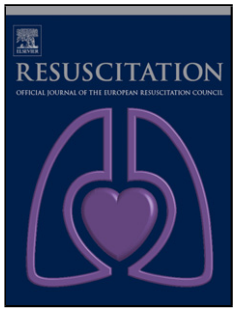


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# Oxygen titration after resuscitation from out-of-hospital cardiac arrest: a multi-centre, randomised controlled pilot study (the EXACT pilot trial).

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## Abstract

Introduction: Recent studies suggest the administration of 100% oxygen to hyperoxic levels following return-of-spontaneous-circulation (ROSC) post-cardiac arrest may be harmful. However, the feasibility and safety of oxygen titration in the prehospital setting is unknown. We conducted a multi-centre, phase-2 study testing whether prehospital titration of oxygen results in an equivalent number of patients arriving at hospital with oxygen saturations SpO2≥94%.

Methods: We enrolled unconscious adults with: sustained ROSC; initial shockable rhythm; an advanced airway; and an SpO2≥95%. Initially (Sept 2015–March 2016) patients were randomised 1:1 to either 2 litres/minute (L/min) oxygen (titrated) or >10L/min oxygen (control) via a bag-valve reservoir. However, one site experienced a high number of desaturations (SpO2<94%) in the titrated arm and this arm was changed (April 2016) to an initial reduction of oxygen to 4L/min then, if tolerated, to 2L/min, and the desaturation limit was decreased to <90%.

Results: We randomised 61 patients to titrated (n=37: 2L/min=20 and 2-4L/min=17) oxygen or control (n=24). Patients allocated to titrated oxygen were more likely to desaturate compared to controls ((SpO2<94%: 43% vs. 4%, p=0.001; SpO2<90%: 19% vs. 4%, p=0.09). The majority of desaturations (81%) occurred at 2L/min. On arrival at hospital the majority of patients had a SpO2 ≥94% (titrated: 90% vs. control: 100%) and all patients had a SpO2 ≥90%. One patient (control) re-arrested. Survival to hospital discharge was similar.

Conclusion: Oxygen titration post-ROSC is feasible in the prehospital environment, but incremental titration commencing at 4L/min oxygen flow may be needed to maintain an oxygen saturation >90% (NCT02499042).

**Key words:** oxygen, hyperoxia, out-of-hospital cardiac arrest, heart arrest, post-resuscitation care.

**Word count:** 2940

**Introduction**

A recent review by the International Liaison Committee in Resuscitation (ILCOR) found that the evidence surrounding the optimal delivery of oxygen after successful resuscitation from cardiac arrest is of very low quality.(1) Currently, out-of-hospital cardiac arrest (OHCA) patients who achieve return of spontaneous circulation (ROSC) receive 100% oxygen during transport to hospital and during the initial period in the emergency department (ED). The administration of 100% oxygen for the first hours post-ROSC is largely based on the perceived benefit of high oxygen levels and not on supportive clinical data. Historically, it has been thought that maximizing oxygen delivery during this period is beneficial in a cardiac arrest patient who has suffered profound tissue hypoxia. There is also a perceived risk that the early lowering of inspired oxygen might result in episodes of hypoxia.

However, recent data suggest the administration of 100% oxygen to hyperoxic levels (partial pressure oxygen [PaO2] >300mmHg) may be harmful. Hyperoxia is seen on the first arterial blood gas in approximately 20% of OHCA patients(2, 3), and is experienced by 38% in the first six hours of hospitalisation.(4) Systematic reviews of experimental data(5) and a meta-analysis of human observational studies(6) indicate that hyperoxia during the early post-ROSC period may lead to additional neurological injury, and thus result in worse clinical outcomes. These findings are biologically plausible given that the administration of additional oxygen increases the production of oxygen free-radicals which are known to injure neurones.(7) However, it remains unknown from these observational studies whether the hyperoxia is simply an association with illness severity rather than a contributor to poor outcome.(8) A recent prospective observational study suggests hyperoxia is independent of illness severity as a predictor or mortality, but there are currently no large randomised controlled trials in

this area.(9) Clinical trials testing different oxygen targets in the post cardiac arrest period has been described as a priority area for research in this setting.(10)

Given the potential harm of hyperoxia and the paucity of clinical experience with titration of oxygen in the prehospital setting, we aimed to conduct a pilot study to determine the feasibility of paramedic titration of oxygen delivery in adult patients who have been resuscitated after OHCA. Specifically, we tested the hypothesis that prehospital oxygen titration would not reduce the proportion of patients who arrived at the emergency department (ED) with a SpO2 greater than or equal to 94%.

