British Journal of Anaesthesia, 124 (1): 8–12 (2020)
doi: 10.1016/j.bja.2019.09.009
Advance Access Publication Date: 17 October 2019

Salvaging remote ischaemic preconditioning as a therapy for perioperative acute kidney injury

Alexander Zarbock[1,**], John A. Kellum[2], Alexander V. Gourine[3] and Gareth L. Ackland[3,4,*]

[1]Department of Anaesthesiology, Intensive Care Medicine and Pain Medicine, University Hospital Münster, Münster, Germany, [2]Center for Critical Care Nephrology, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA, USA, [3]Centre for Cardiovascular and Metabolic Neuroscience, Neuroscience, Physiology and Pharmacology, University College London, London, UK and [4]Translational Medicine & Therapeutics, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK

*Corresponding author.

**Corresponding author. E-mails: zarbock@uni-muenster.de, g.ackland@qmul.ac.uk

This editorial accompanies the following articles: Remote ischaemic preconditioning does not modulate the systemic inflammatory response or renal tubular stress biomarkers after endotoxaemia in healthy human volunteers: a single-centre, mechanistic, randomised controlled trial by Zwaag et al., *Br J Anaesth* 2019:123:177–185, doi: 10.1016/j.bja.2019.03.037
Early remote ischaemic preconditioning leads to sustained improvement in allograft function after live donor kidney transplantation: long-term outcomes in the REnal Protection Against Ischaemia-Reperfusion in transplantation (REPAIR) randomized trial by Veighey et al., *Br J Anaesth* 2019:123:584–591, doi: 10.1016/j.bja.2019.07.019

> *das Kind mit dem Bade ausschütten* (to throw out the baby with the bathwater)
>
> Thomas Murner, *Narrenbeschwörung* (*Appeal to Fools*), 1512

For such an apparently simple perioperative intervention that promised so much, remote ischaemic preconditioning (RIPC) appears to be hovering above the same sinkhole through which many other interventions have disappeared. RIPC, induced by brief episodes of ischaemia and reperfusion in a distant organ before a subsequent injury occurs, reduces the extent of organ injury, potentially conferring protection at remote sites, including the brain, heart, lung, kidney, skeletal muscle, and intestine.[1] Based on laboratory data, RIPC appears to be mediated by humoral mediator(s) because the protective effect is dialysable, transferable from individual to individual across species, and receptor mediated.[2] It has been shown that plasma from animals treated with RIPC is cardioprotective when applied to an isolated ischaemic heart.[3] However, RIPC may recruit several other mechanisms involving systemic anti-inflammatory, humoral, and neuronal autonomic signalling pathways.

Lost in translation?

Despite substantial progress in translating experimental evidence for RIPC into clinical practice, randomised clinical trials in the perioperative setting have reported equivocal benefits in reducing organ injury. As has been highlighted, assuming that findings in the non-anaesthetised state fit neatly into the surgical setting, with apparent disregard for the perioperative milieu, is highly flawed.[4] As it turns out, the contribution of anaesthesia/perioperative medicine is likely to be pivotal to interpreting the results of trials involving RIPC, both within and beyond the perioperative setting. Two papers recently published by the *British Journal of Anaesthesia* (BJA) have revisited both the clinical and translational aspects of RIPC in kidney injury. In concert with many currently hot topics in perioperative medicine, these studies graphically illustrate the paramount need for enhanced mechanistic understanding[5] and longer-term follow-up[6] of perioperative interventions.

Need for perioperative renal protection

Patients with co-morbidities and those who are undergoing complex procedures have a particularly high risk for developing acute kidney injury (AKI).[7,8] For example, after abdominal surgery, the pooled incidence of AKI in 82 514 patients was 13.4% (95% confidence interval [CI]: 10.9–16.4%).[9] The relative risk of death in the presence of postoperative AKI was 12.6-fold (95% CI: 6.8–23.4).[9] The incidence of AKI amongst critically ill patients can be as high as 60%, with an in-hospital mortality of up to 50% when AKI is part of the multiple organ dysfunction syndrome.[10] Clearly, AKI should be regarded as an important surgical outcome measure and a potential target for clinical interventions.

