Queen's University

DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB

Thursday, 11 April, 2024
1800 HOURS

LOCATION:
The Shuroop Sushi
(in the upstairs dining room)
354 King St E, Kingston, ON K7L 3B6

PRESENTING ARTICLES:
Dr. Jason Erb & Dr. Derek Dionne

SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
QUEEN'S UNIVERSITY

Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?

ORIGINAL ARTICLE

Restrictive or Liberal Transfusion Strategy in Myocardial Infarction and Anemia

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ABSTRACT

BACKGROUND

A strategy of administering a transfusion only when the hemoglobin level falls below 7 or 8 g per deciliter has been widely adopted. However, patients with acute myocardial infarction may benefit from a higher hemoglobin level.

METHODS

In this phase 3, interventional trial, we randomly assigned patients with myocardial infarction and a hemoglobin level of less than 10 g per deciliter to a restrictive transfusion strategy (hemoglobin cutoff for transfusion, 7 or 8 g per deciliter) or a liberal transfusion strategy (hemoglobin cutoff, <10 g per deciliter). The primary outcome was a composite of myocardial infarction or death at 30 days.

RESULTS

A total of 3504 patients were included in the primary analysis. The mean (±SD) number of red-cell units that were transfused was 0.7±1.6 in the restrictive-strategy group and 2.5±2.3 in the liberal-strategy group. The mean hemoglobin level was 1.3 to 1.6 g per deciliter lower in the restrictive-strategy group than in the liberal-strategy group on days 1 to 3 after randomization. A primary-outcome event occurred in 295 of 1749 patients (16.9%) in the restrictive-strategy group and in 255 of 1755 patients (14.5%) in the liberal-strategy group (risk ratio modeled with multiple imputation for incomplete follow-up, 1.15; 95% confidence interval [CI], 0.99 to 1.34; P=0.07). Death occurred in 9.9% of the patients with the restrictive strategy and in 8.3% of the patients with the liberal strategy (risk ratio, 1.19; 95% CI, 0.96 to 1.47); myocardial infarction occurred in 8.5% and 7.2% of the patients, respectively (risk ratio, 1.19; 95% CI, 0.94 to 1.49).

CONCLUSIONS

In patients with acute myocardial infarction and anemia, a liberal transfusion strategy did not significantly reduce the risk of recurrent myocardial infarction or death at 30 days. However, potential harms of a restrictive transfusion strategy cannot be excluded. (Funded by the National Heart, Lung, and Blood Institute and others; MINT ClinicalTrials.gov number, NCT02981407.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Carson can be contacted at jeffrey.carson@rutgers.edu or at the Department of Medicine, Rutgers Robert Wood Johnson Medical School, Clinical Academic Bldg., 125 Paterson St., New Brunswick, NJ 08901.

*A complete list of the investigators in the MINT trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Carson and Brooks contributed equally to this article.

This article was published on November 11, 2023, at NEJM.org.

This is the *New England Journal of Medicine* version of record, which includes all *Journal* editing and enhancements. The Author Accepted Manuscript, which is the author's version after external peer review and before publication in the *Journal*, is available at PubMed Central.

N Engl J Med 2023;389:2446-56.
DOI: 10.1056/NEJMoa2307983

Anemia is common in patients with acute myocardial infarction.[1,2] Indications for red-cell transfusion remain controversial in such patients, given the paucity of evidence. Three small randomized trials that have compared transfusion thresholds in a total of 820 patients with myocardial infarction have shown inconsistent results. The largest trial showed the noninferiority of a restrictive strategy as compared with a liberal strategy for preventing major adverse cardiac events at 30 days.[3-5] From a mechanistic perspective, blood transfusion may decrease ischemic injury by improving oxygen delivery to myocardial tissues and reduce the risk of reinfarction or death. Alternatively, administering more blood could result in more frequent heart failure from fluid overload, infection from immunosuppression, thrombosis from higher viscosity, and inflammation.

Randomized trials that have compared a restrictive transfusion strategy with a liberal strategy in more than 21,433 patients have shown a decrease of 50% in blood use without differences in morbidity or mortality.[6] Guidelines for red-cell transfusion have identified patients with myocardial infarction as a population in which more clinical trial data are needed.[7,8]

The primary objective of the Myocardial Ischemia and Transfusion (MINT) trial was to determine whether the risk of death or myocardial infarction through 30 days differed between a restrictive transfusion strategy (hemoglobin threshold, 7 to 8 g per deciliter) and a liberal transfusion strategy (hemoglobin threshold, <10 g per deciliter) among patients with an acute myocardial infarction and anemia.

Methods

Trial Design and Oversight

We conducted this open-label, randomized trial at 144 sites in the United States, Canada, France, Brazil, New Zealand, and Australia. The trial rationale and design have been reported previously.[9] The trial protocol (available with the full text of this article at NEJM.org) was approved by the institutional review board or ethics committee at each trial site. Patients or their surrogates provided written informed consent.

The trial was designed and led by executive and steering committees that included representatives of the clinical coordinating center, data coordinating center, trial sites, and the National Heart, Lung, and Blood Institute (NHLBI). The first two authors wrote the first draft of the manuscript and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. An independent data and safety monitoring committee reporting to the NHLBI reviewed unmasked data every 6 months to ensure patient safety and reviewed protocol-specified formal interim efficacy analyses annually.

Trial Population

We enrolled adults (≥18 years of age) with ST-segment elevation or non–ST-segment elevation myocardial infarction, defined in accordance with the Third Universal Definition of Myocardial Infarction,[10] along with anemia (hemoglobin level, <10 g per deciliter within 24 hours before randomization). Patients with type 1, 2, 4b, or 4c myocardial infarction were eligible for enrollment; diagnosis and categorization of myocardial infarction were performed by site investigators. Patients were ineligible for enrollment if they had uncontrolled bleeding, were receiving palliative treatment, were scheduled for cardiac surgery during the current admission, or had declined to receive blood transfusion.[9] Trial staff members identified potential patients with acute myocardial infarction and low hemoglobin levels during the index hospitalization, confirmed eligibility criteria, and confirmed that the patient's attending physician approved enrollment.

Randomization Procedures

Patients were randomly assigned in a 1:1 ratio to a restrictive or liberal transfusion strategy by means of a Web-based system and a permuted-block design with random block sizes of 4 and 6, stratified according to clinical site. The randomization sequence was created at the data coordinating center by an independent statistician.

Transfusion Strategies

In the restrictive-strategy group, transfusion was permitted but not required when the hemoglobin level was less than 8 g per deciliter and was strongly recommended when the level was less than 7 g per deciliter or when anginal symptoms were not controlled with medications. In the liberal-strategy group, one unit of packed red cells was administered after randomization and red cells were transfused to maintain the hemoglobin level

at or above 10 g per deciliter until the time of hospital discharge or 30 days. With both strategies, transfusion was administered one unit at a time, followed by measurement of the hemoglobin level. The transfusion protocol was paused if the clinician judged that active bleeding required immediate transfusion. Transfusion could be delayed in patients with volume overload until adequate diuresis or on the day of dialysis in patients with end-stage renal disease. After randomization, the transfusion strategy was not masked to site investigators or patients.

MEASUREMENTS AND ASSESSMENTS

Assessment by means of electrocardiography and measurements of hemoglobin and troponin levels were required within 24 hours before randomization and daily for 3 days after randomization (with two troponin measures required on day 1). Patients were contacted by telephone 30 days after randomization to assess vital status, quality of life, and readmission to the hospital or emergency department; patients were also contacted at 6 months to assess vital status. Trial staff members reviewed the medical records of the patients who had been readmitted to the hospital or emergency department within 30 days after randomization to identify and report the occurrence of clinical events and to record all available troponin levels.

OUTCOMES

The primary outcome was a composite of myocardial infarction or death from any cause up to 30 days after randomization. Death was ascertained from medical records during the index hospitalization and by telephone follow-up at 30 days after randomization, with subsequent review of medical records. The clinical events committee, whose members were unaware of treatment assignments, systematically screened for suspected recurrent myocardial infarction by examining all recorded troponin values, and clinical sites reported suspected myocardial infarction. The committee reviewed hospital records and adjudicated recurrent myocardial infarction using the Third Universal Definition of Myocardial Infarction.[10] The only trial outcome that was centrally adjudicated was myocardial infarction.

The prespecified secondary outcomes were the individual components of the primary outcome (myocardial infarction or death at 30 days) and the composite outcome of death, myocardial infarction, ischemia-driven unscheduled coronary revascularization, or readmission to the hospital for an ischemic cardiac condition within 30 days. Other clinically relevant 30-day outcomes were recorded as defined in the protocol and the Supplementary Appendix, available at NEJM.org. The cause of death was classified as cardiac, noncardiac, or undetermined.

PRESPECIFIED SUBGROUPS

Prespecified baseline subgroups included the type of myocardial infarction (type 1 [occlusion of a coronary artery because of atherosclerotic plaque disruption] or type 2 [supply–demand mismatch without atherothrombotic plaque disruption]), myocardial infarction presentation (ST-segment elevation or non–ST-segment elevation), revascularization for the index myocardial infarction (yes or no), heart failure (a composite of a history of heart failure, left ventricular ejection fraction of <45%, or acute heart failure) or no heart failure, prerandomization hemoglobin level (<8, 8 to <9, or 9 to <10 g per deciliter), type of anemia (chronic or acute), renal function (undergoing dialysis or an estimated glomerular filtration rate of <30, 30 to 59, or ≥60 ml per minute per 1.73 m^2 of body-surface area), a history of diabetes therapy (yes or no), sex, and age (<60, 60 to 69, 70 to 79, or ≥80 years). Subgroups that were defined according to race and Hispanic ethnic group were evaluated among the patients from the United States, Canada, New Zealand, and Australia.

