wonders what the long-term DFS for this sub-group of extremely premature babies that need laparotomy for NEC really is . . .

This scenario happens weekly at most tertiary university medical centres, and the moral and ethical implications of potentially producing not DFS, but massive disability survival (MDS), are mindboggling. In my personal opinion the cut off for DFS and NNS should be set at exceptionally low levels in this setting, as if and when we produce MDS we subject patients and their families to unwarranted suffering for extended periods of time, sometimes decades. Although my main concerns are of an ethical nature, one cannot shy away from the fact that creating MDS is also associated with substantial and unnecessary economic burden on various health care systems. It will also result in negative consequences for other patients that cannot get fair and timely care as a result of health care budget money wrongly spent on producing MDS. We should take a step back and reconsider our current practice.

For ethical reasons, it is important to determine what the DFS and NNS are regarding various clinical scenarios. We should start thinking along the lines of DFS and NNS.

Declaration of interest

None declared.

References

1. Shulman M, Myles P. Measuring perioperative outcome. *Curr Opin Anaesthesiol* 2016; **29**: 733–8
2. Boney O, Moonesinghe SR, Myles PS, Grocott MP. Standardizing endpoints in perioperative research. *Can J Anaesth* 2016; **63**: 159–68
3. Shulman MA, Myles PS, Chan MT, McIlroy DR, Wallace S, Ponsford J. Measurement of disability-free survival after surgery. *Anesthesiology* 2015; **122**: 524–36
4. Hutchinson PJ, Kolias AG, Timofeev IS, RESCUEicp Trial Collaborators, *et al*. Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension. *N Engl J Med* 2016; **375**: 1119–30
5. Rysavy MA, Li L, Bell EF, Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, *et al*. Between-hospital variation in treatment and outcomes in extremely preterm infants. *N Engl J Med* 2015; **372**: 1801–11
6. Platt MJ, Cans C, Johnson A, *et al*. Trends in cerebral palsy among infants of very low birthweight (<1500 g) or born prematurely (<32 weeks) in 16 European centres: a database study. *Lancet* 2007; **369**: 43–50
7. Guillén Ú, Weiss EM, Munson D, *et al*. Guidelines for the management of extremely premature deliveries: a systematic review. *Pediatrics* 2015; **136**: 343–50
8. Serenius F, Källén K, Blennow M, EXPRESS Group, *et al*. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden. *JAMA* 2013; **309**: 1810–20

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Remote ischaemic preconditioning: an intervention for anaesthetists?

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The great tragedy of science—the slaying of a beautiful hypothesis by an ugly fact.

Thomas Huxley

Remote ischaemic preconditioning (RIC) was first described in 1993,[1] and since then numerous laboratory studies have shown that RIC using transient limb ischaemia reduces ischaemia–reperfusion injury and protects vulnerable organs, including the heart, kidneys, lungs, and liver.[2 3] The fact that the RIC intervention can be translated to humans simply by repeated cycles of inflating and deflating an ordinary blood pressure cuff on the upper arm has led to widespread clinical interest.[4] Several early clinical studies showed that RIC limits cardiac injury associated with both cardiac surgery and myocardial infarction.[5–11] A meta-analyses of 23 cardiac and vascular surgery randomized controlled trials (RCTs) with 2200 patients showed a cardioprotective effect based on biomarker end points.[12] Too few studies reported clinical end points to enable conclusions to be drawn about the potential clinical benefit of RIC.

More recently, two large double-blind, multicentre RCTs of RIC in cardiac surgery (ERRICA and RIPHeart) found no clinical benefit with RIC. The ERICCA study enrolled 1612 patients from 30 cardiac centres in the UK and showed no benefit with RIC for the composite primary end point of death from cardiovascular causes, non-fatal myocardial infarction, coronary revascularization, or stroke at 12 months [212 RIC patients (26.5%) *vs* 225 sham-RIC patients (27.7%), P=0.58].[13] In the RIPHeart trial (1385 patients from 14 German centres), there was no difference between groups for the composite primary end point of postoperative in-hospital death, myocardial infarction, stroke, or acute renal failure ([99 patients (14.3%) in RIC group *vs* 101 (14.6%) in the sham-RIC group, P=0.89].[14] A multicentre, double-blind 2×2 factorial designed RCT (REPAIR) investigating RIC for live donor renal transplantation in 406 donor–recipient

pairs assessed glomerular filtration rate at 12 months.[15] For the primary end point, iohexol clearance, the RIC group had a higher glomerular filtration rate at 12 months, although the evidence for an effect was weak. The estimated glomerular filtration rate at 12 months was increased by ~5 ml min^{-1} (1.73 m)$^{-2}$; a difference that could translate into a 2–3 yr increase in the lifespan of a transplanted kidney.

