

Research Article

Use of Near Infrared Spectroscopy to Assess Remote Ischemic Preconditioning in Skeletal Muscle

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Received 1 November 2012; Revised 23 January 2013; Accepted 23 January 2013

Academic Editor: Michael S. Wolin

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Remote ischemic preconditioning (IPC) is a procedure during which brief periods of ischemia protect distant organ from ischemia-reperfusion injury. Applying IPC on an upper arm, this phenomenon has been demonstrated in several studies. Skeletal muscle tissue oxygenation at rest (StO₂) and StO₂ deoxygenation rate during vascular occlusion can be measured using near infrared spectroscopy (NIRS). We aimed to investigate the effects of remote upper arm IPC on StO₂ and flow-mediated dilatation (FMD) in healthy male volunteers. In a randomized controlled crossover trial, resting StO₂, StO₂ deoxygenation rate, and FMD were measured on testing arm at baseline and after 60 minutes. After basal measurements IPC protocol on a contralateral arm was performed. StO₂ deoxygenation rate was significantly lower after remote, the IPC cycles in comparison to deoxygenation rate at baseline (9.7 ± 2.6 versus $7.5 \pm 2.5\%$, $P = 0.002$). Comparison of deoxygenation rates showed a significant difference between the IPC and the control protocol ($F = 5.512$, $P = 0.003$). No differences were observed in FMD before and after remote IPC and in the control protocol. In healthy young adults, remote IPC reduces StO₂ deoxygenation rate but has no significant impact on FMD. NIRS technique offers a novel approach to assess skeletal muscle adaptation in response to remote ischemic stimuli.

1. Introduction

Ischemia-reperfusion injury is a systemic event resulting in damage to local and remote organs. Restoration of blood supply to an organ after a critical period of ischemia causes additional tissue damage and organ dysfunction leading to significant morbidity and mortality. It has been described in a number of clinical settings: acute coronary occlusion, cardiopulmonary bypass procedures, organ transplants, and shock [1–3]. Remote ischemic preconditioning (IPC) is a procedure where brief periods of ischemia in one tissue prior to sustained ischemia reduce ischemia-reperfusion injury in another remote tissue [4, 5]. After early experiments in animals [6], both in vitro and in vivo studies suggested the significance of this protective effect in humans, particularly in the setting of myocardial ischemia [7–10]. However, there is still no agreement about standardized IPC protocol.

The precise mechanisms involved in IPC are not yet established. A possible pathway involves the generation of nitric oxide and an effect on endothelial function [5, 8]. Molecular mechanism is not completely understood, but probably involves the released humoral mediators from ischemic tissue, including adenosine, bradykinin, and opioids, which react with the cell surface receptors and activate protein kinase cascades. The end-effectors may be mitochondrial ATP-dependent potassium channels and mitochondrial permeability transition pores, whose opening during ischemia may be lethal [11–14].

Skeletal muscle has been investigated as a remote stimulus for either distant skeletal muscle or cardiac protection in several studies [9, 15–18]. Ischemic conditioning of the skeletal muscle on an upper or lower limb is a noninvasive, readily reproducible method for studying the effects on other

remote organs and, therefore, might be easily translated into clinical practice.

Near infrared spectroscopy (NIRS) has been used to assess peripheral microvascular function in a variety of clinical settings [19–23]. Illuminating an infrared band of 680–800 nm NIRS exploits the difference in absorption spectra between the oxygenated and deoxygenated hemoglobin and partly myoglobin and thus assesses the balance between local arterial supply and cellular oxygen consumption within the muscle tissue. NIRS enables continuous monitoring of skeletal muscle tissue oxygenation (StO_2), which reflects this balance between oxygen delivery and consumption. With the stagnant ischemia provoked by vascular occlusion test (VOT), dynamic changes in StO_2 and thus microvascular function/tissue metabolism can be followed and evaluated [24].

