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Clinical Paper

HyperOxic Therapy OR NormOxic Therapy after out-of-hospital cardiac arrest (HOT OR NOT): A randomised controlled feasibility trial[☆]



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ABSTRACT

Aims: To investigate the feasibility of delivering titrated oxygen therapy to adults with return of spontaneous circulation (ROSC) following out-of-hospital cardiac arrest (OHCA) caused by ventricular fibrillation (VF) or ventricular tachycardia (VT).

Methods: We used a multicentre, randomised, single blind, parallel groups design to compare titrated and standard oxygen therapy in adults resuscitated from VF/VT OHCA. The intervention commenced in the community following ROSC and was maintained in the emergency department and the Intensive Care Unit. The primary end point was the median oxygen saturation by pulse oximetry (SpO₂) in the pre-hospital period.

Results: 159 OHCA patients were screened and 18 were randomised. 17 participants were analysed: nine in the standard care group and eight in the titrated oxygen group. In the pre-hospital period, SpO₂ measurements were lower in the titrated oxygen therapy group than the standard care group (difference in medians 11.3%; 95% CI 1.0–20.5%). Low measured oxygen saturation (SpO₂ < 88%) occurred in 7/8 of patients in the titrated oxygen group and 3/9 of patients in the standard care group ($P=0.05$). Following hospital admission, good separation of oxygen exposure between the groups was achieved without a significant increase in hypoxia events. The trial was terminated because accumulated data led the Data Safety Monitoring Board and Management Committee to conclude that safe delivery of titrated oxygen therapy in the pre-hospital period was not feasible.

Conclusions: Titration of oxygen in the pre-hospital period following OHCA was not feasible; it may be feasible to titrate oxygen safely after arrival in hospital.

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1. Introduction

Despite oxygen being a ubiquitous therapy in patients resuscitated from out-of-hospital cardiac arrest (OHCA), there is little high quality evidence to guide clinicians about how best to use oxygen in this patient group. With the exception of one pilot trial,¹ no

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previous prospective study of different oxygen regimens following resuscitation from OHCA has been performed. There is a sound scientific basis supporting the hypothesis that avoidance of hyperoxia after resuscitation from OHCA might reduce neurological injury.² On the other hand, although exposure to hyperoxia appears to be associated with increased in-hospital mortality in observational studies,^{3–5} significant heterogeneity in the results of the existing studies means that there is uncertainty about this association.⁶ Furthermore, even if the association proved to be robust, it is possible that arterial hyperoxia is a marker of illness severity rather than a determinant of outcome.⁷ For example, the presence of poor peripheral perfusion could potentially lead clinicians to increase the inspired oxygen concentration (FiO₂) on the basis of spuriously low peripheral pulse oximetry (SpO₂) recordings. Moreover, even if hyperoxia were truly harmful, any attempt to reduce oxygen exposure in post-resuscitation management may carry with it the potential risk of exposing patients to hypoxia which is also consistently associated with increased mortality risk.^{4,7}

As a result of the current uncertainty, a high quality prospective trial evaluating the effect of titrated oxygen therapy on patient outcomes after OHCA is a research priority.⁸ With the eventual objective of conducting such a trial, we undertook a feasibility study to evaluate whether or not an individualised oxygen titration regimen designed to limit exposure to hyperoxia in patients with return of spontaneous circulation (ROSC) after OHCA led to an effective reduction in oxygen exposure compared to standard care without exposing patients to a greater incidence and severity of hypoxia.

2. Methods

2.1. Trial design and setting

We performed a prospective, multi-centre, single-blind, parallel-groups, feasibility and safety randomised controlled trial (RCT) comparing titrated oxygen administration to standard care with high concentration oxygen in adults resuscitated from OHCA. This trial was conducted in New Zealand. We intended to enrol patients in Auckland, Christchurch, the Hutt Valley, and Wellington. However, at the time the trial was terminated, site initiation had not been completed in Auckland or Christchurch and, as a result, no participants enrolled were from these centres.

2.2. Participants

Patients who were ventilated *via* a laryngeal mask airway or endotracheal tube were potentially eligible for study inclusion if they had an estimated age of 16–90 years and had ROSC following an OHCA due to a suspected primary cardiac cause with an initial rhythm of VF or VT. Patients were excluded if they were obviously pregnant, living in supported care or a nursing home, were known to have a terminal disease, or if more than 20 min had elapsed since ROSC.

