British Journal of Anaesthesia, 125 (5): 642–646 (2020)
doi: 10.1016/j.bja.2020.08.007
Advance Access Publication Date: 6 September 2020

Aetiology of perioperative myocardial injury: a scientific conundrum with profound clinical implications

Simon J. Howell[1,*], Oliver I. Brown[2] and W. Scott Beattie[3]

[1]Leeds Institute of Medical Research at St James's, University of Leeds, St James's University Hospital, Leeds, UK, [2]Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK and [3]Department of Anaesthesia, University of Toronto, Toronto, ON, Canada

*Corresponding author. E-mail: s.howell@leeds.ac.uk

This editorial accompanies: MicroRNA signatures of perioperative myocardial injury after elective noncardiac surgery: a prospective observational mechanistic cohort study by May et al., *Br J Anaesth* 2020:125: 661–671, doi: 10.1016/j.bja.2020.05.066

Keywords: complication; myocardial infarction; myocardial injury; myocardial ischaemia; perioperative outcome; troponin

Perioperative myocardial infarction has been recognised as an important complication of anaesthesia and surgery for more than half a century. In 1961, Driscoll and colleagues[1] reported postoperative ECG changes consistent with myocardial ischaemia or infarction in 42 of 496 patients undergoing surgery under general anaesthesia. Studies in the succeeding decades have reinforced the impact of perioperative cardiac complications and have led to protracted debate regarding the aetiology of perioperative myocardial infarction.[2] It is now clear that perioperative acute myocardial injury is common, occurring in up to 25% of patients, and has been reproducibly shown to be associated with an increased incidence of major postoperative morbidity, including death.[3–7] It is therefore critical that we understand the mechanisms of this injury, as safe and effective prophylaxis and treatment depend on this knowledge. In this issue of the *British Journal of Anaesthesia*, May and colleagues[8] present preliminary data suggesting an aetiology for this emerging perioperative problem.

May and colleagues[8] investigated the potential mechanism of postoperative troponin elevations in surgical patients who did not have the other diagnostic criteria (e.g. ECG changes) for myocardial infarction. The specific objective of the report was ' … to assess whether the subgroup of patients with postoperative troponin concentrations indicative of myocardial injury, but who did not sustain myocardial infarction, share the same microRNA profile as seen in acute myocardial ischaemia'.

The mechanism of postoperative myocardial injury is controversial. Evidence from the perioperative ischemic evaluation (POISE) trial suggested that many of the patients who sustain myocardial injury in the postoperative period do not satisfy the diagnostic criteria for myocardial infarction. In a *post hoc* analysis, a proportion of the patients with postoperative troponin elevations, but without the criteria to diagnose myocardial infarction, had poor outcomes.[3] It was speculated that these patients may have been misclassified. As most postoperative myocardial infarctions have no symptoms or ECG changes, patients who had sustained a myocardial infarction could have been missed. Some investigators have called for a new postoperative myocardial infarction definition. It was in this spirit that Botto and colleagues[9] proposed that 'myocardial injury *caused by ischemia* (that may or may not result in necrosis), has prognostic relevance and occurs during or within 30 days after noncardiac surgery'.

Using data from the first vascular events in noncardiac surgery patients cohort evaluation (VISION) study publication, Botto and colleagues[9] proposed the nosological entity of myocardial injury after noncardiac surgery (MINS). The clinical and laboratory criteria for this diagnosis are based on there being cardiac troponin (cTn) release in the absence of a demonstrable noncardiac cause. MINS is defined utilising high-sensitivity cardiac troponin T (hscTnT) exclusively. Patients who have *symptomatic* noncardiac conditions associated with elevated troponin concentrations (patients with pulmonary embolism, sepsis, and chronic renal failure) are not considered to have MINS and are excluded from this diagnosis. The postoperative hscTnT concentration elevation required to make a diagnosis of MINS depends on whether the preoperative troponin concentration was evaluated. If the preoperative hscTnT is above the upper reference limit (URL), a postoperative increase of >5 ng L^{-1} is required. If there is no preoperative troponin concentration available, a postoperative troponin concentration >30 ng L^{-1} is defined as MINS. Although this definition includes patients who do fulfil the diagnostic criteria of myocardial infarction, there is no requirement for the patient to display any ischaemic features. However, the definition presumes that the myocardial injury is caused by ischaemia with the statement that MINS is ' …

DOI of original article: 10.1016/j.bja.2020.05.066.

