BJA

REVIEW ARTICLE

Cardioprotection by remote ischaemic preconditioning[†]

S. R. Walsh[1]*, T. Tang[1], U. Sadat[1], D. P. Dutka[2] and M. E. Gaunt[1]

[1]*Cambridge Vascular Research Unit, Box 201, Level 7, Addenbrooke's Hospital and* [2]*Department of Cardiology, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 2QQ, UK*
*Corresponding author. E-mail: srwalsh@doctors.org.uk

Perioperative myocardial infarction is a leading cause of morbidity and mortality after major non-cardiac surgery. Pharmacological agents such as beta-blockers may reduce the risk but are associated with side-effects and may be contra-indicated in some patients. Basic scientific experiments and preliminary clinical trials in humans suggest that remote ischaemic preconditioning (RIPC), where brief ischaemia in one tissue confers resistance to subsequent sustained ischaemic insults in another tissue, may provide a simple, cost-effective means of reducing the risk of perioperative myocardial ischaemia. The Medline and Pubmed databases were searched for articles concerning RIPC. The mechanism may be humoral, neural, or a combination of both, and involves adenosine, opioids, bradykinins, protein kinase C, and K-ATP channels, although the precise end-effector remains unclear. Small randomized trials in humans undergoing major surgery suggest that RIPC induced by brief lower limb ischaemia significantly reduces myocardial injury. It may also reduce other ischaemic complications of surgery and anaesthesia. Small studies provide some evidence that RIPC could reduce myocardial injury and other ischaemic complications of surgery. However, large-scale clinical trials to assess the effect of RIPC on mortality and morbidity are required before RIPC can be recommended for routine clinical use.

Br J Anaesth 2007; **99**: 611–16

Keywords: complications, myocardial infarction; heart, ischaemia; surgery, postoperative care

Perioperative myocardial injury has a significant impact on both short- and long-term outcomes after major non-cardiac surgery.[31] Adverse cardiac events complicate about 1 million surgical procedures every year in the USA.[21] Worldwide, it is estimated that between 500 000 and 900 000 patients suffer perioperative cardiac death, non-fatal myocardial infarction, or non-fatal cardiac arrest every year.[10] Perioperative myocardial infarction (PMI) is associated with mortality rates of up to 40%.[32 45] Non-fatal PMI independently increases the risk of both cardiovascular death and a further non-fatal myocardial infarction in the first 6 months after major non-cardiac surgery.[36]

Hospital stay is prolonged in patients who sustain perioperative cardiac complications,[16] increasing the burden on available health services with estimated costs of about $20 billion annually.[17] Reducing the incidence of perioperative cardiovascular events would have significant benefits. Research has focused on determining the optimum method of identifying high-risk patients. Importantly, they provide no information over and above that provided by simple clinical risk scores such as the Goldman index.[21] Once a high-risk patient has been identified, therapeutic strategies are needed to reduce that individual's risk of a perioperative cardiac event. Coronary revascularization, beta-blockade, α_2-adrenoceptor agonists, aspirin, and statins have all been assessed in major non-cardiac surgery.[46] However, the aetiology of PMI involves many factors such as catecholamine and cortisol release, hypoxia, anaemia, pain, fluid shifts, hypothermia, fasting, tracheal instrumentation, and surgical trauma. These factors may lead to plaque fissuring and thrombosis or myocardial ischaemia due to relative myocardial hypoxia, culminating in a myocardial infarction when the myocardial oxygen supply decreases below a critical point.[10] Therapeutic agents tend to target one or more, but not all, potential triggers. For example, statins may cause plaque stabilization, but this will not prevent a 'haemodynamic' PMI if flow across a stable stenotic plaque is reduced by systemic hypotension.

An alternative approach to prevention of PMI would be to make the myocardium resistant to damage from ischaemia, regardless of the trigger. Experimental data suggest that remote ischaemic preconditioning (RIPC) may represent a novel and inexpensive method of reducing perioperative ischaemic complications.[26 27 35] Clinical data from randomized controlled trials encourage the view that

---

[†]This article is accompanied by Editorial I.

this technique could potentially reduce the incidence of PMI.[2 7] Moreover, it has the potential to reduce the risk of other ischaemic complications of surgery such as acute tubular necrosis or stroke.[41 51] We conducted a literature review of the background, putative mechanisms, and potential clinical utility of RIPC.

