

Prophylactic Postoperative High Flow Nasal Oxygen Versus Conventional Oxygen Therapy in Obese Patients Undergoing Bariatric Surgery (OXYBAR Study): a Pilot Randomised Controlled Trial

Author

Fulton, Rachel, Millar, Jonathan E, Merza, Megan, Johnston, Helen, Corley, Amanda, Faulke, Daniel, Rapchuk, Ivan L, Tarpey, Joe, Fanning, Jonathon P, Lockie, Philip, Lockie, Shirley, Fraser, John F

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1 **Prophylactic post-operative high flow nasal oxygen versus conventional oxygen therapy in obese**
2 **patients undergoing bariatric surgery (OXYBAR study): a pilot randomised controlled trial**

3 R. Fulton,^{1,2} J. E. Millar,^{2,3,4} M. Merza,⁵ H. Johnston,⁵ A. Corley,^{2,6} D. Faulke,⁵ I.L. Rapchuk,^{3,5} J.
4 Tarpey,⁵ J. P. Fanning,^{2,3} P. Lockie,⁵ S. Lockie,⁵ J. F. Fraser^{2,3}

5 1. Department of Anaesthesia and Critical Care, Queen Elizabeth University Hospital, Glasgow,
6 United Kingdom

7 2. Critical Care Research Group, The Prince Charles Hospital, Brisbane, Australia

8 3. Faculty of Medicine, University of Queensland, Brisbane, Australia

9 4. Roslin Institute, University of Edinburgh, Edinburgh, United Kingdom

10 5. St. Andrew's War Memorial Hospital, Brisbane, Australia

11 6. Griffith University, Griffith, Australia

12 **Correspondence to:**

13 Prof John F Fraser

14 Critical Care Research Group

15 The Prince Charles Hospital

16 Rode Road

17 Brisbane

18 Queensland 4032

19 Australia

- 20 Dr Rachel Fulton – Specialist Registrar in Anaesthesia; r.fulton.04@aberdeen.ac.uk
- 21 Dr Jonathan E Millar – Clinical Lecturer in Intensive Care Medicine; jonathan.millar@ed.ac.uk
- 22 Ms Megan Merza – Critical Care Research Nurse; mlsimpson1511@gmail.com
- 23 Ms Helen Johnston – Critical Care Physiotherapist; Helen.Johnston@uhealth.com.au
- 24 Ms Amanda Corley – Nurse Researcher; amanda.corley@health.qld.gov.au
- 25 Dr Daniel Faulke – Consultant Anaesthetist; dfaulke@hotmail.com
- 26 A/Prof Ivan L Rapchuk – Consultant Anaesthetist; ivan.rapchuk@health.qld.gov.au
- 27 Dr Joe Tarpey – Consultant Anaesthetist; jotarpey@yahoo.co.uk
- 28 Dr Jonathon P Fanning – Senior Lecturer and Consultant in Anaesthesia and Intensive Care;
- 29 jonathon_fanning@me.com
- 30 Dr Philip Lockie – Consultant Bariatric and General Surgeon; plockie@icloud.com
- 31 Ms Shirley Lockie – Specialist Nurse in Bariatric Medicine; slockie@me.com
- 32 Prof John F Fraser – Professor of Intensive Care Medicine; fraserjohn001@gmail.com
- 33 * *Preliminary results of this study were presented at the Society for Bariatric Anaesthesia UK Annual*
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40 Summary

