

# ISCHEMIC PRECONDITIONING BLUNTS ECCENTRIC EXERCISE-INDUCED MUSCLE DAMAGE DUE TO REDUCED OXIDATIVE STRESS?

*Jan-Frieder Harmsen<sup>1</sup>, Alexander Franz<sup>1</sup>, Constantin Mayer<sup>2</sup>, Michael Behringer<sup>3</sup>, Bjoern Braunstein<sup>4,5,6</sup>, Robert Rein<sup>7</sup> & Christoph Zilkens<sup>1</sup>*

Department of Orthopedics, University Hospital Duesseldorf,  
Duesseldorf, Germany<sup>1</sup>

Department of Orthopedics, University Hospital Essen, Essen,  
Germany<sup>2</sup>

Faculty of Sport Sciences, Goethe University Frankfurt, Frankfurt,  
Germany<sup>3</sup>

Institute of Biomechanics and Orthopaedics, German Sport  
University, Cologne, Germany<sup>4</sup>

German Research Centre for Elite Sport, German Sport University, Cologne,  
Germany<sup>5</sup>

Centre for Health and Integrative Physiology in Space, Cologne, Germany<sup>6</sup>

Institute of Training Sciences and Sport Informatics,  
German Sport University, Cologne, Germany<sup>7</sup>

The purpose of this study was to investigate if ischemic preconditioning (IPC) prior to eccentric exercise of the elbow flexors leads to alterations in muscle oxygen saturation ( $SmO_2$ ) during loading. Additionally, parameters of muscle damage, like serum creatine kinase, were assessed following the loading protocol. Nineteen untrained males were allocated into two groups: (1) performing IPC prior to eccentric exercise (IPC+ECC;  $n=10$ ) and (2) performing eccentric exercise only ( $n=9$ ). Muscle damage parameters were significantly lower in IPC+ECC ( $p<0.05$ ). The drop of  $SmO_2$  during eccentric loading (ischemia) as well as the subsequent increase of  $SmO_2$  (reperfusion) were lower in IPC+ECC ( $p<0.05$ ). These findings indicate that reduced oxidative stress might have contributed to the blunted muscle damage response seen after IPC.

**KEYWORDS:** ischemia, reperfusion, regeneration, elbow flexors, muscle damage.

**INTRODUCTION:** Ischemic preconditioning (IPC) is a technique to improve resistance against ischemia of tissues like the heart, brain, liver etc. (Le Page & Prunier 2015). In clinical practice, IPC has been shown to reduce the formation of muscle damage induced by prolonged ischemic disposition with subsequent reperfusion during orthopedic surgery (Van M et al. 2008). This is supposedly due to a reduced formation of metabolic stress (Van M et al. 2008) and proinflammatory responses (Sullivan et al. 2009). However, the exact mechanism for this protection is unclear.

Franz et al. (2017) recently showed that IPC can even protect the skeletal muscle from eccentric exercise-induced muscle damage. In their study, the IPC treated participants demonstrated a faster recovery of the contractile properties of the exercised muscle, assessed by tensiomyography (TMG). Additionally, pain sensation and serum creatine kinase (CK) was reduced. Muscle oxygen saturation ( $SmO_2$ ) of the elbow flexor, indirectly reflecting oxidative stress, was also assessed. Oxidative stress is one factor leading to muscle damage (Schoenfeld 2013). Therefore, we analyzed the  $SmO_2$  data to detect possible relationships between oxidative stress and the reduced muscle damage seen after IPC.

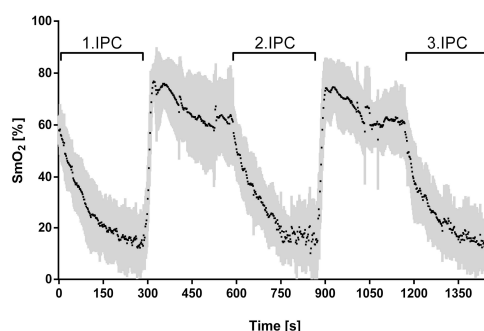
**METHODS:** Nineteen participants (Mean $\pm$ SD age: 25 $\pm$ 4 years, height: 183 $\pm$ 6 cm, body mass: 81 $\pm$ 7 kg) volunteered in a cross-sectional parallel study design. During the first visit, participants' individual concentric one repetition maximum (1RM) of the elbow flexors was determined using a barbell. Participants were equally matched to the IPC intervention group (IPC+ECC) or the eccentric-only control group (ECC) based on the measures of CK activity