2.3. Randomisation

Eligible patients were randomly assigned to either 'titrated oxygen' or 'standard care' in a 1:1 ratio. Randomisation was achieved by sequential numbered sealed envelopes prepared by a third party who received a randomisation schedule generated by a statistician. There was block randomisation with a block size of six, stratified by Intensive Care Unit (ICU) randomisation centre. For participants in Wellington and the Hutt Valley, randomisation was performed by the attending paramedic who phoned a charge nurse at the Wellington ICU randomisation centre. The ICU charge nurse then opened the next opaque envelope in the numerical sequence and provided the treatment allocation to the paramedic. Where the 'first

responder' to the cardiac arrest was the Fire Service,⁹ paramedics were still able to randomise patients provided that randomisation could be achieved within 20 min of ROSC.

2.4. Interventions

In patients assigned to titrated oxygen therapy, the prescribed goal was to achieve an SpO₂ of 90–94%. In the pre-hospital period patients were ventilated using a self-inflating resuscitation bag and titration of oxygen delivery was achieved by adjusting the flow of oxygen.¹⁰ Once patients arrived in hospital, the FiO₂ on the ventilator was adjusted as required. In the event that, in the judgement of the attending paramedic, reliable pulse oximetry recordings were not possible in the pre-hospital period, the protocol initially specified that oxygen should be delivered at 1 litre per minute which corresponds to an FiO₂ of approximately 0.40.¹⁰ After enrolment of six patients, the study protocol was amended because of a reported adverse event where a patient assigned to the titrated oxygen group had an unrecognised tension pneumothorax in the pre-hospital period and reliable pulse oximetry recordings could not be obtained. After this amendment, to avoid any risk of severe undetected hypoxia, if pulse oximetry could not be established or stopped working in the pre-hospital period, paramedics were instructed to give the highest FiO₂ possible until such time as working pulse oximetry could be established. Throughout the study, once patients arrived in the hospital, oxygen was titrated according to arterial blood gases if pulse oximetry was believed to be unreliable. In these circumstances, the oxygen delivery was titrated to the arterial oxygen saturation (SaO₂) rather than the partial pressure of oxygen (PaO₂). We chose a target SpO₂ of 90–94% in the titrated oxygen group in order to achieve the greatest separation in SpO₂ levels possible compared to standard care without exposing patients to significant hypoxaemia.

In the pre-hospital period, patients assigned to standard care received oxygen delivered into the self-inflating bag at the highest flow possible. In the emergency department and the ICU the treating clinician determined the oxygen target for the standard care group but a target SpO₂ > 95% was suggested.

If a patient had a further cardiac arrest after initial ROSC, high concentration oxygen was administered irrespective of which group the patient was assigned to. In these circumstances, if the patient was successfully resuscitated, oxygen was again administered according to the treatment strategy to which the patient had been assigned.

The duration of study treatment was from the time of randomisation until 72 h later or until extubation (whichever was sooner). Patients were blinded as to the treatment allocation; however, due to the nature of the intervention, blinding of investigators was not possible. Apart from the randomised oxygen interventions, patients received standard post resuscitation care which routinely included therapeutic hypothermia.

2.5. Outcomes

The primary end point was the median SpO₂ in the pre-hospital period. Pre-hospital SpO₂ data (maximum one value per minute) were those recorded along with other variables for clinical purposes.

Secondary end points included a range of assessments of oxygen exposure in the emergency department and the ICU. These were the SpO₂ on arrival and every 30 min thereafter while in the emergency department, the SpO₂ and PaO₂ recorded every 6 h up until extubation or 72 h in the ICU, and the number of patients with hypoxia episodes (SpO₂ < 88%) in the ICU. In addition to the oxygenation-related study end points, we measured the arterial partial pressure

of carbon dioxide (PaCO₂) every 6 h in the ICU up until extubation or 72 h (whichever was first). The purpose of determining the PaCO₂ was to determine whether or not titrated oxygen therapy had confounding effects on PaCO₂ levels.

