Ischemic preconditioning: Potential impact on exercise performance and underlying mechanisms

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Abstract Originally, in clinical settings, ischemic preconditioning (IPC) has been used to delay cardiac cell injury and protect against myocardial and vascular damage. Furthermore, as this manipulation is relatively easy and noninvasive, previous studies have examined how IPC may have beneficial effects on exercise performance. However, because of various factors, such as different populations, exercise modes and intensities, and IPC protocols, not enough evidence is available to achieve a consensus on the impact of IPC on exercise performance, e.g., time to failure during exercise, time trial performance, and peak power. Existing evidence suggests that IPC seems not to impair exercise performance, though one study found an impairment. However, about half of the previous studies showed beneficial effects of IPC on exercise performance. Similarly, the physiological responses from IPC are varied. It is still possible that various factors, such as exercise mode and intensity, heterogeneous population and IPC protocol may affect exercise performance. Previous studies showed that effective blood flow via an increase in nitric oxide and the improvement of metabolic efficiency might be candidate factors that can explain the effect of IPC on exercise performance, although no direct evidence has been obtained. This review aims to identify potential sources of variation in these effects on exercise performance with IPC.

Keywords: blood flow, metabolic efficiency, training status, whole-body exercise, local muscle contraction

Introduction

Ischemic preconditioning (IPC) relates to repeated periods of ischemia followed by reperfusion, which has been originally described to delay cardiac cell injury and protect against myocardial and vascular damage. Generally, the IPC protocol involves three or four cycles of 5 min circulatory occlusion above systolic blood pressure, followed by a 5 min reperfusion period. As this method is relatively easy to conduct and noninvasive, IPC may have various advantages in athletic and clinical settings. Regarding clinical relevance, the effects of repeated tissue exposure to ischemic preconditioning on cardiovascular function and potential mechanisms have been extensively reviewed. However, the mechanisms on how IPC may influence exercise performance are largely unknown; either vascular function or metabolic efficiency may relate to exercise performance in response to IPC. A common understanding on whether IPC may improve exercise performance is lacking.

In this review, we summarize studies that have investigated the impact of IPC on exercise performance and physiological responses. We also describe the potential physiological mechanisms that contribute to exercise performance in response to IPC.

Exercise performance in response to IPC

Recently, many studies have investigated the effects of IPC on exercise performance (mainly whole-body exercise). Table 1 shows a summary of studies that investigated the effects of IPC on exercise performance. Obtaining consensus has been difficult because of the large number of variables involved, such as age, gender, training status, intensity and exercise modality, and IPC protocol, including the number of ischemia/reperfusion injury cycles, applied sites, and time to pre-exercise after IPC (early or late), all of which may influence IPC effects. In the following section, we discuss the influence of IPC on exercise performance with regard to classification of exercise mode on the basis of current findings.

Sprint (cycle) performance. Recent research demonstrated that IPC increases the maximal power output during 6 s cycle sprint, whereas two studies did not show any beneficial effects during 6 s cycle sprint and/or the Wing-
ate test\textsuperscript{5-6,8}. Similarly, IPC did not improve 30 m\textsuperscript{3} and 40 m sprint time\textsuperscript{3,9}. Interestingly, one study revealed that IPC decreased the peak power output and the total anaerobic power during the Wingate test\textsuperscript{8}.

**Maximal incremental or constant load cycling performance.** Findings on the impact of IPC on maximal incremental or constant load cycling performance have been equivocal. IPC prolonged the time to failure during maximal incremental leg cycling\textsuperscript{10,13} and constant load leg cycling\textsuperscript{11,12}. Similarly, IPC improved peak power output during maximal incremental leg cycling\textsuperscript{5,10,13}. By contrast, other studies reported no effect of IPC on exhaustion time during maximal incremental leg cycling\textsuperscript{14}, constant load leg cycling at an intensity of 130\% of the peak power output\textsuperscript{10}, the time needed to cycle 100 kJ of total work\textsuperscript{15}. Additionally, IPC did not show any beneficial effects on increasing the maximal power output during maximal incremental leg cycling\textsuperscript{16}.

**Swim and water sport performance.** Some studies have investigated the effect of IPC on swimming or water sport performance. Marocolo et al. (2015) reported that IPC improved the 100 m swimming sprint time compared to the control condition (without cuff inflation), but no difference was observed between IPC (applied pressure: \textasciitilde{}220 mmHg) and SHAM (lower applied pressure: \textasciitilde{}20 mmHg), suggesting that the improvement in sprint time with IPC was merely a placebo effect\textsuperscript{17}. On the other hand, a recent study demonstrated that IPC improved 50 m swim sprint performance without the placebo effect\textsuperscript{18}. IPC also improved the 100 m swim sprint time\textsuperscript{19} and prolonged the underwater swimming distance, 1-km rowing time, and static breath hold time\textsuperscript{20}.

