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Brief Report

Remote Ischemic Preconditioning in Noncardiac Surgery: The End of a Promising Hypothesis?

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ABSTRACT

Postoperative myocardial injury remains a major determinant of morbidity and mortality after noncardiac surgery, prompting sustained interest in preventive strategies such as Remote Ischemic Preconditioning (RIPC). Initially supported by compelling experimental data and numerous small-randomized trials, RIPC has been widely perceived as a low-cost, low-risk intervention with potential systemic organ-protective effects. The PRINCE randomized clinical trial represents the most rigorous and definitive evaluation of RIPC in this setting to date. Conducted across 25 centres in eight countries and enrolling more than 1,200 high-risk patients, PRINCE used a double-blind, sham-controlled design, avoided propofol anaesthesia, and selected postoperative myocardial injury, defined by troponin elevation as a clinically meaningful primary endpoint. The trial demonstrated no reduction in myocardial injury or secondary outcomes, including myocardial infarction, stroke, acute kidney injury, or mortality, with RIPC compared with sham treatment. Moreover, modest safety signals, including increased limb petechiae and hospital readmissions, further weaken the rationale for routine use. This editorial place PRINCE in the broader context of perioperative research, highlighting the recurrent discordance between small, single-centre trials and large multicentre randomized studies. The findings decisively challenge the clinical utility of RIPC in noncardiac surgery and underscore the importance of adequately powered methodologically robust trials before adopting biologically appealing interventions into standard perioperative practice.

Keywords: Remote ischemic preconditioning, Noncardiac surgery, Myocardial injury after surgery, Perioperative cardioprotection and Randomized controlled trial.

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BACKGROUND

Perioperative myocardial injury remains one of the most vexing challenges in modern noncardiac surgery because it is common, frequently silent, multifactorial in origin, and strongly linked to adverse outcomes, yet difficult to prevent or treat effectively.[1,2] A substantial proportion of high-risk surgical patients develop postoperative troponin elevations, often in the absence of chest pain or electrocardiographic changes, leading to underdiagnosis and missed opportunities for intervention.[3-5] The pathophysiology is complex and heterogeneous, encompassing supply-demand mismatch, plaque instability, microvascular dysfunction, inflammation, anaemia, hypotension, hypoxia, and perioperative stress responses, which vary widely across patients and surgical contexts.[1,6] This biological complexity limits the effectiveness of single, targeted preventive strategies. Moreover, perioperative myocardial injury frequently occurs outside the operating room, in the early postoperative period, when monitoring is less intense and symptoms are masked by analgesia or sedation.[1,6] Evidence-based therapies are also limited: while myocardial injury is strongly associated with short- and long-term mortality, there is no universally accepted treatment pathway once it is detected, and preventive interventions that appeared promising in early studies have often failed in large-randomized trials.[1,6,7] Together, these factors render perioperative myocardial injury a persistent and unresolved challenge in contemporary noncardiac surgical care. Despite advances in anaesthetic techniques, perioperative monitoring, and risk stratification, postoperative myocardial injury (often clinically silent yet prognostically ominous) continues to affect a substantial proportion of surgical patients and is strongly associated with short- and long-term mortality.[1,6-8] Against this backdrop, Remote Ischemic Preconditioning (RIPC) emerged over two decades ago as an elegant, low-cost, and biologically appealing strategy for organ protection.[9,10] The PRINCE randomized clinical trial now provides the most definitive evaluation to date of this intervention in noncardiac surgery and delivers a sobering verdict.[11]

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From Experimental Promise to Clinical Uncertainty