To the best of our knowledge, no reports about the effect of remote IPC on dynamic changes in StO_2 of skeletal muscle, measured by NIRS are available. In previous studies, positive effects of IPC on skeletal muscle were shown as prevention of the endothelial dysfunction and systemic neutrophil activation [8, 12, 17, 18].

The aim of our study was to evaluate the effect of remote IPC on skeletal muscle StO_2 using NIRS technique. Considering the ischemia-induced deoxygenation rate of the tissue oxygenation curve as a surrogate for tissue oxygen consumption, we hypothesized that this technique might detect the ability of skeletal muscle adaptation to remote ischemic stimuli applied in the contralateral arm. We also evaluated the effect of remote IPC on endothelial function using flow-mediated dilatation method (FMD).

2. Materials and Methods

2.1. Study Design. The study was designed as a randomized controlled crossover trial. The study protocol was approved by the National Ethics Committee of Slovenia.

2.2. Subjects. Fourteen male healthy volunteers with no significant past medical history were enrolled in the study. Exclusion criteria were any chronic illness, medication, and smoking. The subjects were investigated in two experiments. They were randomly assigned to the remote IPC or the control protocol and were then crossed over to another protocol after at least one week in a random sequence. The two experiments for each subject were performed in the morning after an overnight fast and after 10 minutes of rest in supine position. The selected testing arm was the left, nondominant arm in all subjects. All participants gave written informed consent before any study-related procedure.

2.3. Skeletal Muscle Near Infrared Spectroscopy and Vascular Occlusion Test. StO_2 was measured by NIRS using the InSpectra 325 tissue oxygenation monitor (Hutchinson Technology Inc., West Highland Park Drive NE, MN, USA), which measures tissue absorbance values between 650 and 900 nm. The tissue absorbance values (four wavelengths data) are transformed into scaled second derivative absorbance

values to provide a tissue spectral measurement that is robust to total hemoglobin and optical path length changes [25, 26]. 25 mm InSpectra probe (source-detector separation 25 mm, penetration depth 23 mm, and 95% signal threshold) was used [22, 23]. Probe was moved over the thenar prominence in order to localize the maximum StO_2 and then fixed with InSpectra Shield. StO_2 data was monitored and stored onto a computer using InSpectra software.

After measuring resting StO_2 for 30 seconds, VOT was performed as described earlier [22, 23]. In short, testing arm was subjected to ischemia by inflating a blood pressure tourniquet, placed around the forearm, to a pressure of 250 mmHg for 3 minutes and then rapidly released. StO_2 was continuously measured over the thenar muscle of the testing arm before, during and 5 minutes after VOT. All VOTs were done using the same blood pressure tourniquet.

The dynamic StO_2 curve parameters reported in this study are resting StO_2 (%), StO_2 deoxygenation rate (%/min), which was measured during vascular occlusion, StO_2 reoxygenation rate (%/min), and maximal StO_2 (%), measured after release of vascular occlusion. InSpectra analysis software 2.0 was used to automatically calculate StO_2 slope gradient.

2.4. Flow-Mediated Dilatation. Endothelial function was assessed by measuring FMD of the brachial artery using a Vivid 4 ultrasound machine (GE Medical Systems, USA) with a 7 MHz linear array transducer as described [27]. The brachial artery was scanned in the longitudinal section 2–15 cm above the elbow finding the clearest images of the anterior and posterior wall layers. The mean arterial diameter was measured at the end of diastole, which was determined by simultaneous monitoring of the electrocardiogram. At least three cardiac cycles were analyzed for each scan and the measurements averaged. The flow velocity was measured at a fixed incident angle of 60° to the vessel with the range gate of 1.5 mm located in the centre of the artery. The basal flow was estimated by multiplying the velocity time integral of the Doppler flow signal (corrected for incident angle) by the vessel cross-sectional area. Flow after VOT was recorded within the first 15 seconds and diameter measurements were taken 30–90 seconds after cuff deflation. FMD was expressed as the percentage change of the diameter after reactive hyperemia relative to the basal diameter. Ultrasound data included basal diameter of the brachial artery (mm), basal flow (mL/min), flow after AOT (mL/min), and FMD (%).