**Methods**

Trial design

We conducted a phase 2, multi-centre, parallel, single-blinded, randomised (1:1) controlled trial in the Australian cities of Melbourne and Adelaide. The study was approved by the Monash University Human Ethics Committee (CF14/2953 – 2014001634) and the Royal Adelaide Hospital Ethics Committee (141011). The trial was registered on ClinicalTrials.gov (NCT02499042).

Initially, patients were randomly assigned to either 2 litres/minute (L/min) oxygen (titrated) or >10 L/min oxygen (control) with the oxygen administered via a bag-valve reservoir (BVR), otherwise known as a self-inflating bag. However, following a high number of desaturations (SpO2<94% in 8/20 patients) at the main recruiting site, the titrated arm was changed at this site (April 2016) to an initial reduction of oxygen to 4 L/min, and then if tolerated, to 2 L/min. The study was terminated early (n=61) due to the introduction of mechanical ventilators at

the main recruiting site, and the inability to replicate the equivalent FiO2 of the protocol using these ventilators.

Participants

Eligible participants were: adults (age≥18 years), unconscious (Glasgow Coma Scale <9) with an advanced airway (endotracheal tube [ETT] or supraglottic airways [SGA]) in situ and sustained ROSC following an OHCA of presumed cardiac cause, and an initial monitored rhythm assessed as shockable (ventricular fibrillation or pulseless ventricular tachycardia). Exclusion criteria were: paramedic witnessed OHCAs, Sp02 <95% or no pulse oximetry trace, known or suspected to be pregnant; dependant on others for activities of daily living (i.e. facilitated care or nursing home residents); and evidence of a "Not for Resuscitation" order.

Setting

The study took place in two Australian cities between July 2015 and May 2017. Melbourne, the capital city of the state of Victoria with a population over 4.5 million, is serviced by Ambulance Victoria. The second city, Adelaide, is the capital city of South Australia (SA) and has a population of almost 1.2 million with emergency ambulance services provided by the SA Ambulance Service.

The ambulance services are detailed elsewhere(11), however there were differences between the two ambulance services in airway management at the time of this study. At Ambulance Victoria, SGAs are used during the arrest and are replaced by endotracheal tubes (ETT) either during CPR or soon after ROSC is achieved. If airway reflexes are present, intubation is facilitated using fentanyl and suxamethonium. Sedation is maintained after intubation with a midazolam and opiate infusion. In the SA Ambulance Service, no muscle relaxants are used,

and an ETT or SGA is inserted either during CPR or immediately post–ROSC. Sedation using midazolam may be used to maintain the airway.

Intervention

Intra-arrest oxygen delivery and ambulance cardiac arrest care was unchanged over the study period, and followed the Australian and New Zealand Committee on Resuscitation (ANZCOR) Guidelines. All prehospital oxygen was delivered by hand ventilation using a BVR.

Following ROSC, oxygen was delivered at a flow rate of ≥10 L/min via BVR connected to the airway until a satisfactory pulse oximeter trace and reading was achieved. If eligibility criteria were met, the paramedics randomised the patients by the opening of an opaque envelope containing a computer-generated allocation to either the control or titrated group.

Patients in the control group continued to receive oxygen at ≥10 L/min. Patients in the titrated group had oxygen reduced to either 2 or 4 L/min. Oxygen saturations were continuously measured by pulse oximetry via a finger probe. Oxygen flow into the BVR in the titrated group was to be immediately increased to ≥10 L/min if the patient rearrested, if their pulse oximeter trace failed despite adequate probe placement, or if they desaturated (Sp02 <94% on initial protocol and Sp02 <90% on amended protocol in Victoria).

If a patient's advanced airway was removed post-randomisation because of improving conscious state, then standard care was used (i.e. face mask with oxygen ≥10 L/min). For patients who were to be intubated post-ROSC, ventilation with high-flow oxygen continued during the intubation process and randomisation was delayed until two minutes after the ETT was confirmed as correctly placed and the SpO2 was ≥95%.