Methods

The Medline, Embase, and Pubmed databases were searched between 1986 and 2006 for relevant articles. The first description of ischaemic preconditioning (IPC) appeared in the literature in 1986.[38] Combinations of the search terms 'ischaemic', 'ischemic', 'preconditioning', 'tolerance', 'remote', and 'preconditioning at a distance' were used. Additional papers were obtained from the reference lists of articles identified by the electronic database search.

Results

Ischaemic preconditioning

IPC describes the situation where tissues exposed to brief, non-lethal periods of ischaemia are rendered relatively resistant to damage from a subsequent prolonged ischaemic insult. The first published description[38] found that the size of the myocardial infarction in canine hearts subjected to 40 min of coronary occlusion was significantly reduced if the heart was first exposed to four cumulative 5 min periods of ischaemia with reperfusion between each episode. This pivotal observation stimulated a flurry of experiments aimed at identifying the underlying mechanism, confirming cross-species preservation of IPC and assessing the potential clinical utility of IPC. The experiment proved to be reproducible in a number of different animal models.[24 29 34] The effect was also observed in a range of non-cardiac tissues exposed to ischaemia,[20 37 49 62] suggesting that an innate protective mechanism existed in mammalian tissue that could be exploited to protect against ischaemic injury.

The clinical utility of IPC has been investigated in clinical situations that involved direct interference with a tissue's blood supply. In open heart surgery, it was shown that preconditioning led to relative preservation of myocardial adenosine triphosphate levels at the end of a subsequent 10 min ischaemic insult.[60] A further study from the same group found that postoperative serum troponin T concentrations after coronary artery bypass grafting were significantly reduced if patients were exposed to several brief periods of reversed ischaemia before the fashioning of the first anastomosis.[25] In a small study of 20 patients undergoing pulmonary surgery, there was a significant increase in superoxide dismutase and pulmonary vein oxygenation in the 10 patients who underwent preconditioning by temporary pulmonary artery occlusion, suggesting that the preconditioning reduces pulmonary ischaemia–

reperfusion injury.[6] Preconditioning produced a significant reduction in postoperative serum transaminase peaks after major hepatic resection.[9] It also reduces haemodynamic instability during major hepatic surgery.[8]

Although IPC reduces ischaemic injury, its clinical utility is limited to scenarios in which there is easy access to temporarily occlude the target organ's blood supply, such as cardiology, cardiothoracic surgery, transplant, and plastic surgery. However, preconditioning one vascular bed also appears to protect organs in other vascular beds. This is RIPC or 'preconditioning at a distance'.

Experimental evidence for RIPC

Analysis of canine models of cardiac IPC demonstrated that the size of infarctions in preconditioned hearts tended to increase in proportion to the area of the left ventricle at risk and, furthermore, that the distance between the edge of the infarct and the margin of the risk area increased as the risk region decreased. Conversely, this lateral distance remained the same in control hearts as the area at risk increased.[48] These observations were formulated into a mathematical model, which suggested that a trigger generated in non-ischaemic tissue may contribute to the myocardial protection produced by conventional direct IPC.[56]

The model implied that ischaemia induced in one coronary vascular bed may protect myocardium in another coronary vascular bed, a hypothesis subsequently confirmed in the canine heart. Dogs were randomized to undergo temporary occlusion of the circumflex coronary artery or not. They were then subjected to 1 h of ischaemia in the left anterior descending coronary bed. The extent of necrosis in the LAD bed was significantly reduced by preconditioning the circumflex bed.[47] From a clinical perspective, this 'intracardiac' preconditioning was of limited utility, as it still requires direct interference with the coronary circulation.