2.5. IPC Protocol. The subjects rested in the supine position for 10 minutes before measurements. Baseline NIRS measurements were performed before and during the first VOT on a testing arm. FMD was assessed according to the changes in arterial diameter before and after VOT. After baseline measurements, remote IPC was applied by three cycles of 5 minutes of ischemia and 5 minutes of reperfusion on the contralateral upper arm. Ischemia was induced by inflating a blood pressure tourniquet around the upper arm to a pressure 50 mmHg above the subject's resting systolic blood pressure. After completion of ischemia and reperfusion cycles, the subjects rested for another 30 minutes. The second NIRS

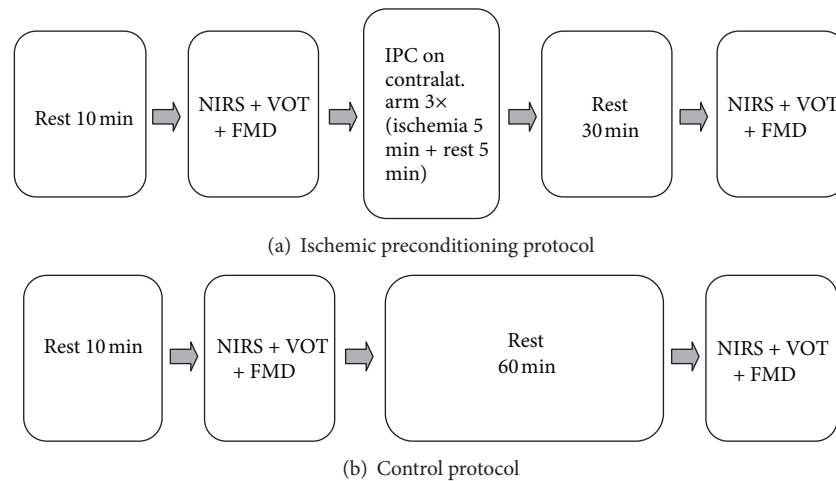


FIGURE 1: Flow chart of the experiment. NIRS: near infrared spectroscopy; VOT: vascular occlusion test; FMD: flow-mediated dilatation; IPC: ischemic preconditioning.

measurements and VOT were then performed on a testing arm in the same way, 60 minutes after baseline measurements and FMD was assessed.

2.6. Control Protocol. The subjects rested in the supine position for 10 minutes before measurements. Baseline NIRS measurements were performed before and during the first VOT on a testing arm and FMD was assessed. Following 60 minutes of rest, the second VOT with NIRS and FMD measurements were performed. The protocols are schematically illustrated in Figure 1.

2.7. Data Analysis. Data is presented as mean \pm standard deviation (SD) or mean (range). Data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 10.0, SPSS Inc., Chicago, IL, USA). Skeletal muscle StO_2 data in the IPC and the control protocol were compared using One way repeated measures analysis of variance with all pairwise multiple comparison procedure by Holm-Sidak method. P values < 0.05 were regarded as significant. In individual subject, ultrasound data in the IPC and the control protocol were compared using paired samples Student's t -test with P values < 0.05 regarded as significant.

3. Results

A total of fourteen male healthy volunteers with mean (range) age of 32 (26–47) years, body weight 76 (57–105) kg, height 181 (162–204) cm, body mass index 25.3 (21.7–28.4), and systolic blood pressure 110 (100–155) mmHg participated in the study.

There was no difference in resting StO_2 at baseline and after 60 minutes in the IPC protocol ($85 \pm 2\%$ versus $85 \pm 2\%$, $P = 0.9$), nor in the control protocol ($85 \pm 2\%$ versus $85 \pm 2\%$, $P = 0.9$). There was also no difference in resting StO_2 between both protocols (P between groups = 0.93).

