The impact of oxygen and carbon dioxide management on outcome after cardiac arrest

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Purpose of review
To describe the impact of oxygen and carbon dioxide management on patient outcomes following cardiac arrest.

Recent findings
Although there are no data that suggest that supplemental oxygen administration during cardiopulmonary resuscitation is harmful, there is concern that 100% oxygen during the postresuscitation phase may be undesirable. The evidence to avoid hyperoxia is limited to animal studies and retrospective clinical studies that examine the association between exposure and outcome. There is a correlation between end-tidal carbon dioxide values during cardiopulmonary resuscitation and resuscitation outcome, yet this correlation is likely to reflect low or absent cardiac output and be a biomarker of illness severity rather than a mediator of injury. Additionally, very limited high-level human data exist on the relationship between arterial carbon dioxide tension and outcome following cardiac arrest. Retrospective studies have identified hypocapnia in the intensive care unit as being independently associated with worse neurological and mortality outcomes in cardiac arrest patients. Although there appears to be sufficient evidence to recommend avoiding hypocapnia after resuscitation, observational data suggest that hypercapnia may be independently associated with a greater likelihood of discharge home amongst cardiac arrest survivors.

Summary
Current data for oxygen and carbon dioxide management following resuscitation suggest that hyperoxia and hypocapnia may be injurious and should be avoided, and that mild hypercapnia may increase the likelihood of discharge home amongst survivors. Such data should be viewed as hypothesis generating. Randomized controlled trials have commenced to clarify the safety, feasibility and efficacy of targeting different oxygen and carbon dioxide tensions following cardiac arrest.

Keywords
carbon dioxide, cardiac arrest, hypercapnia, hyperoxaemia, hyperoxia, hypocapnia, oxygen, resuscitation, ventilation

INTRODUCTION

Cardiac arrest leads to immediate cessation of blood flow to the brain and other vital organs. The brain is particularly susceptible to ischaemic damage during cardiac arrest [1], because although it represents less than 2% of total body weight, it usually receives 15–20% of the cardiac output and accounts for 20% of total body oxygen consumption. Unconsciousness occurs within seconds of cardiac arrest and irreversible neuronal damage occurs within a few minutes unless blood flow to the brain is restored. Like the brain, the heart is dependent on oxygen, and the chances of achieving return of spontaneous circulation (ROSC) may depend on adequate delivery of oxygen to the heart. Elevated arterial carbon dioxide content ($PaCO_2$) may increase coronary artery blood flow, and so there could also be interplay between $PaCO_2$ levels and myocardial oxygen delivery that affects the likelihood of successful resuscitation.

Although ROSC aids in the restoration of energy-dependent cellular processes, it also heralds the onset of reperfusion injury. Reperfusion is a complex process which alters the function of

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KEY POINTS

- The heart and brain are particularly susceptible to damage associated with ischaemia and following return of spontaneous circulation (ROSC) reperfusion injury.
- Arterial oxygen (PaO_2) and carbon dioxide ($PaCO_2$) may play a role in restoring and preserving cardiac and neurological function after cardiac arrest.
- The safety and efficacy of titrated oxygen therapy and mild hypercapnia following cardiac arrest should be investigated, and the findings of prospective randomized trials used to inform future guideline development. Clinical trials currently underway are comparing the effects of targeted oxygen strategies (ACTRN12612001054808) and carbon dioxide concentration targets (ACTRN12612000690853) in cardiac arrest patients during the immediate and early postresuscitation period, respectively.

approximately 500 genes within a few hours [1]. Although delivery of oxygen to the heart may be important for achieving ROSC, it is possible that unregulated oxygen administration after ROSC exacerbates reperfusion injury [2]. Similarly, cerebral and myocardial blood flow changes in response to $PaCO_2$ levels might also modulate reperfusion injury.

In this article, we review the recent advances in knowledge related to oxygen and carbon dioxide management during and after resuscitation from cardiac arrest.