The possibility of 'inter-organ' preconditioning was then explored. Gho and colleagues[19] assessed the effect of transient coronary, mesenteric, or renal ischaemia on infarct size after 60 min of coronary occlusion. There was a significant reduction in infarction size with coronary and mesenteric preconditioning at normothermia, but not with renal preconditioning. Induction of hypothermia produced some enhancement of the coronary preconditioning effect, minimal improvement in the mesenteric preconditioning but unmasked a significant effect for renal preconditioning. Permanent mesenteric occlusion abolished the protection, implying that reperfusion was an essential element in obtaining the remote protection. These observations were subsequently confirmed in other studies.[33 42 43 50 52 53 57 59]

The kidneys and, to a lesser extent, the intestine are vulnerable to damage from even brief periods of ischaemia. The blood supply of these organs is also inaccessible in many clinical scenarios, rendering them unsuitable as the remote stimulus for cardioprotection. Skeletal muscle, on the other hand, is relatively resistant to damage from ischaemia, and it

is easily accessible, and a direct preconditioning effect has been observed in animal models of skeletal muscle flaps.[37]

Skeletal muscle has been investigated as a remote stimulus for cardioprotection. Birnbaum and colleagues induced 30 min of skeletal muscle ischaemia in a rabbit model by means of a 55–65% reduction in femoral artery blood flow combined with electrical stimulation of the gastrocnemius muscle. When the animals were subsequently exposed to 30 min of coronary occlusion followed by 4 h of reperfusion, infarct sizes were considerably smaller in the animals that had received skeletal muscle preconditioning.[3] Other investigators also found that transient limb ischaemia in rats protected against reperfusion tachyarrhythmias after 30 min of ischaemia[40] while it also reduced infarction size in pigs exposed to 40 min of coronary occlusion.[28] These animal models implied that RIPC of the heart could be achieved clinically by transient limb ischaemia.

Mechanisms of RIPC

The precise mechanisms involved in direct preconditioning are not yet established, although the K-ATP channels appear to have a fundamental role. Bradykinin, opioids, and adenosine act on cell surface receptors. Delta-opioid and bradykinin B2 bind to protein kinase C (PKC) and a tyrosine kinase via interactions with PI3-kinase, oxygen radicals, and mitochondrial K-ATP channels. Adenosine acts via a more direct pathway, coupling with PKC via A1/A3 receptors. The kinases are thought to then act on the end-effector, which may be mitochondrial K-ATP, to prevent opening of a mitochondrial transition pore.[61]

Less is known about the mechanisms underlying RIPC. In general, signalling from one tissue to another may be achieved by humoral or neural pathways. Gho and colleagues[19] found that reperfusion was an essential requirement for obtaining a preconditioning effect, implying that ischaemic tissue releases some mediator which triggers preconditioning in distant tissues if it enters the general circulation, that is, a humoral pathway. Dickson and colleagues[12] demonstrated that the preconditioning effect can be transferred between isolated hearts in a modified Langendorff apparatus. One group of isolated rabbit hearts were preconditioned. Fluid washed through the coronary vasculature was then collected and infused into separate isolated receptor hearts. Receptor hearts which received effluent from preconditioned donor hearts demonstrated reduced infarction size when subsequently subjected to prolonged ischaemia compared with hearts which received effluent from control, non-preconditioned donor hearts.[11–14]

Adenosine, bradykinin, and opioid release from ischaemic tissues do appear to be involved in the RIPC pathway, just as they play a role in direct preconditioning. The administration of a PKC blocker abolishes the cardioprotective effect of transient infra-renal aortic occlusion or mesenteric occlusion and the direct preconditioning effect of transient coronary occlusion,[55 57] suggesting that PKC activation is an event common to both direct and remote

pathways. Moreover, PKC activation is higher in remote preconditioned hearts compared with controls.[57] This PKC activation in RIPC may be triggered by adenosine, bradykinin, or opioids. An adenosine-receptor antagonist abolishes the cardio-protective effect of both direct cardiac preconditioning and remote renal preconditioning.[43 52] A bradykinin-receptor antagonist blocks the cardioprotective effect of mesenteric preconditioning,[50] by inhibiting activation of PKC,[57] whereas infusion of bradykinin into the mesenteric circulation mimics the cardioprotective effect.[50] δ_1-opioid receptor inhibition abolishes both direct and remote cardiac preconditioning.[55] However, although inhibition of endogenous free radicals has little effect on infarct size in directly preconditioned myocardium, it reduces the protection provided by RIPC.[5 55]