Compared to baseline StO_2 deoxygenation rate was significantly lower after the IPC protocol ($9.7 \pm 2.6\%/min$ versus

$7.5 \pm 2.5\%/min$, $P = 0.002$). StO_2 deoxygenation rates in the control protocol were found to be similar compared to baseline ($10.0 \pm 3.4\%/min$ versus $9.5 \pm 4.0\%/min$, $P = 0.4$). Comparison of StO_2 deoxygenation rates showed a statistically significant difference between the IPC and the control protocol ($F = 5.512$, $P = 0.003$). A graphical representation of skeletal muscle StO_2 during VOT in both protocols in an individual subject is shown in Figure 2. Individual data of skeletal muscle StO_2 deoxygenation of the study population is shown Figure 3. There was no difference in basal StO_2 , reoxygenation rate, and maximal StO_2 in all study analyses (Table 1).

No differences were observed in the basal diameter of the brachial artery, basal flow, flow after VOT, and FMD before and after IPC in the IPC protocol and in the control protocol. There were no differences between both protocols (Table 2).

4. Discussion

Our study investigated the ischemic adaptation of skeletal muscle induced by IPC using NIRS methodology in healthy subjects. After remote ischemic cycles, we confirmed reduced StO_2 deoxygenation rate during vascular occlusion, demonstrating reduced muscle oxygen consumption. Current study confirmed the usefulness of NIRS technology to assess remote IPC in skeletal muscle.

IPC by ischemic cycles applied on skeletal muscle was tested in a variety of clinical studies, which proved that remote IPC has beneficial effect on distant, treated organs. Greatly the studies were focused on IPC of the heart since cardiovascular diseases account nowadays for significant morbidity and mortality. The beneficial effect of IPC was first studied in children undergoing surgery for congenital heart defects that showed lower troponin levels and less inotropic requirement if the patients were subjected to IPC [16]. In adult patients who underwent elective coronary artery bypass graft surgery, remote IPC consisting of ischemic cycles of the upper arm resulted in a significant reduction