OXYGEN THERAPY DURING CARDIOPULMONARY RESUSCITATION

A recent retrospective cohort study of 145 out-of-hospital cardiac arrest (OHCA) patients who had arterial blood gases (ABGs) performed during cardiopulmonary resuscitation (CPR) demonstrated a linear increase in survival with increasing arterial oxygen tension (PaO_2) [3]. Amongst those who survived until hospital discharge, patients exposed to higher PaO_2 concentrations during CPR were more likely to have a good neurological outcome than those with lower PaO_2 concentrations. However, this study does not provide information regarding the most effective strategy for oxygen management during CPR, as all of the patients were ventilated with 100% oxygen via an endotracheal tube when ABGs were performed.

In a study of inhospital cardiac arrest (IHCA) patients, cerebral venous oxygen saturation was measured during CPR using near-infrared spectroscopy (NIRS) [4]. NIRS uses an algorithm to display a value (rSO_2) which appears to correspond to cerebral venous saturation and has a normal range of 60–80%. When oxygen demand exceeds supply, cerebral venous oxygen saturation falls. In this study, during CPR rSO_2 was significantly higher in survivors than nonsurvivors. Similarly, amongst OHCA patients who arrived in an emergency department in Western Japan with CPR ongoing, increasing rSO_2 levels correlated with an increased likelihood of survival [5]. In both studies, despite the use of airway adjuncts and high concentration oxygen, none of the patients had rSO_2 levels above the normal reference range. Thus, during cardiac arrest, even with effective CPR, it seems likely that tissue oxygen demand exceeds supply because of poor tissue perfusion [5]. This conclusion is consistent with animal data indicating that brain tissue oxygenation remains low during CPR and ventilation with 100% oxygen [6]. Randomized controlled trial data evaluating the utility of supplemental oxygen during CPR have not been performed; however, one animal study suggests that the chance of achieving ROSC is higher if supplemental oxygen is administered [7]. Given that ROSC may be more likely with high fraction of inspired oxygen (FiO_2) CPR and that such CPR does not appear to expose the brain to tissue hyperoxia, it seems prudent to continue to provide 100% oxygen during CPR at this stage (Table 1).

PREHOSPITAL OXYGEN THERAPY FOLLOWING RETURN OF SPONTANEOUS CIRCULATION

If an inspired oxygen concentration of 100% is maintained following resuscitation, data from experimental cardiac arrest in pigs have shown that brain tissue oxygen levels rise dramatically to supranormal levels [6]. As such, exposure to supranormal oxygen levels could potentially increase the risk of brain damage from reperfusion injury. The effect of early hyperoxia following resuscitation from cardiac arrest has been evaluated in a small number of animal studies summarized in a recent systematic review and meta-analysis [8▪]. Six animal studies [7,9–13] were included in the meta-analysis. The administration of 100% oxygen therapy after ROSC (100% oxygen during CPR and for 60 min following ROSC) was associated with worse neurological outcomes and greater histological evidence of brain damage than the use of lower concentrations of oxygen (21% oxygen during CPR and titrated thereafter).

Despite the above observations, the clinical relevance of the animal data is questionable. The animals did not receive treatment with mild

Table 1. Impact and influence of oxygen and carbon dioxide management after cardiac arrest

Oxygen management	Carbon dioxide management
O_2 therapy during CPR	CO_2 management during CPR
No available data exist indicating oxygen administration during CPR is harmful.	Limited data are available on the relationship between the $PaCO_2$ and outcome in CA patients. Existing data have focussed on $ETCO_2$ values drawn from observational or retrospective studies to confirm correct endotracheal tube placement, CPR quality, as a predictor of ROSC and patient outcome or its role in guiding ventilation strategies to avoid hypocapnia.
High FiO_2 during CPR does not appear to expose brain tissue to hyperoxic injury.	
Prehospital O_2 therapy	Inhospital CO_2 management following ROSC
Exposure to high FiO_2 during the prehospital resuscitation period was associated with greater histological evidence of brain injury.	Investigators are beginning to evaluate the relationship between $PaCO_2$ tensions and outcome following ROSC.
It remains unclear whether it is possible to deliver titrated oxygen in the prehospital period in a manner that avoids arterial hyperoxaemia, and if oxygen controlled can be achieved, whether or not this influences clinical outcomes	Like adults, children exposed to hypocapnia during the inhospital postresuscitation period experience worse clinical outcomes than those with normocapnia.
	Whether it is better to manage $PaCO_2$ values of CA patients using alpha-stat or pH-stat remains unknown.
Inhospital O_2 therapy following ROSC	
Limited available evidence, based on a series of retrospective studies, exists to support avoidance of hyperoxia in the hospital setting, though animal data suggestive of potential harm associated with hyperoxia.	
Although inhospital increased PaO_2 may be marker of illness severity after ROSC, emerging data suggest that increasing maximum PaO_2 measured during the first 24 h is associated with increasing hospital mortality and poor neurological status at hospital discharge.	