**Long distance running performance.** Bailey et al. (2012a) found that IPC improved 5 km treadmill running time\textsuperscript{21}. Meanwhile, Tocco et al. (2015) reported that 5000 m self-paced running test results on an outdoor track were not improved\textsuperscript{22}.

**Resistance exercise performance.** In addition to whole body exercise such as cycling, swimming and running, only a comparatively few studies examined the effect of IPC on the performance of local resistance exercise. For example, IPC prolonged the time to failure during rhythmic handgrip at an intensity of 45\% of maximal voluntary contraction (MVC)\textsuperscript{23}. Marocolo et al. (2016a) also reported that IPC and SHAM conditions resulted in significantly greater repetitions versus the control condition on the first and second sets, but not on the third set during leg extension at a 12 RM load\textsuperscript{24}. Furthermore, the authors reported that the number of repetitions during elbow flexion exercise significantly increased in the early sets, but they tended to decrease over four trials\textsuperscript{25}. These two studies suggest that IPC has minor beneficial effects, but these apparently fade over time and may possibly have a placebo effect because, compared with control (CON), the SHAM condition also improved repetitions along with IPC\textsuperscript{24,25}. Beaven et al. (2012) compared the early (immediate) and late (24 h later) effects of IPC on power production, and they found that IPC showed beneficial effects in both periods\textsuperscript{8}. In addition, a recent study investigated the effects of IPC on static leg extension exercise and found that the endurance time to task failure was significantly longer in IPC than in CON\textsuperscript{26}. Compared to its performance in whole-body exercise, it is possible that IPC may be more effective in improving exercise performance during local muscle contraction.

**Physiological responses at maximal work load**

Whether IPC may improve cardiorespiratory variables at a higher exercise intensity, e.g., failure to maintain exercise, remains to be established. In fact, the maximal or peak oxygen uptake (VO\textsubscript{max} or VO\textsubscript{peak}) was not improved with IPC during maximal incremental exercise and during constant-load leg cycling at a work load of 130\% peak power\textsuperscript{10} or at 70\% of the difference between the VO\textsubscript{2} at the gas exchange threshold and VO\textsubscript{2peak}\textsuperscript{12}. Likewise, the heart rate peak (HR\textsubscript{peak}) was not increased with IPC during maximal incremental leg cycling\textsuperscript{13,14}, during constant load leg cycling until exhaustion\textsuperscript{11,12}, maximal HR during a 5 km running time trial\textsuperscript{13}, and 100 m swimming\textsuperscript{21}. Additionally, maximum pulmonary ventilation (V\textsubscript{Emax}) during maximal incremental leg cycling\textsuperscript{13,14} was not affected by IPC.

By contrast, some studies showed the beneficial effects of IPC on VO\textsubscript{2peak} during maximal incremental leg cycling\textsuperscript{13,14} or constant load leg cycling until exhaustion at an exercise intensity of 100\% VO\textsubscript{2peak}\textsuperscript{11}. IPC also resulted in increases in HR\textsubscript{max} and V\textsubscript{Emax} during maximal incremental leg cycling\textsuperscript{13,14}. Because the peak values of blood lactate concentration (LA\textsubscript{peak}) after exercise may be an indicator of anaerobic capacity, several studies compared the LA\textsubscript{peak} between IPC and the control (or SHAM), and no effect in LA\textsubscript{peak} after exercise with IPC was found\textsuperscript{4,9-14,18,19,22}. Two studies focused on muscle activity, assessed by electromyography (EMG), between IPC and CON, and no differences in EMG were found during cycle sprints\textsuperscript{4} or isometric leg extension\textsuperscript{26}.