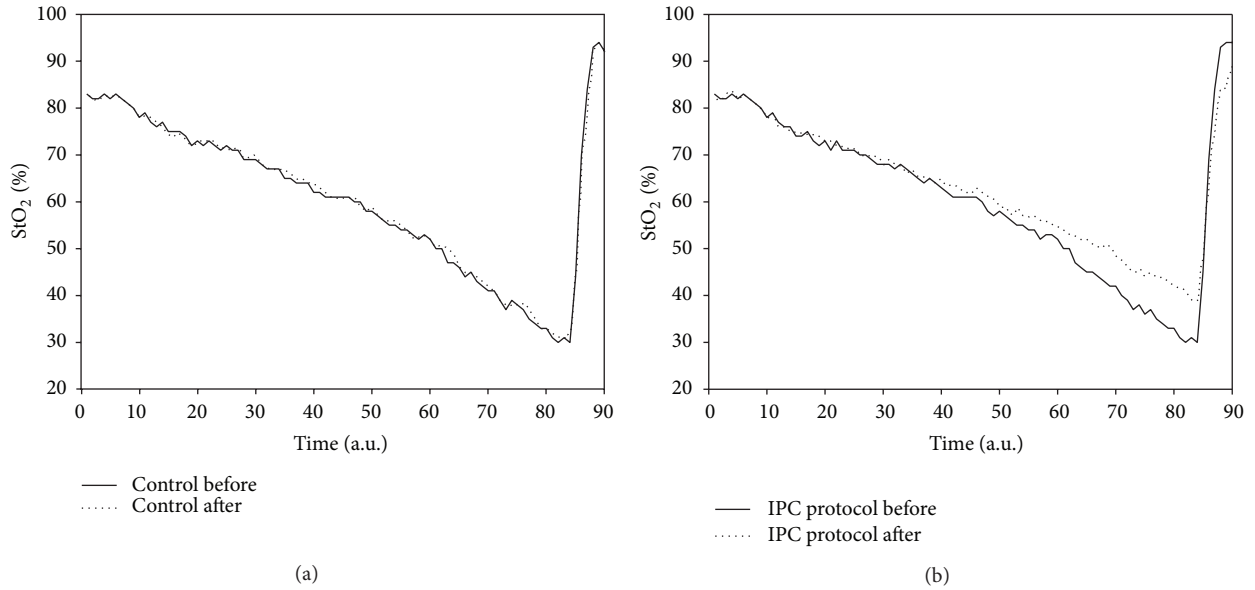


FIGURE 2: Skeletal muscle StO_2 during vascular occlusion test in both experiments in an individual subject. Control before: skeletal muscle StO_2 in the control protocol at baseline; control after: skeletal muscle StO_2 in the control protocol after 60 minutes of rest (at the end of the protocol); IPC protocol before: skeletal muscle StO_2 in the ischemic preconditioning protocol at baseline; IPC protocol after: skeletal muscle ischemic preconditioning in the ischemic preconditioning protocol at the end of the protocol.

TABLE 1: Skeletal muscle tissue oxygenation (StO_2) during vascular occlusion test.

Variable	IPC protocol ($n = 14$)			Control ($n = 14$)			Statistics between treatments
	Before	After	Statistics	Before	After	Statistics	
Basal StO_2 (%)	85 ± 2	85 ± 2	ns	85 ± 3	84 ± 4	ns	0.934
Deoxygenation rate (%/min)	9.7 ± 2.6	7.5 ± 2.5	0.002	9.5 ± 4.0	10.0 ± 3.4	0.4	0.003
Reoxygenation rate (%/min)	230 ± 72	230 ± 100	ns	232 ± 123	250 ± 113	ns	0.922
Maximal StO_2 (%)	94 ± 2	94 ± 1	ns	95	95	ns	0.955

IPC protocol before: skeletal muscle StO_2 data in the ischemic preconditioning protocol at baseline; IPC protocol after: skeletal muscle StO_2 data in the ischemic preconditioning protocol at the end of the protocol; control before: skeletal muscle StO_2 data in the control protocol at baseline; control after: skeletal muscle StO_2 data in the control protocol after 60 minutes of rest; and ns: nonsignificant.

in troponin release following surgery [9]. Even in a large group of patients undergoing elective percutaneous coronary intervention, those who were treated by remote upper arm IPC were more likely to have undetectable troponin release following intervention and better morbidity results at 6 months [28]. In patients presenting with acute myocardial infarction, remote IPC by repeated limb ischemia before hospital admission increased myocardial salvage measured by myocardial perfusion imaging [15].

NIRS technology has been used as a noninvasive, readily accessible method for assessing tissue microcirculation in a number of different research and clinical settings. In response to ischemia, it also allows evaluation of dynamic changes in microcirculation. Using NIRS, the changes in skeletal muscle oxygenation have been demonstrated in chronic heart failure patients at rest and during exercise [20, 29], in patients undergoing haemodialysis [21], during abdominal aortic and cardiac surgery [30, 31], and in patients with peripheral arterial disease [32], cirrhosis [33], septic shock [22, 23], and metabolic myopathies [34]. NIRS has been

already applied to demonstrate the effect of IPC on changes in myocardial oxygenation in dogs; IPC has been induced by repeated periods of coronary occlusion [35]. No previous study, however, utilized NIRS to demonstrate the effect of remote IPC on skeletal muscle in humans.