CA, cardiac arrest; CPR, cardiopulmonary resuscitation; $ETCO_2$, end-tidal carbon dioxide; FiO_2, fraction of inspired oxygen; PaO_2, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension; ROSC, return of spontaneous circulation.

therapeutic hypothermia or other forms of supportive care that would be standard for intensive care patients. Moreover, neurological deficits were usually assessed relatively early at 24 h. Finally, all animal studies involved only brief periods of CPR. This final point is particularly pertinent because one recent rat model study, which involved more prolonged resuscitation, paradoxically demonstrated that 1 h of hyperoxaemic reperfusion resulted in improved myocardial function with higher blood pressure, less metabolic acidosis, better diastolic dysfunction, improved cardiac mitochondrial function, and less nitrooxidative stress in the cardiac tissues than normoxic resuscitation [7].

The only prospective randomized trial of different regimens of oxygen therapy following cardiac arrest compared 30% oxygen with 100% oxygen in the prehospital period following OHCA [14]. This 28-patient study was not powered to detect differences in clinically important outcomes and there was no overall difference in neuron-specific enolase (NSE, a biomarker of brain injury) levels between the treatment groups. The study findings suggest that it might be possible to safely deliver less than 100% oxygen in the prehospital period. However, even the patients in the low oxygen group were exposed to significant arterial hyperoxaemia (mean PaO_2 >150 mmHg). One potential impediment to delivering low concentration oxygen in the prehospital period is that ambulances generally ventilate patients with a self-inflating bag with a reservoir attached to an oxygen flow meter. Although recent data suggest that delivery of a wide range of oxygen concentrations by simple adjustment of oxygen flow is possible [15], the viability of using this approach to titrate oxygen in clinical practice has not been established. Furthermore, the reliability of pulse oximetry in the prehospital cardiac arrest environment has not been systematically studied. Thus, in the absence of ABG analysis, attempting to reduce exposure to hyperoxia may lead to inadvertent hypoxia. Overall, it remains unclear whether it is possible to deliver titrated oxygen in the prehospital period in a manner that avoids the risk of

arterial hyperoxaemia and, even if this can be achieved, whether or not this influences clinical outcomes (Table 1).

INHOSPITAL OXYGEN THERAPY FOLLOWING RETURN OF SPONTANEOUS CIRCULATION

Existing animal data suggesting potential harm associated with hyperoxia compared the oxygen regimens administered for up to an hour after ROSC. In current practice, high flow oxygen until hospital arrival is the norm. There are no animal data examining the effect of avoiding exposure to hyperoxia after prior early hyperoxia. Instead, the evidence to support hyperoxia avoidance in the hospital setting is limited to retrospective studies that examine the association between exposure to hyperoxia and outcome. Two studies [16,17] of the same cohort of patients found an association between hyperoxia, based on the ABG measurement after ICU admission, and inhospital mortality. In contrast, the third study of the 'worst ABG' measurement in patients admitted to Australia and New Zealand ICUs after cardiac arrest did not demonstrate this association after adjustment for potential confounding factors including illness severity and inspired oxygen concentration [18]. These initial studies have a number of limitations. Firstly, they did not include important predictors of clinical outcome in cardiac arrest patients such as initial rhythm, duration of cardiac arrest, and whether bystander CPR was provided. Secondly, in the case of the North American dataset, mild therapeutic hypothermia was not generally applied. Given that mild therapeutic hypothermia appears to alter the ischaemia and reperfusion pathways and reduces apoptotic cell death, this is an important consideration [19].