Tertiary end points designed to aid in assessment of the feasibility of our study design and to aid in planning for a future study were the recruitment rate (based on the number of patients recruited into the study as a proportion of the total number of eligible patients), the proportion of patients with sufficiently good neurological function to be discharged home or to a rehabilitation facility, the ICU and hospital length of stay, and quality of life at six months assessing using the EQ5D.

Because the study was stopped early because of concern about the feasibility of safely titrating oxygen in the pre-hospital period, the proportion of patients with hypoxia (SpO₂ < 88%) at any time during the pre-hospital period was added as a *post hoc* end point.

2.6. Data collection

Study data were collected by trained ICU research co-ordinators using ambulance and medical records. Demographic and baseline data were collected in line with the Utstein definitions for reporting of out of hospital cardiac arrest.¹¹ All eligibility and outcome data were source verified by a study monitor from the co-ordinating centre.

2.7. Sample size calculations and statistical methods

Our planned sample size was 42 patients; however, our study was terminated early after the recruitment of 18 patients after consultation between the Data Safety Monitoring Board and Study Management Committee. Our original sample size calculations were based on data obtained from a previous trial investigating the use of therapeutic hypothermia after resuscitation from community cardiac arrest which demonstrated that the mean \pm SD SpO₂ on hospital arrival in the study population was 97.3 \pm 3.7%.¹² Assuming a constant standard deviation and using a two-sided test, a sample size of 42 patients is sufficient to detect a decrease in mean SpO₂ at this time to 94% at 80% power, and an alpha of 0.05.

Descriptive data are presented as mean (SD) or median [IQR] as appropriate. The Mann–Whitney test was used to compare median oxygen and carbon dioxide levels over time by treatment group presented as Hodges–Lehman differences in median (standard minus titrated oxygen) with 95% confidence intervals. A *P* value of <0.05 was used to determine statistical significance. For this feasibility study no adjustment was made for multiple comparisons. SAS version 9.3 was used for all analyses.

2.8. Trial registration and ethics approval

This study was prospectively registered on the Australian New Zealand Clinical Trials Registry (ANZCTR12612001054808). The full study protocol can be obtained online at <http://wellingtonicu.com/Data/Trials/HOTorNOT%20protocol%20v2.doc>. Ethics approval was granted by the Northern A Health and Disability Ethics Committee (12/NTA/13). Assent for ongoing study participation was sought from relatives after patients arrived in the ICU when this was appropriate and delayed consent for ongoing study participation was obtained from participants where possible.

Table 1
Demographics and arrest characteristics by treatment arm.

	Standard oxygen (n = 9)	Titrated oxygen (n = 8)
<i>Demographics</i>		
Age (years; mean(SD))	61.4 (20.8)	71.6 (10.7)
Male gender (n/N; %)	9/9; 100	7/8; 87.5
Ethnicity (n/N; %)		
NZ European	6/9; 67	4/8; 50
Maori	3/9; 33	2/8; 25
Pacific Islander	0/9; 0	1/8; 12.5
Other	0/9; 0	2/8; 25
<i>Arrest characteristics</i>		
Witnessed Arrest (n/N; %)	6/9; 67	6/8; 75
Bystander CPR (n/N; %)	7/9; 78	6/8; 75
Ambulance call to defibrillation time (mins; mean(SD))	12.6 (4.5)	9.9 (3.8)
Ambulance arrival to ROSC time	21.0 (14.1)	19.1 (12.6)
Ambulance call to ROSC time	30.8 (16.3)	28.6 (12.2)
Adrenaline (epinephrine) doses (mean (SD))	2.3 (1.8)	2.3 (1.8)
Number of defibrillations (mean (SD))	5.8 (5.3)	4.3 (2.8)

3. Results

3.1. Participants

Between 13/10/2012 and 21/09/2013 159 cardiac arrests were screened and 18 participants were randomised (Fig. 1). One non-eligible patient was randomised but received no study treatment and was not included in the analyses. Data for the primary end point were available for the other 17 participants. The trial was terminated early because ongoing review of accumulated data led the Data Safety Monitoring Board and the study management committee to conclude that safe delivery of titrated oxygen therapy in the pre-hospital period was not feasible. This review of data was not part of a planned interim analysis.