RIPC, achieved by brief cycles of limb ischemia and reperfusion, was initially shown to reduce myocardial infarct size in animal models and early human studies.[9,10,12] RIPC has been implemented using a variety of methods that differ in timing, anatomical site, number and duration of ischemia–reperfusion cycles, and clinical context, reflecting both experimental evolution and pragmatic constraints. The most used approach involves the application of a standard blood-pressure cuff to an upper or lower limb, inflated to supra-systolic pressures (typically 180–220 mmHg) to induce transient arterial occlusion, followed by deflation to allow reperfusion.[9,10,12] Protocols most frequently employ three or four cycles of ischemia lasting 5 minutes each, interspersed with 5-min reperfusion periods, although shorter or longer cycles have also been explored. The choice of limb varies, with upper-limb conditioning favoured for ease and safety, while lower-limb conditioning may generate a larger ischemic stimulus but carries a higher risk of local adverse effects. Timing is another major variable, RIPC may be administered immediately before surgery (early or classic preconditioning), during ischemia of the target organ, or hours to days before the insult (delayed or second-window preconditioning), each thought to activate distinct protective pathways. Alternative methods include repeated daily RIPC sessions, particularly in chronic ischemic conditions, and device-assisted automated conditioning systems to improve protocol fidelity.[13,14] This wide methodological heterogeneity has contributed to inconsistent clinical results and underscores the challenge of translating RIPC from controlled experimental models into reproducible perioperative benefit.

Mechanistic studies suggest that the protective effects of remote ischemic preconditioning arise from an integrated network of neural, humoral, and intracellular signalling pathways that converge on mitochondrial preservation and cellular survival.[15,16] Transient limb ischemia activates afferent sensory nerves, particularly through nociceptive and autonomic pathways, which relay signals to the central nervous system and trigger efferent cardioprotective responses via the Vagus nerve. In parallel, brief ischemia-reperfusion episodes stimulate the release of circulating humoral mediators, including adenosine, bradykinin, opioids, nitric oxide–related metabolites, stromal-derived factors, microRNAs, and extracellular vesicles, which travel to distant organs and activate pro-survival signalling cascades.[17,18] These neural and humoral signals converge at the cellular level on intracellular kinase pathways such as PI3K-Akt, ERK1/2, and JAK-STAT, collectively referred to as the Reperfusion Injury Salvage Kinase (RISK) and Survivor Activating Factor Enhancement (SAFE) pathways.[19,20] Activation of these pathways ultimately targets the mitochondria, stabilizing mitochondrial membranes, reducing calcium overload, limiting reactive oxygen species generation, and preventing the opening of the mitochondrial permeability transition pore at reperfusion. Through these coordinated mechanisms, RIPC is thought to enhance cellular resistance to ischemia-reperfusion injury, reduce apoptosis and necrosis, and preserve organ function, although the translation of these mechanistic insights into consistent clinical benefit has proven challenging.[19,20] These findings have generated enormous enthusiasm, reinforced by numerous small-randomized trials and meta-analyses suggesting reductions in biomarker release, postoperative complications, and even mortality in surgical patients. However, the RIPC literature has long been characterized by heterogeneity: small single-centre trials, variable protocols, inconsistent blinding, diverse anaesthetic regimens, and outcomes driven largely by surrogate biomarkers.[21,22] Importantly, the history of perioperative medicine is replete with interventions that appeared promising in early trials but failed to withstand rigorous multicentre evaluation. PRINCE was explicitly designed to resolve this uncertainty.[11]

The PRINCE Trial: Methodological Rigor at Scale

PRINCE is the largest randomized controlled trial of RIPC in noncardiac surgery to date, enrolling 1,213 high-risk patients across 25 centres in eight countries.[11] Its methodological strengths are substantial: a double-blind, sham-controlled design; centralized randomization; pragmatic inclusion criteria reflecting real-world practice; and near-complete postoperative troponin surveillance.[11] Importantly, the investigators addressed one of the most persistent criticisms of prior RIPC studies by avoiding propofol, an anaesthetic agent thought to blunt preconditioning effects. The primary endpoint, postoperative myocardial injury defined by troponin elevation above the 99th percentile was clinically meaningful and biologically relevant. Myocardial injury after noncardiac surgery is now recognized as a powerful predictor of mortality, even in the absence of ischemic symptoms, making it an appropriate and pragmatic outcome for a trial of this scale.

Large-scale, multicentre Randomized Controlled Trials (RCTs) like PRINCE represent a substantial economic undertaking, reflecting both the complexity of their design and the high costs of rigorous clinical research.[23,24] Key cost drivers include patient recruitment across multiple international centres, standardized training and protocol adherence, centralized randomization, and extensive postoperative monitoring such as serial troponin measurements. Blinding procedures and sham interventions further increase logistical and personnel costs.[23,24] However, such investments are justified by the potential for high-impact results that can influence clinical guidelines, improve patient outcomes, and reduce downstream healthcare expenditures associated with postoperative complications. Moreover, robust trial designs that minimize bias and confounding, like PRINCE's avoidance of propofol and pragmatic inclusion criteria, enhance the likelihood that findings are generalizable, thereby maximizing the return on investment in terms of clinical and economic value.