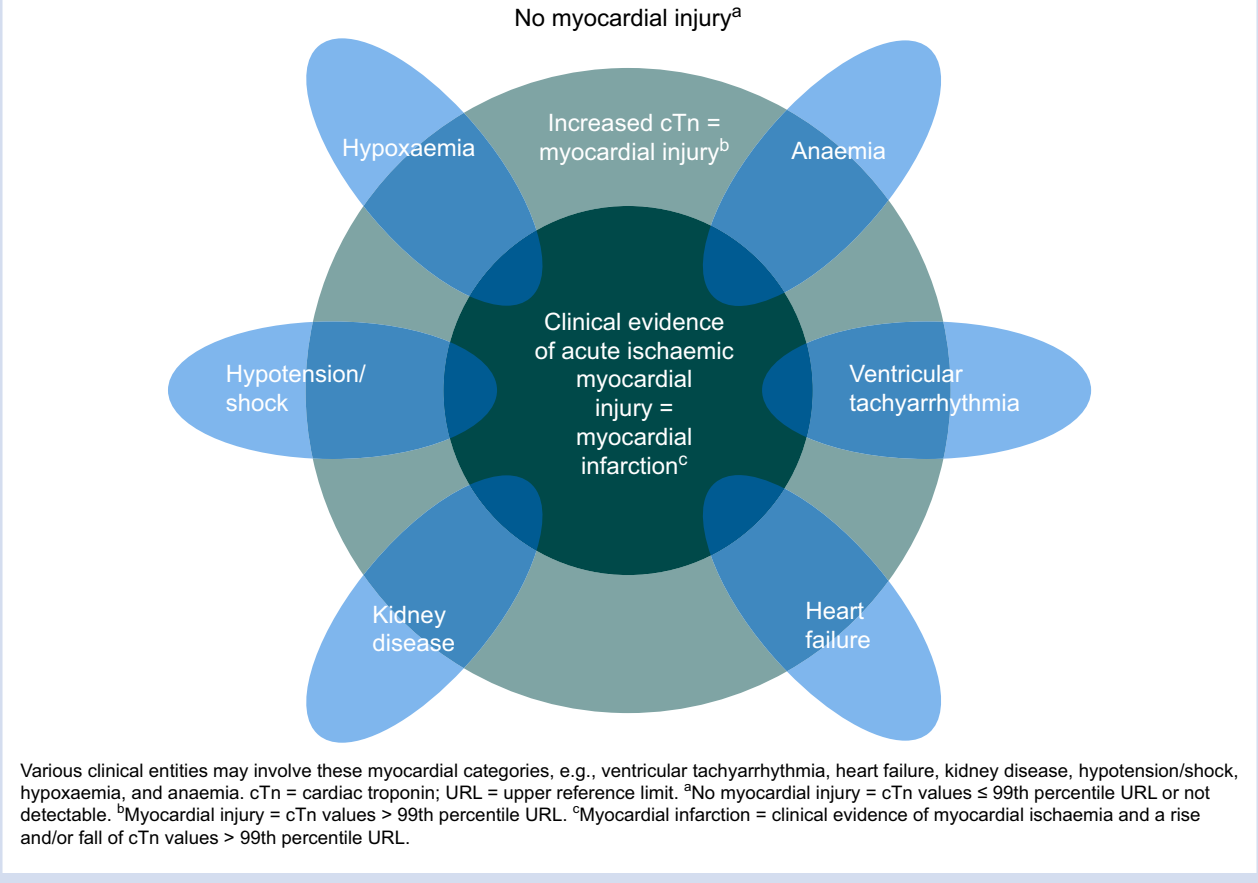
myocardial injury caused by ischaemia that may or may not result in necrosis … '.

