INTERDISCIPLINARY DOCTORAL SCHOOL

Faculty of Medicine

Cezar-Dumitrel LUCA

# The role of ischemic preconditioning in patients undergoing surgical revascularization

SUMMARY

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## 1.Introduction – Theoretical Foundations of Remote Ischemic Preconditioning (RIPC)

Remote ischemic preconditioning (RIPC) has emerged as a promising cardioprotective strategy with significant clinical relevance in the context of coronary artery bypass grafting (CABG). RIPC involves the induction of short episodes of ischemia and reperfusion in a remote tissue region (e.g., upper or lower limb), with the aim of triggering systemic protective mechanisms against myocardial ischemia-reperfusion injury [1–4].

The concept evolved from classical ischemic preconditioning (IPC), first described by Murry et al. in 1986 [5], and later extended by Przyklenk in 1993 into its remote form [8,9]. The clinical applications of RIPC have expanded due to its non-invasive nature and its potential for easy integration into perioperative protocols [10–13].

The mechanisms of action of RIPC are complex and include:

- activation of neurohumoral pathways and the RISK (Reperfusion Injury Salvage Kinase) signaling pathway, involving proteins such as Akt and ERK1/2, which are responsible for cell survival and inhibition of apoptosis [16,17,19];
- release of humoral mediators such as adenosine, bradykinin, and nitric oxide, which activate specific receptors on cardiomyocytes [16–20];
- opening of ATP-sensitive potassium channels, helping to stabilize the cell membrane and prevent calcium overload [18–20];
- inhibition of NLRP3 inflammasome activation, reducing IL-1β production and systemic inflammatory responses [26,27];
- upregulation of antioxidant enzymes, especially superoxide dismutase-1 (SOD-1), catalase, and heme oxygenase-1 (HO-1), counteracting oxidative stress during reperfusion [27,41–43,45];
- modulation of LOX-1 receptor, which plays a role in recognizing oxidized LDL and promoting oxidative stress and vascular inflammation [38,44–46].

Furthermore, RIPC influences key biomarkers, including the reduction of high-sensitivity troponin I (hs-cTnI) [65,92–94], the CK-MB isoenzyme [98–101], and C-reactive protein (CRP), with a favorable impact on postoperative outcomes, including renal function and the incidence of atrial fibrillation [106–109].

The benefits of RIPC have also been documented in:

- **renal function** – through reduced incidence of acute kidney injury (AKI), as demonstrated in studies such as Zarbock et al. [48] and confirmed in meta-analyses [51];
- **platelet function** – with reduced platelet activation and prevention of thromboembolic complications [54];
- **neutrophil inflammatory response** – with lower neutrophil-to-lymphocyte ratio and reduced neutrophil adhesion and migration [53,55–57].

However, the literature also reflects inconsistencies regarding the impact of RIPC on hard clinical endpoints (e.g., mortality, myocardial infarction, stroke), as shown in large trials such as ERICCA and RIPHeart [11,23,26,65]. These discrepancies may be attributed to variability in RIPC protocols (number, duration, and timing of cycles), differences in study populations, the type of anesthesia used (sevoflurane vs. propofol), and patient comorbidities [26,43,59–61].

Available meta-analyses (Yi et al. [10]; Pierce et al. [64]; Long et al. [66]) generally support the beneficial effects of RIPC on myocardial biomarkers and renal function, but emphasize the need for standardization of protocols and identification of patient subgroups who may benefit most from this intervention.

## 2. Materials and Methods

This study was designed as a prospective, randomized, case-control investigation, conducted between January 2020 and November 2022 at Clinicco Hospital, Brașov. A total of 80 adult patients with severe coronary artery disease scheduled for elective coronary artery bypass grafting (CABG) were enrolled. Patients were randomly assigned into two equal groups: an intervention group receiving remote ischemic preconditioning (RIPC) and a control group undergoing the standard surgical protocol.