STATISTICAL ANALYSIS

We determined that the enrollment of 3500 patients would provide the trial with 80% power to detect a 20% relative between-group difference in the incidence of the primary outcome, assuming an overall incidence of myocardial infarction or death of 16.4% and using a two-sided test with an alpha level of 0.05. All the analyses were conducted in the intention-to-treat population with two-sided hypothesis tests for superiority. Risk ratios were used to assess the risk with the restrictive strategy as compared with the liberal strategy (with values of >1 favoring the liberal strategy), in accordance with the methods described in transfusion literature.[6]

For the primary analysis, we used a log-binomial regression model that included a fixed effect for the assigned transfusion strategy and a random

effect for clinical sites. Multiple imputation by chained equations (MICE) was used to impute missing outcome data for patients who withdrew or were lost to follow-up before 30 days without a primary-outcome event after adjustment for all measured variables potentially associated with missing data (see the Supplementary Appendix for details).

For all trial outcomes, we report crude 30-day risk according to the assigned group, without multiple imputation, and risk ratios with 95% confidence intervals. All available data from randomization through 30 days were used to identify trial outcomes, and we assumed that no event occurred after the final day of data collection for patients with incomplete follow-up when computing these estimates.

As a secondary analysis, we used Kaplan–Meier methods to assess the cumulative risk of a primary-outcome event according to the assigned group and used log-rank statistics with data censoring at the time of the patient's withdrawal and at 30 days to compare the two cumulative risk curves. The crude risk ratios and 95% confidence intervals for the primary outcome are reported within prespecified subgroups. A post hoc analysis was conducted by creating a log-binomial regression model for the primary outcome according to the assigned group after adjustment for baseline prognostic factors that were prespecified as subgroup variables. We did not adjust for multiple comparisons for any secondary outcome or subgroup, so 95% confidence intervals should not be used for hypothesis testing.

RESULTS

PATIENTS

A total of 3506 patients were enrolled from April 2017 through April 2023, and 3504 were included in the analyses after 2 patients did not approve the use of their data (Fig. S1 in the Supplementary Appendix). The mean age of the patients was 72.1 years, and 45.5% of the patients were women (Table 1 and Table S1). The patients had frequent coexisting illnesses; approximately a third had a history of myocardial infarction, percutaneous coronary intervention, or heart failure, and nearly half had renal insufficiency. Among the patients who were undergoing coronary angiography and assessment of left ventricular function before randomization, the presence of multivessel disease and reduced left ventricular systolic function was common.

A majority of the patients (55.8%) had type 2 myocardial infarction; the second most common form (in 41.7%) was type 1. The prerandomization mean hemoglobin level was 8.6 g per deciliter, and the median creatinine level was 1.4 mg per deciliter (124 μmol per liter). Follow-up at 30 days was complete for 3447 patients (98.3%) who had undergone randomization (Fig. S1).

IMPLEMENTATION OF ASSIGNED INTERVENTIONS

The mean hemoglobin level was lower in the restrictive-strategy group than in the liberal-strategy group by 1.3 g per deciliter (95% confidence interval [CI], 1.2 to 1.4) on day 1 and lower by 1.6 g per deciliter (95% CI, 1.5 to 1.7) on day 3 (Fig. 1). The total number of units of red cells that were transfused in the liberal-strategy group was 3.5 times the number that were transfused in the restrictive-strategy group (4325 units vs. 1237 units). The mean (±SD) number of red-cell units that were transfused in the liberal-strategy group was 2.5±2.3, as compared with 0.7±1.6 in the restrictive-strategy group. The median duration of hospitalization from randomization until discharge, withdrawal, or death was 5 days (interquartile range, 2 to 10) in the two groups.

Discontinuation of the protocol in the restrictive-strategy group occurred in 46 patients (2.6%); 24 of these discontinuations were for clinical reasons, including surgery and bleeding. Discontinuation of the protocol in the liberal-strategy group occurred in 241 patients (13.7%); clinical reasons were provided for 89 of these patients and included adverse effects, fluid overload, dialysis, and transfusion reactions. Other reasons for discontinuation were patient preference (in 68), provider preference (in 53), and other reasons (in 31), including blood-supply shortages and staffing issues.

TRIAL OUTCOMES

Myocardial infarction or death from any cause at 30 days (the primary outcome) occurred in 295 of 1749 patients (16.9%) in restrictive-strategy group and in 255 of 1755 patients (14.5%) in the liberal-strategy group. The crude risk ratio (restrictive vs. liberal) was 1.16 (95% CI, 1.00 to 1.35) (Fig. 2). According to a log-binomial model after adjustment for site and incomplete follow-up in 57 patients (20 with the restrictive strategy and 37 with

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	All Patients (N=3504)	Restrictive Strategy (N=1749)	Liberal Strategy (N=1755)
Age — yr	72.1±11.6	72.2±11.5	72.1±11.6
Female sex — no. (%)	1593 (45.5)	774 (44.3)	819 (46.7)
Race or ethnic group — no. (%)†			
White	2474 (70.6)	1229 (70.3)	1245 (70.9)
Black	440 (12.6)	217 (12.4)	223 (12.7)
Other	244 (7.0)	129 (7.4)	115 (6.6)
Missing	346 (9.9)	174 (9.9)	172 (9.8)
Medical history — no./total no. (%)			
Myocardial infarction	1138/3504 (32.5)	589/1749 (33.7)	549/1755 (31.3)
Percutaneous coronary intervention	1200/3503 (34.3)	623/1749 (35.6)	577/1754 (32.9)
Coronary-artery bypass grafting	762/3504 (21.7)	372/1749 (21.3)	390/1755 (22.2)
Heart failure	1066/3504 (30.4)	527/1749 (30.1)	539/1755 (30.7)
Angiography — no./total no. (%)			
Results available before randomization	1738/3504 (49.6)	885/1749 (50.6)	853/1755 (48.6)
Multivessel coronary artery disease: >50% obstruction	1103/1679 (65.7)	565/856 (66.0)	538/823 (65.4)
Left ventricular ejection fraction			
Quantitative assessment available — no. (%)	2558 (73.0)	1282 (73.3)	1276 (72.7)
Most recent result in past year — %	47.4±13.5	47.3±13.4	47.5±13.7
Categorical assessment available — no./total no. (%)			
30 to <45%: moderate	807/2929 (27.6)	397/1460 (27.2)	410/1469 (27.9)
<30%: severe	292/2929 (10.0)	145/1460 (9.9)	147/1469 (10.0)
Index myocardial infarction — no. (%)			
NSTEMI	2848 (81.3)	1430 (81.8)	1418 (80.8)
Type 1	1460 (41.7)	730 (41.7)	730 (41.6)
Type 2	1955 (55.8)	967 (55.3)	988 (56.3)
Medical finding or therapy before randomization			
Revascularization for treatment of index myocardial infarction — no. (%)	1002 (28.6)	509 (29.1)	493 (28.1)
In-hospital heart failure — no. (%)	780 (22.3)	377 (21.6)	403 (23.0)
Mechanical ventilation — no. (%)	481 (13.7)	250 (14.3)	231 (13.2)
Active bleeding — no. (%)	459 (13.1)	246 (14.1)	213 (12.1)
Red-cell transfusion — no. (%)	1237 (35.3)	599 (34.2)	638 (36.4)
Hemoglobin — g/dl	8.6±0.8	8.6±0.8	8.6±0.8
Median creatinine (IQR) — mg/dl	1.4 (0.9–2.5)	1.4 (0.9–2.6)	1.4 (0.9–2.5)
Renal dialysis — no./total no. (%)	415/3503 (11.8)	203/1748 (11.6)	212/1755 (12.1)

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. IQR denotes interquartile range, and NSTEMI non–ST-segment elevation myocardial infarction.
† Race or ethnic group was reported by the patients. The "other" category included patients who identified as Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, First Nations Inuit or Metis, or multiracial. Data were missing for 323 patients in France (where racial data are not reported) and for 23 patients in other countries.

the liberal strategy) with multiple imputation, the estimated risk ratio for the primary outcome was 1.15 (95% CI, 0.99 to 1.34; P=0.07). The estimate for the primary outcome from the model after adjustment for baseline prognostic factors (risk ratio, 1.16; 95% CI, 1.00 to 1.36) was consistent with the previous two calculations.