**Physiological responses at submaximal work load**

Unlike the situation of exhaustion during exercise, i.e., at a submaximal work rate during exercise, lower physiological variables, such as a lower VO\textsubscript{2}, HR, and LA, may indicate a more effective energy turnover to optimize exercise performance. IPC had no beneficial effects on the mean VO\textsubscript{2}, V\textsubscript{E}, and HR during a 5 km running time trial\textsuperscript{23}, the submaximal VO\textsubscript{2} during maximal incremental leg cycling\textsuperscript{13,14}, or during leg cycling at an exercise...
intensity of 90% VO2peak at the gas exchange threshold. However, IPC decreased LA at the submaximal running speed compared to SHAM. A recent study also demonstrated that muscle deoxygenation (HHb) profiles, which are indicators of arterial-venous O2 differences, increased at the onset of exercise during moderate-intensity exercise. Altogether, the IPC protocol involves three or four cycles of 5 min circulatory occlusion above systolic blood pressure, followed by a 5 min reperfusion period. Indeed, applied pressure, cuff width, and IPC parts, may have affected exercise performance. As these confounding factors could not be ruled out, future studies that describe the optimal protocols for the implementation of IPC prior to exercise are therefore warranted.

Effect of repeated IPC on exercise performance. As shown in Table 1, all studies examined the acute effects of IPC on exercise performance; therefore, little is known of the possible effects of repeated IPC. To the best of our knowledge, only one study investigated the effects of a regular routine of IPC on vasculature and fitness level for a period of eight weeks. As this recent study mainly focused on the effects of repeated IPC on vascular function, detailed outcomes with regard to exercise performance were not evaluated; the study failed to observe improvement in aerobic fitness level. Since this study is insufficient evidence of repeated IPC effects on exercise performance, future studies are needed.

Population differences

When we take into account the effects of IPC on exercise performance, we should consider population differences, as well. Previous studies used various populations, such as healthy volunteers and trained subjects (Table 1). Although an accurate classification is difficult because the detailed information of subjects is often not available, we attempted to classify subjects into 3 groups: healthy (including recreationally active) subjects, trained athletes, and elite athletes. This classification showed that the studies did not reach a consensus on the effects of IPC on exercise performance across different populations, i.e., different training levels. Six of eight studies on healthy (recreationally active) subjects showed an improvement in exercise performance (75%), whereas only four of 13 studies of trained athletes showed positive effects with IPC (31%). We identified only two studies of elite athletes that resulted in an improvement in exercise performance (100%). In general, highly trained athletes have higher baseline values, e.g., higher aerobic capacity. This observation may suggest that the higher the exercise capacity, the more difficult it is to improve exercise performance; however, the literature did not necessarily support this. In addition to different training levels, we should acknowledge individual differences, as well, such as responders versus non-responders, suggesting that additional evidence is needed.

