PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol for IMPRoVE: a multicentre prospective observational cohort study of the incidence, impact and mechanisms of perioperative right ventricular dysfunction in non-cardiac surgery
AUTHORS	Keast, Thomas; McErlane, James; Kearns, Rachel; McKinlay, Sonya; Raju, Indran; Watson, Malcolm; Robertson, Keith; Berry, Colin; Greenlaw, Nicola; Ackland, Gareth; McCall, Philip; Shelley, Benjamin

VERSION 1 – REVIEW

REVIEWER	Raina, Amresh Allegheny General Hospital, Cardiovascular Institute
REVIEW RETURNED	02-May-2023

GENERAL COMMENTS	This manuscript details a study protocol for the Improve multi center perspective observational study, evaluating the incidence, clinical significance and mechanisms of perioperative right ventricular dysfunction. The study plans to assess preoperative and postoperative right ventricular function with echocardiography as well as with cardiac biomarker testing. A sub-study is going to evaluate patients with cardiac MRI pre and postoperatively to evaluate for evidence of myocardial inflammation or infarct. The study topic is quite interesting in the sense that few studies have evaluated the incidence and mechanisms of RV dysfunction around the time of non-cardiac surgery. The primary endpoint is incidence of right ventricular dysfunction as measured by postoperative right ventricular longitudinal strain, as well as the impact right ventricular dysfunction has on postoperative outcome. Right ventricular strain is a well validated echocardiographic endpoint and shows relatively superior inter observer variability in terms of measurement versus other typically used measures of RV function such as TAPSE and fractional area change. The study is clear, well written and has a very clear rationale and focus. Overall I think it is well designed. It does not appear that the study is ongoing at this point. Therefore, I have some suggestions with regards to the methodology. I do wonder whether it would be most prudent to exclude patients who have pre-existing right ventricular dysfunction or known ischemic heart disease. For example, patients with previous bypass surgery or other cardiac surgery will typically have impaired longitudinal contraction of the right ventricle and/or commonly have some degree of right ventricular dysfunction preoperatively. Consequently I would wonder that excluding these patients would make this study cleaner if this was feasible/possible. Alternatively, if it is not possible to amend the

	actual study protocol, it would be beneficial in the manuscript to explain the rationale for not excluding these patients. With regards to the patients getting cardiac MRI as part of the sub study with ten in each surgical group, can the authors mention if there was a power calculation or how they arrived at this number of patients in each group. It would seem to me that given the relatively small number of patients getting MRIs in each study group, it would be difficult show statistically significant differences in MRI metrics even if there were some between the various MRI parameters in the different study groups with the sample size they have. Again, can the authors comment on this?

REVIEWER	Magunia, Harry Eberhard Karls University Tübingen Faculty of Medicine
REVIEW RETURNED	23-Jun-2023

GENERAL COMMENTS	Thank you very much for giving me the opportunity to review this protocol. The study seeks to answer important clinical questions: does right ventricular function change after (different) surgical procedures? and if so, does this affect patient outcome? The answer to these questions is very exciting, as it has been proven, for example, that RV dysfunction is an independent predictor for various (negative) outcome variables in cardiac diseases and procedures. The present study protocol is well written and uses up to date diagnostics to detect RV dysfunction. During review of the manuscript several points raised that could be clarified and addressed in a revised manuscript: * the title could be specified by the words "in non-cardiac surgery" * p.7 l.148: lung resection solely or together with single lung ventilation leads to increased RV afterload what can translate into structural RV changes detctable with CMR or echo - the possible patho-mechanism could be added * hypothesis 2) it is not completely clear for me how cardiac inflammation will be assessed (lab values? CMR?), according to the study protocol there will be only blood samples taken for troponin and NT-BNP measurements * hypothesis 3) is not part of the study protocol and can be removed * inclusion criteria: the manuscript states that patients with "planned elective primary hip or knee joint replacement under spinal anaesthesia" will be included, what about patients with the same procedures receiving general anaesthesia? * exclusion criteria: patients with pre-existing right heart disease/dysfunction or pulmonary hypertension should be excluded (or analysed in a sub-group, but case number could be too low) - can the authors please comment on this patient group? * table 1: schedule of assessment: are there any standard lab analyses that are planned to be performed or recorded? * In terms of the various diagnostic procedures, 3D techniques could be added to echocardiography to achieve an even more comprehensive analysis of the ventricles. * Sections dealing with potential limitations and pitfalls could be added to the manuscript.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Amresh Raina, Allegheny General Hospital