41 Obesity has become a global pandemic, as a result surgical intervention for weight loss has increased
42 in popularity. Obese patients undergoing operative intervention pose several challenges in respect of
43 their peri-operative care. A prominent feature is the alteration in respiratory mechanics and
44 physiology evident in the obese. These combine to predispose individuals to a reduction in end
45 expiratory lung volume (EELV) and atelectasis after anaesthesia. Consequently, the incidence of post-
46 operative pulmonary complications (PPC) in this cohort has been reported to be in excess of 35%. High
47 flow nasal oxygen (HFNO) has been suggested as a means of increasing EELV in post-operative
48 patients, reducing the likelihood of PPC. We conducted a single centre, pilot, randomised controlled
49 trial (RCT) of conventional oxygen therapy versus HFNO in patients after bariatric surgery. The aim of
50 the study was to investigate the feasibility of using Electrical Impedance Tomography (EIT) as a means
51 of assessing respiratory mechanics and to inform the design of larger, definitive RCT. Fifty patients
52 were randomised during a 10-month period (conventional O₂ n=25 vs. HFNO n = 25). One patient
53 crossed over from conventional O₂ to HFNO. There was no loss to follow-up. and analyses were
54 performed on an intention-to-treat basis. Delta EELI was higher at 1 hour in patients receiving HFNO
55 (mean difference = 831 Au (95% CI -1636 – 3298), p = 0.5). Continuous EIT beyond 1 hour was poorly
56 tolerated. At 6 hours, there were no differences in PaO₂/FiO₂ ratio or PaCO₂. ICU and hospital LOS
57 were comparable. Only one patient developed a PPC (in the HFNO group). In a secondary analysis,
58 delta EELI was positively correlated with increasing BMI. These data suggest that a large-scale
59 randomised controlled trial of HFNO after bariatric surgery in an 'all-comers' population is likely
60 infeasible. Furthermore, while EIT is a useful tool for assessing respiratory mechanics in this group it

61 could not be considered a patient-centred outcome in a larger study. Similarly, the infrequency of PPC
62 precludes its use as a primary outcome in a definitive trial. Future studies should focus on identifying
63 patients most at risk for post-operative pulmonary complications and those in whom HFNO is likely to
64 confer greatest benefit.

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90 Introduction

91 Obesity is a global pandemic, with over 2 billion individuals now classed as overweight or obese [1].
92 As a result, the use of surgical intervention in the management of obesity has increased in popularity
93 [2]. Surgery, in selected individuals, has been shown to be a safe and effective means of achieving
94 sustained weight loss [3]. Despite the success of operative interventions, patients undergoing these
95 procedures continue to represent a challenge in respect of their peri-operative and anaesthetic
96 management.

97 Obesity is associated with a higher mortality after non-cardiac surgery and with an increased risk of
98 developing a variety of post-operative complications, including myocardial infarction and wound
99 infection [4]. The adverse impact of obesity on respiratory mechanics and ventilation is also well
100 described. Obesity tends to increase the work of breathing and promote rapid, shallow breathing. In
101 turn, end expiratory lung volume (EELV) is reduced, disposing the individual toward atelectasis and
102 ventilation/perfusion mismatching [5-8]. In those undergoing bariatric surgery, the prevalence of post-
103 operative atelectasis has been reported to be as high as 38% [9]. However, the ability to directly
104 translate these physiological alterations into observable morbidity and mortality remains uncertain
105 [10-12].

106 The post-operative application of high flow nasal oxygen (HFNO) has been suggested as a means of
107 reducing the risk of pulmonary complications [13]. Previous studies have reported the physiological
108 benefits of HFNO in the post-operative period, associating its use with improvements in EELV and gas
109 exchange [14].

110 We conducted a pilot, randomised controlled trial of HFNO versus conventional oxygen therapy after
111 bariatric surgery to investigate the physiological action of HFNO in the obese, assess the feasibility of
112 using an Electrical impedance Tomography (EIT) measure of EELV as an outcome, and to inform the
113 design of a larger, definitive trial.

114 Methods

115 This single centre study was approved by the UnitingCare Health and Human Research Ethics
116 Committee (UCH/HERC/1709). The trial was prospectively registered with the Australian New Zealand
117 Clinical Trials Registry (ACTRN12617000694314). Prospective written informed consent was obtained
118 from all patients prior to their inclusion in the study. This study has been reported in compliance with
119 the CONSORT extension for pilot randomised and feasibility trials [15].

120 Study setting

121 St. Andrew's War Memorial Hospital (SAWMH), Brisbane, is a tertiary referral centre with a 15-bed
122 general adult ICU. Bariatric surgical services are provided by a single specialist surgeon, conducting
123 over 250 procedures per year, including; laparoscopic gastric bypass, sleeve gastrectomy, and gastric
124 banding. All patients scheduled to undergo laparoscopic surgical intervention for weight loss were
125 screened for eligibility between April 2017 and January 2018. The trial was scheduled to finish after
126 the inclusion of 50 patients. This number was based on an audit of surgical workload over a 12-month
127 period, with an assumed randomisation to screening ratio of 1:2 (10% loss to follow-up) and a planned
128 study period of 14 months.