Alternatively, the criterion for a diagnosis of myocardial injury, as defined in the Fourth Universal Definition of Myocardial Infarction,[10] is detection of an elevated cTn value above the 99th percentile URL. The injury is considered acute if there is an increase or decrease of cTn values. Importantly, the type of troponin assay is not specified. In contrast to the definition of MINS, the mechanism or aetiology is not specified. The Fourth Universal Definition of Myocardial Infarction makes clear that myocardial injury can be as a result of anaemia, hypoxaemia, hypotension, renal failure, heart failure, tachyarrhythmia, and pulmonary embolism (Fig. 1). This diagram shows that myocardial injury occurs in some of the patients that display these entities and can also, at times, be associated with myocardial infarction. The diagnosis of non-fatal myocardial infarction can only be made if the troponin elevation is associated with any ECG changes consistent with ischaemia, clinical symptoms of ischaemia, or imaging evidence. The distinction between a myocardial infarction and myocardial injury is, however, critically important both prognostically and mechanistically. The demonstration of myocardial infarction criteria (troponin elevations and ischaemic symptoms or ECG changes) has been reproducibly shown to carry more than a two-fold increase in all-cause mortality than myocardial injury alone at both 30 days[4,6] and 1 yr.[7,11]

The question, in a nutshell, is whether perioperative troponin release in the absence of ECG changes or other markers of myocardial ischaemia should be considered one of the other (non-ischaemic) causes of myocardial injury as identified in the Universal Definition of Myocardial Infarction, or whether it inevitably has an ischaemic aetiology. It is this issue that the current paper seeks to address.

The study by May and colleagues[8] is the first to utilise microRNAs (miRNAs) to explore the nature of myocardial injury. MicroRNAs are a diverse class of small single-stranded non-coding RNA. MicroRNAs modulate gene expression post-transcriptionally by inhibiting the translation of their target complementary messenger RNA (mRNA) and promoting the degradation of mRNA.[12,13] They are produced by all cell types and are secreted extracellularly within microparticles (exosomes, apoptotic bodies, and micro-vesicles) or bound to proteins.[14] The stability of circulating miRNAs has led to them being proposed as potential biomarkers for diseases, including cancer, viral infections, and cardiovascular disease.

Measuring circulating concentrations of miRNA can be challenging. The most robust method is with reverse transcription quantitative real-time polymerase chain reaction (RT–qPCR). Technical and analytical considerations



Various clinical entities may involve these myocardial categories, e.g., ventricular tachyarrhythmia, heart failure, kidney disease, hypotension/shock, hypoxaemia, and anaemia. cTn = cardiac troponin; URL = upper reference limit. [a]No myocardial injury = cTn values ≤ 99th percentile URL or not detectable. [b]Myocardial injury = cTn values > 99th percentile URL. [c]Myocardial infarction = clinical evidence of myocardial ischaemia and a rise and/or fall of cTn values > 99th percentile URL.

Fig 1. Reproduced from the Fourth Universal Definition of Myocardial Infarction,[10] with permission.

(including collection modality, storage conditions, and transcription efficiency) can cause significant variability in miRNA measurement.[15] This can be reduced by normalisation, which involves using mathematical modelling to rank the expression stability of candidate genes compared with a 'normaliser' or reference standard. Normalisers include exogenous synthetic oligonucleotides, endogenous miRNAs, and the geometrical mean of the quantification cycle (Cq) of all the miRNA sequences analysed.[15] Cq values represent the number of amplification cycles needed to detect a target miRNA and are therefore inversely related to the quantity of target miRNA. There is no universally accepted method of normalisation. This reduces the ability to compare results between studies and the appropriateness of pooling of data with meta-analysis.