The particular issue of the impact of therapeutic hypothermia on the influence of oxygen exposure after cardiac arrest was recently addressed in a single-centre study of 173 consecutive comatose cardiac arrest patients [20▪]. Using a multivariate logistic regression model adjusting for age, time to ROSC, presence of shock, bystander CPR and initial rhythm, the investigators demonstrated that higher levels of PaO_2 were significantly associated with an increased risk of inhospital mortality [odds ratio (OR) 1.439; 95% confidence interval (CI) 1.028–2.015; $P = 0.034$] and poor neurological outcome at hospital discharge (OR 1.485; 95% CI 1.032–2.136; $P = 0.033$). An important confounding factor in understanding this association is that pulse oximetry assessments may be inaccurate in the settings of poor peripheral perfusion and may lead clinicians to increase oxygen delivery, thus making PaO_2 a marker of illness severity. In an attempt to account for this, the presence of shock defined by the requirement for a vasoactive infusion was included in the multivariate analysis. However, a requirement for vasopressor support is not necessarily predictive of a state of peripheral perfusion. Thereby, a high PaO_2 is a marker of illness severity rather than a direct mediator of adverse outcome (Table 1).

The relationship between oxygen exposure and outcome after cardiac arrest has been evaluated in children in three studies [21–23] which report similar findings to those of adult cardiac arrest studies. These suggest that in children, as may be the case in adults, the association between hyperoxia and outcome is confounded by the administration of high concentration oxygen to patients who have a higher mortality risk.

All retrospective studies are limited because of the potential for unmeasured confounders to affect outcome. With this in mind, one group has attempted to identify the factors associated with hyperoxia in cardiac arrest patients [24]. In a single-centre retrospective analysis of a prospectively collected cohort of cardiac arrest patients treated in an Australian tertiary hospital [24], patients exposed to hyperoxia were more likely to have suffered OHCA than IHCA. Furthermore, the safety and efficacy of titrated oxygen therapy following cardiac arrest should be evaluated in prospective randomized clinical trials. With this in mind, we are currently recruiting patients into a randomized trial comparing targeted oxygen strategies (ACTRN12612001054808) in cardiac arrest patients during the immediate postresuscitation period.

CARBON DIOXIDE MANAGEMENT DURING CARDIOPULMONARY RESUSCITATION

Arterial carbon dioxide tension ($PaCO_2$) is a major determinant of cerebral blood flow [25] and changes in $PaCO_2$ in the hours following cardiac arrest may have a significant impact on neurological outcomes [26,27]. To date, there are very limited data on the relationship between the $PaCO_2$ and outcome in cardiac arrest patients. Existing data have focussed on the value of end-tidal carbon dioxide ($ETCO_2$) values drawn largely from observational or retrospective studies. Such studies evaluated the role of $ETCO_2$ to confirm correct endotracheal tube placement, to monitor CPR quality, usefulness as a predictor of ROSC and patient outcome [28] or its role in guiding ventilation strategies to avoid hypocapnia [29] (Table 1).

Capnography has the potential to inform the immediate clinical decisions related to the

likelihood of ROSC. A recent systematic review of 23 observational studies [28] evaluated the prognostic value of $ETCO_2$ to predict the outcome of resuscitation following cardiac arrest. The authors concluded that $ETCO_2$ values during CPR were significantly higher in patients who achieved ROSC compared to those who did not, though this finding was not consistent across all studies. However, there is no $ETCO_2$ threshold that reliably predicts favourable outcome and $ETCO_2$ values alone cannot predict outcome. Further, larger multicentre studies powered to established the ability of $ETCO_2$ values to predict short-term (e.g. ROSC) and long-term outcome (e.g. hospital discharge and neurological outcome) in conjunction with other prognostic factors are warranted. Furthermore, there are no data evaluating whether titration of ventilation during CPR to particular $ETCO_2$ values affects the likelihood of ROSC or alters the neurological outcomes.