RIPC and perioperative renal protection

Experimental studies and small clinical trials first suggested that RIPC may prevent perioperative kidney injury after cardiac and vascular surgery.[11] The Right Ventricular Remodeling in Pulmonary Arterial Hypertension (REPAIR) trial investigated the effect of RIPC on long-term outcome of allograft function after live-donor kidney transplantation.[6] The long-term follow-up of the REPAIR trial for up to 5 yr after transplantation, recently

DOIs of original article: 10.1016/j.bja.2019.03.037, 10.1016/j.bja.2019.07.019.

published in the BJA, reported that RIPC was associated with sustained improvement of the estimated glomerular filtration rate (adjusted mean difference: 5 ml min^{-1} (1.73 m)$^{-2}$ [95% CI: 2–8]; P=0.004).[6] This suggests that RIPC before live-donor transplantation can substantially improve long-term kidney allograft function and subsequently extend the life of the allograph by several years. Consistent with these findings, the RenalRIPC investigators reported that RIPC applied in 240 patients at high risk of AKI before cardiac surgery reduced AKI from 53% to 38% (absolute risk reduction [ARR]: 15% [95% CI: 3–27%]), and renal replacement therapy (ARR: 10% [95% CI: 2–18%]).[12] The effectiveness of RIPC was strongly associated with the release of tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth-factor-binding protein-7 (IGFBP7), biomarkers for cell-cycle arrest indicative of renal tubular stress. Also in the BJA, Zwaag and colleagues[5] recently reported that RIPC alone induced the release of TIMP-2 and IGFBP7 in 30 healthy male volunteers, but RIPC neither modulated systemic cytokine release nor attenuated inflammation-induced tubular stress after low-dose endotoxin, a Toll-like receptor-4 (TLR-4) agonist. Notably, endotoxin preconditioning reduces renal ischaemia/reperfusion injury by hypoxia-inducible factor-2α activation in endothelial cells, which is associated with improved renal microvascular perfusion and reduced ischaemic tubular damage.[13] It is, therefore, striking that RIPC triggers a similar molecular stress response in cardiac[14] and renal tissue that is also triggered by TLR-4 agonists that induce renal protection. However, the injurious effects of RIPC through this stressor mechanism cannot be ruled out.[14,15] This may, in part, explain why RIPC failed to reduce the occurrence of AKI in the two largest multicentre trials in cardiac surgical patients comprising >3000 patients, which included AKI as a secondary outcome.[16,17]

Perioperative RIPC: unanswered questions

Reconciling the positive and neutral results of perioperative trials in RIPC demands a critical reconsideration of the many shortcomings in trial design and, rather more fundamentally, mechanistic understanding of RIPC. First, an objective readout that would define a clinically useful therapeutic range for RIPC remains unknown. Thus far, no clinical studies have shown that RIPC elicits a reproducible cellular or molecular signature (such as that described by Zwaag and colleagues[5]). It is also unknown whether RIPC is 'toxic' or what the minimally effective dose might be. Basic and human experimental studies show that neural (autonomic) modulation is a major component of the mechanisms underlying RIPC.[18] The impact of anaesthesia on the autonomic mechanisms of RIPC is pivotal in understanding trial results and in considering whether the fundamental biological mechanisms underpinning RIPC can be manipulated to maximise the clinical benefit.

Autonomic mechanisms of RIPC: a key perioperative link

Both the sympathetic[19] and parasympathetic[20] components of the autonomic nervous system contribute to RIPC-mediated organ protection (Fig. 1). Ischaemic activation of sensory (afferent) C-fibre neurones[21] in a distant organ triggers a vagal reflex that confers cardiac protection, independently of HR changes.[20] Additionally, stimulation of the vagus nerve 24 h before ischaemia–reperfusion injury reduces kidney injury in mice[22] and systemic inflammation in patients with rheumatoid arthritis.[23] A major component of experimental renal protection is conferred by a neuro-immune mechanism,