3.2. Baseline data and co-interventions

Baseline demographic data and clinical characteristics of the study participants assigned to titrated oxygen therapy and standard care were similar (Table 1). Therapeutic hypothermia was used in all study participants except for one participant in the standard care group. Two of the study participants (both assigned to the titrated oxygen group) had a coronary angiogram performed prior to or during their ICU admission. Both of these patients had angioplasties and were also treated with intra-aortic balloon pumps. 2/9 and 2/8 of participants in the standard care and titrated oxygen groups respectively required inotropes or vasopressors in ICU. Pre-hospital and emergency department oxygen data were available for all participants. ICU data were available for all 16 participants who survived until ICU admission. The number of pre-hospital and emergency department SpO₂ recordings, in particular, varied between participants due to missing data and variability in the amount of time spent in each location (supplementary appendix).

3.3. Outcome data

Measured SpO₂ levels were lower in the titrated oxygen group than the standard care group throughout the study (Table 1). In the pre-hospital period SpO₂ levels were significantly lower in the titrated oxygen therapy group than the standard care group (difference in medians 11.3%; 95% CI 1.0–20.5%). 7/8 of patients in the titrated oxygen group and 3/9 of patients in the standard care

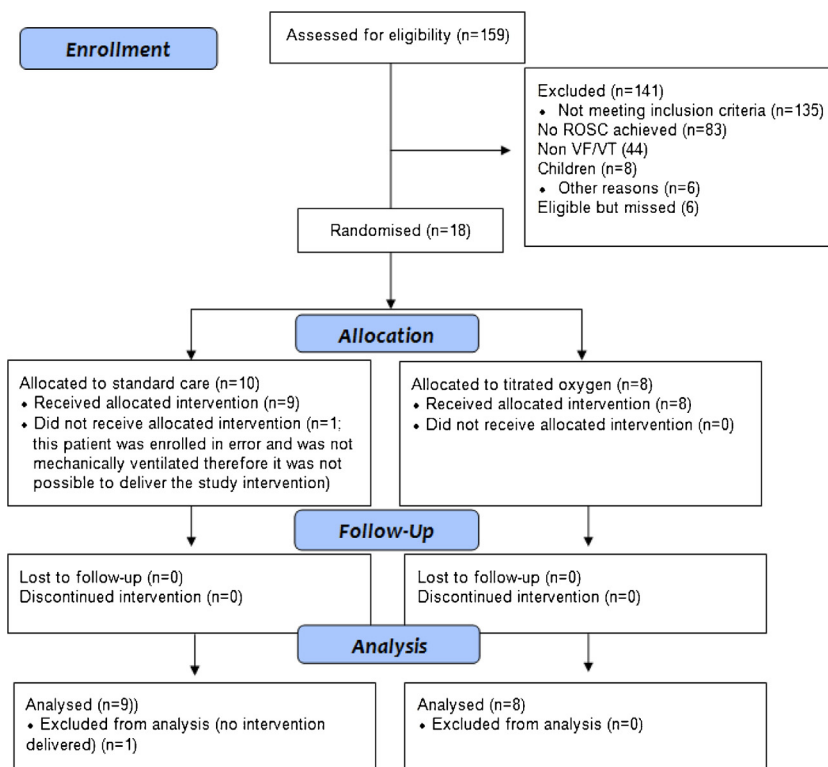


Fig. 1. Participant flow.

group had at least one documented SpO₂ measurement <88% in the pre-hospital period ($P=0.05$). In both groups, in a number of individual patients, a very wide range of SpO₂ recordings were obtained (Fig. 2).

At the time of hospital arrival the difference in median SpO₂ between the treatment groups was 9.5%; 95% CI 4.0–15.0%. This difference persisted at 30 min after admission (difference in median saturation recordings 7.0%; 95% CI 2.0–16.0%). Statistical comparisons were not undertaken beyond the 30 min time point in the emergency department because the number of available recordings was too small. However, SpO₂ measurements were generally lower in the titrated oxygen therapy group.

