultaneously measured using a rapid sampling frequency-domain multi-distance near infrared spectrometer (NIRS; OptiplexTS; ISS, Champaign, IL) before and within 5 min after the 30 min retrograde shear rate intervention. The NIRS device was calibrated prior to each experimental session per manufacturer specifications. Briefly, the NIRS probe consisted of eight light emitting diodes operating at two wavelengths (690 and 830 nm) and a single detector fiber bundle (source detector separation of 2.0–3.5 cm). This system provides absolute values of oxygenated and deoxygenated microvascular tissue hemoglobin + myoglobin and were used to calculate microvascular tissue saturation (TSI%), which provides an integrative measure of the dynamic changes in local tissue perfusion relative to local metabolism. Due to similar absorption properties of the NIRS light wavelengths, distinction between hemoglobin and myoglobin cannot routinely be made. Total microvascular hemoglobin + myoglobin concentration ($[Hb]_{\text{total}}$) measured and used as an index of changes in total microvascular hemoglobin concentration which can occur due to changes in regional blood volume. Correct placement of the NIRS probe was confirmed by obtaining an ultrasound image of the muscle tissue below the probe. During each test the data were sampled at 50 Hz and averaged into 1 s bins for off-line analysis. No movement of the probe occurred during the procedures. Throughout the procedure, participants were supine with both the Treatment and Control legs placed on a 10 cm elevated foam pad.

Following a 5 min resting baseline period a specialized pneumatic cuff, attached to a rapid inflation/deflation pneumatic system (D.E. Hokanson, Bellevue, Wash), was positioned on the upper legs at the level of the femoral artery and inflated to > 250 mm Hg for 5 min to fully occlude the femoral artery. TSI% and $[Hb]_{\text{total}}$ were measured during a 2 min baseline period and following the release of the > 250 mm Hg cuff (i.e., post-occlusion; Fig. 1). Similar to previous investigations evaluating microvascular reactivity (Doerschug et al., 2007), the following post-occlusive microvascular reactivity variables were assessed: 1) TSI% reperfusion rate calculated as the upslope of a 10 s window following cuff release 2) peak TSI% defined as the highest value obtained during the post-occlusive period, 3) change peak TSI%, defined as the difference between baseline and peak TSI% values, 4) total post-occlusive microvascular reactivity response calculated as the area under the TSI% response curve, 5) peak $[Hb]_{\text{total}}$ defined as the highest value obtained during the post-occlusive period, and 6) change

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