129 Inclusion, exclusion, and randomisation

130 Patients were eligible for inclusion in the study if they were aged ≥ 18 years and had a body mass index
131 (BMI) ≥ 30 kg/m². We excluded patients if they had a contraindication to the use of HFNO, had a chest
132 circumference too large to allow for the use of an Electrical Impedance Tomography (EIT) belt (> 150
133 cm), or if they had evidence of pre-operative hypoxaemia (SpO₂ $< 92\%$ on air) and/or severe chronic
134 lung disease.

135 Prior to surgery, patients were randomised in a 1:1 fashion (using a computer-generated sequence
136 based on block sizes of 4, 6, or 8). An investigator, not involved in the peri-operative care of patient,
137 obtained the allocation in a sealed envelope and informed the Intensive Care Unit staff. The surgical

138 and anaesthetic teams were blinded to the patient's allocation until return to the ICU, after which
139 treatment allocation was unblinded.

140 Study protocol

141 The study protocol was pre-defined and has been published online [16]. In brief, the conduct of
142 general anaesthesia was at the discretion of the responsible anaesthetist. Given the nature of the
143 surgery, all patients underwent endotracheal intubation and mechanical ventilation. All patients were
144 extubated in theatre and received supplemental oxygen via a Hudson mask at 6 L/min before
145 immediate transfer to the ICU. Those randomised to the conventional oxygen group continued to
146 receive supplemental oxygen via a face mask, titrated to achieve a peripheral oxygen saturation (SpO_2)
147 $\geq 95\%$. If the patient consistently achieved or exceeded this target, the level of support was reduced
148 in stages to a minimum of standard nasal cannula providing 2 L/min oxygen. Patients randomised to
149 the intervention group received supplemental oxygen via high flow nasal cannulae (Airvo™ 2, Fisher
150 & Paykel, New Zealand). HFNO was commenced at a flow rate of 50 L/min and set to provide an
151 inspired fraction of oxygen (FiO_2) of 0.5. Inspired oxygen concentrations were titrated to maintain a
152 $SpO_2 \geq 95\%$. A constant flow was maintained for the duration of the study. Oxygen therapy was
153 protocolised for 6 hours after which care reverted to the discretion of the treating intensivist. HFNO
154 could be continued if deemed desirable by the clinical team. Patients were discharged from the ICU
155 on post-operative day one, unless a higher level of care was judged to be required by the intensive
156 care team. Timing of hospital discharge was decided upon by the admitting surgeon.

157 Outcome assessment

158 The primary outcome of the study was change in end expiratory lung impedance ($\Delta EELI$) at 60 minutes,
159 measured using EIT (Pulmovista 500, Dräger, Lübeck, Germany). EIT is a non-invasive, bedside imaging
160 technique used to acquire data on regional lung ventilation and volume. It's use as a tool for
161 investigating patients receiving HFNO is well validated [14, 17, 18]. Previous studies have shown that
162 changes in End Expiratory Lung Impedance (EELI), measured using EIT are positively correlated with

163 changes in EELV [14]. Likewise, tidal variation, measured by EIT, is related to changes in tidal volumes
164 [14].