The RIPC protocol consisted of four cycles of ischemia and reperfusion (5 minutes of occlusion followed by 5 minutes of reperfusion), performed using a pneumatic cuff inflated to 200 mmHg on either the upper or lower limb, prior to the induction of anesthesia. The SYNTAX score was used to assess the severity of coronary lesions based on angiographic findings.

The biomarkers analyzed included the pro-inflammatory cytokines IL-1 and IL-6, the antioxidant enzyme SOD-1, and the LOX-1 receptor, along with high-sensitivity cardiac troponin I (hs-cTnI). Blood samples were collected preoperatively, at 2 hours postoperatively, and at 7 days after surgery. Laboratory analyses were conducted using ELISA and chemiluminescence techniques.

Clinical parameters such as length of stay in the intensive care unit, total hospitalization duration, and postoperative complications were also evaluated.

Statistical analysis was performed using JASP software. Differences between groups were assessed using Student's t-test or the Mann–Whitney U test, with statistical significance defined as $p<0.05$. The study was approved by the Ethics Committee of Transilvania University of Brașov and conducted in accordance with the Declaration of Helsinki.

## 3. Results and Discussion

### 3.1. **Study No. 1: The Impact of RIPC on the Inflammatory Response in Patients Undergoing CABG**

Study No. 1 investigated the effects of remote ischemic preconditioning (RIPC) on the systemic inflammatory response in the context of coronary artery bypass grafting (CABG), a major surgical procedure associated with ischemia-reperfusion (IR) injury and enhanced inflammation. Specifically, changes in the levels of interleukin-1 (IL-1) and interleukin-6 (IL-6)—two key proinflammatory cytokines involved in the postoperative immune activation cascade—were analyzed.

The study was conducted on a cohort of 80 patients diagnosed with severe coronary artery disease, eligible for elective CABG. Patients were randomized into two equal groups: an intervention group (RIPC) and a control group. The RIPC protocol involved four cycles of ischemia and reperfusion (5 minutes of occlusion using a pneumatic cuff inflated to 200 mmHg, followed by 5 minutes of reperfusion) applied to a limb prior to anesthesia induction. The groups were confirmed to be homogeneous based on clinical, demographic, and surgical characteristics, including SYNTAX score, aortic cross-clamp time, and use of extracorporeal circulation.

The results showed a significant reduction in IL-1 and IL-6 levels in the RIPC group compared to the control group. Immediately postoperatively (V2), IL-1 levels were significantly lower in the RIPC group ($2.85 \pm 2.24$ pg/mL) versus the control group ($5.56 \pm 4.90$ pg/mL, $P = 0.002$); this difference persisted at 7 days (V3: $2.75 \pm 2.06$ vs. $6.54 \pm 5.10$ pg/mL, $P < 0.001$). Similarly, IL-6 levels were significantly reduced in the RIPC group both at V2 ($16.43 \pm 9.73$ vs. $22.83 \pm 13.39$ pg/mL, $P = 0.01$) and V3 ($2.75 \pm 2.06$ vs. $6.54 \pm 5.10$ pg/mL, $P < 0.001$).

On the other hand, no significant differences were found between groups regarding markers of myocardial injury (high-sensitivity troponin I – hsTnI) or nonspecific inflammation (C-reactive

protein – CRP). Furthermore, hospital stay duration and intensive care unit admission were similar in both groups, with no statistically significant differences.

These findings suggest that RIPC exerts a clear systemic anti-inflammatory effect by attenuating the IR-induced inflammatory response, but does not produce a measurable reduction in myocardial injury or immediate clinical recovery improvement. This indicates that the protective mechanisms of RIPC may be predominantly immunomodulatory rather than directly cardioprotective in all cases.

The limitations of the study include the relatively small sample size and the lack of long-term follow-up. Further research, with larger cohorts and extended monitoring, is needed to clarify the real-world clinical applicability of RIPC and to identify subgroups of patients who may benefit most from this therapeutic strategy.