There is also evidence of a potential neural pathway in RIPC. The gastroprotective effects of RIPC in a rat model are significantly reduced by capsaicin-denervation or truncal vagotomy.[4] Ganglion blockade with hexamethonium prevents PKC activation in rats, impeding the RIPC effect when the stimulus is brief mesenteric occlusion,[57] although not when the stimulus is infra-aortic occlusion.[54] In a pig model of heart transplantation, RIPC with transient limb ischaemia in the recipient animals reduced the extent of myocardial infarctions in subsequently transplanted hearts.[30] The effect was abolished by administration of glibenclamide, a K-ATP channel blocker.[30] Given that transplanted hearts have no innervation, these data appear to suggest that RIPC cannot be produced by a neural mechanism. On the other hand, a recent study in humans found that administration of a ganglion blocker attenuated the effect of RIPC on endothelial ischaemia–reperfusion injury assessed by flow-mediated vasodilation.[35]

There may be some overlap between potential humoral mediators and neural pathways. Experiments in a rabbit model of RIPC using renal ischaemia as the stimulus demonstrated that adenosine released by the ischaemic kidney acted locally on the afferent renal nerves to trigger myocardial protection.[15] A series of experiments using a rat model demonstrated that adenosine released locally during small intestinal ischaemia stimulates afferent nerves in the mesenteric bed during early reperfusion, triggering a neural pathway that activates myocardial adenosine receptors.[33]

RIPC in humans

Although the mechanism of RIPC has yet to be clarified, several groups have produced preliminary results of trials of RIPC as a cardioprotective technique in humans. A study of eight male patients undergoing coronary artery bypass surgery, four of whom received brief periods of upper limb ischaemia after bypass, was inconclusive, probably due to an inadequate sample size.[22] Brief upper limb ischaemia reduced endothelial dysfunction in human volunteers subjected to subsequent prolonged ischaemia in the contralateral arm.[28]

These small *proof of concept* trials have been followed by two studies designed to assess the effect of transient lower limb ischaemia on myocardial injury after major surgery. Cheung and colleagues[7] studied children undergoing open heart surgery and randomized them to receive four 5-min cycles of lower limb ischaemia as a RIPC stimulus. The method of randomization was not stated. Ischaemia was induced by inflating a blood pressure cuff to a pressure of 15 mm Hg greater than the systolic arterial pressure obtained via an arterial line. RIPC was performed about 5–10 min before the initiation of cardiopulmonary bypass. The patients underwent a range of cardiac procedures, including ventricular and atrial septal defect repair, valve repair, surgery for tetralogy of Fallot, and transposition of the great arteries. There were no significant differences in the distribution of surgical procedures between the RIPC and control arms, although the sample was small. However, the control patients tended to be older and larger. Again, this probably reflects the small sample size and it seems likely that the two groups were not entirely similar in terms of age, weight, or surgical procedure performed. However, the cross-clamp and bypass times were comparable. Of 37 patients recruited, 17 were assigned to the RIPC arm. The RIPC patients had significantly less myocardial damage (lower serum troponin I concentrations), but both groups exhibited a similar pattern of troponin elevations, with an immediate rise in the first few hours, tailing off by 24 h. Thus, RIPC reduced but did not eliminate myocardial injury. RIPC also produced a statistically significant reduction in inotrope requirements, although the actual reduction was only on the order of 2–3 μg kg^{-1}min^{-1}.[7] Despite the apparent reduction in myocardial damage and inotrope requirements, the length of the postoperative critical care stay was unchanged, the RIPC group requiring a mean stay of 54.2 (40.7) h compared with 39.5 (25.7) h for the control group. In this small study, RIPC did not appear to produce a tangible clinical benefit.[7]