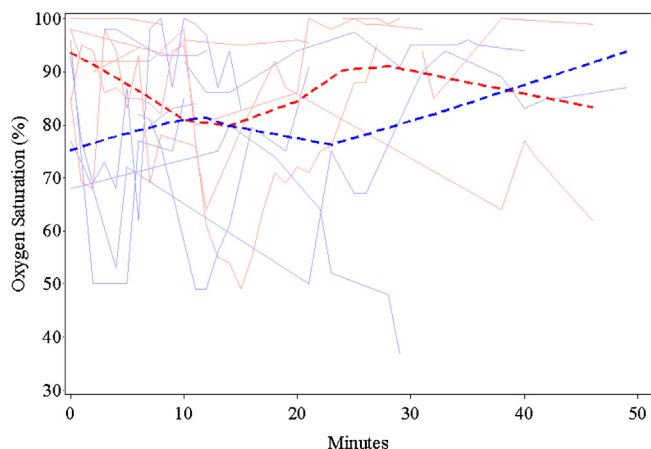


Fig. 2. Pre-hospital oxygen saturation recordings*. Joined line plots of oxygen saturation by participant with LOESS scatter plot smoother (smoothing parameter 0.7) as the heavy dotted lines. Red is Standard and Blue is Titrated oxygen.
* Oxygen saturation (SpO₂) data in the pre-hospital period were obtained from the Lifepak® defibrillator and could potentially be recorded minutely; however, they were only recorded when the vital signs were logged on the defibrillator by the paramedic as part of routine clinical care.

In the ICU, there was good separation of oxygen exposure achieved between the titrated oxygen therapy group and the standard care group. In general, the SpO₂ values obtained were within the target ranges (Fig. 3). Three patients in the titrated oxygen therapy group had a documented SpO₂ in the ICU of <88% compared to no patients in the standard care group ($P=0.08$). The PaO₂ and PaCO₂ measurements obtained from all patients in the ICU are demonstrated graphically in Fig. 4 with estimates of differences in oxygenation and carbon dioxide parameters shown in Table 2.

Data related to the tertiary end points are presented in the supplementary appendix.

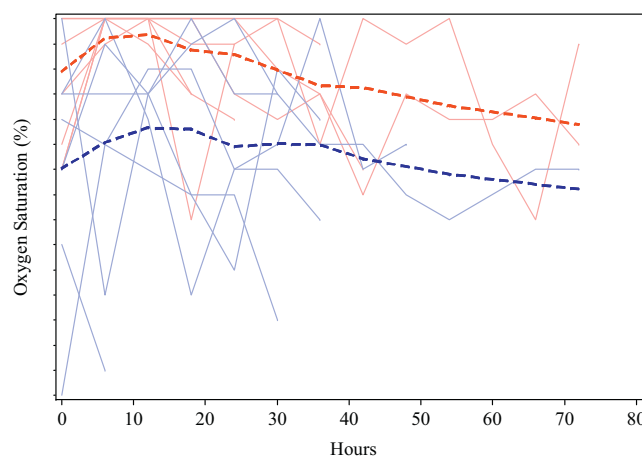


Fig. 3. ICU oxygen saturation recordings. Joined line plots of oxygen saturation (SpO₂) by participant with LOESS scatter plot smoother (smoothing parameter 0.5) as the heavy dotted lines. Red is Standard and Blue is Titrated oxygen. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Oxygen and carbon dioxide levels by treatment arm.