A large number of miRNAs (including, but not limited to, miRNA-1, miRNA-133, miRNA-145, miRNA-208, and miRNA-499) have some degree of cardiac specificity.[16] Their roles are diverse, but include regulation of angiogenesis, apoptosis, cardiac myocyte differentiation, and repression of cardiac hypertrophy.[14] May and colleagues[8] used miRNA-1, miRNA-21, miRNA-133, miRNA-146, miRNA-208, and miRNA-499 as signatures for acute coronary syndrome, justifying their use from the results of the recent meta-analysis by Cheng and colleagues.[17] This correlated established serum biomarkers of acute coronary syndrome with miRNA-1, miRNA-21, miRNA-133, miRNA-146, miRNA-208, and miRNA-499, and demonstrated that the sensitivities and specificities of these miRNAs for the diagnosis of myocardial infarction were 63% and 89%, respectively.[17] However, there are significant limitations of this meta-analysis. Firstly, not all of the included studies used the Universal Definition of Myocardial Infarction. The majority of included studies are case–control in design and have a risk of selection bias. There are significant differences in characteristics of cases and controls in some of the included studies. Finally, different studies use different normalisation strategies that can significantly impact the outcome of RT–qPCR miRNA quantification. Therefore, we cannot say with certainty that miRNA-1, miRNA-21, miRNA-133, miRNA-146, miRNA-208, and miRNA-499 are entirely sensitive or specific for acute coronary syndrome.

Notwithstanding these limitations, after adjusting for Type 1 error, May and colleagues[8] found that increases in troponin were not associated with miRNA changes characteristic of ischaemic myocardial injury. Looking beyond the miRNA signature of ischaemic injury, the two studies presented by May and colleagues[8] offer interesting insights into the cellular and genomic pathways involved with perioperative myocardial injury. The authors identify an association between SLC8A1 (NCX1 sodium–calcium exchanger) and miRNAs elevated after surgery. The NCX1 sodium–calcium exchanger regulates cytoplasmic Ca^{2+} concentration in the cardiac myocyte, exporting calcium into the extracellular space.[18] Ischaemia/reperfusion injury and adrenergic stress both can affect the NCX1 sodium–calcium exchanger, leading to dysfunctional intracellular handling of calcium and ultimately cardiac myocyte death.[19]

May and colleagues[8] propose a loss of cardioprotective mechanisms as a potential mechanism of perioperative myocardial injury, because of an aberrant inflammatory response mediated by reduced expression of miRNA-146a. Secretion of pro-inflammatory cytokines (including interleukin-6, interleukin-8, cytokine MCP-1, and CCL20) is reduced by miRNA-146a *ex vivo* in human adipocytes *via* a negative feedback loop.[20] Targeted inhibition of selected pro-inflammatory cytokines improves clinical outcome. In the recent CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) trial, inhibition of interleukin-1β (central to the interleukin-6 inflammatory pathway) with canakinumab was shown to reduce cardiovascular events in patients with myocardial infarction when compared with placebo.[21] In addition, Ackland and colleagues[22] have shown that an elevated neutrophil-to-lymphocyte ratio (a marker of systemic inflammation) is independently associated with elevated troponin and increased release of radical oxygen species in a large cohort of patients undergoing noncardiac surgery. In addition to the limitations noted previously, the studies conducted by May and colleagues[8] have small sample sizes, and they did not provide any comparisons to the ischaemic (infarction) cohort. This is likely related to the fact that only 28 (2%) of the population experienced the primary outcome.[23]

All extant investigations into perioperative acute myocardial injury have important limitations. There is no consensus on which troponin assay should be used. Use of a high-sensitivity assay doubled the detected incidence of injury and infarction in a surgical population.[24] In a non-operative population, high-sensitivity troponin T and high sensitivity troponin I assays both equally diagnosed myocardial infarction, but hscTnT was a better predictor of long-term noncardiac death.[25] The analytical sensitivity (limit of detection) of cTn assays varies 10-fold. Assays are not standardised, making it impossible to compare values from one to another.[10] These limitations make it impossible to compare incidences of injury between studies.