Some studies examined the effects of IPC on the exercise performance of patients with coronary and peripheral arterial disease, and no improvements in exercise performance were found. However, these previous studies showed a significant improvement in clinically relevant markers. Notably, these studies used remote IPC, not IPC on the primary engaged limbs. In many clinical
| Author (year)          | Groups       | Age | Sex | IPC cycle (pressure) | IPC parts | Exercise mode                     | Findings                                      | Effect  |
|-----------------------|--------------|-----|-----|----------------------|-----------|-----------------------------------|----------------------------------------------|---------|
| Gibson et al. (2013)  | Trained      | 23  | 16M, 9F | 3 × 5 min (220mmHg) | Leg       | 3 × 30 m sprint                   | Sprint time                                  |         |
| Paixão et al. (2014) | Trained      | 30  | 15M | 4 × 5 min (250mmHg)  | Leg       | Wingate test                      | Peak power, Anaerobic power                  |         |
| Gibson et al. (2015)  | Trained      | 24  | 7M, 9F | 3 × 5 min (220mmHg) | Leg       | 5 × 6 s cycle sprints              | Peak power, Total work                       |         |
| Lalonde and Curnier (2015) | Healthy      | 29  | 8M, 9F | 4 × 5 min (>50mmHg SBP) | Arm       | 6 × 6 s cycle sprint, Wingate test | Peak and mean power                           |         |
| Patterson et al. (2015) | Trained      | 30  | 14M | 4 × 5 min (220mmHg)  | Leg       | 12 × 6 s cycle sprint             | Peak power                                   |         |
| De Groot et al. (2010) | Trained      | 27  | 12M, 3F | 3 × 5 min (220mmHg) | Leg       | Incremental cycling               | VO2max, HRpeak, LApeak, submax VO2           | +       |
| Crisafulli et al. (2011) | Active      | 35  | 17M | 3 × 5 min (>50mmHg SBP) | Leg       | Incremental cycling               | Time to failure, Peak power, Vpeak, HRmax, VO2max | +       |
| Foster et al. (2011)  | Trained      | 39  | 6M, 2F | 4 × 5 min (>20mmHg SBP) | Leg       | Cycle sprint up to 100kJ          | Time to failure, Vpeak, VO2peak, LApeak     | ~       |
| Clevidence et al. (2012) | Trained      | 27  | 12M | 3 × 5 min (220mmHg)  | Leg       | Incremental cycling               | Time to failure, Vpeak, LApeak, submax VO2   | ~       |
| Hüttinger et al. (2015) | Trained      | 30  | 15M | 4 × 5 min (>15 mmHg SBP) | Leg       | Incremental cycling               | Time to failure, VO2peak                      | +       |
| Cruz et al. (2015)    | Trained      | 20-36 | 12M | 4 × 5 min (220mmHg)  | Leg       | Cycling at 100 % Wpeak            | Time to failure, Wpeak, HRpeak, LApeak      | ~       |
| Kido et al. (2015)    | Healthy      | 24  | 15M | 3 × 5 min (>300mmHg) | Leg       | Moderate and severe cycling       | Time to failure, HHb (speeding up)            | +       |
| Kjeld et al. (2014)   | Elite        | 23  | 10M, 4F | 4 × 5 min (>40 mmHg SBP) | Arm       | 1 km rowing, Static breath hold   | VO2peak, LApeak, HRpeak, submax VO2         | ~       |
| Marocolo et al. (2015) | Trained      | 21  | 15M | 4 × 5 min (220mmHg)  | Arm       | 100 m swim                       | Rowing time, Breath hold time                 | +       |
| Author (year)            | Groups   | Age | Sex | IPC cycle (pressure) | IPC parts | Exercise mode       | Findings               | Effect |
|-------------------------|----------|-----|-----|----------------------|-----------|---------------------|------------------------|--------|
| Ferreira et al. (2016)  | Trained  | 30  | M, F| 3×5 min (220mmHg)    | Leg       | 6×50 m swim         | Swim time              | +      |
|                         |          |     |     |                      |           |                     | LA                     | ~      |
| Bailey et al. (2012a)   | Healthy  | 25  | M   | 4×5 min (220mmHg)    | Leg       | 5 km treadmill running | Running time            | +      |
|                         |          |     |     |                      |           |                     | HR<sub>peak</sub>      | ~      |
|                         |          |     |     |                      |           | Incremental treadmill running | LA (at submax)         | +      |
|                         |          |     |     |                      |           |                     | VO<sub>2</sub>, VE, HR | ~      |
| Tocco et al. (2015)     | Trained  | 35  | M   | 4×5 min (>50mmHg SBP)| Leg       | 5 km running         | Running time, LA<sub>peak</sub>, VO<sub>2</sub>, VE, HR (mean), | ~      |
| Beaven et al. (2012)    | Healthy  | 32  | M, F| 2×3 min (220mmHg)    | Leg       | Squat jump, Leg press, 40 m sprint | Jump, Maximal strength, Sprint time | +      |
| Barbosa et al. (2015)   | Active   | 25  | M   | 3×5 min (200mmHg)    | Leg       | Rhythmic hand grip at 45 % MVC | Time to failure         | +      |
|                         |          |     |     |                      |           |                     | Blood flow, EMG, HHb   | ~      |
| Marocolo et al. (2016a) | Trained  | 26  | M   | 4×5 min (220mmHg)    | Leg       | Leg extension (12RM load) | Repetitions, LA        | ~      |
| Marocolo et al. (2016b) | Active   | 27  | M   | 4×5 min (220mmHg)    | Arm, Leg  | Elbow flexion (12RM load) | Repetitions            | ~      |
| Tanaka et al. (2016)    | Healthy  | 22  | M   | 3×5 min (>300mmHg)   | Leg       | Isometric leg extension | Time to failure, HHb (time delay) | +      |
|                         |          |     |     |                      |           |                     | EMG                    | ~      |

IPC: ischemic preconditioning, M: males, F: females, SBP: systolic blood pressure, W: work, RM: repetition maximum, MVC: maximal voluntary contraction, VO<sub>2</sub>: oxygen uptake, VE: pulmonary ventilation, HR: heart rate, LA: blood lactate concentration, HHb: muscle deoxygenation, EMG: electromyography.

+ indicates positive effects, − indicates negative effects, and ~ indicates no effects. If IPC improved exercise performance compared with the control, with no differences between the IPC and SHAM conditions, we identified this as no improvement in exercise performance, i.e., ‘~’ mark was checked.
studies, regular, repeated remote IPC has shown positive effects on vascular\textsuperscript{29,34-37}, cardiac\textsuperscript{38-40}, and brain functions\textsuperscript{41,42}. Together, IPC did not improve exercise performance in these populations; however, it appears that remote IPC may have positive effects in clinical outcomes.