At 30 days, death had occurred in 173 of 1749 patients (9.9%) in the restrictive-strategy group and in 146 of 1755 patients (8.3%) in the liberal-strategy group (risk ratio, 1.19; 95% CI, 0.96 to 1.47), and myocardial infarction had occurred in 8.5% and 7.2% of the patients, respectively (risk ratio, 1.19; 95% CI, 0.94 to 1.49) (Fig. 2). Death, myocardial infarction, ischemia-driven unscheduled coronary revascularization, or readmission to the hospital for an ischemic cardiac condition within 30 days occurred in 19.6% of the patients in the restrictive-strategy group and in 17.4% of those in the liberal-strategy group (risk ratio, 1.13; 95% CI, 0.98 to 1.29). Figure 3 shows Kaplan–Meier estimates of the 30-day cumulative incidence of myocardial infarction or death from any cause (the primary outcome) and of death from any cause with censoring of data for patients at the time of withdrawal or loss to follow-up.

Cardiac death was more common in the restrictive-strategy group than in the liberal-strategy group (5.5% and 3.2%, respectively; risk ratio, 1.74; 95% CI, 1.26 to 2.40); the risk of other clinical-outcome events did not differ significantly between the two groups (Fig. 2 and Table S2). The risk of heart failure at 30 days was similar in the restrictive-strategy group and the liberal-strategy group (5.8% and 6.3%, respectively; risk ratio, 0.92; 95% CI, 0.71 to 1.20), although there were fewer transfusion-associated cardiac overload (TACO) events in the restrictive-strategy group than in the liberal-strategy group (0.5% and 1.3%, respectively; risk ratio, 0.35; 95% CI, 0.16 to 0.78). Pulmonary embolism or deep venous thrombosis was infrequent in both the restrictive-strategy group and the liberal-strategy group (1.5% vs. 1.9%; risk ratio, 0.77; 95% CI, 0.46 to 1.27). Transfusion reactions were uncommon, and the absolute differences in the incidence between the two groups were small (Table S2).

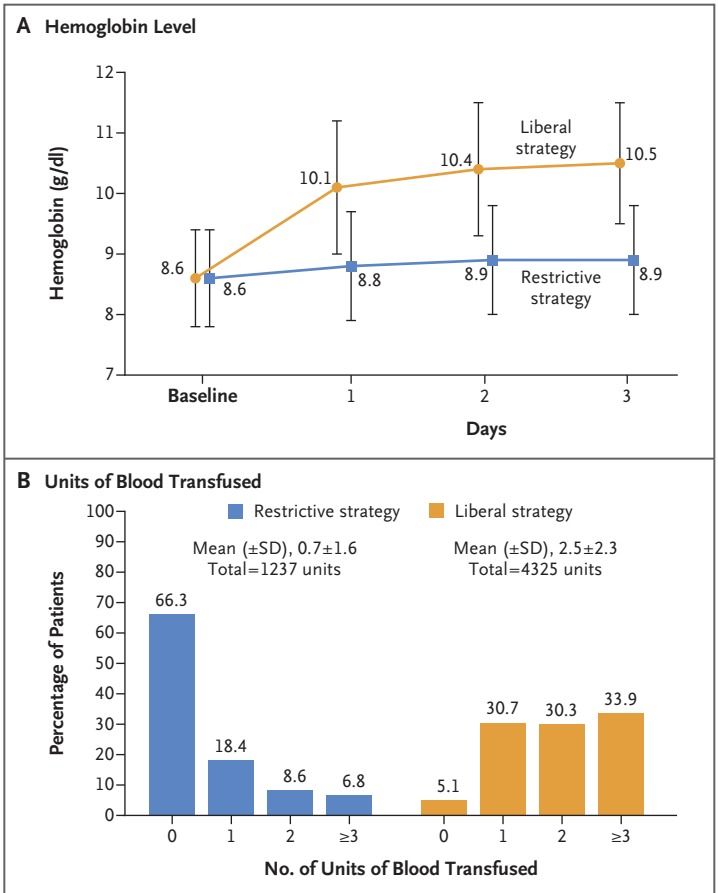

Figure 1. Hemoglobin Level and Number of Units of Red-Cell Transfusions.
Panel A shows the mean (±SD) hemoglobin level at baseline, day 1, day 2, and day 3 in the restrictive-strategy group and the liberal-strategy group. I bars indicate 95% confidence intervals. Panel B shows the number of units of red cells transfused in the two groups.

SUBGROUP ANALYSES

The effect of the restrictive as compared with the liberal transfusion strategy on the primary outcome was consistent across all prespecified subgroups (Fig. 4 and Table S3). Among the patients with type 1 myocardial infarction, the restrictive strategy led to more primary-outcome events than the liberal strategy (risk ratio, 1.32; 95% CI, 1.04 to 1.67), with no apparent effect among the patients with type 2 myocardial infarction (risk ratio, 1.05; 95% CI, 0.85 to 1.29).

DISCUSSION

In the MINT trial, we did not find a significant difference in the incidence of recurrent myocardial infarction or death at 30 days between patients with acute myocardial infarction and anemia who were assigned to a restrictive transfusion strategy

and those who were assigned to a liberal transfusion strategy. However, the liberal transfusion strategy was consistently favored in point estimates for the primary outcome and for death, cardiac death, recurrent myocardial infarction, and the composite of death, myocardial infarction, ischemia-driven unscheduled coronary revascularization, or readmission to the hospital for an ischemic cardiac condition. The frequency of heart failure, a more comprehensive measure of volume overload than TACO, and other safety-outcome events was similar in the two transfusion groups.

The findings in our trial contrast with the results from previous transfusion trials conducted across a wide range of patient populations and treatments (including cardiac surgery) in our Cochrane meta-analysis.[6] In the other clinical situations involving patients without acute myocardial infarction, a restrictive strategy decreased blood use by 50% without adversely affecting clinical outcomes.[11,12]

Of three transfusion trials involving patients with acute myocardial infarction, a cost-effectiveness study that enrolled 668 patients showed that a restrictive transfusion strategy was less costly and was clinically noninferior to a liberal strategy with respect to the risk of major adverse cardiac events (including death, reinfarction, stroke, and emergency revascularization) at 30 days.[3] One-year outcomes were similar in the two groups, and the restrictive strategy did not meet the prespecified noninferiority threshold.[13] In the MINT pilot study involving 110 patients, there were 7 deaths in the restrictive-strategy group and 1 death in the liberal-strategy group.[4] In the CRIT trial, which involved 45 patients, point estimates favored the restrictive group.[5] In our trial, the enrollment was four times as large as the enrollment in all three of the other studies combined.

Although the between-group difference in the primary outcome in our trial did not reach the prespecified level of significance, it was not because of poor implementation of the transfusion strategy, given the large difference (by a factor of three) in blood use, the hemoglobin differences between the trial groups, or the occurrence of the estimated primary-outcome events overall. The trial was designed to detect a 20% relative between-group difference, and the observed effect was a relative difference of approximately 15%. The smaller-than-expected difference may have occurred as a result of introducing more hetero-

Outcome	Restrictive Strategy	Liberal Strategy	Risk Ratio (95% CI)
	no. of patients/total no. (%)		
Primary outcome			
Myocardial infarction or death	295/1749 (16.9)	255/1755 (14.5)	1.16 (1.00–1.35)
Secondary outcomes			
Death	173/1749 (9.9)	146/1755 (8.3)	1.19 (0.96–1.47)
Myocardial infarction	149/1749 (8.5)	126/1755 (7.2)	1.19 (0.94–1.49)
Death, myocardial infarction, revascularization, or rehospitalization	342/1749 (19.6)	305/1755 (17.4)	1.13 (0.98–1.29)
Other outcomes			
Heart failure	102/1749 (5.8)	111/1755 (6.3)	0.92 (0.71–1.20)
Death, myocardial infarction, or unstable angina	338/1749 (19.3)	300/1755 (17.1)	1.13 (0.98–1.30)
Unscheduled revascularization	43/1749 (2.5)	39/1755 (2.2)	1.11 (0.72–1.70)
Cardiac death	97/1749 (5.5)	56/1755 (3.2)	1.74 (1.26–2.40)
Stroke	30/1749 (1.7)	26/1755 (1.5)	1.16 (0.69–1.95)
Pulmonary embolism or deep venous thrombosis	26/1749 (1.5)	34/1755 (1.9)	0.77 (0.46–1.27)
Pneumonia or bacteremia	166/1749 (9.5)	153/1755 (8.7)	1.09 (0.88–1.34)

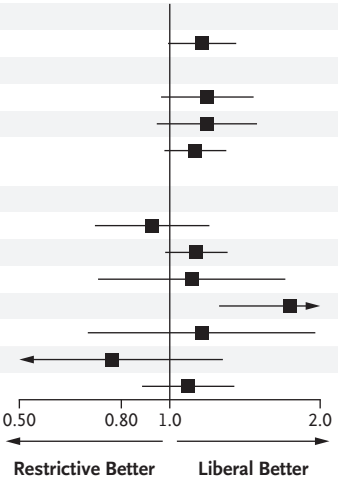

Figure 2. Trial Outcomes at 30 Days.

Shown are the unadjusted risk ratios for the primary, secondary, and other outcomes in patients assigned to a restrictive transfusion strategy as compared with those assigned to a liberal transfusion strategy. The estimate for the primary model with imputed missing data was a risk ratio of 1.15 (95% CI, 0.99 to 1.34; P=0.07).

geneity of the treatment effect than anticipated with the enrollment of a broad group of patients with acute myocardial infarction, including a large percentage of patients with demand ischemia (type 2 myocardial infarction).