The question remains what the underlying mechanism of the decreased deoxygenation rate is. In animal studies, it has been shown that ischemia-reperfusion injury alters the mitochondrial oxidative phosphorylation and that IPC preserves mitochondrial enzyme activities [36]. So we can speculate that decreased deoxygenation rate demonstrated in our study reflects certain degree of beneficial tissue adaptation on remote ischemic conditions, possibly through modification of mitochondrial oxygen metabolism. However, NIRS does not measure mitochondrial function and other explanations for decreased deoxygenation rate should be considered. The rate of postischemic vasodilatation might be enhanced in response to IPC, but there were no differences in reoxygenation rate and maximal StO_2 between the control and the IPC protocols in our study. There were also

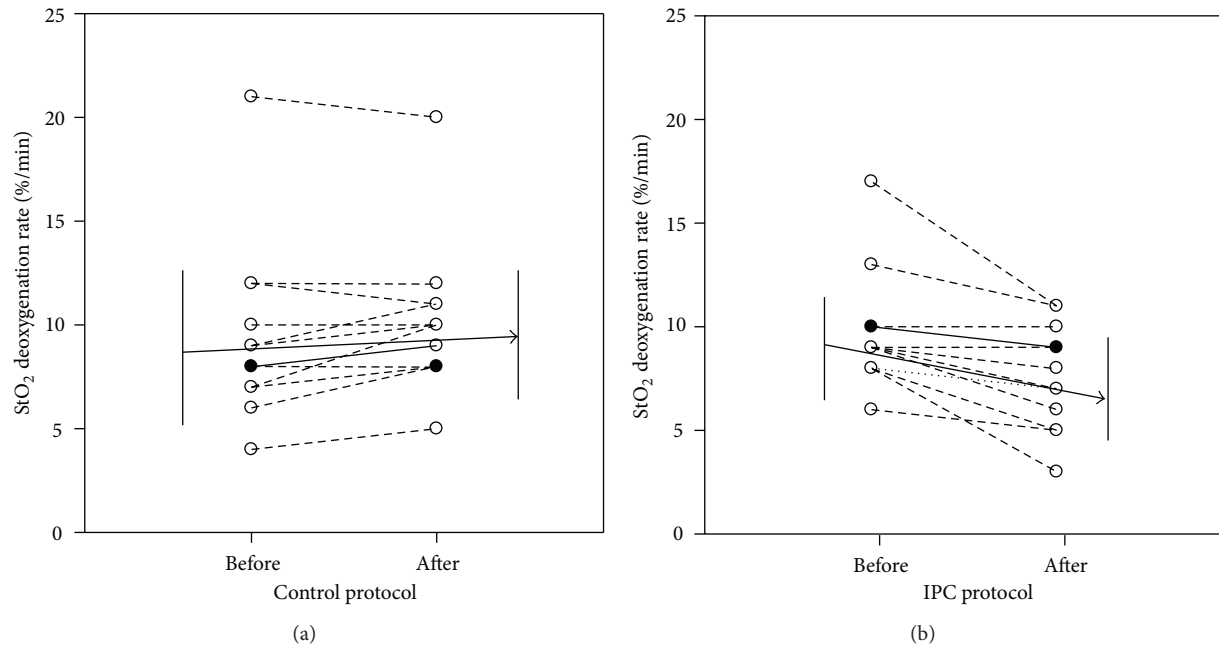


FIGURE 3: Individual data of skeletal muscle StO_2 deoxygenation of the study population in the ischemic preconditioning (IPC) and the control protocol. Compared to baseline, StO_2 deoxygenation rate was significantly lower after the IPC protocol ($9.7 \pm 2.6\%/min$ versus $7.5 \pm 2.5\%/min$, $P = 0.002$). StO_2 deoxygenation rates in the control protocol were found to be similar compared to baseline ($10.0 \pm 3.4\%/min$ versus $9.5 \pm 4.0\%/min$, $P = 0.4$). Comparison of StO_2 deoxygenation rates showed a statistically significant difference between the IPC and the control protocol ($F = 5.512$, $P = 0.003$). In the figure, there are less lines than the actual number of the study participants ($n = 14$) because three pairs of data in the control and two pairs of data in the IPC protocol were the same (black points).

TABLE 2: Flow-mediated dilatation—ultrasound data.