**Potential factors**

Although not enough evidence is available to explain the underlying mechanisms of IPC on exercise performance, secondary improvements in vascular function and/or metabolic efficiency may explain the impact of IPC on exercise performance. The underlying principle of this unorthodox technique is that the occlusive cuff pressure is higher than the systolic blood pressure; in this condition, ischemic reperfusion induced by cuff deflation simulates shear stress, followed by greater vasodilation and/or enhanced blood flow\textsuperscript{43,44}. Indeed, as maximal dilation is observed after ischemic exercise\textsuperscript{45}, IPC (repeated ischemia/reperfusion condition) might possibly have beneficial effects on vasculature, resulting in an improvement in exercise performance. For example, Kimura et al. (2007) was the first to examine the effects of repeated IPC on arterial endothelial function, and they found that arterial endothelial function was enhanced via increases in nitric oxide\textsuperscript{46}. Similarly, repeated IPC may improve endothelial function\textsuperscript{47} and increase the flow velocity of coronary vessels\textsuperscript{46,47}. Furthermore, Bailey et al. (2012b) found that acute IPC could prevent a decline in vascular function, which is typically observed after strenuous exercise\textsuperscript{48}. These results suggest that either acute or chronic IPC may have positive effects on vascular function. During exercise, an increase in muscle oxygen saturation during 6 s cycle sprints was reported with IPC\textsuperscript{49}. Further functional sympatholysis was improved (increase in muscle oxygen saturation in response to acute sympathetetic stimulation) with IPC during dynamic handgrip exercise with an intensity of 25% MVC\textsuperscript{49}. Although muscle oxygen saturation represents only the tissue oxygenation level, these results may indicate that IPC-mediated increases in blood flow during exercise were induced. However, the failure of remote IPC to affect blood flow during rhythmic handgrip exercise compared with CON was also reported\textsuperscript{50}.

Another potential explanation might be an improvement in metabolic efficiency via activation of KATP channels. In animal experiments, prolonged ischemia of the skeletal muscle demonstrates that IPC attenuates ATP depletion\textsuperscript{50-53}, secondary to the activation of KATP channels\textsuperscript{53-57}. Previous work showed that the activation of KATP channels may contribute to more effective blood flow redistribution during exercise\textsuperscript{58,59}. Furthermore, IPC suppressed ischemia-induced glycogen depletion\textsuperscript{60} and lactate production\textsuperscript{50,51} in skeletal muscles. These results may suggest that IPC can reduce muscle energy demand, resulting in an improvement in metabolic efficiency during muscle contraction. Indeed, several studies found that the LA at submaximal exercise with IPC was lower during exercise\textsuperscript{21}, and mean response time in muscle HHb was accelerated at the onset of moderate cycling exercise\textsuperscript{21}, and during isometric leg extension\textsuperscript{69}. Conversely, whole-body VO\textsubscript{2} did not show any differences between IPC and CON\textsuperscript{70}.

In summary, whether IPC can enhance actual volumetric blood flow and/or improve muscle metabolic efficiency, followed by a reduction in whole-body VO\textsubscript{2}, remains unclear. Further studies should be conducted to explain the potential mechanisms by which IPC affects exercise performance.

**Summary and future perspectives**

In this review, we focused on what is currently known (Table 1) about the impacts of IPC on exercise performance and the potential mechanisms to explain such effects. Current evidence, except for the findings of one study\textsuperscript{59}, suggests that either IPC or remote IPC does not impair exercise performance. However, no consensus has been reached on whether IPC may have benefits in improving exercise performance. The relationship between exercise performance and physiological responses with IPC may also be different and more complex. Previous studies on IPC and exercise performance were mostly conducted on healthy and young trained athletes and elite athletes (see Table 1). All studies, except for one by Jones et al. (2014)\textsuperscript{59}, were cross-sectional studies. Further research is therefore needed to explain the effects of training status (level) with IPC and/or repeated IPC on exercise performance. To date, no research has examined whether IPC may improve exercise performance for middle-aged and aged people. Similarly, previous studies investigated only male subjects or a combination of male and female subjects, so no direct evidence has been obtained on the effects of gender differences on exercise performance with IPC, including the impact of aging. Different IPC protocols, including but not limited to applied pressure, applied location, number of ischemia/reperfusion cycles, and time to pre-exercise after IPC, may have possibly affected exercise performance and physiological responses. However, the optimal methodology to implement IPC has yet to be established.

**Conflict of Interests**

The author declare that there is no conflict of interests regarding the publication of this article.

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