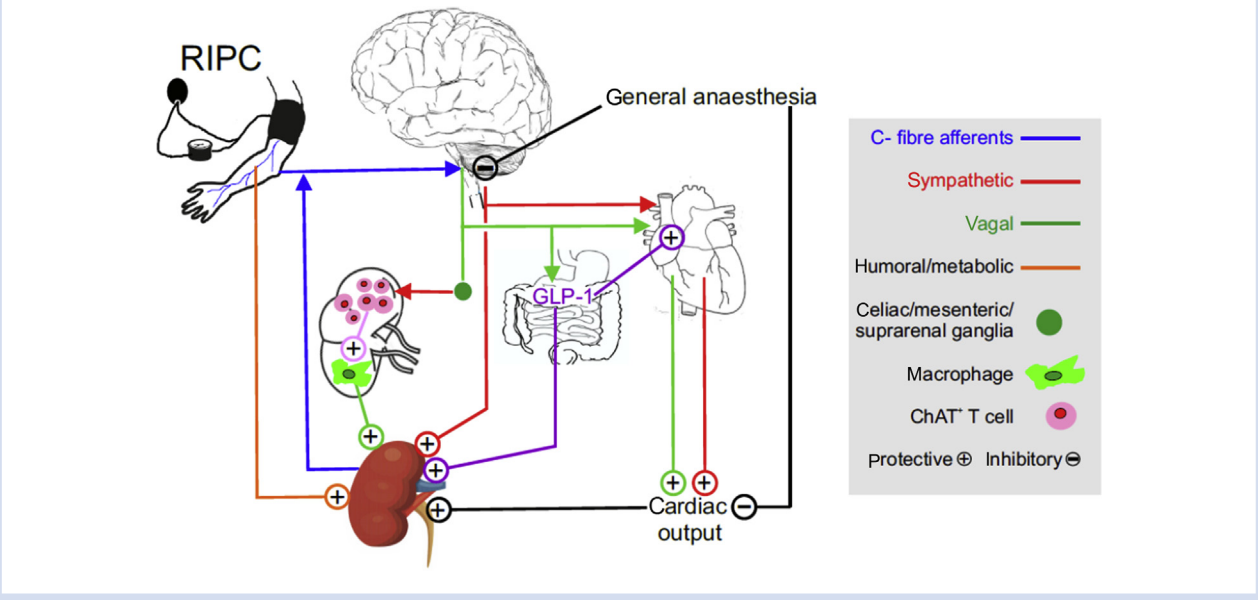

Fig 1. Potential mechanisms of remote ischaemic preconditioning (RIPC) involved in reducing perioperative acute kidney injury. Experimental data show that RIPC confers renal protection through humoral and neural autonomic pathways. Efferent vagal activity mediates the release of glucagon-like peptide-1 (GLP-1) from the gastrointestinal tract, which confers cardiac and renal protection. Vagally mediated postganglionic splenic nerve releases norepinephrine, which binds to β-2 adrenergic receptors expressed on T cells and stimulates the release of acetylcholine from $CD4^{+}CD44^{high}CD62L^{low}$ memory T cells, which in turn reduces the macrophage release of pro-inflammatory cytokines via α-7 nicotinic acetylcholine receptors. Direct anti-inflammatory β-2 adrenergic-receptor-mediated renal protection can also occur. Preserving adequate cardiac output, and hence renal perfusion, requires maintenance of both efferent sympathetic and parasympathetic activities, both of which are impaired by the deleterious effects of general anaesthesia.

which has also been shown to operate in cardioprotection after experimental haemorrhage.[24] Increased vagal nerve activity triggers the release of norepinephrine by splenic nerve terminals via the suprarenal ganglia, which in turn activates splenic choline-acetyltransferase-positive T lymphocytes to release acetylcholine in a beta-adrenergic-receptor-dependent manner.[25] Binding of acetylcholine to nicotinic cholinergic receptors expressed on macrophages that reside close to these T cells leads to suppression of inflammatory cytokines, and hence, reduced inflammation. Loss of vagal innervation prevents this anti-inflammatory action. RIPC also triggers effects mediated by glucagon-like peptide-1 (GLP-1) receptors, likely through GLP-1 release from viscera innervated by the posterior gastric branch of the vagus nerve.[26] GLP-1R agonists confer renal protection independent of their beneficial effects in improving glycaemic control.[27]

The sympathetic regulation of inflammation is coordinated by pre-sympathetic C1 neurones residing in the ventrolateral medulla via projections to sympathetic neurones.[19] Multiple stressors activate C1 cells, including inflammation, hypoxia, pain, hypotension, and short periods of physical restraint stress. Combined with vagally mediated reductions in HR or augmentation of cardiac output,[28] the parasympathetic activation by RIPC activates mechanisms that confer organ protection.