165 *A priori*, we defined Δ EELI at 6 hours as the primary outcome measure [16]. During the trial it became
166 apparent that the continuous placement of an EIT belt for > 2-3 hours was intolerable for most
167 patients. Removal and re-application of the belt invalidates the measurement of EELI and thus 60
168 minutes was adopted as a primary endpoint prior to the completion of the trial and analysis of the
169 data. EIT analysis was conducted using the manufacturers software (EIT Data Analysis Tool v6.1,
170 Dräger, Lübeck, Germany) according to our previously published methods [14]. Pre-defined secondary
171 outcomes were: Δ EELI at 15 and 30 minutes; tidal variation at 15, 30 and 60 minutes (measured by
172 EIT); change in PaO₂/FiO₂ ratio, PaCO₂ and respiratory rate (RR) at 60 minutes, 3 and 6 hours; change
173 in modified Borg dyspnoea score [19] at 60 minutes, 3 and 6 hours; simple numeric pain reporting
174 scale at 60 minutes, 3, and 6 hours; requirement for escalation of oxygen therapy; ICU length of stay;
175 re-admission to the ICU; hospital length of stay; and hospital re-admission in the first 6 weeks. In
176 addition, patients were followed up until 6 weeks post-operatively to identify those with a diagnosis
177 of a new post-operative pulmonary complication (PPC), defined as any pulmonary abnormality,
178 disease, or dysfunction that adversely affected the clinical course of the patient.

179 Statistical analysis

180 All analyses were on an intention-to-treat basis and performed with GraphPad Prism v8.0.1 (GraphPad
181 Software, San Diego, CA, USA). Data are expressed as mean (\pm SD) if normally distributed or median
182 (IQR) if non-normally distributed. Longitudinal data were analysed by fitting a mixed model. This mixed
183 model used a compound symmetry covariance matrix and was fit using Restricted Maximum
184 Likelihood (RML). Where a significant interaction was observed between groups or between time and
185 group, post-hoc comparisons were undertaken using Fisher's Least Significant Difference (LSD) test.
186 Alternatively, non-longitudinal data were compared using an unpaired t-test if normally distributed,
187 or a Mann-Whitney test if non-normally distributed. Categorical data were compared using the chi-

188 squared test. Adjustment for multiple comparisons was made using a False Discovery Rate (FDR)
189 method (Benjamini-Hochberg). The FDR was restricted to 5%. Correlation between variables was
190 assessed using Pearson's correlation co-efficient. A *P* value < 0.05 was considered significant.

191 **Results**

192 Fifty-six patients were screened for enrolment, of whom 50 were randomised (25 patients per group)
193 (Fig. 1). All patients completed the study protocol. One patient randomised to receive conventional
194 oxygen was escalated to HFNO at hour 4 due to hypoxaemia. There was no loss to follow-up. Baseline
195 characteristics and intra-operative parameters are detailed in Table 1. There were no adverse events
196 related to either HFNO or EIT use.

197 End expiratory lung impedance and tidal variation

198 Overall, 46 (92%) patients had ≥ 3 analysable EIT recordings (conventional O₂ n = 23 vs. HFNO n = 23).
199 One patient in each group did not have EIT data fit for analysis due to corruption of the baseline
200 recording. There were no significant differences in change in EELI from baseline (Δ EELI) between
201 groups (Fig. 2). However, the group receiving HFNO showed a consistent increase in EELI over 60
202 minutes, while the group receiving conventional oxygen therapy had a diminishing improvement over
203 the first 30 minutes and failed to match the improvement seen at baseline by 60 minutes (HFNO vs.
204 conventional O₂ mean difference at 60 minutes = 831 Au (95% CI -1636 – 3298), *p*.adj = 0.5). There
205 were no significant differences in tidal variation between groups (Fig. 2).

206 Oxygenation and gas exchange

207 Oxygenation, as measured by PaO₂/FiO₂ ratio, was similar between groups throughout the study (Fig.
208 3). This was despite the conventional oxygen group receiving a significantly lower FiO₂ from 1 hour
209 onwards. Both groups exhibited a progressive reduction in PaCO₂ during the study period (Fig. 3).

210 Dyspnoea and pain scores

211 Patient reports of dyspnoea, measured using a modified Borg score, were universally low. There were
212 no differences observed between groups (Table 2). Pain scores varied across time points and were
213 higher in those receiving HFNO at 6 hours (Table 2).

214 Length of stay and post-operative complications

215 Intensive care unit and hospital length of stay (LOS) were equivalent between groups. One patient in
216 the conventional O₂ group required readmission to ICU after revisional surgery for an anastomotic
217 leak. Only one patient (from the HFNO group) was diagnosed with a PPC during the 6-week follow-up
218 period, in this case atelectasis with small bilateral pleural effusions. Four patients in the HFNO required
219 readmission to hospital following their initial discharge, none of these incidents were related to
220 pulmonary complications.