Ischaemia–reperfusion injury, usually manifesting as perioperative cardiac, kidney, or neurological complications, is a major cause of perioperative harm, including death. As an intervention, RIC has huge appeal because it is easy, inexpensive, and relatively non-invasive, without any known side-effects. The translation of RIC from basic science into clinical practice has turned out to be very challenging, however, and maybe things are not as simple and straightforward as we thought.[16] Are the clinical findings from the recent RCTs[13–15] the death knell for RIC or should we look for explanations as to why it has failed to fulfil its preclinical promise in the recent RCTs? To address this, we need to consider the impacts that anaesthesia, patient factors, the type of surgery, and the choice of preconditioning intervention have on the effectiveness of the RIC intervention.

Anaesthetic technique

In patients undergoing cardiac surgery, propofol can interfere and diminish the protective effect of RIC.[17 18] Propofol infusion was used for all the patients in the RIPHeart study, 90% of ERICCA participants,[13 14] and an unknown number in the REPAIR study.[15] Experimental studies show that volatile anaesthetics and opioids are cardioprotective and have an 'anaesthetic preconditioning' effect.[16 19] Evidence from two recent meta-analyses shows that a volatile-based anaesthetic for cardiac surgery is associated with a reduced mortality.[20 21] The mitochondria are the energy hubs of cells, where adenosine triphosphate (ATP) is generated via oxidative phosphorylation, and not surprisingly, they perform a central role in the mechanism of ischaemia–reperfusion injury.[22] The pathways of intracellular protection target the mitochondria, and it has been shown that both the inhibition of the opening of the mitochondrial permeability transition pore and activation of the mitochondrial ATP-dependent potassium channels play a role in protective mechanisms.[19 22] Propofol has dose-dependent effects on mitochondria, and studies suggest that propofol at high doses can reduce ATP synthesis, cause mitochondrial damage, and have cytotoxic effects.[23] The optimal anaesthetic technique may well be different for various disease conditions. When patients are at risk of ischaemia–reperfusion injury, the choice of anaesthetic appears to favour a volatile anaesthetic technique, and it may be prudent to standardize the anaesthetic technique to include a volatile anaesthetic instead of propofol in future RIC trials.

Patient factors

Pre-existing diabetes and medications that affect mitochondrial ATP-dependent potassium channels (e.g. sulfonylureas and nicorandil) have been shown to inhibit the beneficial effects of RIC.[24–26] In addition, angina, transient ischaemic attacks, or claudication themselves have a protective preconditioning effect on patients.[27] Diabetic patients are more vulnerable to myocardial ischaemia–reperfusion injury, but also seem to be resistant to known cardioprotective strategies.[16 26] An earlier phase II trial showed that diabetic patients treated with sulfonylurea drugs and anaesthetized with volatile anaesthetics for coronary revascularization had no RIC-induced decrease in troponin concentrations, whereas an RIC-induced decrease in troponin concentrations was seen in non-diabetic patients.[28] In the ERICCA and RIPHeart studies, about a quarter of the patients had a diagnosis of diabetes mellitus; this could have contributed to the lack of effect shown by the RIC intervention in the trials.