The intervention ceased at ED handover, at which time the patient received oxygen therapy as determined by the treating emergency medicine physician.

Outcomes

The primary outcome was a SpO2 ≥94% on arrival at hospital. Secondary outcomes were a SpO2 ≥90% on arrival at hospital, re-arrest during ambulance transport and survival at hospital discharge.

Data Collection

Study data were collected from the ambulance patient care record (PCR) by trained trial staff. Hospital survival was collected by the Victorian Ambulance Cardiac Arrest Registry (VACAR)(12) and the SA Ambulance Service Cardiac Arrest Registry.(13) Data collected included demographics, arrest characteristics (using Utstein definitions)(14), randomisation allocation, vital signs at randomisation and hospital arrival, airway type, medications, desaturations , changes in oxygen flow, and re-arrests during pre-hospital care. No hospital data was collected other than hospital discharge survival. Final Sp02 on arrival at hospital was recorded by paramedics and extracted from the PCR.

Sample size and analysis

The intended sample size was determined from existing data from the VACAR. For January to June 2014, there were 102 patients who met the inclusion criteria and had an oxygen saturation recorded by paramedics on arrival to the ED. All these patients received 100% oxygen (oxygen flow at 10L/min into the BVM). Pulse oximetry data at ED arrival on 100% oxygen were: SpO2 <94% in 31%, SpO2 =94-96% in 14% and SpO2 >96% in 55% of cases. It was anticipated that a titration of oxygen strategy to a target oxygen saturation of 94-96%

would be achieved in 33% of titrated oxygen patients compared to 14% in the 100% oxygen group. A sample of 88 patients in each arm (n=176) would be needed to achieve 80% power (alpha 0.05).

Descriptive data are presented as mean (standard deviations [SD]) or median (interquartile range [IQR]). Mann-Whitney and Student T-tests were used to compare continuous data and Fisher's Exact test for categorical data. A p-value <0.05 was considered statistically significant. All analyses were performed in STATA (Version15).

Ethics

The study was granted a waiver of consent by the two approving Ethics Committees. At both sites, survivors were notified of enrolment approximately two months after hospital discharge and were given contact details for further information and the option to opt out of data collection.

**Results**

We randomised 62 patients to titrated (n=37) or control (n=25) groups (Figure 1). No patients were lost in follow-up and one patient requested data withdrawal (control arm). The demographics, arrest and clinical characteristics between the groups of the remaining 61 patients were similar (Table 1).

The majority of patients had an SGA inserted initially (95%), and were intubated post-ROSC. Use of sedation and paralysis were similar between groups (Table 2), however slightly more patients in the control group received post-ROSC adrenaline (67% vs 49%).

On average the titration of oxygen commenced 35 minutes after ROSC (Table 2). Overall, oxygen delivery in the titrated group was increased per protocol due to desaturations in 16

(43%) patients. All patients who desaturated responded to the increase in oxygen (≥10L/min), with 100% arriving at ED with SpO2 >90%. The majority of desaturations (81%) occurred following the titration to 2L/min . Table 3 compares the characteristics and outcomes by desaturation (<94% and <90%) in the titrated oxygen group. Although the numbers were small for statistical comparisons, patients who desaturated were less likely to have factors associated with improved outcomes (e.g. shorter downtimes and witnessed arrests). These patients were also more likely to have been intubated intra-arrest and to have received sedation, particularly morphine and midazolam.

On arrival at hospital the majority of patients had a SpO2 ≥94%: 33/37 (90%) titrated and 24/24 (100%) control (Table 4). There was reasonable separation in mean oxygen saturation on arrival at ED between the groups (titrated: 97% vs. control: 99%, p=0.004). One patient in the control group re-arrested. Survival to hospital discharge was similar between the groups (titrated: 51% vs. control: 54%), and when examined by desaturation status in the titrated group (desaturated <94%: 56% vs. no desaturation: 48%, p=0.74).

**Discussion**

We found that the titration of oxygen post-ROSC is feasible in the prehospital environment using a simple decrease in the oxygen flow into a bag/valve device with oxygen reservoir. We observed no significant adverse events, and desaturations were brief and correctable. There were no re-arrests in the titrated arm and no difference between the groups in hospital survival. While we observed brief desaturations in 43% of titrated cases, the majority (81%) of these occurred following titration to low-flow oxygen (2L/min).