Variable	IPC protocol ($n = 14$)			Control ($n = 14$)			Statistics between treatments
	Before	After	Statistics	Before	After	Statistics	
Brachial artery diameter (mm)	4.3 ± 4	4.2 ± 3	ns	4.1 ± 2	4.2 ± 3	ns	0.226
Basal flow (mL/min)	157 ± 81	175 ± 51	ns	169 ± 62	163 ± 57	ns	0.788
Flow after VOT (mL/min)	902 ± 384	937 ± 373	ns	930 ± 326	900 ± 233	ns	0.929
FMD (%)	9.4 ± 3.8	9.5 ± 3.8	ns	9.9 ± 3.4	9.9 ± 3.4	ns	0.941

IPC protocol before: ultrasound data in the ischemic preconditioning protocol at baseline; IPC protocol after: ultrasound data in the ischemic preconditioning protocol at the end of the protocol; control before: ultrasound data in the control protocol at baseline; control after: ultrasound data in the control protocol at the end of the protocol; VOT: vascular occlusion test; FMD: flow-mediated dilatation; and ns: nonsignificant.

no changes in FMD; therefore we could not identify the modulation of oxygen delivery. According to our data, we can conclude that IPC induces tissue metabolic changes instead of changes of blood flow. However, 5 minutes of ischemic time that we used were relatively short in comparison to other studies where 20 minutes of ischemia were applied [8]. This might be the reason why we could not demonstrate any differences in FMD in our experiments, not even reduced FMD after VOT, which was possibly too short in duration to cause measurable effects. Our conclusions are similar to the findings of Kilian et al. [37], who otherwise confirmed a significantly reduced FMD after 10 minutes of ischemia but failed to reproduce its prevention by remote IPC using shorter IPC stimuli and shorter time delay between stimuli and ischemic event.

Major limitation of our study is that the NIRS device that was used does not provide absolute concentrations of

oxyhemoglobin, deoxyhemoglobin, and total hemoglobin; so we were not able to calculate oxygen consumption as proposed in previous studies either by arterial or venous occlusions [38–40]. Venous occlusion is preferable to arterial occlusion because the procedure is less inconvenient for the subjects and can be repeated at short time intervals. However, venous occlusion is more prone to variations in flow within the arm due to the changes in blood pressure and local vasoreactivity, whereas these influences are negligible during arterial occlusion that characterizes closed compartment, temporary cut-off from centrally mediated variations. It seems that arterial occlusion method has higher reproducibility as compared to venous occlusion [39]. Calculations of the skeletal muscle oxygen consumption are prone to errors due to changes in the optical properties of the tissue and can be expressed in milliliters of oxygen per minute per 100 grams only after assuming tissue density. Absolute values of

the skeletal muscle oxygen consumption are clinically not important; that is why we decided to monitor only tissue desaturation (deoxygenation rate), which is a surrogate of oxygen consumption.

5. Conclusions

Our findings confirm that remote ischemic cycles provide adaptation of skeletal muscle in terms of decrease oxygen consumption when exposed to ischemia that was demonstrated by NIRS technology. In spite of its recognized powerful effect, the precise mechanism of this phenomenon is still unknown. There are several factors influencing the extent of IPC effects. The length and magnitude of the ischemic event as well as the intensity of remote ischemic stimuli seem to play a role. It has been recognized that aging and other cardiovascular risk factors, such as diabetes, smoking, hyperlipidemia, hypertension, and obesity, are associated with lower protective effect of IPC, but the threshold for protection is unclear [41]. Skeletal muscle NIRS during vascular occlusion test can be applied to quantitatively determine the effectiveness of IPC. In accordance with our findings, we could propose NIRS to test various preconditioning protocols with ischemic or even pharmacological stimuli in a different population of patients who might benefit from preconditioning therapeutic strategy with the aim to find individual threshold for protection. Further studies would be necessary to confirm these assumptions.

Acknowledgment

This work was supported by Research Program P3-0043, Slovenian Research Agency. The authors thank all subjects, doctors, nurses, and technical support staff for their assistance in this study. They declare no conflict of interests.

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