-"It does not appear that the study is ongoing at this point. Therefore, I have some suggestions with regards to the methodology. I do wonder whether it would be most prudent to exclude patients who have pre-existing right ventricular dysfunction or known ischemic heart disease. For example, patients with previous bypass surgery or other cardiac surgery will typically have impaired longitudinal contraction of the right ventricle and/or commonly have some degree of right ventricular dysfunction preoperatively. Consequently, I would wonder that excluding these patients would make this study cleaner if this was feasible/possible. Alternatively, if it is not possible to amend the actual study protocol, it would be beneficial in the manuscript to explain the rationale for not excluding these patients."

Many thanks to Dr Raina for raising this important point. The study has now commenced recruitment, with the first patient recruited in May this year.

When the study was designed this issue was a cause for debate between the study authors. However, our consensus opinion was that we felt the study offers an opportunity to determine the prevalence of pre-operative RVD (itself a neglected area of research as we point out on lines 96-9). Additionally, those patients with pre-existing RVD may be impacted most by peri-operative insults to the RV meaning we felt we could not exclude this important patient group.

We have added a statement underneath the "Exclusion criteria" section (lines 200-204) which now reads 'Risk factors for RVD are likely to be overrepresented in patients presenting for surgery and participants with pre-existing RVD could represent an important population that may face greater consequences of acute perioperative insults to the RV. For this reason, although not a specific inclusion or exclusion criteria, patients with pre-existing RVD, including when identified on pre-op echocardiography will be included in the study.'

To account for pre-existing RVD, we will perform sensitivity analyses to identify the incidence of patients that develop new post operative RVD, and identify the incidence of those that have pre-existing RVD maintained through to the postoperative period (lines 355-362).

-“With regards to the patients getting cardiac MRI as part of the sub study with ten in each surgical group, can the authors mention if there was a power calculation or how they arrived at this number of patients in each group. It would seem to me that given the relatively small number of patients getting MRIs in each study group, it would be difficult show statistically significant differences in MRI metrics even if there were some between the various MRI parameters in the different study groups with the sample size they have. Again, can the authors comment on this?”

Again, we appreciate the raising of this point. The main power calculations were performed on the co-primary endpoints of reduced peak longitudinal RV strain and reduced DAH30. Further CMR imaging is on an exploratory basis and will provide useful pilot data for future studies in this patient population. Ten participants per group was a pragmatic and achievable number for the CMR substudy. Previous work by our group (in submission) has shown a very clear signal for association between CMR correlates of RV myocardial inflammation and ventricular function in ten post-operative patients following lung resection surgery (1).

Reviewer: 2

Dr. Harry Magunia, Eberhard Karls University Tübingen Faculty of Medicine
Comments to the Author:

"the title could be specified by the words 'in non-cardiac surgery'"
Thank you Dr Magunia and we agree. This statement has now been added to the title.

"* p.7 l.148: lung resection solely or together with single lung ventilation leads to increased RV afterload what can translate into structural RV changes detectable with CMR or echo - the possible patho-mechanism could be added2-
Thank you for raising this point. The causes of post-operative RVD remain unclear. There may be intrinsic myocardial damage or increased afterload or as you point out a combination of the two. One lung-ventilation is well known to bring about a temporary increase in pulmonary vascular resistance and this could well cause an inflammatory 'hit' on the RV (similar to that seen in rat models of pulmonary embolism (2)).

The recruitment of different surgical populations aims to differentiate between these potential insults. Orthopaedics patients undergoing spinal anaesthesia will have no positive pressure ventilation (and as such act as a negative control- with the caveat that they will be exposed to bone cement), the vascular patients will be ventilated for their open procedures, the colorectal patients will primarily be undergoing laparoscopic procedures (and thus encounter the effects of pneumoperitoneum) and the upper-GI patients undergoing oesophagectomy will undergo a sustained period of one-lung ventilation but without lung resection.

To clarify this, we have added the statement on line 131 so that it now reads 'Positive pressure ventilation- especially one-lung ventilation'.