In major vascular surgery,[2] we studied 82 patients undergoing elective open abdominal aortic aneurysm repair who were randomized to receive RIPC or not. The RIPC protocol used clamping to each common iliac artery sequentially for 10 min followed by 10 min reperfusion. Cross-clamping was performed only once the second leg had been allowed to reperfuse for 10 min. Significant troponin elevations (>0.2 ng ml^{-1}) occurred in 15 of 41 control patients (36%) compared with three of 41 preconditioning patients (7%), a significant reduction ($P=0.002$). Postoperative myocardial injury (serum troponin >1.5 ng ml^{-1}) or infarction was significantly lower in the preconditioned group (2/41 patients *vs* 13/41; $P=0.002$). Mean critical care stay was reduced from a mean of 2 (2.3) days in the control group to 1.0 (0.2) days ($P=0.007$). This appears to demonstrate a clinical benefit in favour of RIPC. However, no risk stratification was incorporated into the trial design. Preoperative renal impairment was present in 23% of the control arm but only in 12% of the RIPC arm. Renal impairment significantly increases the risk of postoperative complications,[39] so the control arm may have been a higher risk group.

Other potential applications of RIPC

At present, most work has focused on RIPC as a cardioprotective technique. However, it could protect other organs from ischaemia–reperfusion injury. Cheung and colleagues[7] reported reduced airway resistance in patients exposed to RIPC, providing human data to support the observation that RIPC reduces lung ischaemia–reperfusion injury in animals.[58] Other animal studies suggest that RIPC may protect against renal ischaemic injury.[41] It also protects distant muscle beds from ischaemic injury[1] and has a protective effect on the central nervous system.[23] Initial clinical trials of RIPC as a reno-protective and neuro-protective technique in major vascular surgery are underway in our unit.

Further studies

Although there is conflicting evidence of clear clinical benefit from RIPC,[2 7] the technique could have the potential to reduce perioperative myocardial injury. The optimum preconditioning protocol (clamping of the iliacs or tourniquet-induced ischaemia) is unclear, as both have demonstrated some benefit. On a practical level, however, tourniquet-induced ischaemia is easier. Data on effect of RIPC on hard clinical end-points such as perioperative death, cardiac arrest, and hospital stay are lacking. Large clinical trials are required to determine whether there is a true clinical benefit to RIPC or whether it merely reduces biochemical markers without affecting prognosis. Some form of risk stratification should be incorporated into the design of any such trial in order to ensure an even distribution of risk between the arms of the study. In addition, anaesthetic techniques should be standardized, as volatile anaesthetics have a preconditioning effect.[18 44 63]

Conclusion

The mechanisms of RIPC are complex and poorly understood. However, initial results from clinical trials suggest that this technique could potentially reduce perioperative myocardial injury. It raises the possibility of ameliorating the consequences of ischaemic injury in other tissues.

Funding

References

1 Addison PD, Neligan PC, Ashrafpour H, *et al*. Noninvasive remote ischemic preconditioning for global protection of skeletal muscle against infarction. *Am J Physiol Heart Circ Physiol* 2003; **285**: H1435–43

2 Ali ZA, Callaghan CJ, Lim E, *et al*. Remote ischaemic preconditioning reduces myocardial and renal injury after elective abdominal aortic aneurysm repair: a randomized controlled trial. *Circulation*, 2007; **116** (Suppl.): i98–105

3 Birnbaum Y, Hale SL, Kloner RA. Ischemic preconditioning at a distance: reduction of myocardial infarct size by partial reduction of blood supply combined with rapid stimulation of the gastrocnemius muscle in the rabbit. *Circulation* 1997; **96**: 1641–6

4 Brzozowski T, Konturek PC, Pajdo R, *et al*. Importance of brain-gut axis in the gastroprotection induced by gastric and remote preconditioning. *J Physiol Pharmacol* 2004; **55**: 165–77

5 Chen YS, Chien CT, Ma MC, *et al*. Protection 'outside the box' (skeletal remote preconditioning) in rat model is triggered by free radical pathway. *J Surg Res* 2005; **126**: 92–101

6 Chen S, Li G, Long L. Clinical research of ischemic preconditioning on lung protection. *Hunan Yi Ke Da Xue Xue Bao* 1999; **24**: 357–9