Neutral Results, Decisive Implications

The findings are unequivocal. RIPC failed to reduce postoperative myocardial injury, which occurred in approximately 38% of patients in both groups.[11] No signal of benefit emerged for any secondary endpoint, including myocardial infarction, stroke, acute kidney injury, ICU admission, length of stay, or 30-day mortality. These results were consistent across intention-to-treat, per-protocol, and sensitivity analyses, and robust to subgroup exploration. Notably, an unexpected signal emerged in patients receiving lower-limb RIPC, where myocardial injury appeared more frequent though this finding should be interpreted cautiously.[11] While likely due to chance or unmeasured confounding, it nevertheless reinforces the absence of a protective effect and raises questions about the biological plausibility of uniform benefit across different RIPC protocols. Equally important is the safety signal. Although serious RIPC-related adverse events were rare, limb petechiae and higher rates of hospital readmission were more common in the intervention group. While clinically concerning, these findings undermine the notion that RIPC is entirely benign and further weaken the argument for its routine use.

Reconciling PRINCE with Prior Evidence

How should clinicians reconcile the neutral findings of PRINCE with earlier meta-analyses suggesting benefit? The answer likely lies in the well-recognized limitations of aggregate evidence derived from small, heterogeneous trials. Meta-analyses are only as reliable as the studies they include, and when dominated by small, single-centre trials with low fragility indices, they are particularly vulnerable to bias and random error. The proliferation of meta-analyses in recent years has raised concerns about the potential for misleading conclusions when methodological rigor is not critically assessed. While meta-analyses can provide valuable synthesis of evidence, their reliability depends entirely on the quality, size, and design of the included studies. When a field is dominated by small, single-centre trials with low fragility indices, combining them without careful evaluation can amplify biases, overestimate treatment effects, and create a false sense of certainty. The routine publication of large numbers of meta-analyses without thorough scrutiny of study quality, heterogeneity, and statistical robustness risks cluttering the literature with conclusions that may not be clinically meaningful, potentially influencing practice guidelines and policy decisions based on flawed evidence. This underscores the need for a more critical, methodologically grounded approach before accepting or publishing meta-analytic findings. PRINCE joins a growing list of large, rigorously conducted trials both in cardiac and noncardiac surgery that have failed to confirm the benefits of RIPC suggested by earlier studies.[25-27] This pattern mirrors the trajectory of many perioperative interventions, where biological plausibility and early enthusiasm ultimately yield to the sobering reality of large-scale randomized evidence.

Implications for Practice and Research

The clinical implications of PRINCE are clear. RIPC should not be used routinely to prevent myocardial injury in noncardiac surgery. In an era increasingly focused on value-based care and evidence-driven practice, interventions without demonstrable benefit even if inexpensive and conceptually attractive should be abandoned. For researchers, PRINCE offers important lessons. First, it underscores the necessity of large, multicentre, blinded trials before widespread adoption of perioperative interventions. Second, it highlights the limitations of surrogate endpoints when disconnected from consistent clinical benefit. Finally, it invites a reassessment of whether the biological mechanisms underlying ischemic conditioning translate meaningfully into the complex physiological milieu of modern surgery and anaesthesia. Future investigations may yet identify niche populations, alternative conditioning paradigms (such as delayed or repeated preconditioning), or mechanistically distinct strategies for organ protection. However, any such efforts must proceed with humility, methodological rigor, and a clear recognition of the lessons learned from PRINCE.

CONCLUSION

In conclusion, the PRINCE trial represents a landmark in perioperative cardiovascular research. By definitively demonstrating the absence of benefit of remote ischemic preconditioning in high-risk noncardiac surgery, it closes an important chapter in the search for simple cardioprotective strategies. More importantly, it reinforces a central tenet of perioperative medicine: promising physiology must always be tested and retested by robust clinical trials before it earns a place in routine care.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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