after the 1RM test. After two weeks participants performed an eccentric loading protocol consisting of 3 sets of 10 repetitions with 60 s rest in-between sets, using 80% of their 1RM. Only in IPC+ECC, the eccentric strength protocol was preceded by IPC consisting of 3 x 5 min of occlusion interspersed by 5 min of reperfusion (Figure 1). IPC was induced by a blood pressure cuff, which was applied proximally to the both upper arms to occlude the brachial artery entirely with a pressure of 200 mmHg. During IPC and eccentric exercise, SmO<sub>2</sub> was assessed via near-infrared spectroscopy (NIRS; Moxy Monitor, Fortiori Design LLC, Hutchinson, MN, USA) which was placed on the muscle belly of the biceps brachii. The device measured with a sampling frequency of 0.5 Hz. In addition to SmO<sub>2</sub>, pain on the visual analog scale, Dm by tensiomyography, and CK were assessed as indicators of muscle damage. A one-way repeated measures ANOVA was used to assess significant effects over time within SmO<sub>2</sub> data of the 3 x 5 min IPC period. To test whether SmO<sub>2</sub> increases in the reperfusion period compared to baseline, each reperfusion period was divided into 10 x 30 s intervals calculating the mean SmO<sub>2</sub> of each interval. A two-way repeated-measures ANOVA was used to assess significant main effects (group, time) and interaction within SmO<sub>2</sub> data between the IPC+ECC and ECC group. Assessment for normality of data was carried out by using the Kolmogorov–Smirnov test. Because normal distribution was rejected in CK and pain data, the Spearman’s rank correlation coefficients were calculated to determine the relationship between SmO<sub>2</sub> data and muscle damage parameters (CK, pain, Dm). More specifically, we correlated the mean individual SmO<sub>2</sub> drop during the eccentric loading as well as the mean subsequent increase with the relative maximal individual increase of CK, pain and the relative maximal individual drop of Dm. Statistical significance was set at  $p < 0.05$  and means with respective standard deviations (SD) are used to present data in the running text. All statistical analyses were performed using the Graphpad Prism 6 software package (Graphpad Software, San Diego, CA).

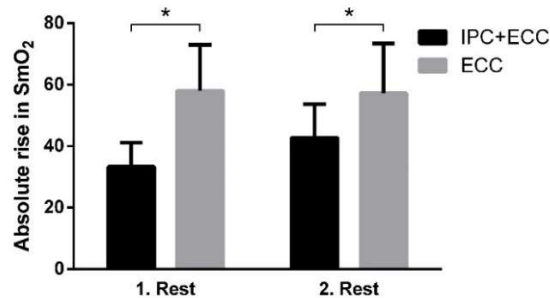
**RESULTS:** In terms of muscle damage, IPC+ECC showed a significant increase of CK only after 72h ( $996.1 \pm 1243.6 \text{ U} \cdot \text{L}^{-1}$  compared to  $216.6 \pm 125.8 \text{ U} \cdot \text{L}^{-1}$  at baseline;  $p = 0.03$ ), whereas the ECC group showed a significant higher increase after 24h, 48h and highest values after 72h ( $24,316.0 \pm 18,752.4$ ;  $p < 0.01$ ). Maximal pain sensation was highest after 24h and was significantly higher in the ECC group ( $39 \pm 15 \text{ mm}$  vs.  $8 \pm 4 \text{ mm}$ ;  $p < 0.001$ ) (Franz et al. 2017). The course of SmO<sub>2</sub> over time during 3 x 5 min IPC can be seen in Figure 1. During the IPC period, a significant SmO<sub>2</sub> increase compared to baseline ( $62.2 \pm 5.1\%$ ) was found in the first 30 s after the first 5 min occlusion period ( $76.6 \pm 7.0\%$ ;  $p < 0.001$ ) and after 30-60 s ( $74.9 \pm 9.6\%$ ;  $p = 0.03$ ).