INHOSPITAL CARBON DIOXIDE MANAGEMENT FOLLOWING RETURN OF SPONTANEOUS CIRCULATION

Currently, the International Liaison Committee on Resuscitation [30] recommended normocapnia ($PaCO_2$ 40–45 mmHg) as the target for mechanically ventilated cardiac arrest survivors. In a retrospective analysis study of cardiac arrest registry data, investigators evaluated the association between postresuscitation $PaCO_2$ and neurological outcome [31]. Findings revealed that 27% of patients had hypocapnia only ($PaCO_2$ $\leq$30 mmHg), 33% had hypercapnia only ($PaCO_2$ $\geq$50 mmHg), and 9% had both hypocapnia and hypercapnia exposure. Overall, 74% of patients (142 out of 193 patients) had poor neurological outcome at hospital discharge (Cerebral Performance Category score $\geq$3). These investigators acknowledge that cerebral blood flow was not directly measured and that hypercapnia may reflect lung, and thus dyscarbia may remain a marker of illness severity (Table 1).

In a larger retrospective observational study, a different group of investigators also evaluated the association of early $PaCO_2$ values with clinical outcomes [32▪▪]. In this study 16 542 cardiac arrest patients admitted to 125 Australia and New Zealand ICUs between 2000 and 2011 were reviewed. Following multivariate analysis, these investigators found that hypocapnic patients ($PaCO_2$ <35 mmHg) Hg) had worse outcomes compared with normocapnic ($PaCO_2$ 35–45 mmHg) or hypercapnic ($PaCO_2$ >45 mmHg) for mortality and discharge home. Importantly, compared with normocapnia, hypocapnia was independently associated with worse clinical outcomes and hypercapnia with a greater likelihood of discharge home for survivors. Although 'discharged home' does not represent a full assessment of neurological recovery, it is a robust patient-centred endpoint that is likely to be free from bias and indicative of a better neurological outcome than discharged to hospital level care or rehabilitation.

The association between mean $PaCO_2$ during the early resuscitation period and inhospital mortality and neurological outcome after cardiac arrest was addressed in a single-centre retrospective study of 213 patients treated with therapeutic hypothermia [33]. Of 1704 $PaCO_2$ values obtained between ROSC and end of therapeutic hypothermia, 557 (32.7%) were hypocapnic and 321 (18.8%) values were hypercapnic. Following a multivariate analysis, hypocapnia was no longer associated with poor neurological outcome. Overall, this study [33], together with the previous studies [23,32▪▪] indicate that hypocapnia has a more robust relationship with mortality and may lead to poorer neurological outcomes in survivors, though larger multicentre studies are required to explicitly demonstrate any such relationships.

The safety and efficacy of mild hypercapnia following cardiac arrest should be evaluated in prospective randomized clinical trials. Accordingly, we are currently recruiting patients into a randomized trial (ACTRN12612000690853) comparing normocapnia and mild hypercapnia ($PaCO_2$ 50–55 mmHg) in the early ICU management of patients following cardiac arrest. Preliminary analysis of ABG data has shown that separation in the $PaCO_2$ levels between groups is achievable (see Fig. 1). Additional trial outcomes include differences in NSE at baseline, 24 h, 48 h and 72 h; ICU and hospital outcome; and quality-of-life assessment at 6 months after cardiac arrest.

Resuscitated cardiac arrest patients in the ICU typically have their ABGs assessed based on the values corrected to 37°C (alpha-stat). However, the impact and outcome of assessing ABG according to the patient's actual body temperature (pH-stat) remains unclear. Finnish investigators [34] performed a prospective randomized crossover study of eight adult OHCA patients treated with induced mild therapeutic hypothermia with a focus on $PaCO_2$. The main finding was that mild hypocapnia, and the lower threshold of normocapnia with pH-stat, resulted in lower jugular bulb oxygen saturation. Hence, the use of alpha-stat $PaCO_2$ values to guide ventilation decisions may prove safer than pH-stat values. Yet, further evaluation of the impact of assessing ABG according to the patient's actual body temperature on the management and outcome for resuscitated cardiac arrest patients appears desirable (Table 1).