"* hypothesis 2) it is not completely clear for me how cardiac inflammation will be assessed (lab values? CMR?), according to the study protocol there will be only blood samples taken for troponin and NT-BNP measurements"

Thank you again for this astute observation. CMR will be used to assess for image correlates of myocardial inflammation in the 50 patients enrolled in the T1-CMR substudy. As mentioned in the above response, this is on an exploratory basis, but we have demonstrated association between CMR correlates of myocardial inflammation (T1) and ventricular function in previous cohorts undergoing lung resection. In addition, we will explore association between these CMR measures and systemic markers of inflammation (CRP and neutrophil-lymphocyte ratio) and markers of myocardial injury (BNP and hsTn).

"* hypothesis 3) is not part of the study protocol and can be removed"

We agree and have removed this. Thank you.

"* inclusion criteria: the manuscript states that patients with "planned elective primary hip or knee joint replacement under spinal anaesthesia" will be included, what about patients with the same procedures receiving general anaesthesia?"

We will not be recruiting patients who are planned to undergo general anaesthesia. All orthopaedic patients will be recruited from the GJNH which is the site of the National Waiting Times Orthopaedic Treatment Centre in Scotland and the standard of care for patients undergoing primary lower limb arthroplasty is spinal anaesthesia.

"* exclusion criteria: patients with pre-existing right heart disease/dysfunction or pulmonary hypertension should be excluded (or analysed in a sub-group, but case number could be too low) - can the authors please comment on this patient group?"

This point was raised by Dr Raina in their review too. Please may we direct you our reply to their first point. As detailed there, we have also added a statement underneath the 'Exclusion criteria' section (lines 200-204).

Specifically, regarding patients with specifically with pulmonary hypertension, we do not believe that patients with known significant PH would be referred for major elective surgery. If during the study any patients are identified as having significantly raised PA pressures (or any significant incidental findings on echo or CMR after safety reporting) the patient's clinical teams will be made aware so they can take appropriate action.

"* table 1: schedule of assessment: are there any standard lab analyses that are planned to be performed or recorded."

Thanks again. We plan to record results of routine clinical blood samples (FBC, U+Es, LFTs and CRP) taken peri-operatively. These results will collected as now described on lines 285-8 and we have added a line to the schedule of assessments table

"* In terms of the various diagnostic procedures, 3D techniques could be added to echocardiography to achieve an even more comprehensive analysis of the ventricles."

We agree that 3D echo has significant advantages for analysis on an exploratory basis. Availability of 3D echo is not universal across our recruiting sites meaning it cannot be incorporated into this protocol. Incidentally, previous experience by our group demonstrated low availability of 3D RVEF (<50% [unpublished]) but high availability of RV-FWLS (>96%) in patients following lung resection (3).

"* Sections dealing with potential limitations and pitfalls could be added to the manuscript."

Thank you. We have included our main limitation on lines 75-6 in the "Strengths and limitations of this study" section. The main issue is due to the paucity of data on the incidence and impact of RVD in non-thoracic surgery. We have tried to be as open as we can with the effects this may have on our power calculations (please see line 386-91)

References:

1. Murphy E, Glass A, McCall P, Shelley B. Myocardial inflammation after major non-cardiac thoracic surgery. British Journal of Anaesthesia. 2021;126:e80-e1.
2. Watts JA, Zagorski J, Gellar MA, Stevinson BG, Kline JA. Cardiac inflammation contributes to right ventricular dysfunction following experimental pulmonary embolism in rats. J Mol Cell Cardiol. 2006;41(2):296-307.
3. McCall P, Soosay A, Kinsella J, Sonecki P, Shelley B. The utility of transthoracic echocardiographic measures of right ventricular systolic function in a lung resection cohort. Echo Res Pract. 2019;6(1):7-15.

VERSION 2 – REVIEW

REVIEWER	Raina, Amresh Allegheny General Hospital, Cardiovascular Institute
REVIEW RETURNED	08-Aug-2023

GENERAL COMMENTS	In the response to the Editorial and Reviewer's comments, the investigators appear to have appropriately addressed my questions and comments as well as the questions raised by the second reviewer. I think that the manuscript is acceptable for publication in its current version. I do not have any additional comments.

REVIEWER	Magunia, Harry Eberhard Karls University Tübingen Faculty of Medicine
REVIEW RETURNED	08-Aug-2023

GENERAL COMMENTS	thank you very much for the detailed discussion of my points and the revision of the manuscript.