The SmO<sub>2</sub> drop during eccentric loading had a higher absolute drop in the ECC group than in IPC+ECC within the first ( $53.7 \pm 14.7$  vs.  $32.1 \pm 12.9$ ,  $p = 0.01$ ) and the second set ( $52.6 \pm 18.0$  vs.  $32.9 \pm 8.0$ ,  $p = 0.02$ ). Also, a higher absolute increase after the first ( $58.0 \pm 15.0$  vs.  $33.3 \pm 7.9$ ,  $p < 0.001$ ) and the second set ( $57.2 \pm 16.2$  vs.  $42.8 \pm 10.8$ ,  $p = 0.04$ ) was apparent in the ECC group compared to IPC+ECC (Figure 2).

The mean SmO<sub>2</sub> drop during eccentric loading showed significant correlations to the relative maximal rise of CK ( $r = -0.58$ ), pain ( $r = -0.47$ ) and the relative maximal drop in Dm ( $r = 0.54$ ;  $p < 0.05$ ). The mean SmO<sub>2</sub> increase showed significant correlations to CK ( $r = 0.65$ ), pain ( $r = 0.60$ ), and Dm ( $r = -0.68$ ;  $p < 0.01$ ).



**Figure 1: SmO<sub>2</sub> during IPC (n=10). Black dots represent group averages ( $\pm$ SD, gray shading).**



**Figure 2: The absolute rise of SmO<sub>2</sub> after eccentric contractions within 60 s rest in-between sets. Values are means  $\pm$  SDs. \*significantly different from IPC+ECC ( $p < 0.05$ )**

**DISCUSSION:** We were able to show that IPC reduced the oxidative stress during the following eccentric loading. This reduction might have led to the blunted muscle damage response found within the following three days of post-assessments. Interestingly, significant correlations between the indicators of muscle damage (CK, pain and Dm) and SmO<sub>2</sub> data were shown. In fact, the mean rise of SmO<sub>2</sub> associated with reperfusion showed higher correlations than the mean drop of SmO<sub>2</sub> associated with ischemia. We suspect that especially the higher degree of reperfusion in the ECC group induced the greater muscle damage response. By contrast, the IPC+ECC group already experienced high degrees of reperfusion without mechanical stress during IPC, potentially inducing some kind of short-term repeated-bout effect.

Another strategy that has been shown to induce very similar fluctuations in SmO<sub>2</sub> due to prolonged ischemia and subsequent reperfusion is continuous stretching (Trajano et al. 2014). Behm and colleagues (2016) concluded in a recent review that stretching prior to exercise is ineffective in reducing soreness or other symptoms of muscle damage. To our knowledge, only one study found lowered muscle damage markers with repeated static stretching performed before eccentric exercise (Chen et al. 2015). Therefore, future studies need to clarify if stretching is also suitable as a preconditioning technique blunting muscle damage occurring after subsequent exhaustive exercise. However, the potential preconditioning effect of stretching likely diminishes due to the simultaneous mechanical elongation stress acting on the muscle. Either way, as stretching is known to impair performance outcomes (Behm et al. 2016), this effect might be neglectable or rather irrelevant in a practical sports setting.

Many studies have investigated the effects of IPC on exercise performance. Generally, studies assumed that IPC may have positive effects on sprint, anaerobic performance (de Groot et al. 2010), endurance and physiological responses such as blood lactate levels (Bailey et al. 2012) in different populations. Other studies did not find beneficial effects on performance outcomes (Gibson et al. 2015, Lalonde & Curnier, 2015) and Marocolo and colleagues (2015) go as far as to suggest that improvements in performance could possibly represent a placebo effect. Based on our study, conclusions regarding performance enhancement cannot be drawn, as we focused on the potential benefit of IPC in terms of muscle recovery after resistance exercise. To the best of our knowledge, this is the first study investigating the protective effect of IPC prior to eccentric loading. In this context, it has to be emphasized that this study only deals with acute effects of IPC, whereas chronic effects of applying IPC frequently remain unknown. As i.a. Schoenfeld (2013) supposes muscle damage to be an essential anabolic signal for adaptations leading to muscle hypertrophy and increases in strength, we would expect IPC to blunt also long-term adaptations. But this needs to be studied in the future.