### 3.2. **Study No. 2: The Impact of RIPC on LOX-1 and SOD-1 Modulation in Combating Oxidative Stress**

Study No. 2 aimed to assess the effect of remote ischemic preconditioning (RIPC) on oxidative stress and inflammatory response in the context of myocardial revascularization surgery via coronary artery bypass grafting (CABG). The focus was placed on two central biomarkers involved in cellular redox balance: LOX-1 (lectin-like oxidized LDL receptor), associated with endothelial dysfunction and vascular inflammation, and superoxide dismutase-1 (SOD-1), a key intracellular antioxidant enzyme.

Eighty patients with severe coronary artery disease were enrolled and randomized into two equal groups: one that received RIPC prior to anesthesia induction (four cycles of limb ischemia-reperfusion), and a control group undergoing the standard surgical protocol. Both groups were balanced in terms of clinical characteristics and cardiovascular risk factors.

The results revealed a significant postoperative decrease in LOX-1 levels in the RIPC group compared to the control group, both at 2 hours (V2: 427.52 ± 718.44 vs. 604.27 ± 403.41 pg/mL, $p < 0.001$) and at 7 days (V3: 569.99 ± 607.80 vs. 749.36 ± 614.75 pg/mL, $p < 0.001$), indicating a reduction in vascular inflammation and oxidative stress. In parallel, SOD-1 levels increased significantly in the RIPC group immediately postoperatively (V2: 2.99 ± 0.93 vs. 0.97 ± 0.79 pg/mL, $p < 0.001$), and remained elevated at 7 days (V3: 2.20 ± 1.22 vs. 1.41 ± 1.33 pg/mL, $p < 0.01$), reflecting an enhanced endogenous antioxidant capacity.

However, no significant differences were observed between groups regarding high-sensitivity troponin I (hsTnI), C-reactive protein (CRP), hemoglobin, or creatinine levels. Likewise, the

duration of hospitalization, ICU stay, and postoperative complications did not differ significantly between groups.

These findings suggest that RIPC favorably modulates the oxidative-inflammatory balance by reducing LOX-1 and enhancing SOD-1 expression, contributing to notable cellular and endothelial protection during the perioperative period. Nevertheless, these molecular benefits did not translate into a clear clinical effect on myocardial injury or immediate postoperative recovery.

Study limitations include the moderate sample size, single-center design, short follow-up period (7 days), and absence of direct functional myocardial assessment (e.g., echocardiography or cardiac MRI). Additionally, interactions between RIPC and other cardioprotective strategies (e.g., pharmacological or postconditioning approaches) were not explored.

In conclusion, this study demonstrates that RIPC exerts significant beneficial effects on oxidative stress and vascular inflammation, supporting its potential as an adjunctive cardioprotective strategy in cardiovascular surgery. However, larger clinical trials with extended follow-up are needed to validate its translational relevance.

### 3.3. **Study No. 3: Connections Between Oxidative Stress, Inflammation, and Cardiovascular Risk Factors in Patients Undergoing CABG and RIPC**

Study No. 3 explored the effects of remote ischemic preconditioning (RIPC) on the balance between oxidative stress, inflammation, and cardiovascular risk factors in patients with severe coronary artery disease undergoing coronary artery bypass grafting (CABG). The primary objective was to evaluate whether RIPC application could favorably influence inflammatory markers (IL-1, IL-6) and the endogenous antioxidant SOD-1, with potential implications for myocardial protection and postoperative recovery.

The study cohort included 80 patients, randomized equally into RIPC and control groups. Both groups were comparable in terms of age, comorbidities, and operative parameters. RIPC was applied preoperatively through four cycles of limb ischemia-reperfusion.

Results showed a significant decrease in IL-1 and IL-6 levels in the RIPC group, both immediately postoperatively (V2: IL-1 = 2.85 ± 2.24 vs. 5.56 ± 4.90 pg/mL; IL-6 = 16.43 ± 9.73 vs. 22.83 ± 13.39 pg/mL) and at 7 days (V3: IL-1 = 2.75 ± 2.06 vs. 6.54 ± 5.10 pg/mL; IL-6 = 2.75 ± 2.06 vs. 6.54 ± 5.10 pg/mL, all $p < 0.001$). In parallel, SOD-1 levels increased significantly in the RIPC group (V2: 2.99 ± 0.93 vs. 0.97 ± 0.79 pg/mL, $p < 0.001$; V3: 2.20 ± 1.22 vs. 1.41 ± 1.33 pg/mL, $p < 0.01$), indicating a sustained antioxidant protective effect.