Type of surgery

In preclinical studies supporting the use of RIC, and where the duration of experimental ischaemia was carefully timed and controlled, it was recognized that the protective effect of RIC was diminished for prolonged ischaemic insults. Indeed, RIC appears to limit rather than completely abolish ischaemia–reperfusion injury.[1–3 16] In clinical settings, the complexity of surgery and duration of ischaemia and reperfusion affect perioperative outcomes and will impact on clinical trials studying RIC. Our feasibility RCT on RIC in patients undergoing elective abdominal aortic aneurysm repair showed that the allocation scheme for a trial should take into account both the surgical procedure and its complexity to avoid confounding the effect of the RIC intervention.[29] Patients in both the ERICCA and RIPHeart studies underwent coronary artery surgery (no restriction on number of grafts), with or without combined cardiac valve surgery. Therefore, levels of ischaemia, cardiopulmonary bypass time, length of surgery, and hypothermia (not commented on) varied.[13 14]

Intervention

If RIC is considered as a therapeutic drug, very little is known about its pharmacokinetics or pharmacodynamics. There is no agreed dose (number and length of inflations and cuff inflation pressure), nor agreement on whether it requires adjustment according to the type, duration, or both of the ischaemia–reperfusion injury. It is also not known which of the upper or lower limbs might be more effective if used for the RIC intervention. Four cycles of 5 min of arm ischaemia was used in ERICCA, RIPHeart, and REPAIR, but researchers could choose to use either the right or the left arm for the interventional cuff inflations.[13–15] In a large single-centre study in patients undergoing cardiac surgery in which only the left arm was used for the RIC intervention, there was a significant decrease in troponin-T release and an improvement in clinical outcomes, with a reduced risk of myocardial infarction and all-cause death with RIC.[8] Anaesthetists have an important role in determining which limb is used for the RIC intervention, taking into account the need for vascular access, patient positioning, and the type of surgery. For example, studies using the left arm for RIC would predetermine that only the right arm is used for arterial and venous access. Other considerations include the need for surgical access to an arm for obtaining vascular grafts during cardiac surgery. In most clinical trials, including ERICCA and RIPHeart, the RIC intervention was carried out during general anaesthesia. The RIC intervention also seems to be well tolerated by awake patients. In the REPAIR trial, only nine out of 307 patients withdrew because of discomfort associated with cuff inflation on their arm.[15] This opens the possibility of starting the RIC intervention before anaesthesia starts.

Remote ischaemic preconditioning is an anaesthetic-led intervention that has a potential role in procedures with an ischaemia–reperfusion injury, such as cardiovascular and neurosurgical procedures, transplantation surgery, partial nephrectomy, plastic surgical free flaps, and all surgical

procedures where tourniquets are used. This is in addition to a role in critical care settings. For example, experimental studies suggest beneficial effects of RIC during cardiopulmonary resuscitation.[30] Although more studies are needed, it appears that RIC is unlikely to be the magic bullet that cures all, but as a simple intervention it might provide real gains in perioperative patient outcomes. The ERICCA, RIPHeart, and REPAIR trials are valuable and highlight the important role anaesthetists will have in implementing the lessons learnt for future trials. Anaesthetists are best placed to lead on understanding the role of remote ischaemic preconditioning to overcome the harmful effects of ischaemia and reperfusion.

Failure is only the opportunity to begin again, only this time more wisely.

Henry Ford

Authors' contributions

Equal contribution to all aspects of this manuscript; concept and design, writing, editing, and approval of the final submitted version: R.M., J.S.