Our trial has several strengths. It was pragmatic, since it was designed to maximize the generalizability of the results. With few exclusions, the enrollment of 3504 patients included a wide variety of older patients who had a variety of myocardial infarction diagnoses, including both ST-segment elevation and non–ST-segment elevation and both type 1 and type 2 myocardial infarctions. In addition, the patients had many coexisting illnesses and were generally representative of patients in clinical practice with acute myocardial infarction and anemia. In making these inclusion decisions, we may have included patients who had an increased severity of illness, who had an increased number of coexisting illnesses, and who were less likely to benefit from a liberal transfusion strategy. Transfusion protocols were also straightforward and easy to manage and closely approximated clinical practice in a variety of settings and health systems. The transfusion protocol made accommodations for patients with heart failure and for transfusing during dialysis. The protocol also advised transfusion in patients with ongoing ischemic symptoms who did not have a response to intensification of medical therapy or who had hemorrhage. The trial transfusion protocol led to large differences in the number of blood transfusions and clinically meaningful differences in hemoglobin levels between the two groups. The trial outcomes were clinically relevant, and other interventions were applied according to standard clinical practice. Follow-up for the 30-day primary outcome was complete for 98.3% of the patients. The myocardial infarction component of the primary outcome was centrally adjudicated in a blinded fashion by an expert committee that examined all available troponin levels and clinical information over the 30-day follow-up period.

Our trial also has several limitations. As in all transfusion-threshold trials, the assigned intervention was not masked from health professionals caring for the patients. This factor may have influenced the use of revascularization or other interventions or the classification of cause of death. Death from cardiac causes was a prespecified outcome,[9] but it was not designated as a primary, secondary, or tertiary outcome and was not adjudicated, and fewer than half the deaths were classified as cardiac. The qualifying myocardial infarction and the outcomes, other than myocardial infarction, were not centrally adjudicated. Adherence to the hemoglobin threshold of less than 10 g per deciliter in the liberal-strategy group was moderate (86.3% at hospital discharge); this lapse was frequently due to clinical discretion, such as concern about fluid overload, and

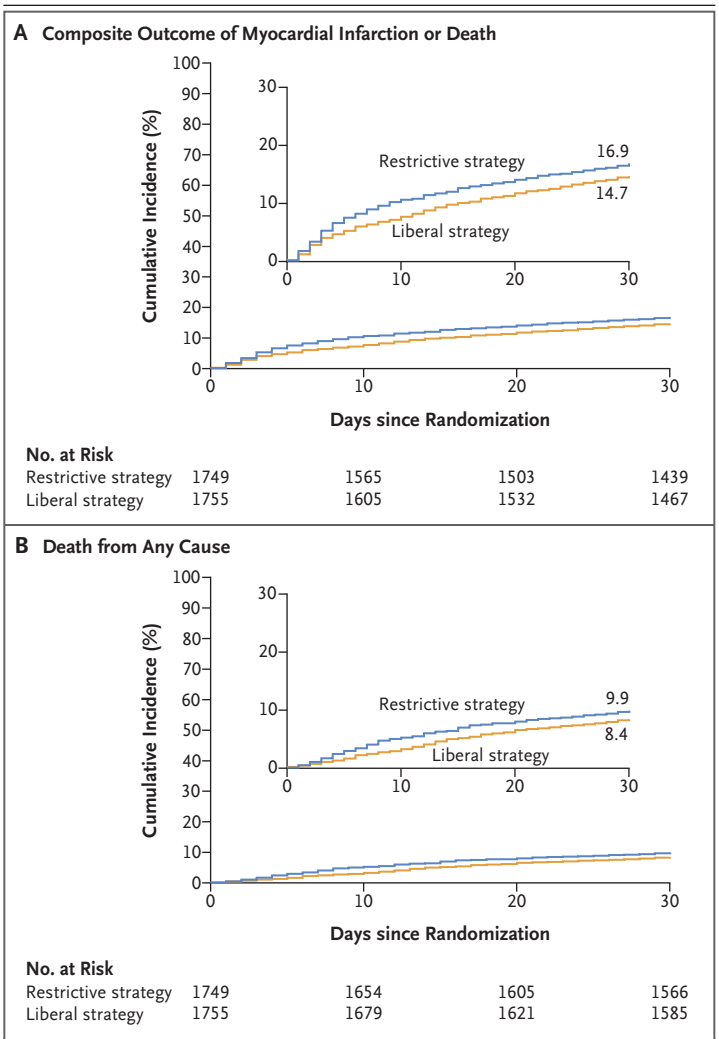

Figure 3. Cumulative Incidence of Myocardial Infarction or Death (Primary Outcome) or Death from Any Cause at 30 Days.

Shown are Kaplan–Meier estimates of the cumulative 30-day incidence of a composite of myocardial infarction or death (Panel A) and death from any cause (Panel B) after the censoring of data for patients at the time of withdrawal or loss to follow-up. The insets in each panel show the same data on an expanded y axis.

Subgroup	Restrictive Strategy	Liberal Strategy	Risk Ratio (95% CI)
	no. of patients/total no. (%)		
All patients	295/1749 (16.9)	255/1755 (14.5)	1.16 (1.00–1.35)
Type of index myocardial infarction			
Type 1	133/730 (18.2)	101/730 (13.8)	1.32 (1.04–1.67)
Type 2	153/967 (15.8)	149/988 (15.1)	1.05 (0.85–1.29)
STEMI or NSTEMI			
STEMI	49/319 (15.4)	50/337 (14.8)	1.04 (0.72–1.49)
NSTEMI	246/1430 (17.2)	205/1418 (14.5)	1.19 (1.00–1.41)
Revascularization before randomization			
No	218/1240 (17.6)	190/1262 (15.1)	1.17 (0.98–1.40)
Yes	77/509 (15.1)	65/493 (13.2)	1.15 (0.84–1.56)
CHF, acute HF, or low LVEF			
No	115/831 (13.8)	105/802 (13.1)	1.06 (0.83–1.35)
Yes	180/918 (19.6)	150/953 (15.7)	1.25 (1.02–1.52)
Hemoglobin category			
<8 g/dl	74/404 (18.3)	73/386 (18.9)	0.97 (0.72–1.30)
8 to <9 g/dl	107/662 (16.2)	89/677 (13.1)	1.23 (0.95–1.59)
9 to <10 g/dl	114/681 (16.7)	93/686 (13.6)	1.23 (0.96–1.59)
Type of anemia			
Chronic	144/902 (16.0)	116/914 (12.7)	1.26 (1.00–1.58)
Acute	103/539 (19.1)	92/539 (17.1)	1.12 (0.87–1.44)
Renal function			
Renal dialysis at baseline	34/203 (16.7)	41/212 (19.3)	0.87 (0.57–1.31)
eGFR <30 ml/min/1.73 m^2	88/406 (21.7)	63/396 (15.9)	1.36 (1.02–1.83)
eGFR 30 to 59 ml/min/1.73 m^2	89/505 (17.6)	69/493 (14.0)	1.26 (0.94–1.68)
eGFR ≥60 ml/min/1.73 m^2	84/633 (13.3)	80/646 (12.4)	1.07 (0.81–1.43)
History of diabetes therapy			
No	132/801 (16.5)	117/807 (14.5)	1.14 (0.90–1.43)
Yes	163/948 (17.2)	138/948 (14.6)	1.18 (0.96–1.45)
Sex			
Male	167/975 (17.1)	133/936 (14.2)	1.21 (0.98–1.49)
Female	128/774 (16.5)	122/819 (14.9)	1.11 (0.88–1.39)
Age			
<60 yr	27/238 (11.3)	24/250 (9.6)	1.18 (0.70–1.99)
60–69 yr	63/421 (15.0)	54/459 (11.8)	1.27 (0.91–1.78)
70–79 yr	126/631 (20.0)	106/598 (17.7)	1.13 (0.89–1.42)
≥80 yr	79/459 (17.2)	71/447 (15.9)	1.08 (0.81–1.45)

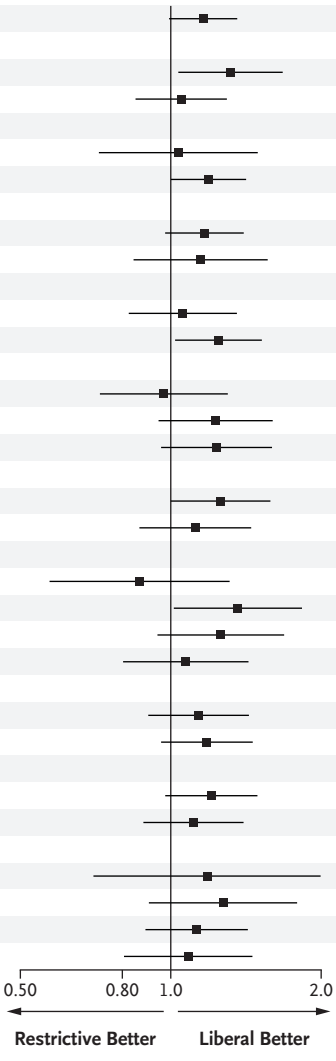

Figure 4. Subgroup Analysis of Myocardial Infarction or Death.