However, no statistically significant differences were observed in myocardial injury biomarkers (hsTnI), CRP, serum creatinine, length of hospital stay, or postoperative ejection fraction. A post-hoc power analysis showed a detection power of 59.8% (Cohen's d = 0.5), indicating a moderate ability to detect true effects, particularly subtle ones.

Interpretation of these findings suggests that RIPC exerts a relevant anti-inflammatory and antioxidant effect, although it did not translate into a measurable immediate clinical benefit regarding myocardial injury or recovery during hospitalization. These outcomes may have been influenced by factors such as comorbidities (e.g., diabetes, hypertension), individual variability in response, and study limitations (single-center design, moderate sample size, short follow-up).

In conclusion, RIPC demonstrates a favorable biological profile and emerges as a promising adjunct strategy in cardiac surgery. However, its direct clinical benefits require further validation through multicenter trials with larger cohorts and extended follow-up. This research provides important evidence on the role of RIPC in modulating oxidative stress and inflammation, strengthening the scientific rationale for its integration into perioperative protection protocols.

**4. Discrepancies Between Study Findings and the Scientific Literature**

While existing literature describes clear cardioprotective effects of remote ischemic preconditioning (RIPC)—including troponin reduction, preservation of left ventricular function, and shorter hospital stays [112–116]—our studies did not consistently confirm these benefits. Specifically, postoperative levels of high-sensitivity troponin I (hsTnI), C-reactive protein (CRP), serum creatinine, and hospitalization duration did not show significant differences between the RIPC and control groups.

These discrepancies may be explained by:

- variations in RIPC protocols (timing, number and duration of cycles, anatomical location),
- patient comorbidities (e.g., hypertension, diabetes, dyslipidemia),
- influence of anesthesia type (propofol vs. volatile agents),
- sample size and study design (single-center, short follow-up),
- and individual biological variability.

Such differences between experimental and clinical data reflect the complexity of translating RIPC from the laboratory setting into real-world cardiac surgery.

**5. Statistical Power Analysis of the Study**

Post-hoc statistical analysis revealed an overall detection power of 59.8% (for Cohen's d = 0.5), indicating a moderate ability to detect medium-sized effects. For large effects (Cohen's d ≥ 0.8), the detection probability increased substantially (>95%).

This level of power is below the conventional threshold of 80%, suggesting that non-significant results (e.g., for hsTnI or CRP) do not rule out the existence of real effects, but may reflect a lack of statistical sensitivity due to sample size or high data variability.

Therefore, the interpretation of results should be done cautiously, considering the potential risk of Type II error (false negatives), especially for biomarkers with high biological variability.

**6. Clinical Relevance and Implications for Medical Practice**

Although RIPC did not demonstrate a direct clinical effect on myocardial necrosis markers or other postoperative recovery parameters, its evident biological benefits—reduction in IL-1, IL-6, and LOX-1 levels, and increase in SOD-1—support its potential as a perioperative adjunctive strategy.

Its clinical relevance lies in:

- reducing systemic inflammation, which is associated with major cardiovascular complications,
- improving redox balance, with possible implications for endothelial health and organ function,
- a favorable safety and cost profile, making RIPC suitable for broad implementation in cardiac surgery centers.

The integration of RIPC into clinical practice could help optimize perioperative management, especially in high-risk patient groups (e.g., elderly, diabetics, chronic kidney disease), but this requires further validation through additional multicenter studies with extended follow-up.

**7. General Conclusions**

The research conducted in this thesis supports the notion that remote ischemic preconditioning:

- significantly reduces systemic inflammation (via decreased IL-1 and IL-6 levels),
- improves cellular antioxidant status (via increased SOD-1 expression),

- reduces expression of the LOX-1 receptor, a key mediator of vascular inflammation and oxidative stress.