Declaration of interest

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References

1. Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischaemic preconditioning protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation* 1993; **87**: 893–9
2. Heusch G, Bøtker HE, Przyklenk K, Redington A, Yellon D. Remote ischemic conditioning. *J Am Coll Cardiol* 2015; **65**: 177–95
3. Candilio L, Malik A, Hausenloy DJ. Protection of organs other than the heart by remote ischemic conditioning. *J Cardiovasc Med* 2013; **14**: 193–205
4. Kharbanda RK, Mortensen UM, White PA, *et al*. Transient limb ischemia induces remote ischemic preconditioning in vivo. *Circulation* 2002; **106**: 2881–3
5. 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
6. Hausenloy DJ, Mwamure PK, Venugopal V, *et al*. Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial. *Lancet* 2007; **370**: 575–9
7. Hoole S, Heck PM, Sharples L, *et al*. Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP Stent) Study: a prospective, randomized control trial. *Circulation* 2009; **119**: 820–7
8. Thielmann M, Kottenberg E, Kleinbongard P, *et al*. Cardioprotective effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial. *Lancet* 2013; **382**: 597–604
9. Bøtker HE, Kharbanda R, Schmidt MR, *et al*. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *Lancet* 2010; **375**: 727–34
10. Crimi G, Pica S, Raineri C, *et al*. Remote ischemic post-conditioning of the lower limb during primary percutaneous coronary intervention safely reduces enzymatic infarct size in anterior myocardial infarction: a randomized controlled trial. *JACC Cardiovasc Interv* 2013; **6**: 1055–63
11. Sloth AD, Schmidt MR, Munk K, *et al*. Improved long-term clinical outcomes in patients with ST-elevation myocardial infarction undergoing remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention. *Eur Heart J* 2014; **35**: 168–75
12. Healy DA, Khan WA, Wong CS, *et al*. Remote preconditioning and major clinical complications following adult cardiovascular surgery: systematic review and meta-analysis. *Int J Cardiol* 2014; **176**: 20–31
13. Hausenloy DJ, Candilio L, Evans R, *et al*. Remote ischemic preconditioning and outcomes of cardiac surgery. *N Engl J Med* 2015; **373**: 1408–17
14. Meybohm P, Bein B, Brosteanu O, *et al*. A multicenter trial of remote ischemic preconditioning for heart surgery. *N Engl J Med* 2015; **373**: 1397–407
15. MacAllister R, Clayton T, Knight R, *et al*. REmote preconditioning for Protection Against Ischaemia–Reperfusion in renal transplantation (REPAIR): a multicentre, multinational, double-blind, factorial designed randomised controlled trial. *Efficacy Mech Eval* 2015; **2**: 1–84
16. Xia Z, Li H, Irwin MG. Myocardial ischaemia reperfusion injury: the challenge of translating ischaemic and anaesthetic protection from animal models to humans. *Br J Anaesth* 2016; **117 Suppl 2**: ii44–62
17. Kottenberg E, Thielmann M, Bergmann L, *et al*. Protection by remote ischemic preconditioning during isoflurane but not propofol—a clinical trial. *Acta Anaesthesiol Scand* 2012; **56**: 30–8
18. Kottenberg E, Musiolik J, Thielmann M, Jakob H, Peters J, Heusch G. Interference of propofol with signal transducer and activator of transcription 5 activation and cardioprotection by remote ischemic preconditioning during coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2014; **147**: 376–82
19. Kunst G, Klein AA. Peri-operative myocardial preconditioning and protection – cellular mechanisms and clinical relevance in cardiac anaesthesia. *Anaesthesia* 2015; **70**: 467–82
20. Landoni G, Greco T, Biondi-Zoccai G, *et al*. Anaesthetic drugs and survival: a Bayesian network meta-analysis of randomized trials in cardiac surgery. *Br J Anaesth* 2013; **111**: 886–96
21. Uhlig C, Bluth T, Schwarz K, *et al*. Effects of volatile anesthetics on mortality and postoperative pulmonary and other complications in patients undergoing surgery: a systematic review and meta-analysis. *Anesthesiology* 2016; **124**: 1230–45
22. Halestrap AP, Richardson AP. The mitochondrial permeability transition: a current perspective on its identity and role in ischaemia/reperfusion injury. *J Mol Cell Cardiol* 2015; **78**: 129–41
23. Yuan J, Cui G, Li W, *et al*. Propofol enhances hemoglobin-induced cytotoxicity in neurons. *Anesth Analg* 2016; **122**: 1024–30
24. Shim YH, Kersten JR. Preconditioning, anaesthetics, and perioperative medication. *Best Pract Res Clin Anaesthesiol* 2008; **22**: 51–65
25. Cleveland JC Jr, Meldrum DR, Cain BS, Banerjee A, Harken AH. Oral sulfonylurea hypoglycemic agents prevent