There have been two previous pilot trials comparing early oxygen titration with 100% oxygen in patients resuscitated from OHCA.(15, 16) In a Finnish study, patients were randomised to

be ventilated either with a fraction of inspired oxygen (FiO2) of 0.3 or 1.0 for the first 60 minutes post-ROSC.(15) This study concluded that most patients had acceptable oxygenation when ventilated with 30% oxygen during the immediate post-ROSC period. In a New Zealand study, 18 post-ROSC patients were randomised to receive either titrated oxygen (targeting 90-94%) or 100% oxygen commencing in the pre-hospital setting via a BMR.(16) This study was stopped early due to high numbers of desaturations in the titrated arm. However, the accuracy of the readings of the pulse oximeter in this study was uncertain as all readings were downloaded from the monitoring device and not just those readings confirmed by paramedics as having an adequate trace. Thus, many readings may have been included where the recorded oxygen saturation was inaccurate.

In the titrated arm of our original protocol, oxygen was titrated to 2 L/min and delivered by a BVR device. This level was based on bench tests which found that 2 L/min via a BVR provides oxygen at an FiO2 of approximately 50% when delivered at a rate of 14/min and a tidal volume of 600mL.(17) However, our results showed that titration of oxygen to 2L/min in practice resulted in a significant number of patients desaturating below the initially acceptable oxygen saturation level of 94%. Hence, we then performed incremental titration at our major recruiting site, first to 4 L/min then if tolerated to 2 L/min.

The lowest safe oxygen saturation target following resuscitation from cardiac arrest is uncertain. Recently, the Australian and New Zealand Thoracic Society changed the normal low oxygen target from 94% to 92%.(18) Other researchers in this area have also used a lower target. For example, Eastwood et al. ICU study had safely targeted a SpO2 of 88-92%.(19) Based on these changes, we lowered the desaturation limit to <90% in the second period of this trial.

The desaturations (<94%) following the immediate titration to low flow oxygen seen in both this and the Young et al.(16) trial are most likely related to difficulties maintaining BVR inflations at the correct tidal volume and rate with manual ventilation in the prehospital environment. A laboratory investigation found FiO2 levels at low flow oxygen (0.5-6 L/min) is highly dependant on tidal volumes and inflation rates.(17) For example, at 2 L/min, FiO2 varied between 0.27 and 0.62 –with lower oxygen concentrations seen with higher tidal volumes or faster inflation rates. In the prehospital environment, it may be difficult to maintain a consistent ventilation while multitasking and extricating the patient from the scene. This variation may be an issue in future research if unmeasured, but may be corrected with careful monitoring, paramedic education and practice(20) or the use of prehospital mechanical ventilators with standard settings.

Although we examine factors related to desaturation, these results must be interpreted with caution due to the sample size. Not surprisingly the patients who desaturated in the titrated group were more likely to have the factors that may require careful and possibly slower oxygen titration (e.g. older age, longer downtimes, and sedation). Intra-arrest intubation was rare in our study, as it is only used with difficult airways (e.g. copious vomitus or supra-glottic airway failure), but was seen in a high proportion of patients who desaturated. We recommend caution in these patients. Importantly, desaturations were not associated with lower survival. Unfortunately, we were only able to collect hospital survival in this pilot study, so are unable to provide comment of the impact of prehospital oxygen titration on other outcomes, such as neurological status.

Our results are subject to a number of potential limitations. First, we did not achieve our sample size. The main recruiting site introduced mechanical ventilators during the study and

we were unable to include ventilated patients due to differences in achievable FiO2 levels. Second, we were unable to blind paramedics or data collectors to allocation. Third, due to limited funding and the ongoing establishment of the cardiac arrest registry in South Australia we were unable to track reasons why patients were not enrolled in the study. Fourth, while there were no major prehospital adverse events associated with oxygen titration in our study, we did not collect hospital data and so were unable to measure oxygenation using an arterial blood gas analysis or subsequent adverse events. However, such data may be affected by hypoxic events after hospital arrival; which are seen in as many 78% of cases in the first 24-hours.(8) Despite episodes of brief desaturations, all patients in our study had acceptable oxygen saturation levels (>90%) on arrival at hospital and similar survival between groups and in those who desaturated. We did not collect data related to neurological outcome.