However, no significant direct effects were observed on myocardial necrosis (hsTnI), general inflammatory markers (CRP), renal function, or immediate clinical outcomes.

RIPC remains a promising strategy for protecting vital organs during cardiac surgery, particularly as an adjunct to reduce the impact of ischemia-reperfusion injury. Nevertheless, the translation of these biological benefits into measurable clinical outcomes requires further validation through:

- larger sample sizes,
- optimization of RIPC application protocols,
- integration with other protective measures (pharmacological, anesthetic, technical),
- and long-term patient follow-up.

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## 9. List of publications

- ✓ **Romanian Journal of Cardiology -** *Atrial standstill in a young patient treated with left bundle branch area pacing*

  Ecaterina C. , **Dumitrel L.** , & Catalin P.. Atrial standstill in a young patient treated with left bundle branch area pacing. Romanian Journal of Cardiology 2024;34(2):97-101. https://doi.org/10.2478/rjc-2024-0008

- ✓ **Cardiology Research Journal** - *The Impact of Remote Ischemic Preconditioning on Inflammation Markers in Patients Undergoing Coronary Artery Bypass Grafting*

  **Luca C.** , Boieriu A. , Neculoiu C. , & Ţînţ D.. The impact of remote ischemic preconditioning on inflammation markers in patients undergoing coronary artery bypass grafting. Cardiology Research 2024;15(5):369-376. https://doi.org/10.14740/cr1702

- ✓ **Frontiers in Cardiovascular Medicine -** *Cardioprotection in coronary artery bypass graft surgery: the impact of remote ischemic preconditioning on modulating LOX-1 and SOD-1 to counteract oxidative stress*

  **Luca C.** , Boieriu A. , Neculoiu C. , & Ţînţ D.. Cardioprotection in coronary artery bypass graft surgery: the impact of remote ischemic preconditioning on modulating lox-1 and sod-1 to counteract oxidative stress. Frontiers in Cardiovascular Medicine 2024;11. https://doi.org/10.3389/fcvm.2024.1502326

- ✓ **Frontiers in Cardiovascular Medicine -** *The impact of inflammatory and oxidative stress biomarkers on the sympathetic nervous system in severe coronary atherosclerosis*

  Boieriu A. , **Luca C.** , Neculoiu C. , & Ţînţ D.. The impact of inflammatory and oxidative stress biomarkers on the sympathetic nervous system in severe coronary atherosclerosis. Frontiers in Cardiovascular Medicine 2024;11. https://doi.org/10.3389/fcvm.2024.1480925

- ✓ ***Medicina* Journal -** *Endothelial Dysfunction and Oxidative Stress in Patients with Severe Coronary Artery Disease: Does Diabetes Play a Contributing Role?*

  Boieriu A. , **Luca C.** , Neculoiu C. , Bisoc A. , & Ţînţ D.. Endothelial dysfunction and oxidative stress in patients with severe coronary artery disease: does diabetes play a

contributing role?. Medicina 2025;61(1):135. https://doi.org/10.3390/medicina61010135

- ✓ **Research Reports in Clinical Cardiology -** *Flow Mediated Dilation and Its Correlation with Coronary and Systemic Atherosclerosis in Patients Scheduled for Surgical Myocardial Revascularization*

  Boieriu A. , **Luca C.** , & Tint D.. Flow mediated dilation and its correlation with coronary and systemic atherosclerosis in patients scheduled for surgical myocardial revascularization. Research Reports in Clinical Cardiology 2025;Volume 16:1-7. https://doi.org/10.2147/rrcc.s489002

- ✓ **Romanian Journal of Cardiology -** *Connections Between Oxidative Stress, Inflammation, and Cardiovascular Risk Factors in CABG Patients Undergoing Remote Ischemic Preconditioning*

  **Luca C.** , Boieriu A. , Neculoiu D. , & Ţînţ D.. Connections between oxidative stress, inflammation, and cardiovascular risk factors in cabg patients undergoing remote ischemic preconditioning. Romanian Journal of Cardiology 2025. https://doi.org/10.2478/rjc-2025-0006