221 Association between BMI and Δ EELI

222 The association between BMI and Δ EELI was assessed in a post-hoc analysis. There was no significant
223 correlation between BMI and Δ EELI at any time point in the conventional group. However, in those
224 receiving HFNO, increasing BMI was positively correlated with higher Δ EELI values at 30 and 60
225 minutes (Fig. 4).

226 **Discussion**

227 We conducted a single centre, pilot, randomised controlled trial of HFNO versus conventional oxygen
228 therapy, in patients undergoing bariatric surgery. Our principal findings can be summarised as; (1),
229 HFNO failed to produce a significant increase in EELI at 60 minutes, (2), similarly, the use of HFNO was
230 not associated with improvements in PaO₂/FiO₂ ratio, dyspnoea, length of stay, or the incidence of
231 post-operative pulmonary complications, (3), the use of HFNO was associated with higher pain scores
232 at 6 hours, and (4), the effect of HFNO on EELI was enhanced in patients with a higher BMI. EIT was a
233 feasible method of assessing respiratory mechanics in this population, however, in a definitive trial,
234 would not constitute a patient-centred outcome and is not suitable for use over extended periods.

235 Additionally, the low incidence of post-operative pulmonary complication in our study would suggest
236 that its use as a primary outcome would likely require an infeasibly large sample size. Future
237 effectiveness studies in this area may consider enrichment by including patients with a higher BMI or
238 those with other risk factors for post-operative pulmonary complication.

239 The ability of HFNO to improve EELI post-operatively has been studied previously [14, 20]. In a cohort
240 of patients undergoing elective cardiac surgery, Corley et al. described an improvement in EELI in
241 patients transitioning from low flow oxygen therapy to HFNO. The magnitude of this effect was
242 positively correlated with BMI. These findings are consistent with the relationship between EELI and
243 BMI in patients randomised to HFNO in our study. In contrast, Corley et al. did report reductions in
244 dyspnoea and tidal variation. In a mixed critical care population, Zhang et al. evaluated the
245 physiological effects of HFNO following extubation [20]. This study demonstrated the ability of HFNO
246 to increase EELI and reduce atelectasis. However, this was variable, with several patients impervious
247 to recruitment and a minority exhibiting evidence of regional over distension despite an increase in
248 global EELI. There was no difference in BMI between the so-called 'high' and 'low' potential for
249 recruitment groups. Similar to our findings, Zhang et al. failed to record a change in tidal variation.

250 In patients randomised to HFNO in our study, pain scores were higher at 6 hours. The high gas flow
251 rates used during HFNO have been associated with increased abdominal distension [21], of particular
252 concern after gastric surgery and a possible explanation for our findings. An alternative explanation
253 may be the nasal discomfort reported by some patients receiving HFNO [22].

254 The incidence of post-operative pulmonary complications in our study was 2% across both groups.
255 This is much lower than the 25.7% seen in conventional oxygen therapy or 27% in HFNO, described in
256 a recent meta-analysis of trials comparing the two [23]. However, the majority of studies included in
257 this review enrolled patients after cardiac or thoracic surgery. Our findings are more consistent with
258 the incidence of PPC after non-cardiac surgery [24] and in particular with the very low incidence (<1%)
259 of PPC in a large series of bariatric surgical patients [25].

260 This study has several limitations. First, we were unable to perform analyses of EIT data beyond 60
261 minutes. While this was an important finding from the perspective of feasibility, it may be that
262 prolonged observation would have demonstrated a continued and significant divergence in EELI
263 between groups. Second, we chose to start the respiratory support protocol on return to the ICU. This
264 may have permitted decruitment in the period between extubation and commencing therapy, which
265 may have been overcome by choosing to extubate on to HFNO. However, this was a pragmatic
266 decision given the difficulty of transferring patients on HFNO with current technology. Third, this was
267 a single centre study, with patients electively admitted to a critical care bed for at least 24 hours post-
268 operatively, this may not be generalisable to practice elsewhere and may have contributed to the low
269 incidence of post-operative pulmonary complication. Finally, this was a pilot study and was not
270 powered to detect differences in EIT or clinical outcomes and should be interpreted in that light.