Following this pilot study and the growing body of evidence suggesting harm from hyperoxia,(4) we have commenced a Phase 3 randomised control trial (NCT3138005), comparing titration of oxygen to maintain oxygen saturations at either 90-94% or 98-100%. This study will include three Australian cities (Greater Melbourne, Adelaide and Perth) and intends to enrol 1416 OHCA patients. The main study intervention will continue in-hospital and conclude following the first arterial blood gas in the intensive care unit. The primary outcome of the trial will be survival to hospital discharge and numerous secondary outcomes such as: neurological outcome; hypoxic episodes; recurrent cardiac arrest; ICU survival; length of stay; and quality of life and survival at 12-months. The limitations of this pilot study will be addressed in the main study which will include: inclusion of patients on prehospital ventilators and OHCA of all cardiac rhythms; tracking patients not enrolled; a lower level of acceptable oxygen after titration (O2sat <90%); collection of inhospital data and a wider range of outcome data.

In summary, our pilot study found that oxygen titration is feasible in the prehospital environment, but does require incremental titration and careful pulse oximeter monitoring. An increase in oxygen delivery may be required in some patients to avoid hypoxia.

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**Conflicts of Interest**

None.

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EXACT SA Site Investigators: Richard Larsen and Chris Cotton.

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**Figure Legend**

Figure 1. Diagram of study intervention.

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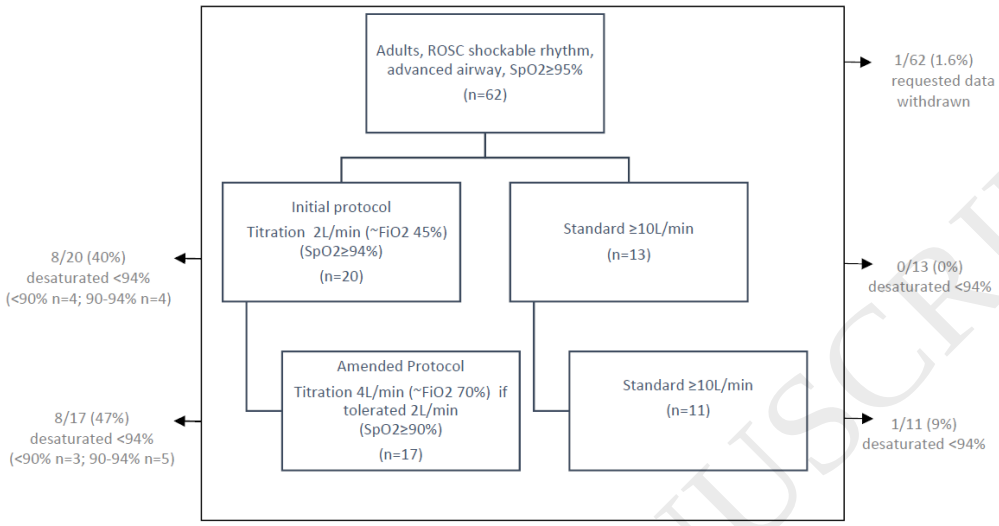

Table 1. Comparison of patient characteristics by study group.

| **N (%)** | **2-4L/MIN (N=37)** | **≥10L/MIN (N=24)** |
|---|---|---|
| Age, mean (SD) | 64 (13.5) | 60.5 (9) |
| Male | 32 (86) | 17 (75) |
| Witnessed arrest | 27 (73) | 18 (75) |
| Bystander cardiopulmonary resuscitation | 31 (84) | 23 (96) |
| Downtime, median (IQR) | 18.5 (16-27) | 19.5 (16-29) |
| Supraglottic airway | 34 (95) | 23 (96) |
| Supraglottic airway only | 2 (5) | 1 (4) |
| Endotracheal tube intra-arrest | 5 (14) | 7 (29) |
| Endotracheal tube post-ROSC | 18 (49) | 9 (38) |
| Rapid sequence intubation post-ROSC | 12 (32) | 7 (29) |
| Midazolam | 29 (78) | 20 (83) |
| Morphine | 25 (68) | 14 (58) |
| Fentanyl | 14 (38) | 9 (38) |
| Pancuronium | 10 (27) | 7 (29) |
| PostROSC adrenaline | 18 (49) | 16 (67) |