7 Cheung MM, Kharbanda RK, Konstantinov IE, *et al*. Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery: first clinical application in humans. *J Am Coll Cardiol* 2006; **47**: 2277–82

8 Chouker A, Schachtner T, Schauer R, *et al*. Effects of Pringle manoeuvre and ischaemic preconditioning on haemodynamic stability in patients undergoing elective hepatectomy: a randomized trial. *Br J Anaesth* 2004; **93**: 204–11

9 Clavien PA, Selzner M, Rudiger HA, *et al*. A prospective randomized study in 100 consecutive patients undergoing major liver resection with versus without ischemic preconditioning. *Ann Surg* 2003; **238**: 843–50

10 Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. *CMAJ* 2005; **173**: 627–34

11 Dickson EW, Blehar DJ, Carraway RE, Heard SO, Steinberg G, Przyklenk K. Naloxone blocks transferred preconditioning in isolated rabbit hearts. *J Mol Cell Cardiol* 2001; **33**: 1751–6

12 Dickson EW, Lorbar M, Porcaro WA, *et al*. Rabbit heart can be 'preconditioned' via transfer of coronary effluent. *Am J Physiol* 1999; **277**: H2451–7

13 Dickson EW, Porcaro WA, Fenton RA, *et al*. 'Preconditioning at a distance' in the isolated rabbit heart. *Acad Emerg Med* 2000; **7**: 311–7

14 Dickson EW, Reinhardt CP, Renzi FP, Becker RC, Porcaro WA, Heard SO. Ischemic preconditioning may be transferable via whole blood transfusion: preliminary evidence. *J Thromb Thrombolysis* 1999; **8**: 123–9

15 Ding YF, Zhang MM, He RR. Role of renal nerve in cardioprotection provided by renal ischemic preconditioning in anaesthetized rabbits. *Sheng Li Xue Bao* 2001; **53**: 7–12

16 Fleischmann KE, Goldman L, Young B, Lee TH. Association between cardiac and noncardiac complications in patients undergoing noncardiac surgery: outcomes and effects on length of stay. *Am J Med* 2003; **115**: 515–20

17 Fleisher LA, Eagle KA. Lowering cardiac risk in noncardiac surgery. *N Engl J Med* 2001; **345**: 1677–82

18 Garcia C, Julier K, Bestmann L, *et al*. Preconditioning with sevoflurane decreases PECAM-1 expression and improves one-year cardiovascular outcome in coronary artery bypass graft surgery. *Br J Anaesth* 2005; **94**: 159–65

19 Gho BC, Schoemaker RG, van den Doel MA, Duncker DJ, Verdouw PD. Myocardial protection by brief ischemia in noncardiac tissue. *Circulation* 1996; **94**: 2193–200

20 Glazier S, O'Rourke D, Graham D, Welsh F. Induction of ischemic tolerance following brief focal ischemia in rat brain. *J Cereb Blood Flow Metab* 1994; **14**: 545–53

21 Grayburn PA, Hills LD. Cardiac events in patients undergoing noncardiac surgery: shifting the paradigm from noninvasive risk stratification to therapy. *Ann Intern Med* 2003; **138**: 506–11

22 Gunaydin B, Cakici I, Soncul H, *et al*. Does remote organ ischaemia trigger cardiac preconditioning during coronary artery surgery? *Pharmacol Res* 2000; **41**: 493–6

23 Gurcun U, Discigil B, Boga M, *et al*. Is remote preconditioning as effective as direct ischemic preconditioning in preventing spinal cord ischemic injury? *J Surg Res* 2006; **135**: 385–93

24 Iwamoto T, Miura T, Adachi T, *et al*. Myocardial infarct size-limiting effect of ischemic reconditioning was not attenuated by oxygen free-radical scavengers in the rabbit. *Circulation* 1991; **83**: 1015–22

25 Jenkins DP, Pugsley WB, Alkhulaifi AM, Kemp M, Hooper J, Yellon DM. Ischaemic preconditioning reduces troponin T release in patients undergoing coronary artery bypass surgery. *Heart* 1997; **77**: 314–8