There is still much to learn about defining elevated troponin concentrations. The URL is defined as the upper 99th percentile of troponin concentration for a 'normal' population. Recent investigations show that the URL differs as the parameters used to define normal are altered, including age and sex.[26,27] Apple and colleagues[26] stated that, 'sex-specific 99th percentile URLs vary according to the hs-assay used to measure cTn and the statistical method used to calculate the 99th percentile'. Whilst not yet part of clinical practice, sex-specific cut-off values for troponin assays increase the diagnostic and prognostic information in women with acute myocardial infarction.[28,29] Asymptomatic pulmonary embolism may also be an underappreciated mechanism of myocardial injury.[30] A further potential phenotype has also emerged. Coronary angiographic studies in non-surgical patients with asymptomatic 'troponaemia' showed that the predominant mechanism was fluid overload.[31] To date, we are unaware of any studies investigating fluid overload and acute postoperative myocardial injury.

The proposed mechanism by May and colleagues[8] of an aberrant inflammatory pathway, miRNAs, and postoperative myocardial injury is certainly interesting and has merit. However, this study does not of itself establish the primary mechanism for perioperative myocardial injury in the absence of evidence of ischaemia. Further studies to elucidate the details of the proposed alternative mechanisms for myocardial injury are needed. Numerous mechanisms have now been proposed for postoperative myocardial injury. The

perioperative community now must come together to study the incidence, severity, treatment, and prognostic implications of each aetiology.

Authors' contributions

All authors contributed equally to the writing and revision of the article.

Declarations of interest

SJH is a board member and director of the *British Journal of Anaesthesia*. OIB and WSB have no conflicts to declare.

Funding

Fellowship from the National Institute for Health Research to OIB.