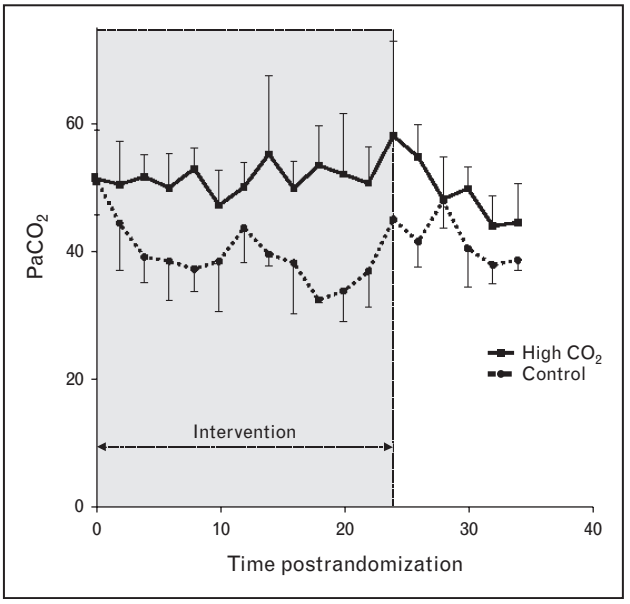

FIGURE 1. Arterial $PaCO_2$ obtained during the first 36 h of intensive care admission of patients after resuscitation from cardiac arrest. This figure shows the degree of $PaCO_2$ separation for the first 10 study patients enrolled in the therapeutic hypercapnia after cardiac arrest clinical trial (ACTRN12612000690853). Patients were randomly allocated to receive either targeted normocapnia ($PaCO_2$ 35–45 mmHg) or mild hypercapnia ($PaCO_2$ 50–55 mmHg) during the first 24 h of intensive care admission. After 24 h, normocapnia was targeted for both groups. $PaCO_2$, arterial carbon dioxide tension.

From the data available, $ETCO_2$ and $PaCO_2$ may be markers of disease severity, a potential target for therapeutic intervention, or both [32▪▪,35]. Studies that have evaluated the impact of $PaCO_2$ derangement and outcome in children [23,36] reported similar findings to adult studies. At present, there is insufficient evidence to support the best approach to the management of $PaCO_2$ for patients admitted to ICU following cardiac arrest. Hypocapnia appears to be associated with worse patient outcomes, whereas mild hypercapnia is not associated with worse patient outcomes. It, therefore, appears prudent for clinicians to avoid unnecessary hypocapnia but be tolerant of mild hypercapnia should it occur during the early management of the cardiac arrest patient.

Carbon dioxide and pH

Arterial carbon dioxide tension is known to influence pH in patients following resuscitation after cardiac arrest. Metabolic acidosis is also often present and is a biomarker of the duration of CPR and the presence of cardiogenic shock. Thus, many patients have a low pH and either a metabolic acidaemia or combined respiratory and metabolic acidaemia. It is not surprising, therefore, that there is an association between pH and outcome on univariate analysis. However, when corrections are made for other clinical characteristics, illness severity, comorbidities, propensity score, temperature, glucose, base excess, bicarbonate or $PaCO_2$, pH fails to achieve an independent association with survival or with discharge home amongst survivors [32▪▪]. No data are available on whether manipulating pH with bicarbonate administration has an impact on the patients' outcome.

CONCLUSION

Current data for oxygen and carbon dioxide management following cardiac arrest should be viewed as hypothesis generating. It is possible that deliberate attempts to limit oxygen exposure or target supranormal carbon dioxide concentrations will lead to unanticipated consequences. Overall, we consider that patients who have suffered from cardiac arrest should currently be managed no differently with respect to oxygen and carbon dioxide management compared to other critically ill patients who require mechanical ventilation. The only exception being that the provision of high-flow oxygen during CPR seems prudent with subsequent reductions in oxygen administration, occurring in situations in which reliable monitoring of arterial oxygen saturation is possible.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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Abnormal $PaCO_2$ values are common within the first 24 h of ICU after a cardiac arrest. Following a multifaceted statistical assessment compared with normocapnia, hypocapnia was associated with an increase in combined mortality and failure to be discharged home and a lower likelihood of discharge home for survivors. In contrast, for survivors, hypercapnia was associated with a higher likelihood of being discharged home.

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