Perioperative medicine: a welcome fly in the RIPC ointment?

Perioperative research has generated two key insights into the mechanisms of RIPC. First, the modulation of autonomic function by general anaesthesia is likely to profoundly alter the effectiveness of RIPC. Although different anaesthetic agents impact locally on the extent of experimental ischaemia–reperfusion injury,[29] differential effects on organ protection involving both neural and humoral components of RIPC are likely. Propofol attenuates the effects of RIPC,[30] an effect that may be attributable to the attenuated expression of preconditioning inflammatory mediators,[31] central inhibition of vagal preganglionic neurones, or both.[32] In the two largest multicentre trials in cardiac surgery, most patients received propofol for anaesthesia, which could have abrogated the potential beneficial effects of RIPC. Second, cardiopulmonary exercise testing has revealed that ~35% of higher-risk patients undergoing major noncardiac surgery have markedly impaired autonomic function.[33,34] In the case of cardiac vagal impairment, this is independently associated with myocardial injury[34] and AKI,[35] suggesting that a loss of intrinsic neural protection mechanisms may promote cardio-renal injury. Pre-existing autonomic impairment may therefore impair the effectiveness of RIPC in conferring organ protection. Acute reductions in sympathetic and parasympathetic activities that typify the perioperative stress response may also impair the operation of intrinsic RIPC mechanisms. The timing of disrupting neural regulatory control mechanisms has major implications for the time frame over which RIPC should be applied.

RIPC: the need for a personalised medicine approach

One explanation for the discordant results from perioperative clinical trials is the failure to target the correct phenotype at the correct time in the most appropriate patient and operative setting. Using RIPC in higher-risk patients significantly reduces the occurrence of AKI,[12] whereas the application of this same intervention in lower-risk patients has no effect on AKI.[16,17] Notably, patients with chronic kidney disease, who are at most risk of perioperative AKI, exhibit markedly lower parasympathetic (cardiac vagal) activity (Fig. 2). As the study by Veighey and colleagues[6] on the BJA shows, the clinical use of RIPC is applicable to many perioperative areas beyond cardiac surgery, many of which remain unexplored. Moreover, application of RIPC in the setting of kidney transplantation highlights the critical importance of timing for RIPC. As Veighey and colleagues[6] have shown, RIPC applied to both donors and recipients before the actual insult occurs is likely to confer a long-term impact for the recipient.

Depending on the applied stimulus and clinical setting, the contribution of humoral and neural signalling pathways may be variably dominant, but it is likely that the different pathways interact with each other. The elegant human model of acute inflammation used by Zwaag and colleagues[5] illustrates the need for further insights into the RIPC-immune interface, which remains in its infancy. Renal tubular epithelial cells express several pattern recognition receptors that respond to injurious exogenous and endogenous stimuli, including damage-associated molecular patterns. Different stressors might trigger a variety of self-protective mechanisms for renal tubular epithelial cells, including cell-cycle arrest and down-regulation of energy-expending ion transport functions.[36] Manipulating the responses of renal tubular epithelial cells to the mediators released in response to RIPC remains poorly understood.

In conclusion, there are several reasons why perioperative RIPC deserves further exploration, not least because the surgical setting enables a targeted, personalised application of the RIPC procedure in highly phenotyped subjects. A better understanding of the underlying mechanisms, clinical effects, and patient selection is still needed before this promising intervention can be fully adopted or dismissed from perioperative use. The perioperative setting affords the ideal conditions to determine whether a personalised medicine approach can refocus RIPC as a scalable therapeutic intervention.