271 In summary, our findings suggest that a large-scale randomised controlled trial of HFNO after bariatric
272 surgery in an 'all-comers' population is likely infeasible. Future studies should focus on identifying
273 patients most at risk for post-operative pulmonary complications and those in whom HFNO is likely to
274 confer greatest benefit.

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370 **Table 1. Patient characteristics at baseline**

371 BMI – body mass index; CPAP – continuous positive airway pressure; COPD – chronic obstructive pulmonary disease; NMB
 372 – neuromuscular blocking drug; OSA – obstructive sleep apnoea.

	Conventional O₂ (n=25)	HFNO (n=25)
Age (years), mean (\pm SD)	46 \pm 9.2	48 \pm 11.1
Female (n (%))	20 (80)	19 (76)
BMI (kg/m ²), mean (\pm SD)	44.4 \pm 6.9	43.1 \pm 7.4
> 40 (n (%))	18 (72)	14 (56)
> 50 (n (%))	9 (36)	5 (20)
Prior respiratory disease (n (%))		
Asthma	4 (16)	4 (16)
OSA	14 (56)	9 (36)
Using CPAP	14 (56)	6 (24)
COPD	0	0
Other	2 (8)	0
Prior cardiac disease (n (%))		
Hypertension	7 (28)	9 (36)
Ischaemic heart disease	1 (4)	0
Other	3 (12)	4 (16)
Smoking status (n (%))		
Never smoked	9 (36)	14 (56)
Ex-smoker	15 (60)	10 (40)
Current smoker	1 (4)	1 (4)
Type of surgery (n (%))		
Gastric band	2 (8)	3 (12)
Sleeve gastrectomy	16 (64)	14 (56)
Gastric bypass	4 (16)	3 (12)
Other	3 (12)	5 (20)
Operative duration (mins), mean (\pm SD)	142 \pm 32	137 \pm 40
Intra-operative crystalloid volume (mL), mean (SD)	1444 \pm 381	1428 \pm 403
Sugammadex NMB reversal (n (%))	19 (76)	20 (80)

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374 **Table 2. Dyspnoea scores, pain scores, and patient outcomes.**

375 ICU – intensive care unit; LOS – length of stay; PPC – post-operative pulmonary complication.

	Conventional O₂ (n=25)	HFNO (n=25)	P value
Borg Dyspnoea Score [0-10] (median (IQR))			
Baseline	0 (0-0)	0 (0-0)	0.387
1 hour	0 (0-0)	0 (0-0)	0.322
3 hours	0 (0-0)	0 (0-0)	0.389
6 hours	0 (0-0)	0 (0-0)	0.180
Pain Score [0-10] (median (IQR))			
Baseline	3 (2-6)	1.5 (0-4.25)	0.107
1 hour	3 (0-5)	3.5 (0-6.25)	0.397
3 hours	3 (1-4)	2.35 (0-3.25)	0.691
6 hours	0 (0-3)	2.79 (1.5-4.5)	0.026
ICU LOS (days)	1 (1-1)	1 (1-1)	0.982
ICU re-admission (n (%))	1 (4)	0	1
Hospital LOS (days)	2 (2-2)	2 (2-2)	0.617
Hospital re-admission (n (%))	0	4 (16)	0.128
PPC in first 6 weeks (n (%))	0	1 (4)	0.128

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390 **Figure legends**

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392 **Figure 1. CONSORT flow chart for the study.**

393 **Figure 2. Electrical impedance tomography parameters.** A. Delta End Expiratory Lung Impedance
394 (Δ EELI). B. Tidal variation. Data are expressed as mean (\pm 95% confidence interval).

395 **Figure 3. Gas exchange parameters.** A. Arterial partial pressure of oxygen to inspired fraction of
396 oxygen ratio ($\text{PaO}_2/\text{FiO}_2$) and median FiO_2 . B. Arterial partial pressure of carbon dioxide (PaCO_2). Data
397 are presented as mean (\pm 95% confidence interval). * $p < 0.01$.