Shown is the unadjusted risk ratio for myocardial infarction or death (primary outcome) in the restrictive-strategy group as compared with the liberal-strategy group, according to prespecified subgroup. CHF denotes chronic heart failure, eGFR estimated glomerular filtration rate, LVEF left ventricular ejection fraction, NSTEMI non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.

to the timing of hospital discharge. The trial analyses were not adjusted for multiplicity, so caution must be used in interpreting the results beyond the primary outcome.

Whether to transfuse is an everyday decision faced by clinicians caring for patients with acute myocardial infarction. We observed that the 95% confidence interval contains values that suggest a clinical benefit for the liberal transfusion strategy and does not include values that suggest a benefit for the more restrictive transfusion strategy. At 30 days, the risk of myocardial infarction or death was 2.4 percentage points lower in the liberal-strategy group than in the restrictive-strategy group, and the risk of death was 1.6 percentage points lower. Furthermore, the

safety profile of the liberal transfusion strategy indicated low risk.

Our results show that in patients with acute myocardial infarction and anemia, a liberal transfusion strategy did not significantly reduce the risk of recurrent myocardial infarction or death at 30 days. Trial end points suggest some benefit of a liberal strategy over a restrictive strategy, but additional studies would be needed to confirm that conclusion.

The views expressed in this article are those of the authors and do not necessarily reflect the official policies of the National Institutes of Health.

Supported by grants (U01 HL133817 and U01HL132853) from the National Heart, Lung, and Blood Institute and by the Canadian Blood Services and Canadian Institutes of Health Research Institute of Circulatory and Respiratory Health.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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BJA

British Journal of Anaesthesia, 130 (1): 103–110 (2023)

doi: 10.1016/j.bja.2021.12.011
Advance Access Publication Date: 11 January 2022
Respiration and the Airway

RESPIRATION AND THE AIRWAY

Apnoeic oxygenation in morbid obesity: a randomised controlled trial comparing facemask and high-flow nasal oxygen delivery

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Abstract

Background: Obesity is a risk factor for airway-related incidents during anaesthesia. High-flow nasal oxygen has been advocated to improve safety in high-risk groups, but its effectiveness in the obese population is uncertain. This study compared the effect of high-flow nasal oxygen and low-flow facemask oxygen delivery on duration of apnoea in morbidly obese patients.

Methods: Morbidly obese patients undergoing bariatric surgery were randomly allocated to receive either high-flow nasal (70 L min^{-1}) or facemask (15 L min^{-1}) oxygen. After induction of anaesthesia, the patients were apnoeic for 18 min or until peripheral oxygen saturation decreased to 92%.

Results: Eighty patients were studied (41 High-Flow Nasal Oxygen, 39 Facemask). The median apnoea time was 18 min in both the High-Flow Nasal Oxygen (IQR 18–18 min) and the Facemask (inter-quartile range [IQR], 4.1–18 min) groups. Five patients in the High-Flow Nasal Oxygen group and 14 patients in the Facemask group desaturated to 92% within 18 min. The risk of desaturation was significantly lower in the High-Flow Nasal Oxygen group (hazard ratio=0.27; 95% confidence interval [CI], 0.11–0.65; P=0.007).

Conclusions: In experienced hands, apnoeic oxygenation is possible in morbidly obese patients, and oxygen desaturation did not occur for 18 min in the majority of patients, whether oxygen delivery was high-flow nasal or low-flow facemask. High-flow nasal oxygen may reduce desaturation risk compared with facemask oxygen. Desaturation risk is a more clinically relevant outcome than duration of apnoea. Individual physiological factors are likely to be the primary determinant of risk rather than method of oxygen delivery.

Clinical trial registration: NCT03428256.

Keywords: apnoeic oxygenation; apnoeic ventilation; bariatric anaesthesia; desaturation risk; high-flow nasal oxygen; obesity; safe apnoea time; THRIVE

Editor's key points

- High-flow nasal oxygenation is useful to prevent hypoxaemia during attempts at securing the airway after induction of anaesthesia, but its efficacy in morbidly obese patients is not clear.
- Compared with morbidly obese patients receiving low-flow oxygenation via a facemask, those receiving

Received: 19 July 2021; **Accepted:** 8 December 2021

high-flow nasal oxygenation were less likely to become hypoxaemic during 18 min of apnoea after induction of anaesthesia.
- Morbid obesity did not preclude apnoeic oxygenation. However, future studies need to establish the role of high-flow nasal oxygenation during apnoea in morbidly obese patients, as 5 of 41 patients became hypoxaemic.

There has been a resurgence in interest in apnoeic oxygenation techniques since the advent of high-flow heated and humidified oxygen delivery systems.[1] Several studies have investigated the influence of oxygen delivery characteristics, notably flow rate and the proximity of fresh gas flow to the respiratory epithelium, on apnoeic oxygenation and ventilation. Broadly, the conclusions have been that these processes are more efficient with higher flow rates of oxygen delivered closer to the lung.[2] The evidence is limited, in particular by the use of surrogate markers of arterial gas tension such as end-tidal concentration. Whether high-flow nasal oxygen (HFNO) delivery promotes apnoeic ventilation remains a subject of debate.[3]

Obesity has been associated with failure of apnoeic oxygenation techniques.[4] In the UK, more than a quarter of adults are obese and obesity is increasingly common worldwide.[5] Obesity presents many challenges to the anaesthetist,[6] and airway-related incidents are more common in obese patients.[7,8] Understanding the factors that influence the efficiency of apnoeic oxygenation in obese patients might improve safety of airway management in this high-risk group. Landmark papers describing apnoeic oxygenation using HFNO at the time of airway surgery concluded that, although apnoea could be reliably extended in non-obese patients using this technique,[9] the safe upper limit of apnoea in the presence of morbid obesity may be as low as 5 min but that this needs confirmation by an experimental human physiological study.[10]

In this physiological study, we explored the safe upper limit of apnoea in morbidly obese patients. We compared the effect of oxygen flow rate and proximity of fresh gas flow to the respiratory epithelium on the duration of apnoea. Our primary outcome was the time to arterial haemoglobin oxygen desaturation to 92%. In addition, we measured arterial oxygen and carbon dioxide tension during apnoea to determine whether higher oxygen flow rate promotes more efficient apnoeic oxygenation, ventilation, or both.

Methods

This study was registered with ClinicalTrials.gov (NCT03428256), approved by the Bloomsbury Research and Ethics Committee (17/LO/0742) and was conducted in a tertiary centre between October 2018 and September 2019. Two experienced bariatric anaesthetists and an operating department practitioner were present at all times. Emergency equipment and drugs were immediately available.

Eligible participants were recruited during a bariatric surgical clinic. Inclusion criteria were patients aged 18–65 yr with BMI >40 kg m^{-2}. Exclusion criteria were inability to give informed consent; significant cardiac, peripheral vascular or respiratory disease; nasal obstruction; and predicted difficult facemask ventilation or intubation. Written, informed consent was obtained.

A secure online service (www.sealedenvelope.com) was used to randomise participants to HFNO or facemask oxygen (FM) groups. Minimisation ensured participants with diagnosed obstructive sleep apnoea using continuous positive airway pressure (CPAP) therapy were balanced between groups.

Participants were positioned at 45° mid-thoracic incline.[6] In addition to standard monitoring,[11] bispectral index (BIS™; Medtronic Limited, Boulder, CO, USA) and invasive arterial blood pressure were monitored throughout the study period.

In both groups, preoxygenation was provided for 3 min. Participants were asked to take vital capacity breaths during the third minute. In both groups, oxygen was delivered during preoxygenation and throughout apnoea.

In the FM group, oxygen was delivered via a tightly fitted anaesthetic facemask connected to a pressure-free circle circuit with 15 L min^{-1} oxygen.

In the HFNO group, oxygen was delivered via Optiflow™ (Fisher & Paykel Healthcare Limited, Auckland, New Zealand). During preoxygenation, flow was 35 L min^{-1} for the first minute, 50–70 L min^{-1} as tolerated for the next 2 min, and thereafter flow was maintained at 70 L min^{-1}. Participants were instructed to keep their mouths closed throughout.

Anaesthesia was induced with fentanyl 2 μg kg^{-1} (predicted body weight [PBW]) and propofol infusion (Marsh model, plasma concentration target 6 μg ml^{-1}). Rocuronium 1 mg kg^{-1} (PBW) was given after loss of verbal contact. An oropharyngeal airway and jaw-thrust manoeuvre were used to optimise airway patency until the study endpoint was reached. The ability to ventilate manually through a facemask was checked with a single insufflation in both groups – if not, the study was abandoned. Propofol infusion was titrated to BIS 40–60. Systolic blood pressure was maintained within 20% of baseline using metaraminol infusion with or without boluses. Further rocuronium doses were permitted at the anaesthetist's discretion if apnoea time exceeded 10 min to ensure optimum intubating conditions.

Onset of apnoea was defined as 1 min after rocuronium administration. Arterial blood gas samples were taken at baseline (before preoxygenation), at the end of preoxygenation, at the onset of apnoea (TA), and at 2, 4, 6, 9, 12, and 18 min (TA+2, 4, …, 18) min thereafter if arterial oxygen saturation (Sao_2) remained >92%; or when Sao_2 reached 92% if this occurred before TA+18. These samples were immediately refrigerated and processed sequentially at the end of the study (GEM Premier 4000; IL GmbH, Berlin, Germany).