**CONCLUSION:** As IPC seems to enhance recovery after exhaustive exercise, it might be an interesting tool in sports that have a short time for regeneration in periods of high competition density (e.g. tournaments). However, before integrating IPC into practice in order to increase stress tolerance, further trials need to be conducted proving the protective effect in larger and wider samples. In the end, especially muscles of the lower extremities and trained individuals have to be investigated to justify the relevance of the IPC technique for most team sports.

## REFERENCES

- Bailey, T.G., Jones, H., Gregson, W., Atkinson, G., Cable, N.T., & Thijssen, D.H.J. (2012). Effect of ischemic preconditioning on lactate accumulation and running performance. *Medicine and Science in Sports and Exercise*, 44(11), 2084–2089.
- Behm, D.G., Blazevich, A.J., Kay, A.D., & McHugh, M. (2016). Acute effects of muscle stretching on physical performance, range of motion, and injury incidence in healthy active individuals: A systematic review. *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme*, 41(1), 1–11.
- Chen, C.-H., Chen, T.C., Jan, M.-H., & Lin, J.-J. (2015). Acute effects of static active or dynamic active stretching on eccentric-exercise-induced hamstring muscle damage. *International Journal of Sports Physiology and Performance*, 10(3), 346–352.
- Franz, A., Behringer, M., Harmsen, J.-F., Mayer, C., Krauspe, R., Zilkens, C., & Schumann, M. (2018). Ischemic Preconditioning Blunts Muscle Damage Responses Induced by Eccentric Exercise. *Medicine and Science in Sports and Exercise*, 50(1), 109–115.
- Gibson, N., Mahony, B., Tracey, C., Fawkner, S., & Murray, A. (2015). Effect of ischemic preconditioning on repeated sprint ability in team sport athletes. *Journal of Sports Sciences*, 33(11), 1182–1188.
- Groot, P.C.E. de, Thijssen, D.H.J., Sanchez, M., Ellenkamp, R., & Hopman, M.T.E. (2010). Ischemic preconditioning improves maximal performance in humans. *European Journal of Applied Physiology*, 108(1), 141–146.
- Lalonde, F., & Curnier, D.Y. (2015). Can anaerobic performance be improved by remote ischemic preconditioning? *Journal of Strength and Conditioning Research*, 29(1), 80–85.
- Le Page, S., & Prunier, F. (2015). Remote ischemic conditioning: Current clinical perspectives. *Journal of Cardiology*, 66(2), 91–96.
- Marocolo, M., da Mota, G.R., Pelegrini, V., & Appell Coriolano, H.J. (2015). Are the Beneficial Effects of Ischemic Preconditioning on Performance Partly a Placebo Effect? *International Journal of Sports Medicine*, 36(10), 822–825.
- Schoenfeld, B.J. (2013). Potential mechanisms for a role of metabolic stress in hypertrophic adaptations to resistance training. *Sports Medicine (Auckland, N.Z.)*, 43(3), 179–194.
- Sullivan, P.J., Sweeney, K.J., Hirpara, K.M., Malone, C.B., Curtin, W., & Kerin, M.J. (2009). Cyclical ischaemic preconditioning modulates the adaptive immune response in human limb ischaemia-reperfusion injury. *The British Journal of Surgery*, 96(4), 381–390.
- Trajano, G.S., Nosaka, K., B Seitz, L., & Blazevich, A.J. (2014). Intermittent stretch reduces force and central drive more than continuous stretch. *Medicine and Science in Sports and Exercise*, 46(5), 902–910.
- Van, M., Olguner, C., Koca, U., Sişman, A.R., Muratli, K., Karci, A., . . . Kilercik, H. (2008). Ischaemic preconditioning attenuates haemodynamic response and lipid peroxidation in lower-extremity surgery with unilateral pneumatic tourniquet application: A clinical pilot study. *Advances in Therapy*, 25(4), 355–366.