26 Kanoria S, Jalan R, Davies NA, Seifalian AM, Williams R, Davidson BR. Remote ischaemic preconditioning of the hind limb reduces experimental liver warm ischaemia–reperfusion injury. *Br J Surg* 2006; **93**: 762–8

27 Kharbanda RK, Li J, Konstantinov IE, *et al*. Remote ischaemic preconditioning protects against cardiopulmonary bypass-induced tissue injury: a preclinical study. *Heart* 2006; **92**: 1506–11

28 Kharbanda RK, Mortensen UM, White PA, *et al*. Transient limb ischemia induces remote ischemic preconditioning in vivo. *Circulation* 2002; **106**: 2881–3

29 Kida M, Fujiwara H, Ishida M, *et al*. Ischemic preconditioning preserves creatine phosphate and intracellular pH. *Circulation* 1991; **84**: 2495–503

30 Konstantinov IE, Li J, Cheung MM, *et al*. Remote ischemic preconditioning of the recipient reduces myocardial ischemia–reperfusion injury of the denervated donor heart via a Katp channel-dependent mechanism. *Transplantation* 2005; **79**: 1691–5

31 Landesberg G. The pathophysiology of perioperative myocardial infarction: facts and perspectives. *J Cardiothorac Vasc Anesth* 2003; **17**: 90–100

32 Lee TH, Marcantonio ER, Mangione CM, *et al*. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999; **100**: 1043–9

33 Liem DA, Verdouw PD, Ploeg H, Kazim S, Duncker DJ. Sites of action of adenosine in interorgan preconditioning of the heart. *Am J Physiol Heart Circ Physiol* 2002; **283**: H29–37

34 Liu Y, Downey JM. Ischemic preconditioning protects against infarction in rat heart. *Am J Physiol* 1992; **263**: H1107–12

35 Loukogeorgakis SP, Panagiotidou AT, Broadhead MW, Donald A, Deanfield JE, MacAllister RJ. Remote ischemic preconditioning provides early and late protection against endothelial ischemia–reperfusion injury in humans: role of the autonomic nervous system. *J Am Coll Cardiol* 2005; **46**: 450–6

36 Mangano DT, Browner WS, Hollenberg M, Li J, Tateo IM. Long-term cardiac prognosis following noncardiac surgery. The Study of Perioperative Ischemia Research Group. *JAMA* 1992; **268**: 233–9

37 Mounsey RA, Pang CY, Boyd JB, Forrest C. Augmentation of skeletal muscle survival in the latissimus dorsi porcine model using acute ischemic preconditioning. *J Otolaryngol* 1992; **21**: 315–20

38 Murry CE, Jennings JB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; **74**: 1124–36

39 O'Brien MM, Gonzales R, Shroyer AL, *et al*. Modest serum creatinine elevation affects adverse outcome after general surgery. *Kidney Int* 2002; **62**: 585–92

40 Oxman T, Arad M, Klein R, Avazov N, Rabinowitz B. Limb ischemia preconditions the heart against reperfusion tachyarrhythmia. *Am J Physiol* 1997; **273**: H1707–12

41 Park KM, Chen A, Bonventre JV. Prevention of kidney ischemia/reperfusion-induced functional injury and JNK, p38, and MAPK kinase activation by remote ischemic pretreatment. *J Biol Chem* 2001; **276**: 1870–6

42 Patel HH, Moore J, Hsu AK, Gross GJ. Cardioprotection at a distance: mesenteric artery occlusion protects the myocardium via an opioid sensitive mechanism. *J Mol Cell Cardiol* 2002; **34**: 1317–23

43 Pell TJ, Baxter GF, Yellon DM, Drew GM. Renal ischemia preconditions myocardium: role of adenosine receptors and ATP-sensitive potassium channels. *Am J Physiol* 1998; **275**: H1542–4

44 Piriou V, Chiari P, Lhuiller F, *et al*. Pharmacological preconditioning: comparison of desflurane, sevoflurane, isoflurane and halothane in rabbit myocardium. *Br J Anaesth* 2002; **89**: 486–91