When the study endpoint was reached (TA+18 or Sao_2 92%), a videolaryngoscope (McGrath™; Medtronic Limited, Watford, UK) was inserted and the trachea intubated.

The study was powered in respect of the primary outcome – time to desaturation to 92%. There were no extant data in obese patients given facemask oxygen during apnoea. In one study, using 5 L min^{-1} oxygen via nasopharyngeal catheter during apnoea in obese subjects, time to desaturation was 317 (standard deviation [SD], 80) s.[12] We used this to estimate time to desaturation in the FM group. We estimated that time to desaturation in the HFNO group would be 20% longer. Allowing for up to 18 min of apnoea, more than double the expected apnoea time, we did not expect any censored events.

Using these estimates, 1:1 randomisation, two-tailed alpha 0.05, and 1-beta 0.9, a sample size of 35 per group was calculated to provide adequate power with respect to the primary

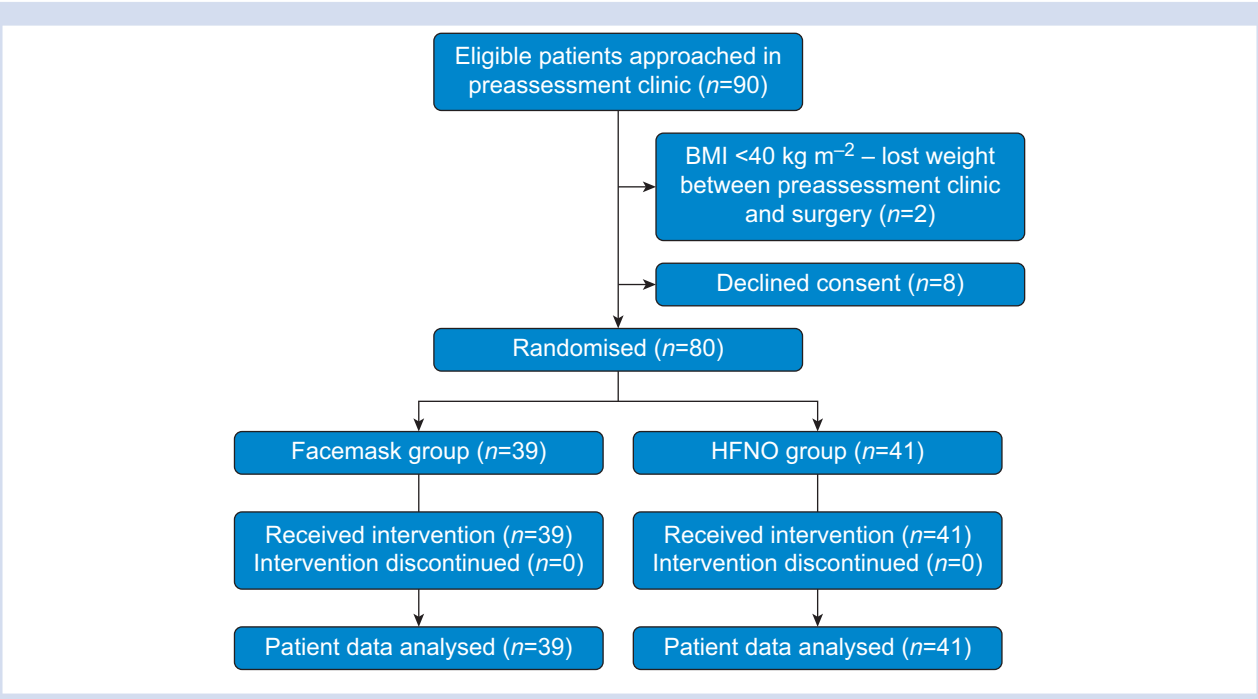


Fig 1. CONSORT diagram. CONSORT, Consolidated Standards of Reporting Trials; HFNO, high-flow nasal oxygen.

outcome, but – given the uncertainty in these estimates – we chose a sample size of 40 per group.

Standard descriptive statistics were used to summarise the presenting features of two groups using mean and SD or median and inter-quartile range (IQR) and 95% confidence interval (95% CI). Time to desaturation is summarised using Kaplan–Meier curves and compared between groups using the log-rank statistic. Continuous data were checked for normality (d'Agostino and Pearson), and between-group differences were evaluated using either an independent *t*-test or Mann–Whitney *U*-test as appropriate. For those who desaturated during the 18 min period, the time to desaturation was compared between groups using the Mann–Whitney *U*-test. Arterial oxygen (Pa_{O2}) and carbon dioxide (Pa_{CO2}) tension were compared between groups using independent *t*-tests. The Holm–Sidak method was used to correct for multiple comparisons. A two-tailed *P* value <0.05 was taken to indicate statistical significance.

Data were collated using Excel 2016 (Microsoft Corporation, Redmond, WA, USA) and analysed using Prism 8.3.0 (GraphPad Software Inc., San Diego, CA, USA). Data and documentation would be securely stored for 10 yr after the completion of the study.

Results

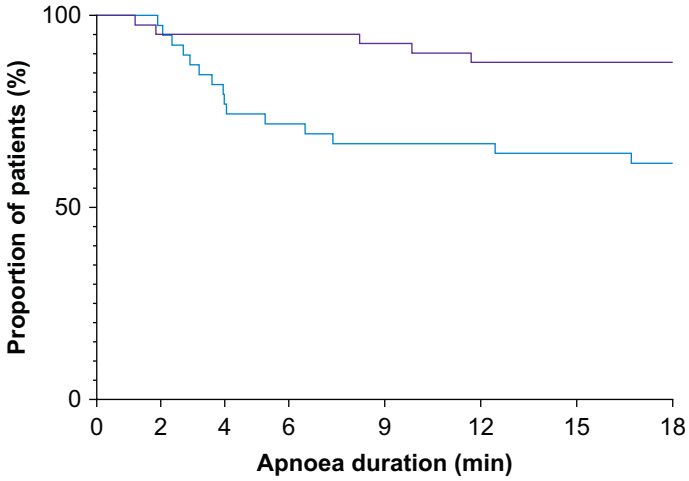
Eighty participants were randomised (41 patients for the HFNO group, 39 for the FM group). All completed the study (Fig. 1). No serious adverse events occurred. Ten participants in each group were using CPAP and baseline characteristics were similar in both groups (Table 1). Fifty-three patients received an additional rocuronium after 10 min of apnoea. Of the 60 patients who reached 18 min of apnoea without desaturation, 54 received an additional dose of rocuronium.

Five patients (12%) in the HFNO group and 15 (38%) in the FM group desaturated to 92% within 18 min of apnoea (Fig. 2). The risk of desaturation was significantly lower in the HFNO group than in the FM group (hazard ratio=0.27; 95% CI, 0.11–0.65; log-rank *P*=0.007).

The median time to desaturation was 18 (IQR 18–18) min in the HFNO group and 18 (IQR 4.1–18) min in the FM group. However, these data are heavily right-censored because the majority of patients in both groups reached the 18 min endpoint without desaturating, and therefore statistical analysis (although significant, Mann–Whitney *U* *P*=0.0068) is

Table 1 Subject characteristics. Continuous variables are presented as median (IQR). CPAP was prescribed to patients diagnosed with obstructive sleep apnoea (OSA). STOP-Bang score is a validated tool to assess risk of OSA where a score ≥5 indicates a high risk of OSA.[38] CPAP, continuous positive airway pressure; IQR, inter-quartile range; FM, facemask oxygen; HFNO, high-flow nasal oxygen.

	FM	HFNO
Participants	39	41
CPAP use	10	10
STOP-Bang score ≥5	10	13
Sex	31 F / 8 M	26 F / 15 M
Age (yr)	48 (38–54)	47 (36–55)
Weight (kg)	130 (122–139)	129 (118–144)
BMI (kg m^{-2})	46.7 (44.4–49.5)	46.6 (43–53.6)
Neck circumference (cm)	40.8 (38.8–44.3)	40.0 (38.0–46.0)
Waist/hip ratio	1.0 (1.0–1.1)	1.0 (1.0–1.1)
Smoker (current/ex/never)	2/13/24	0/16/25



At risk	TA	TA+2	TA+4	TA+6	TA+9	TA+12	TA+15	TA+18
HFNO	41	39	39	39	38	36	36	36
FM	39	38	30	28	26	26	25	24

Fig 2. Risk of desaturation during apnoea. Proportion of study participants in HFNO (purple line) and FM (blue line) groups with oxygen saturation >92% during apnoea. Hazard ratio comparing FM and HFNO groups, 0.27 (95% confidence interval, 0.11–0.65; log-rank P=0.007). TA, onset of apnoea. TA+x, apnoea duration where x denotes min after TA; FM, facemask oxygen; HFNO, high-flow nasal oxygen.

of limited value. Of the 20 patients who desaturated, time to desaturation was longer in HFNO group (median=8.2; IQR 1.5–10.8 min; n=5) compared with the FM group (median=4.0; IQR 2.7–6.5 min; n=15), but this was not statistically significant (Mann–Whitney U P=0.933).

Blood gas data were not available for two baseline samples and two post-preoxygenation samples (separate participants) in the HFNO group and three apnoeic samples (TA+2/+4/+6) in one participant in the FM group. Missing samples were all in participants who completed 18 min of apnoea. Two TA+18 samples (both HFNO) showed a marked reduction in Pa_{co2} (9.4 to 7.8 kPa in one and 9.3 to 7.7 kPa in the other), which were also lower than samples taken after 1 min of ventilation (8.5 kPa in both cases). These samples were excluded from analysis.