398 **Figure 4. Association between BMI and Δ EELI.** Au – arbitrary units.

399

Figure 1.

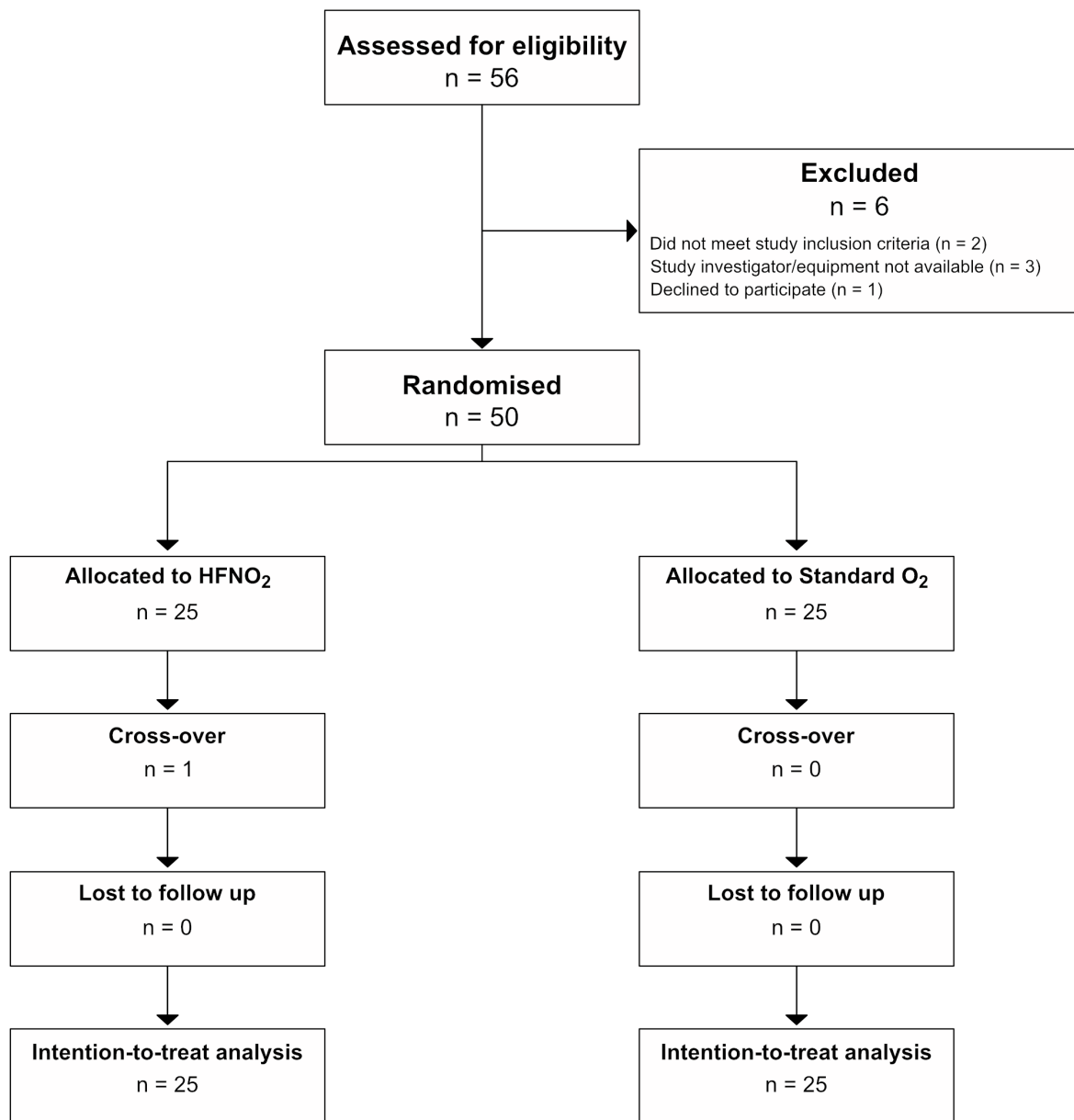


Figure 2.