References

1. Driscoll AC, Hobika JH, Etsten BE, Proger S. Clinically unrecognized myocardial infarction following surgery. *N Eng J Med* 1961; **264**: 633–9
2. Nathoe HM, van Klei WA, Beattie WS. Perioperative troponin elevation: always myocardial injury, but not always myocardial infarction. *Anesth Analg* 2014; **119**: 1014–6
3. Devereaux PJ, Xavier D, Pogue J, et al. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann Intern Med* 2011; **154**: 523–8
4. Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators, Devereaux PJ, Chan MT, *et al*. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2012; **307**: 2295–304
5. van Waes JA, Nathoe HM, de Graaff JC, et al. Myocardial injury after noncardiac surgery and its association with short-term mortality. *Circulation* 2013; **127**: 2264–71
6. Writing Committee for the VISION Study Investigators. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2017; **317**: 1642–51
7. Beattie WS, Wijeysundera DN, Chan MTV, et al. Implication of major adverse postoperative events and myocardial injury on disability and survival: a planned subanalysis of the ENIGMA-II trial. *Anesth Analg* 2018; **127**: 1118–26
8. May SM, Abbott TEF, Arroyo AGD, et al. MicroRNA signatures of perioperative myocardial injury after elective noncardiac surgery: prospective observational mechanistic cohort study. *Br J Anaesth* 2020. https://doi.org/10.1016/j.bja.2020.05.066. Advance Access published on July 25
9. Botto F, Alonso-Coello P, Chan MT, et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology* 2014; **120**: 564–78
10. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. *Circulation* 2018; **138**: e618–51
11. van Waes JA, Grobben RB, Nathoe HM, et al. One-year mortality, causes of death, and cardiac interventions in patients with postoperative myocardial injury. *Anesth Analg* 2016; **123**: 29–37
12. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 2004; **116**: 281–97
13. Zhu K, Liu D, Lai H, Li J, Wang C. Developing miRNA therapeutics for cardiac repair in ischemic heart disease. *J Thorac Dis* 2016; **8**: E918–27
14. Navickas R, Gal D, Laucevicius A, Taparauskaite A, Zdanyte M, Holvoet P. Identifying circulating microRNAs as biomarkers of cardiovascular disease: a systematic review. *Cardiovasc Res* 2016; **111**: 322–37
15. Faraldi M, Gomarasca M, Sansoni V, Perego S, Banfi G, Lombardi G. Normalization strategies differently affect circulating miRNA profile associated with the training status. *Sci Rep* 2019; **9**: 1584
16. Kaur A, Mackin ST, Schlosser K, et al. Systematic review of microRNA biomarkers in acute coronary syndrome and stable coronary artery disease. *Cardiovasc Res* 2020; **116**: 1113–24
17. Cheng C, Wang Q, You W, Chen M, Xia J. MiRNAs as biomarkers of myocardial infarction: a meta-analysis. *PLoS One* 2014; **9**, e88566
18. Eisner DA, Sipido KR. Sodium calcium exchange in the heart: necessity or luxury? *Circ Res* 2004; **95**: 549–51
19. Hudecova S, Kubovcakova L, Kvetnansky R, et al. Modulation of expression of Na^+/Ca^{2+} exchanger in heart of rat and mouse under stress. *Acta Physiol (Oxf)* 2007; **190**: 127–36
20. Roos J, Enlund E, Funcke JB, et al. miR-146a-mediated suppression of the inflammatory response in human adipocytes. *Sci Rep* 2016; **6**: 38339
21. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Eng J Med* 2017; **377**: 1119–31
22. Ackland GL, Abbott TEF, Cain D, et al. Preoperative systemic inflammation and perioperative myocardial injury: prospective observational multicentre cohort study of patients undergoing non-cardiac surgery. *Br J Anaesth* 2019; **122**: 180–7
23. Wijeysundera DN, Pearse RM, Shulman MA, et al. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. *Lancet* 2018; **391**: 2631–40
24. Brown JC, Samaha E, Rao S, et al. High-sensitivity cardiac troponin T improves the diagnosis of perioperative MI. *Anesth Analg* 2017; **125**: 1455–62
25. Welsh P, Preiss D, Hayward C, et al. Cardiac troponin T and troponin I in the general population. *Circulation* 2019; **139**: 2754–64
26. Apple FS, Wu AHB, Sandoval Y, et al. Sex-specific 99th percentile upper reference limits for high sensitivity cardiac troponin assays derived using a universal sample bank. *Clin Chem* 2020; **66**: 434–44
27. Wu AHB, Christenson RH, Greene DN, et al. Clinical laboratory practice recommendations for the use of cardiac troponin in acute coronary syndrome: expert opinion from the academy of the American association for clinical chemistry and the task force on clinical applications of cardiac bio-markers of the international federation of clinical chemistry and laboratory medicine. *Clin Chem* 2018; **64**: 645–55

28. Lee KK, Ferry AV, Anand A, et al. Sex-specific thresholds of high-sensitivity troponin in patients with suspected acute coronary syndrome. *J Am Coll Cardiol* 2019; **74**: 2032–43
29. Bhatia PM, Daniels LB. Highly sensitive cardiac troponins: the evidence behind sex-specific cutoffs. *J Am Heart Assoc* 2020; **9**, e015272
30. Grobben RB, van Waes JAR, Leiner T, et al. Unexpected cardiac computed tomography findings in patients with postoperative myocardial injury. *Anesth Analg* 2018; **126**: 1462–8
31. Stripe B, Rechenmacher S, Jurewitz D, Lee C, Schaefer S. The diagnostic yield of cardiac catheterization in low-risk troponinemia. *JAMA Intern Med* 2013; **173**: 2088–90

British Journal of Anaesthesia, 125 (5): 646–649 (2020)
doi: 10.1016/j.bja.2020.06.050
Advance Access Publication Date: 15 July 2020

Evidence on technology-driven preoperative exercise interventions: are we there yet?