Blood gas data are summarised in Table 2. At baseline and after preoxygenation, there was no significant difference in the mean Pa_{o2} between the two groups.

To allow direct comparison of the effect of oxygen delivery method on the efficiency of apnoeic oxygenation and ventilation,[3] analyses of blood gas tension during apnoea were restricted to the 60 patients who reached 18 min without desaturation. There was no significant difference in the mean Pa_{o2} or Pa_{co2} at any time point during apnoea.

Individual Pa_{o2} and Pa_{co2} curves are shown in Fig. 3. Among participants who reached 18 min of apnoea, the mean rate of Pa_{co2} increase between TA and TA+18 was 0.224 (0.05) kPa min^{-1} in the FM group and 0.232 (0.05) kPa min^{-1} in the HFNO group. This was not significantly different, nor was the rate of increase at any single time point.

Discussion

The principal finding of this study is that, under these experimental conditions, morbid obesity does not preclude apnoeic oxygenation. Overall, 60 (75%) morbidly obese patients

Table 2 Pa_{o2} and Pa_{co2} before and during apnoea. Figures shown are mean (standard deviation) arterial oxygen and carbon dioxide tensions (kPa). TA, onset of apnoea; TA+x, apnoea duration where x denotes min after TA. Figures before apnoea (at baseline breathing air, and at the end of preoxygenation) include data from all participants in the high flow nasal oxygen (HFNO; where data are available, n=39) and facemask oxygen (FM, n=39) groups. During apnoea, figures include data only from the 60 participants who completed 18 min of apnoea (HFNO, n=36; FM, n=24). Comparisons were made using the independent t-test.

		Baseline	After preoxygenation	TA	TA+2	TA+4	TA+6	TA+9	TA+12	TA+15	TA+18
Pa_{o2}	HFNO	12.8 (2.4)	59.9 (8.1)	55.7 (7.2)	40.4 (8.1)	30.4 (8.1)	28.2 (8.2)	26.7 (7.3)	26.0 (7.2)	24.5 (6.7)	23.6 (6.7)
	FM	12.7 (2.3)	60.2 (9.4)	50.7 (9.9)	35.5 (11.6)	30.5 (11.1)	28.7 (10.2)	27.1 (9.9)	25.2 (9.4)	23.8 (9.1)	22.2 (8.3)
	P	0.978	0.978	0.249	0.422	1.000	0.999	0.999	0.999	0.999	0.987
Pa_{co2}	HFNO	5.3 (0.5)	4.5 (0.9)	6.5 (0.9)	7.1 (0.8)	7.7 (0.8)	8.2 (0.8)	9.0 (0.9)	9.6 (0.9)	10.1 (1.0)	10.7 (1.1)
	FM	5.3 (0.5)	5.0 (0.7)	6.6 (0.8)	7.1 (0.7)	7.8 (0.7)	8.3 (0.8)	8.9 (0.8)	9.5 (0.9)	10.0 (1.0)	10.6 (1.1)
	P	0.660	0.009	0.996	0.999	0.999	0.999	0.999	0.999	0.996	0.999

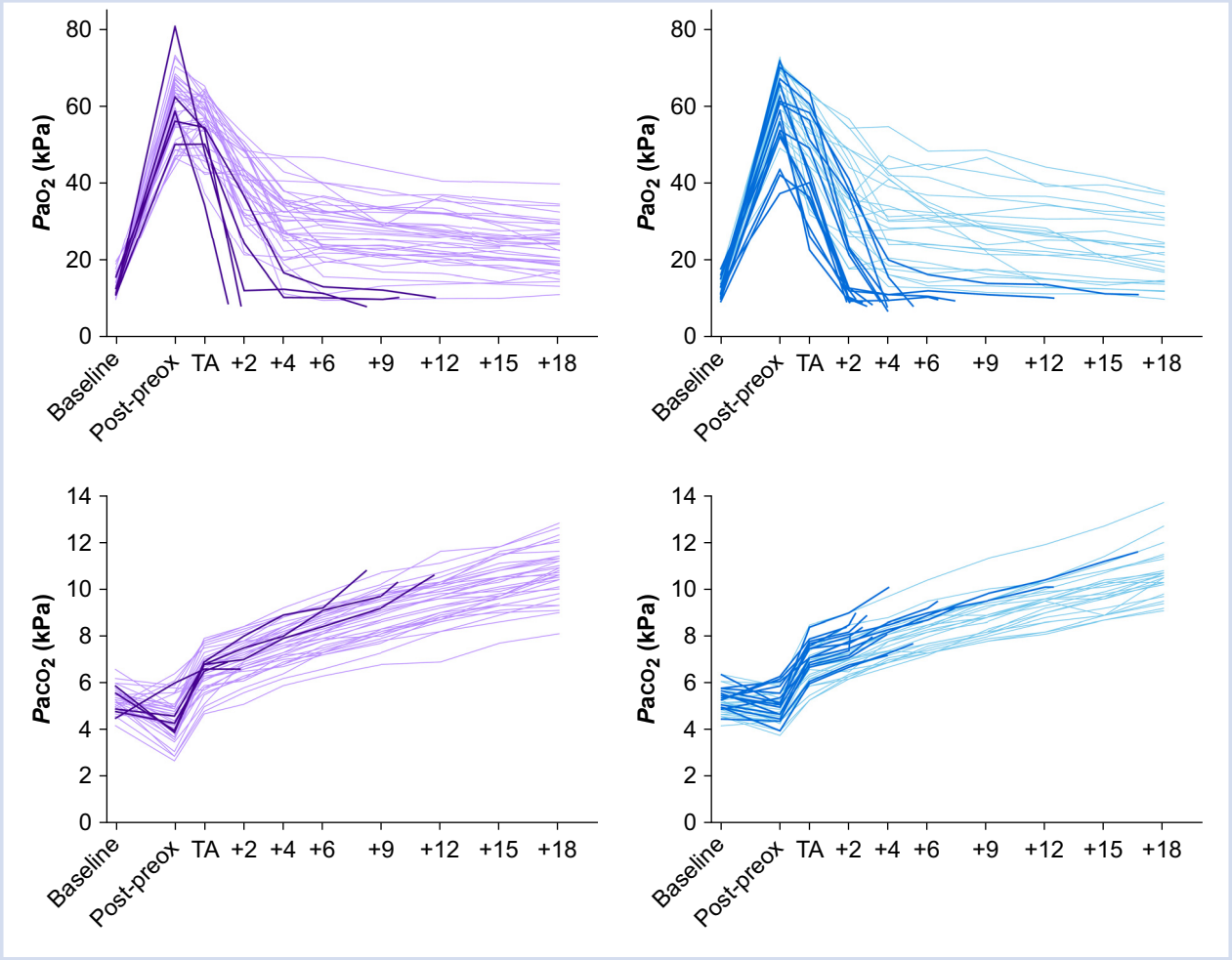


Fig 3. Pa_{o2} and Pa_{co2} change over time during apnoea. Change in arterial oxygen and carbon dioxide tension during apnoea. TA, onset of apnoea; TA+x, apnoea duration where x denotes min after TA. Each line represents an individual participant (purple: high flow nasal oxygen group; blue: facemask group). Light lines represent participants whose oxygen saturation level remained >92% during apnoea throughout the 18 min period. Dark lines represent participants who desaturated to 92% during the study period.

tolerated apnoea for 18 min without desaturation. In the HFNO group, the proportion (36/41, 88%) was similar to that previously reported in non-obese patients[13] although, in contrast to this study, patients in the non-obese case series were in the supine position.

This is the largest RCT of apnoeic oxygenation in morbidly obese patients to date. Before this, apnoea without desaturation in obese patients had been reported using various oxygen delivery techniques. Using our definition of apnoea onset, the maximum apnoea time in these earlier studies was 10.5 min[14] and, subsequently, one trial has extended this to 14 min.[15] There have been no studies of comparable size with the exception of one, studying obese patients, in which the maximum apnoea time was 6 min.[16]

In the FM group, a lower proportion tolerated apnoea without desaturation, suggesting that HFNO improves the efficiency of apnoeic oxygenation. The only directly comparable study is in non-obese older patients which reported similar results.[17] Our findings align with previous studies which report that both flow rate[18] and proximity of fresh gas flow to the respiratory epithelium[19] influence apnoeic oxygenation efficiency.

However, as Fig. 3 shows, there is inter-individual variability in Pa_{o2} trajectory during apnoea. This is not linear, initially decreasing rapidly before decreasing more slowly. There was substantial variation in both the rate of initial descent and the inflexion point. As Table 2 demonstrates, this variability was similar in HFNO and FM groups. The physiological factors that underlie this variability are not thus far clear.