Comparison	Standard oxygen (median; [IQR])	Titrated oxygen (median; [IQR])	Hodges–Lehmann estimate (95% CI)	P value
<i>Prehospital oxygen saturations (%)</i>				
All recordings	95.8 [92.3–96.5]	79.5 [75.8–90.3]	11.3 (1–20.5)	0.046
<i>ED oxygen saturations</i>				
0 h	98 [93.5–99.5]	85 [84–90]	9.5 (4–15)	0.013
30 min	98 [96–100]	91 [88–93]	7 (2–16)	0.028
60 min	98 [95–100]	93 [76–94]	N/A	N/A
90 min	100 [99–100]	96.5 [93–100]	N/A	N/A
<i>Oxygen saturations by pulse oximetry in ICU (%)</i>				
0 h	99 [95–100]	96 [91–97]	3 (–1 to 9)	0.18
6 h	100 [100–100]	96 [89–99]	3.5 (1–11)	0.02
12 h	100 [100–100]	97 [97–97]	3 (2–4)	0.009
18 h	100 [97–100]	96 [93–99]	2 (–1 to 7)	0.25
24 h	99 [97–100]	94 [93–97]	5 (0–7)	0.073
<i>Oxygen saturations by ABG in ICU (%)</i>				
0 h	97 [97–99]	92 [88–94]	5 (0–9)	0.075
6 h	99 [99–99]	95 [95–96]	4 (2–5)	0.006
12 h	99 [98–99]	96.5 [96–97]	2 (1–3)	0.017
18 h	98 [96.5–99]	95.5 [95–97]	2 (–1 to 4)	0.21
24 h	97 [94–99]	96 [95–98]	0 (–3 to 3)	0.94
<i>PaO₂ (ICU)</i>				
0 h	107 [91–120]	73 [64–75]	34 (–5 to 231)	0.11
6 h	106.5 [97.5–117.5]	72 [70–74]	31.5 (23–48)	0.007
12 h	99 [93.5–108]	84 [77–86]	20 (8–44)	0.01
18 h	103.5 [90.5–115]	76.5 [72–79]	26 (–7 to 49)	0.10
24 h	75 [69–101]	80.5 [65–83]	2 (–22 to 25)	0.94
<i>PaCO₂ in ICU (mmHg)</i>				
0 h	43.4 [41–45]	46 [43–49.2]	2.3 (–9 to 5.7)	0.47
6 h	37.6 [30.9–42.6]	35.7 [32.3–38.9]	0.2 (–7 to 7)	0.99
12 h	35.4 [32.4–36.8]	36.0 [31.8–38.7]	–1.3 (–9.8 to 5.4)	0.75
18 h	37.5 [33.2–38.8]	39.4 [35.6–42]	–2.2 (–8.6 to 5.3)	0.42
24 h	33.3 [30.7–37.2]	34.8 [30.2–35.2]	0.45 (–5.9 to 8.9)	0.83

4. Discussion

4.1. Summary of principal findings

We conducted a multicentre feasibility study comparing titrated oxygen therapy to standard oxygen therapy in patients resuscitated from OHCA in New Zealand. The study was stopped early because preliminary data strongly suggested that our approach to delivering titrated oxygen therapy in the pre-hospital setting was not feasible. While targeting an SpO₂ of 90–94% achieved significantly lower SpO₂ measurements than standard care in the pre-hospital period, SpO₂ recordings varied widely, potentially indicating unreliable recordings and/or an increased risk of being exposed to hypoxaemia. In the emergency department and the ICU SpO₂ levels were generally lower in the titrated oxygen therapy group and titrated oxygen therapy was not associated with a significant increase in exposure to hypoxaemia.

4.2. Relationship to previous studies

Our results contrast with those of the only previous study comparing a lower FiO₂ with a higher FiO₂ strategy after OHCA.¹ In this previous study patients were randomly assigned to receive an FiO₂ of 0.30 or 1.0 after ROSC. A lower safety limit of SpO₂ of 95% was set and the FiO₂ was increased in steps of 0.10 if the SpO₂ remained <95% for 5 min. The study included arterial blood gas recordings taken at 10 and 60 min after ROSC using a portable blood gas analyser. While 5/9 patients assigned to the low FiO₂ group required an increase in FiO₂, there were no reported episodes of hypoxaemia. The mean PaO₂ 10 min after ROSC in the low FiO₂ group in this previous study was relatively high (158 ± 111.75 mmHg). We designed our protocol to allow titration of oxygen delivery on an individualised basis in order to avoid the exposure to hyperoxia, which occurred in the previous study. However, our protocol required continuous titration of oxygen delivery against SpO₂ which proved not to be practical in the pre-hospital setting.

Once patients arrive in hospital, titration of oxygen appeared to be potentially feasible. There are no previous studies evaluating titration of oxygen therapy in the emergency department setting after OHCA and the small number of data points available from the emergency department phase of care in our study makes it impossible to draw conclusions about our approach. However, our findings in relation to the ICU phase of care are consistent with a previous study conducted in a general ICU population, which demonstrated that aiming for an SpO₂ of 90–92% appeared to be safe and did not increase hypoxaemia episodes.¹³ Although the three participants with documented SpO₂ <88% in the ICU were in the titrated therapy arm, our sample size was small, and this did not represent a statistically significant increased risk of hypoxaemia. Recent data suggest that carbon dioxide management may affect outcomes in patients resuscitated from cardiac arrest.¹⁴ Our findings suggest that titration of oxygen does not have significant confounding effects on PaCO₂ levels.