Daniel Steffens[1,2,*], Kim Delbaere[3], Jane Young[1,4], Michael Solomon[1,2,4] and Linda Denehy[5,6]

[1]Surgical Outcomes Research Centre (SOuRCe), Royal Prince Alfred Hospital (RPAH), University of Sydney, Sydney, Australia, [2]The University of Sydney, Faculty of Medicine and Health, Central Clinical School, Sydney, Australia, [3]Falls, Balance and Injury Research Centre, Neuroscience Research Australia (NeuRA), University of New South Wales, Sydney, Australia, [4]RPA Academic Institute of Surgery, Royal Prince Alfred Hospital (RPAH), University of Sydney, Sydney, Australia, [5]Department of Allied Health, Peter MacCallum Cancer Centre, Melbourne, Australia and [6]Melbourne School of Health Sciences, Faculty of Medicine Dentistry and Health Sciences, University of Melbourne, Melbourne, Australia

*Corresponding author. E-mail: Daniel.Steffens@health.nsw.gov.au

Keywords: cancer; exercise; morbidity; prehabilitation; preoperative; postoperative outcomes; technology

A number of RCTs have been published in the past few years investigating the effectiveness of a wide range of preoperative exercise interventions on postoperative surgical outcomes, quality of life, and health service costs in patients undergoing cancer surgery.[1–3] Thus far, the most compelling evidence is reported in lung cancer patients, where preoperative exercise was shown to be effective in reducing the rate of postoperative complications and length of hospital stay.[4–6] For other groups of patients undergoing oncological surgery, the evidence is mostly derived from small individual trials reporting a trend towards preoperative exercise as an effective intervention to reduce postoperative morbidity.[7–10]

Many of these programmes are delivered face to face in centralised rehabilitation centres; however, this might not be suitable for patients who live in regional or remote areas, are of low socioeconomic status, or are juggling full-time work, family responsibilities, and medical appointments in the weeks before a surgery. Home-based exercise prescription may help, although poor exercise fidelity and poor adherence to the exercise programme are commonly reported. A potential solution to these limitations would be implementation of a technology-based preoperative exercise intervention, in which patients could perform individualised and unsupervised preoperative exercises, delivered online at home.

Our group recently conducted a systematic review to evaluate the evidence for technology-based preoperative exercise in patients undergoing cancer surgery.[11] For this purpose, technology-driven preoperative exercise interventions were defined as app-based, web-based, videogame, or virtual reality exercise programmes aimed to maintain or increase muscle strength, endurance, respiratory function, or all three. This review aimed to describe the current evidence of efficacy in technology-driven preoperative exercise on postoperative complication rate, length of hospital stay, and quality of life outcomes in patients undergoing cancer surgery. Of the 321 individual articles found in the search, none met the inclusion criteria. This was somewhat surprising, as there are >1000 exercise applications available from App stores. Although clearly not evidenced-based for patients undergoing cancer surgery, we found four studies – three that were originally excluded from our review for reporting on a single arm only (no control)[12–14] and one abstract that was published in a conference proceeding.[15] The characteristics of the four studies are described in Table 1.

The limited literature on this topic highlights that more research is warranted. Recent research has shown that the majority of patients (72%, 74/103) awaiting major gastrointestinal and urological cancer surgeries would prefer to do a preoperative exercise programme at home.[16] Therefore, there is a need to develop an evidence-based technology to deliver a preoperative exercise programme to patients undergoing surgery that can improve exercise fidelity and patient adherence to exercise regimens when performed at home. We have developed a set of recommendations that we consider