ischemic preconditioning in human myocardium. Two paradoxes revisited. *Circulation* 1997; **96**: 29–32
26. Ishihara M, Inoue I, Kawagoe T, *et al*. Diabetes mellitus prevents ischemic preconditioning in patients with a first acute anterior wall myocardial infarction. *J Am Coll Cardiol* 2001; **38**: 1007–11
27. Kloner RA, Shook T, Przyklenk K, *et al*. Previous angina alters in-hospital outcome in TIMI 4. A clinical correlate to preconditioning? *Circulation* 1995; **91**: 37–45
28. Kottenberg E, Thielmann M, Kleinbongard P, *et al*. Myocardial protection by remote ischaemic pre-conditioning is abolished in sulphonylurea treated diabetics undergoing coronary revascularisation. *Acta Anaesthesiol Scand* 2014; **58**: 453–62
29. Mouton R, Pollock J, Soar J, Mitchell DM, Rogers C. Remote ischaemic preconditioning versus sham procedure for abdominal aortic aneurysm repair: an external feasibility randomized controlled trial. *Trials* 2015; **16**: 377–86
30. Madathil RJ, Hira RS, Stoeckl M, Sterz F, Elrod JAB, Nichol G. Ischemia reperfusion injury as a modifiable therapeutic target for cardioprotection or neuroprotection in patients undergoing cardiopulmonary resuscitation. *Resuscitation* 2016; **105**: 85–91

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Think drink! Current fasting guidelines are outdated

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Ever since the formative work of Curtis Mendelson[1] in peripartum women, the need for preoperative fasting has been propagated to help to minimize the risk of pulmonary aspiration of gastric content during anaesthesia. That early work described the catastrophic consequences of particulate matter aspiration but also reported all those who aspirated non-particulate matter (40 patients out of 44 016) survived. This is notable considering the lack of sophisticated postoperative monitoring and care more than seven decades ago. Fasting guidelines and recommendations have been produced as a consequence of this early work, with the majority advocating a 6 h fast for solids, 4 h for breast milk, and 2 h for clear fluids for elective surgery in both adults and children,[2 3] the so-called 6–4–2 rule. Uncertainty remains for trauma patients, whereas obstetric patients are considered to have a full stomach.

Anaesthesia textbooks are full of recommended techniques to reduce the perceived risk of pulmonary aspiration, ranging from rapid sequence induction with cricoid pressure to the pharmacological modification of gastric pH using H_2-receptor blockers, proton-pump inhibitors, antacids, or prokinetics. None has been shown to reduce the incidence or indeed the severity of gastric content aspiration in a prospective clinical trial or data collection.

This is not surprising. Pulmonary aspiration of gastric contents during anaesthesia is not a common event. It occurs in approximately 1:900–1:10 000 in adults and in 2:10 000 children and is more frequent during emergency procedures. The outcomes range from asymptomatic (the majority) to prolonged hospital admission or even death. The outcome of death occurs predominantly in severely ill adults and is caused by acute asphyxia attributable to complete airway obstruction with solids and particulate matter.[4 5] There are no reports of deaths in the paediatric population in any of the several large retrospective or prospective series, with no liquid aspirations resulting in any reported long-term sequelae.[6–9]

Liquid aspiration occurs during normal sleep in almost half of the population and up to 70% of patients with depressed consciousness.[10] This does not usually result in significant clinical consequences, such as pneumonia or hospital admission. Also, what does the term 'empty stomach' mean? No fluid? No solids? No air? There will always be fluids or gastric secretions present. The quantity and composition of this is subject to individual variation depending on many, often non-quantifiable variables.

A sizeable amount of juice (7 ml kg^{-1}) administered to children is all but gone from the stomach within 1 h of ingestion as judged by magnetic resonance imaging.[11] Solids, however, behave differently, both in the speed with which they leave the stomach and in their ability to cause harm on aspiration.[1 12] What is relevant to the practice of anaesthesia is the presence and quantity of solid, particulate matter in the stomach, not fluids.

Reducing the preoperative fasting times has physiological benefits. Children <3 yr old whose preoperative fasting time is minimized by active measures show less reduction in blood pressure on induction and less evidence of a catabolic state.[13] Most strikingly, these changes are seen with a very modest reduction in mean fasting time from 8.5 to 6 h.

Reduction of the postoperative fasting time may also be of benefit according to the article published by Chauvin and colleagues[14] in this edition of the *BJA*. Those children reaching recovery with a high pain score and offered a drink of dilute apple juice in preference to an initial rescue dose of morphine showed a reduction in the pain score, less postoperative vomiting, a shorter recovery stay, and less postoperative rescue opioid ultimately. Of course, the consolability and crying components of the FLACC score used to assess the pain can be elevated because of a number of non-pain factors. Indeed, it is not surprising that many of these children may have been thirsty because children of both arms of the study had been fasted for fluid for more than 11 h before surgery. Taking thirst out of the equation and not