Oxygen delivery characteristics may mitigate the risk of desaturation[18] and this study supports this notion. However, the unexpectedly high proportion of patients in the FM group reaching 18 min without desaturation and the wide variability in Pa_{o2} during apnoea in both groups also suggests that oxygen delivery characteristics are not the primary determinant of whether patients desaturate during apnoea. Indeed, it has been shown that desaturation can occur despite 100% oxygen concentration within the trachea.[20]

This is reinforced by the wide variation seen in results from apnoeic oxygenation studies using similar oxygen delivery techniques. In obese patients, there are no other studies investigating facemask oxygen but three have used HFNO. In one, the mean apnoea time was 261 (77.7) s.[21] In another, censored at 600 s, the median apnoea time was 600 (IQR 296–600) s.[22] In the third, censored at 900 s, the median was 537 (IQR 399–808) s.[15] Notably, in the latter study, there was no difference between apnoea time in patients given high-flow (120 L min^{-1}) and low-flow (10 L min^{-1}) oxygen. It is not clear why these and our results differ, but oxygen delivery method *per se* does not seem to be the reason. These disparities emphasise the complexity of apnoeic oxygenation as a physiological process and the need for deeper understanding of the mechanisms that underpin it.

In our study, patients were semi-recumbent with a 45° mid-thoracic incline, steeper than other studies in which patients were positioned at 30°,[14,21] 25°,[16] or 20°,[13] the 'ramped sniffing' position,[15,18] or supine.[17] Although there is no clear relationship between apnoea time and position among these studies, comparison is limited by other methodological differences. There is, however, evidence that position affects apnoea time,[23,24] and this may have contributed to the apnoea time achieved by patients in our study.

Apnoeic ventilation

Arterial carbon dioxide tension during apnoea initially increases steeply followed by a more gradual incline.[25] The underlying physiology is not well understood but contributory factors are arteriovenous admixture, the Haldane effect, and possibly apnoeic ventilation. Evidence for the latter has been derived from comparison of studies reporting Pa_{co2} increase during apnoea with[25] (~0.45 kPa min^{-1}) and without[9,13,26,27] airway obstruction (as low as 0.15 kPa min^{-1}). However, these comparisons are confounded by experimental design, particularly the use of proxy measures such as end-tidal carbon dioxide concentration,[3] which has been shown to be an imprecise marker of Pa_{co2}.[9]

This study provides direct evidence of Pa_{co2} changes in 60 patients during 18 min of apnoea, the largest such dataset published to date. Overall, the rate of increase was 0.23 (0.05) kPa min^{-1}, which suggests that ventilatory exchange is indeed a phenomenon.[3] This is similar to the rate of increase seen in studies of non-obese patients,[9,13,27] which supports our contention that obesity itself (with appropriate airway management) does not preclude apnoeic gas exchange. Our analysis is limited to those patients who tolerated 18 min of apnoea without arterial oxygen desaturation but our findings suggest that, in this group, the efficiency of this process is not substantially different to that in non-obese patients.

There was no significant difference between HFNO and FM groups in the rate of Pa_{co2} increase during apnoea. This challenges the notion that HFNO delivery improves efficiency of ventilatory exchange[10,28] and, correspondingly, that enhanced carbon dioxide clearance is responsible for any increase in efficiency of apnoeic oxygenation when high gas flows are used.[29]

It has been hypothesised that apnoeic carbon dioxide clearance may become more efficient as alveolar concentration increases.[9] We did not observe a 'plateau' where Pa_{co2} stopped increasing. This may require a longer period of apnoea but it is questionable whether it is clinically relevant, particularly in the context of mounting acidaemia.[30]

Strengths and limitations

This physiological study was conducted in a safe environment by experts in bariatric anaesthesia. These conditions allowed the safe collection of an unprecedented dataset. In comparison with earlier case series, this was a systematic study which minimised risk of confounding. This study was clinically relevant: airway management can be challenging and time-pressured in obese patients owing to rapid desaturation. However, our findings may not be transferable to other populations.

Our primary outcome, in common with most other studies of apnoeic oxygenation, was time to desaturation. In previous studies,[12,14,31] the majority of patients in the intervention groups reached the census point (the maximum duration of apnoea allowed by the study design) without desaturation. This limits the clinical utility of this outcome measure as it is predominantly determined by the choice of census point rather than the physiological performance of the patients. In response, we increased the maximum apnoea time to 18 min. Despite this and unexpectedly, the majority of patients reached this census point without desaturation. This was also a limitation of other studies performed around the same time as ours, which also used longer apnoea periods.[18,20,32]

Time to desaturation as an outcome is therefore sensitive to study design and it does not describe the risk of desaturation during apnoea. In retrospect it is clear that desaturation risk, as used by a recent study in high-risk patients undergoing endoscopy,[33] would have been a better primary outcome. A strength of this study is the temporal resolution of the blood gas dataset, which illustrates the fallibility of time to desaturation as an outcome in apnoeic oxygenation studies (Fig. 3).

The majority of patients who desaturated in this study did so early in apnoea. In these cases the apnoea time was less than 5 min, comparable with time to desaturation in obese patients who were not given supplemental oxygen during apnoea.[14,34] This pattern, an apparent dichotomy between patients who do and do not 'tolerate' apnoea, was reported as early as 1973[35] and has been replicated in studies in both obese[14,18] and non-obese patients.[17]

Clinically, this is an important finding: the implication is that for some patients – whatever the delivery method – supplying oxygen does not greatly increase the duration of apnoea without desaturation. Indeed, it is questionable whether the notion of 'safe apnoea time' is valid.

A technical limitation to this study relates to blood sampling method: blood gas samples were not processed contemporaneously but were refrigerated until completion of an individual patient study run. However, samples were analysed sequentially and each analysis took approximately 2 min, which approximately matches the sampling time difference. Two blood gas samples taken at intubation showed a noticeably lower Pa_{co2} (7.8 and 7.7 kPa) compared with previous (9.4 and 9.3 kPa, respectively) and subsequent samples (both 8.5 kPa after 1 min of mechanical ventilation). In one case, other biochemical markers were consistent with saline contamination. In the other, the reason for the decrease is not clear. These discrepancies were obvious and have been excluded but other sampling discrepancies may have been missed. However, the fact that all of the other blood gas data points followed coherent trajectories (Fig. 3) suggests that this was not a significant methodological concern.

Although we did not monitor neuromuscular block, the protocolised dose of rocuronium (1 mg kg^{-1}) should have been adequate to prevent diaphragmatic movement.[36,37] The majority of patients received additional rocuronium during apnoea, including 54 of the 60 patients who reached 18 min without desaturation, which suggests that this was due to apnoeic oxygenation rather than imperceptible diaphragmatic movement.

In contrast to some studies,[12,14,31] no direct visualisation of the airway was used throughout apnoea. However, an oropharyngeal airway and jaw thrust were used and a check that manual ventilation was possible at the beginning of apnoea confirmed the airway was patent at this point. Theoretically, operator fatigue during prolonged jaw thrust may have led to airway compromise after this but most patients who desaturated did so within the first 5 min, suggesting that this did not materially alter results.

Clinical relevance/application

Although this study demonstrates that apnoeic oxygenation is possible in morbidly obese patients, it was conducted under experimental conditions by bariatric anaesthetists with the experience and resources to manage any complication. Patients were screened to exclude conditions that might put them at predictable risk of complications during apnoea or airway management. This was primarily a physiological study and the experimental conditions do not translate to clinical conditions such as 'tubeless' airway surgery.

Clinically, this study highlights two important, in some ways contradictory, precepts: first, a note of caution that patients may desaturate rapidly during apnoea despite optimal preoxygenation and an adequate oxygen supply. The factors that determine this risk – and which may be present also in non-obese patients – warrant further investigation. Second, the majority, including those in the FM group, tolerated apnoea without desaturation for a duration that substantially exceeds the normal duration of perioperative airway management. This suggests that apnoea is tolerable in most patients using a standard anaesthetic facemask under certain conditions – notably, adequate preoxygenation, head-up position, intravenous anaesthetic delivery, haemodynamic stability, and assiduous attention to mask seal and airway patency.

The safety of this manoeuvre presupposes the ability to facemask ventilate in the event of desaturation. Potential advantages of minimising facemask ventilation relate to the risk of gastric insufflation, which may increase the risk of regurgitation and aspiration of gastric contents, compromise laparoscopy and ventilation, and increase the risk of postoperative nausea and vomiting. Recently, the risk of aerosol generation during facemask ventilation has been a concern, and this technique may be one element among many in the management of this risk.

Authors' contributions

Study concept and design: JC, AL, SJB, AK
Data acquisition: JC, JSW, TW, RS, AK, RK, AA, SP
Data analysis: JSW, JC, TW, RS
Data interpretation: JC, JSW, TW, RS, SJB
Writing of the initial manuscript draft: JSW, TW, JC, RS
Critical revision: JSW, JC, SJB, TW, RS, AK, AL, RK

Declarations of interest

JC has received payments and travel funding from Fisher & Paykel Healthcare, Auckland, New Zealand (Fisher & Paykel) for both UK and overseas lectures. He continues to advise Fisher & Paykel on future developments relating to delivery of humidified oxygen. TW has previously received travel funding from Fisher & Paykel. The other authors have no relevant interests to declare.

Funding

The National Institute for Health Research Imperial Biomedical Research Centre provided infrastructure support. Fisher & Paykel provided high-flow nasal oxygen equipment and disposables, but were not involved with design, data collection, analysis, or interpretation of the study and had no role in the preparation of the manuscript or the decision to submit the manuscript for publication.

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Handling editor: Takashi Asai