4.3. Clinical implications

Our study findings suggest that titration of oxygen therapy may potentially expose patients to inadvertent hypoxaemia and that, in the pre-hospital period continuous oxygen titration against SpO₂ measurements is not feasible. Although our preliminary data suggest that titration of oxygen therapy after arriving in hospital may not expose OHCA patients to a significantly increased risk of hypoxaemia, our findings need to be confirmed in a larger study before a phase III trial to establish the effect of titrated oxygen therapy in hospital on patient-centred outcomes is undertaken.

4.4. Strengths and weaknesses

Our study has several strengths. We evaluated a pragmatic oxygen intervention maintained through the pre-hospital, emergency department, and ICU phases of care. We utilised standard

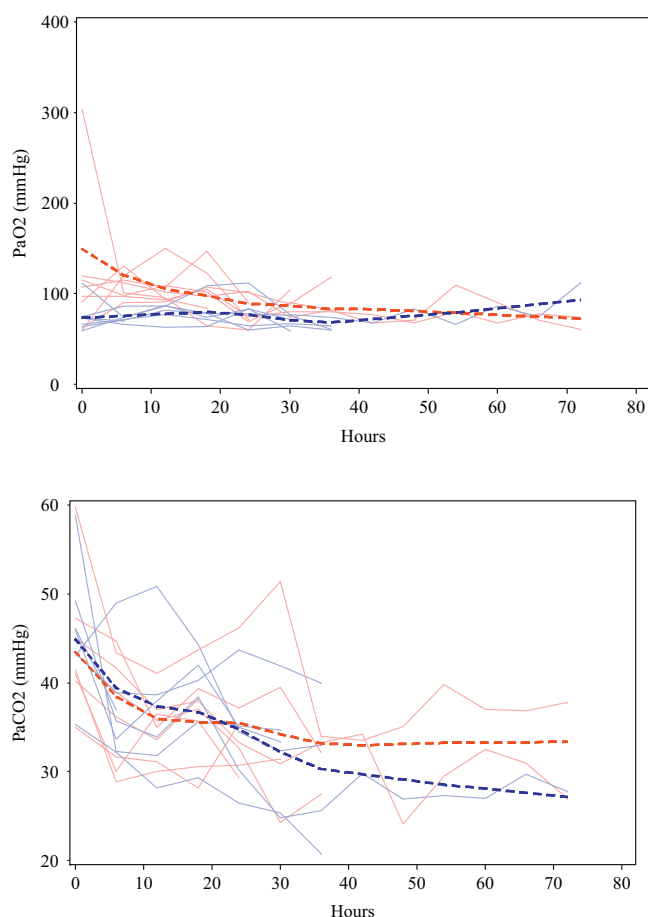


Fig. 4. Arterial partial pressure of oxygen and carbon dioxide in the ICU. Joined line plots of PaO₂ and PaCO₂ by participant with LOESS scatter plot smoother (smoothing parameter 0.5) as the heavy dotted lines. Red is Standard and Blue is Titrated oxygen. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

equipment available in any modern healthcare system, meaning that our intervention, if feasible, would have been generalisable.

Our findings are subject to some limitations. Most importantly, our study was stopped early when only 18 patients out of a planned 42 patients had been enrolled. Stopping the study early increases the risk of bias and, thus, the strength of the associations demonstrated between the intervention and outcomes in our study may overestimate the true effect of the intervention on oxygen exposure. However, the primary factor which demonstrated that our intervention was not feasible in the pre-hospital period was wide range of SpO₂ recordings seen in individual patients. It is likely that some SpO₂ recordings were spurious due to saturation probe mal-positioning or to a poor saturation trace for other reasons. Even if this is the case, our findings still highlight that continuous titration of oxygen delivery against SpO₂ in the pre-hospital setting is not feasible.

5. Conclusions

Titration of oxygen delivery to SpO₂ following resuscitation from OHCA was not feasible in the pre-hospital setting. However, our preliminary data suggest that it may be possible to titrate oxygen after arrival in hospital. The safety and efficacy of any strategy to reduce oxygen exposure in hospital in OHCA patients should be further evaluated through prospective trials.

Conflicts of interest statement

The authors have no conflicts of interest to report.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.resuscitation.2014.09.011>.

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