45 Poldermans D, Boersma E, Bax JJ, *et al*. The effect of bisoprolol on perioperative mortality and myocardial infarction in high risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med* 1999; **341**: 1789–94

46 Priebe HJ. Perioperative myocardial infarction—aetiology and prevention. *Br J Anaesth* 2005; **95**: 3–19

47 Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation* 1993; **87**: 893–9

48 Przyklenk K, Darling CE, Dickson EW, Whittaker P. Cardioprotection 'outside the box'—the evolving paradigm of remote preconditioning. *Basic Res Cardiol* 2003; **98**: 149–57

49 Roth S, Li B, Rosenbaum PS, *et al*. Preconditioning provides complete protection against retinal ischemic injury in rats. *Invest Ophthalmol Vis Sci* 1998; **39**: 777–85

50 Schoemaker RG, van Heijningen CL. Bradykinin mediates cardiac preconditioning at a distance. *Am J Physiol Heart Circ Physiol* 2000; **278**: H1571–6

51 Steiger HJ, Hanggi D. Ischaemic preconditioning of the brain, mechanisms and applications. *Acta Neurochir (Wien)* 2007; **149**: 1–10

52 Takaoka A, Nakae I, Mitsunami K, *et al*. Renal ischemia/reperfusion remotely improves myocardial energy metabolism during myocardial ischemia via adenosine receptors in rabbits: effects of 'remote preconditioning'. *J Am Coll Cardiol* 1999; **33**: 556–64

53 Wang YP, Xu H, Mizoguchi K, Oe M, Maeta H. Intestinal ischemia induces late preconditioning against myocardial infarction: a role for inducible nitric oxide synthase. *Cardiovasc Res* 2001; **49**: 391–8

54 Weinbrenner C, Nelles M, Herzog N, Sarvary L, Strasser RH. Remote preconditioning by infrarenal occlusion of the aorta protects the heart from infarction: a newly identified non-neuronal but PKC-dependent pathway. *Cardiovasc Res* 2002; **55**: 590–601

55 Weinbrenner C, Schulze F, Sarvary L, Strasser RH. Remote preconditioning by infrarenal aortic occlusion is operative via delta1-opioid receptors and free radicals in vivo in the rat heart. *Cardiovasc Res* 2004; **61**: 591–9

56 Whittaker P, Przyklenk K. Reduction of infarct size in vivo with ischemic preconditioning: mathematical evidence for protection via non-ischemic tissue. *Basic Res Cardiol* 1994; **89**: 6–15

57 Wolfrum S, Schneider K, Heidbreder M, Nienstedt J, Dominiak P, Dendorfer A. Remote preconditioning protects the heart by activating myocardial PKCepsilon-isoform. *Cardiovasc Res* 2002; **55**: 583–9

58 Xia Z, Herijgers P, Nishida T, Ozaki S, Wouters P, Flameng W. Remote preconditioning lessens the deterioration of pulmonary function after repeated coronary artery occlusion and reperfusion in sheep. *Can J Anaesth* 2003; **50**: 481–8

59 Xiao L, Lu R, Hu CP, Deng HW, Li YJ. Delayed cardioprotection by intestinal preconditioning is mediated by calcitonin gene-related peptide. *Eur J Pharmacol* 2001; **427**: 131–5

60 Yellon DM, Alkhulaifi AM, Pugsley WB. Preconditioning the human myocardium. *Lancet* 1993; **342**: 276–7

61 Yellon DM, Downey JM. Preconditioning the myocardium: from cellular physiology to clinical cardiology. *Physiol Rev* 2003; **83**: 1113–51

62 Yoshizumi T, Yanaga K, Soejima Y, Maeda T, Ucjiyama H, Sugimacji K. Amelioration of liver injury by ischaemic preconditioning. *Br J Surg* 1998; **85**: 1636–40

63 Zaugg M, Lucchinetti E, Garcia C, Pasch T, Spahn DR, Schaub MC. Anaesthetics and cardiac preconditioning. Part II. Clinical implications. *Br J Anaesth* 2003; **91**: 566–76