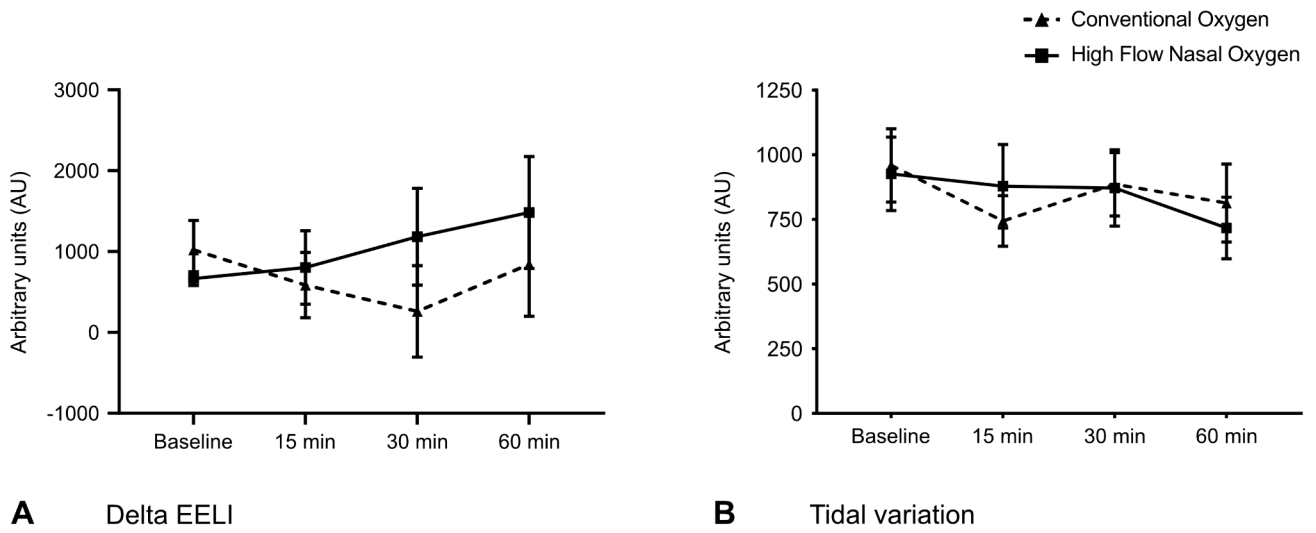
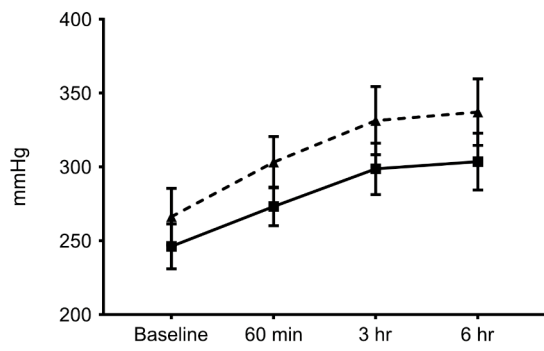
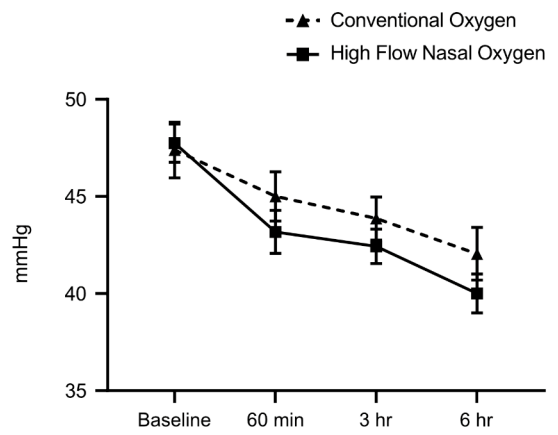


Figure 3.

	Median FiO2			
Conventional O ₂	0.5	0.36*	0.32*	0.32*
HFNO ₂	0.5	0.5	0.5	0.41



A PaO₂/FiO₂ ratio



B PaCO₂

Figure 4.