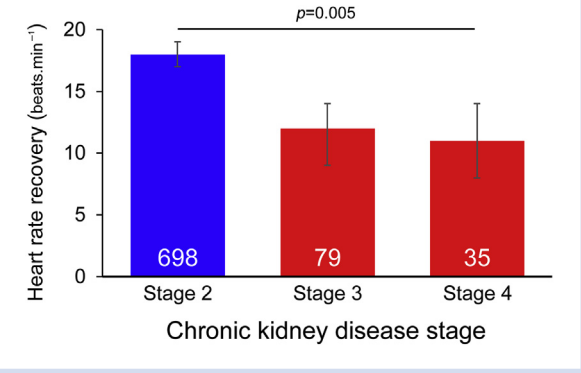

Fig 2. Chronic kidney disease (CKD) and cardiac vagal function. Patients with Stage 3–4 CKD, who are at substantially higher risk of acute kidney injury after surgery, are more likely to have impaired efferent vagal activity, as quantified by slower HR recovery (data from Ackland and colleagues[35]). *P*-value refers to differences in HR recovery between Stage 2 *vs* Stages 3 and 4 CKD (by one-way analysis of variance).

Authors' contributions

Drafting of first version: AZ, GLA.
Review/editing of revised manuscript: all authors.

Declarations of interest

AZ received research grants from DFG, Fresenius, Else Kröner-Fresenius-Stiftung, and Astute Medical, and lecture fees from Astute Medical, bioMérieux, Baxter, Fresenius, and Braun. GLA is an editor of the BJA, whose research work was supported by the British Oxygen Company Research Chair grant, British Heart Foundation programme grant (RG/14/4/30736), and Royal College of Anaesthetists/BJA Basic Science Career Development Award. GLA has also undertaken a consultancy work for GlaxoSmithKline that is unrelated to this work. He is also a member of the editorial advisory board of *Intensive Care Medicine Experimental*. AVG was a recipient of the British Heart Foundation programme grant (RG/14/4/30736) and Wellcome Trust Senior Investigator award. JAK declares that he has no conflict of interest.