ROSC: return of spontaneous circulation

Table 2: Comparison of oxygenation by study group

| **N (%)** | **2-4L/MIN (N=37)** | **≥10L/MIN (N=24)** | **P-value** |
|---|---|---|---|
| SpO2 at randomisation, mean (SD) | 98 (2) | - | - |
| Time from ROSC to randomisation (minutes) , mean (SD) | 35 (17) | - | - |
| Time from randomisation to ED (minutes), mean (SD) | 50 (13) | - | - |
| Oxygen flow level at ED<br>2L/min<br>4L/min<br>10L/min | <br>20 (54)<br>1 (3)<br>16 (43) | <br>0 (0)<br>0 (0)<br>24 (100) | <br><0.001 |
| Lowest SpO2, mean (SD) | 94 (4) | 98 (3) | <0.001 |
| Desaturation<br><94%<br><90% | <br>16 (43)<br>7 (19) | <br>1 (4)<br>1 (4) | <br>0.001<br>0.13 |
| SpO2 at ED, mean (SD)* | 97 (3) | 99 (2) | 0.004 |

*p=0.004

SpO2: oxygen saturation; ROSC: return of spontaneous circulation; ED: emergency department

Table 3. Characteristics and outcomes of those who desaturated (<94% and <90%) in titrated group (n=37).

| N (%) | Desaturated <94% | | | Desaturated <90% | | |
|---|---|---|---|---|---|---|
| | No (n=21) | Yes (n=16) | p-value | No (n=30) | Yes (n=7) | p-value |
| Age, mean (SD) | 64 (12) | 65 (16) | 0.88 | 62.5 (12) | 74 (16) | 0.04 |
| Male | 18 (86) | 14 (88) | 0.99 | 25 (83) | 7 (100) | 0.56 |
| Witnessed | 16 (76) | 11 (69) | 0.72 | 23 (77) | 4 (57) | 0.36 |
| Bystander cardiopulmonary resuscitation | 19 (90) | 12 (75) | 0.21 | 26 (87) | 5 (71) | 0.32 |
| Downtime, median (IQR) | 17 (15.5-26) | 21.5 (15.5-28) | 0.37 | 18 (15-26) | 27 (19-35) | 0.04 |
| Supraglottic airway | 19 (90) | 16 (100) | 0.49 | 28 (93) | 7 (100) | 0.99 |
| Supraglottic airway only | 2 (10) | 0 (0) | 0.20 | 2 (7) | 0 (0) | 0.99 |
| Endotracheal tube intra-arrest | 1 (5) | 4 (25) | 0.07 | 2 (7) | 3 (43) | 0.04 |
| Endotracheal tube post-ROSC | 12 (57) | 6 (37.5) | 0.24 | 15 (50) | 3 (43) | 0.99 |
| Rapid sequence intubation post-ROSC | 6 (29) | 6 (37.5) | 0.57 | 11 (37) | 1 (14) | 0.39 |
| Midazolam | 15 (71) | 14 (87) | 0.42 | 22 (73) | 7 (100) | 0.31 |
| Morphine | 11 (52) | 14 (87.5) | 0.04 | 18 (60) | 7 (100) | 0.07 |
| Fentanyl | 8 (38) | 6 (37.5) | 0.99 | 13 (43) | 1 (14) | 0.22 |
| Pancuronium | 4 (19) | 6 (37.5) | 0.27 | 8 (27) | 2 (29) | 0.99 |
| PostROSC adrenaline | 9 (43) | 9 (56) | 0.52 | 13 (43) | 5 (71) | 0.18 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Survived to hospital discharge | 10 (48) | 9 (56) | 0.60 | 16 (53) | 3 (43) | 0.69 |

Table 4. Comparison of outcomes by study group

| **N (%)** | **2-4L/MIN (N=37)** | **≥10L/MIN (N=24)** |
|---|---|---|
| SpO2 at ED ≥94% | 33 (90) | 24 (100) |
| SpO2 at ED ≥90% | 37 (100) | 25 (100) |
| Re-arrest prehospital | 0 (0) | 1 (4) |
| Survived to hospital discharge | 19 (51) | 13 (54) |

SpO2: oxygen saturation; ED: emergency department