References

1. Zarbock A, Kellum JA. Remote ischemic preconditioning and protection of the kidney—a novel therapeutic option. *Crit Care Med* 2016; **44**: 607–16
2. Kharbanda RK, Nielsen TT, Redington AN. Translation of remote ischaemic preconditioning into clinical practice. *Lancet* 2009; **374**: 1557–65
3. Shimizu M, Tropak M, Diaz RJ, et al. Transient limb ischaemia remotely preconditions through a humoral mechanism acting directly on the myocardium: evidence suggesting cross-species protection. *Clin Sci (Lond)* 2009; **117**: 191–200
4. Zaugg M, Lucchinetti E, Clanachan A, Finegan B. Remote ischemic preconditioning is redundant in patients undergoing coronary artery bypass graft surgery who are already protected by volatile anesthetics. *Circ Res* 2012; **110**. e42–3, author reply e44–5
5. Zwaag J, Beunders R, Warlé MC, et al. Remote ischaemic preconditioning does not modulate the systemic inflammatory response or biomarkers for renal tubular stress following endotoxaemia in healthy human volunteers: a single-centre, mechanistic, randomised controlled trial in healthy volunteers. *Br J Anaesth* 2019; **123**: 177–85
6. Veighey K, Nicholas J, Clayton T, et al. Early remote ischaemic preconditioning leads to sustained improvement in allograft function following live donor kidney transplantation; long term outcomes in the REPAIR randomised trial. *Br J Anaesth* 2019; **11**. https://doi.org/10.1016/j.bja.2019.07.019. Advance Access published on September
7. Hobson CE, Yavas S, Segal MS, et al. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. *Circulation* 2009; **119**: 2444–53
8. Kheterpal S, Tremper KK, Heung M, et al. Development and validation of an acute kidney injury risk index for patients undergoing general surgery: results from a national data set. *Anesthesiology* 2009; **110**: 505–15
9. O'Connor ME, Kirwan CJ, Pearse RM, Prowle JR. Incidence and associations of acute kidney injury after major abdominal surgery. *Intensive Care Med* 2016; **42**: 521–30
10. Singbartl K, Kellum JA. AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. *Kidney Int* 2012; **81**: 819–25
11. Gassanov N, Nia AM, Caglayan E, Er F. Remote ischemic preconditioning and renoprotection: from myth to a novel therapeutic option? *J Am Soc Nephrol* 2014; **25**: 216–24
12. Zarbock A, Schmidt C, Van Aken H, et al. Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial. *JAMA* 2015; **313**: 2133–41
13. He K, Chen X, Han C, et al. Lipopolysaccharide-induced cross-tolerance against renal ischemia–reperfusion injury is mediated by hypoxia-inducible factor-2α-regulated nitric oxide production. *Kidney Int* 2014; **85**: 276–88
14. Albrecht M, Zitta K, Bein B, et al. Remote ischemic preconditioning regulates HIF-1alpha levels, apoptosis and inflammation in heart tissue of cardiosurgical patients: a pilot experimental study. *Basic Res Cardiol* 2013; **108**: 314
15. Zaugg M, Lucchinetti E. Remote ischemic preconditioning in cardiac surgery—ineffective and risky? *N Engl J Med* 2015; **373**: 1470–2
16. Hausenloy DJ, Candilio L, Evans R, et al. Remote ischemic preconditioning and outcomes of cardiac surgery. *N Engl J Med* 2015; **373**: 1408–17
17. 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
18. Basalay MV, Davidson SM, Gourine AV, Yellon DM. Neural mechanisms in remote ischaemic conditioning in the heart and brain: mechanistic and translational aspects. *Basic Res Cardiol* 2018; **113**: 25
19. Guyenet PG, Stornetta RL, Bochorishvili G, Depuy SD, Burke PG, Abbott SB. C1 neurons: the body's EMTs. *Am J Physiol Regul Integr Comp Physiol* 2013; **305**: R187–204
20. Mastitskaya S, Marina N, Gourine A, et al. Cardioprotection evoked by remote ischaemic preconditioning is critically dependent on the activity of vagal preganglionic neurones. *Cardiovasc Res* 2012; **95**: 487–94
21. Basalay M, Barsukevich V, Mastitskaya S, et al. Remote ischaemic pre- and delayed postconditioning—similar degree of cardioprotection but distinct mechanisms. *Exp Physiol* 2012; **97**: 908–17
22. Tanaka S, Okusa MD. AKI and the neuroimmune axis. *Semin Nephrol* 2019; **39**: 85–95
23. Koopman FA, Chavan SS, Miljko S, et al. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. *Proc Natl Acad Sci U S A* 2016; **113**: 8284–9
24. Guarini S, Altavilla D, Cainazzo MM, et al. Efferent vagal fibre stimulation blunts nuclear factor-κB activation and protects against hypovolemic hemorrhagic shock. *Circulation* 2003; **107**: 1189–94
25. Chavan SS, Pavlov VA, Tracey KJ. Mechanisms and therapeutic relevance of neuro-immune communication. *Immunity* 2017; **46**: 927–42
26. Basalay MV, Mastitskaya S, Mrochek A, et al. Glucagon-like peptide-1 (GLP-1) mediates cardioprotection by remote ischaemic conditioning. *Cardiovasc Res* 2016; **112**: 669–76
27. van Baar MJB, van Raalte DH, Muskiet MHA. GLP-1 receptor agonists, CKD, and eGFR trajectory. *Lancet Diabetes Endocrinol* 2018; **6**: 764–5
28. Machhada A, Trapp S, Marina N, et al. Vagal determinants of exercise capacity. *Nat Commun* 2017; **8**: 15097

29. Zaugg M, Wang L, Zhang L, Lou PH, Lucchinetti E, Clanachan AS. Choice of anesthetic combination determines Ca^{2+} leak after ischemia–reperfusion injury in the working rat heart: favorable versus adverse combinations. *Anesthesiology* 2012; **116**: 648–57
30. Kottenberg E, Thielmann M, Bergmann L, et al. Protection by remote ischemic preconditioning during coronary artery bypass graft surgery with isoflurane but not propofol—a clinical trial. *Acta Anaesthesiol Scand* 2012; **56**: 30–8
31. Motayagheni N, Phan S, Eshraghi C, Nozari A, Atala A. A review of Anesthetic effects on renal function: potential organ protection. *Am J Nephrol* 2017; **46**: 380–9
32. Wang X, Huang ZG, Gold A, et al. Propofol modulates gamma-aminobutyric acid-mediated inhibitory neurotransmission to cardiac vagal neurons in the nucleus ambiguus. *Anesthesiology* 2004; **100**: 1198–205
33. Abbott TEF, Pearse RM, Beattie WS, et al. Chronotropic incompetence and myocardial injury after non-cardiac surgery: planned secondary analysis of a prospective observational international cohort study. *Br J Anaesth* 2019; **123**: 17–26
34. Abbott TEF, Pearse RM, Cuthbertson BH, Wijeysundera DN, Ackland GL, METS Study Investigators. Cardiac vagal dysfunction and myocardial injury after non-cardiac surgery: a planned secondary analysis of the measurement of exercise tolerance before surgery study. *Br J Anaesth* 2019; **122**: 188–97
35. Ackland GL, Abbott TEF, Minto G, et al. Heart rate recovery and morbidity after noncardiac surgery: planned secondary analysis of two prospective, multi-centre, blinded observational studies. *PLoS One* 2019; **14**, e0221277
36. Gomez H, Ince C, De Backer D, et al. A unified theory of sepsis-induced acute kidney injury: inflammation, microcirculatory dysfunction, bioenergetics, and the tubular cell adaptation to injury. *Shock* 2014; **41**: 3–11

British Journal of Anaesthesia, 124 (1): 12–14 (2020)
doi: 10.1016/j.bja.2019.09.038
Advance Access Publication Date: 2 November 2019

Is less really more? A critical appraisal of a POPULAR study reanalysis

Thomas Fuchs-Buder[1] and Sorin J. Brull[2,*]

[1]CHRU Nancy, Nancy, France and [2]Mayo Clinic College of Medicine and Science, Jacksonville, FL, USA

*Corresponding author. E-mail: SJBrull@me.com

This editorial accompanies: Use of a train-of-four ratio of 0.95 versus 0.9 for tracheal extubation: an exploratory analysis of POPULAR data by Blobner et al., *Br J Anaesth* 2020:124:63–72, doi: 10.1016/j.bja.2019.08.023

'*You see, but you do not observe*.' Sir Arthur Conan Doyle (1859–1930); *A Scandal in Bohemia*

The POPULAR study[1] was a multicentre, prospective, large-scale observational cohort study in which 22 803 patients from 211 hospitals in 28 European countries were recruited to investigate the potential role of neuromuscular blocking agents on patient safety, particularly postoperative pulmonary complications.[1] In this study, 17 150 patients received a neuromuscular blocking agent. In more than 10 000 patients, intraoperative neuromuscular monitoring was not used at all, and in 11 789 patients, the timing of tracheal extubation was based on clinical criteria. The recommended objective neuromuscular monitoring was used in only 4182 patients, but surprisingly, in 32.1% of patients tracheal extubation occurred before achieving a train-of-four (TOF) ratio of 0.9, thus questioning the utility of quantitative monitoring when quantitative data are ignored.

The POPULAR study led to an initial publication in *The Lancet Respiratory Medicine*.[1] In the current issue of the *British Journal of Anaesthesia*, Blobner and colleagues[2] present a reanalysis of the POPULAR database. At first glance, it may appear that the authors' most recent conclusions are different from those published by the same authors previously.[1] Indeed, the key message of the original publication was, 'The use of neuromuscular monitoring and the administration of reversal agents were not associated with a decreased risk of pulmonary complications. Neither the choice of sugammadex instead of neostigmine for reversal nor extubation at a train-of-four ratio of 0.9 or more was associated with better pulmonary outcome.'[1] Accordingly, it is likely that many clinicians understood the message of the initial publication as follows: neither neuromuscular monitoring nor pharmacological antagonism (with either neostigmine or sugammadex) contributes to decrease the clinical consequences of residual paralysis. This initial message appears to contradict previous studies that unequivocally found that quantitative monitoring and the use of pharmacological antagonists contribute to lowering of postoperative pulmonary complications.[3–5] In the current reanalysis,[2] the key message is '...The presented

DOI of original article: 10.1016/j.bja.2019.08.023.