Direct cerebral perfusion and cooling in experimental cardiac arrest

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ABSTRACT

Background: Cerebral protection is a key priority during cardiac arrest (CA). However, current approaches are suboptimal.

Objective: To test whether direct perfusion and cooling of the anterior cerebral circulation by means of cerebral vessel cannulation and extracorporeal membrane oxygenation (ECMO) increases cerebral oxygenation and induces cerebral hypothermia during CA.

Methods: We performed proof-of-concept animal experiments in sheep. We cannulated the carotid artery (for antegrade perfusion) or the jugular vein (for retrograde perfusion) for direct perfusion and cooling, and the jugular vein on the opposite side for drainage. We connected these cannulae to an ECMO circuit. We induced CA and, after 10 minutes, and during open-chest cardiac massage, we provided ECMO-based perfusion and cooling. We measured cerebral tissue oxygen saturation (Sct_{O_2}) by near infrared spectroscopy (NIRS) and cerebral temperature by means of invasively inserted tissue temperature probes.

Results: In the antegrade perfusion experiments (n = 2), CA markedly decreased the Sct_{O_2} to below 40% over 10 minutes, despite open-chest cardiac massage. ECMO-based cerebral perfusion and cooling increased Sct_{O_2} levels to 60% and lowered cerebral temperature to 25°C within about 3 minutes. With retrograde perfusion (n = 2), ECMO-based cerebral perfusion and cooling was less effective; ECMO increased Sct_{O_2} levels slowly and to a much lesser extent and similarly decreased cerebral temperature slowly and to a lesser extent.

Conclusions: During experimental CA, cerebral perfusion and cooling are possible by means of an ECMO circuit connected to the anterior cerebral circulation. Antegrade perfusion appears to be superior. Further investigations of the antegrade perfusion technique appear justified.

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Cardiac arrest (CA) is a common and catastrophic event with an estimated incidence of about one per 1000 people per year, and with Australian mortality rates varying between 87% and 94%.[1] In 2013–14, Ambulance Victoria attended 5581 out-of-hospital CA (OHCA) events in adults,[2] which was in keeping with such estimates. Of these OHCAs, 48% of patients received an attempt at resuscitation by paramedics, with 39% achieving successful return of spontaneous circulation (ROSC) and reaching an emergency department (ED). However, only 10% of these patients survived to hospital discharge.

Similar to OHCA, in-hospital CA (IHCA) represents a worldwide problem, is common, affects about two per 1000 hospital admissions and carries a similarly bleak outcome, with hospital mortality rates of 60%–80% in Australia[3] and internationally.[4] Irrespective of location, even for patients admitted to the intensive care unit death and neurological injury are the most common outcomes after CA.[5,6] Crucially, while the initial problem is cardiac in nature, the dominant reason for such dismal outcomes is neurological injury.

The disabling effects of CA persist for many years and the human and financial costs of supporting survivors of CA are substantial.[7,8] For each patient who has a CA, is resuscitated and admitted to the ICU, and survives to hospital discharge, costs exceed $120 000.[8] The estimated ongoing cost per CA survivor with a good neurological outcome is $50 000 per quality-adjusted life-year.[8] Therefore, given the devastating neurological impact and financial costs associated with CA, new treatment strategies are warranted to attenuate neurological injury and improve patient-centred outcomes.

It is well understood, and obvious, that CA leads to ischaemic neuronal damage[9] and that neurological injury is a dominant cause of death in these patients. Thus, any approach to the immediate management of these patients should focus on cerebral protection. Such protection may logically be achieved by two means: near immediate delivery of a sufficient flow of oxygenated blood to the brain, and simultaneous cooling of the brain to minimise any injury associated with a period of suboptimal perfusion and to immediately decrease oxygen consumption. Unfortunately, such therapies can only be delivered suboptimally with the current approaches, which are based on external cardiac massage[10] and, more recently, the intravenous infusion of cool fluids.[11] The suboptimal nature of such approaches is confirmed by the dismal outcomes of patients who have had a CA with current management.[12] This has led to the growing application of more advanced and invasive treatment, based on extracorporeal membrane oxygenation (ECMO).[13-15] However, even the use of ECMO has not yet been shown to deliver superior outcomes. This is likely to be because the time between the onset of CA and initiation of

ECMO is often greater than 30 minutes, thus exposing the brain to an excessively long period of suboptimal perfusion before ECMO can be initiated.[13,14]

These failures suggest the need for a completely novel strategy to protect the brain from CA-associated ischaemic injury. We hypothesised that, in this situation, it would be possible to provide rapid cerebral perfusion and cooling by delivery of oxygenated blood by means of an ECMO circuit. The circuit would be connected to cerebral circulation via a cannula inserted into the carotid artery or the jugular vein. We tested this hypothesis with proof-of-concept experiments in an ovine model of CA.

Methods

Animal preparation

All experimental protocols were approved by the animal ethics committee of the Florey Institute of Neuroscience and Mental Health under guidelines established by the National Health and Medical Research Council of Australia.

We induced anaesthesia with intravenous sodium thiopentone (at a rate of 10–15 mg/kg) for intubation with an endotracheal tube (cuffed, size 9). Maintenance of anaesthesia was by means of oxygen, air and isoflurane (end tidal isoflurane concentration, 1.5%–2.0%). The fractional inspired oxygen level was altered to maintain arterial oxygen saturation above 97%, and ventilation was controlled to maintain end tidal CO_2 at about 35 mmHg. We performed several procedures in sheep under general anaesthesia. In two animals, we inserted a right carotid cannula (size 14 Fr) under direct vision and cut-down to enable subsequent antegrade perfusion. Then we inserted a jugular vein cannula (size 16 Fr) on the opposite side, with a similar technique, to enable blood flow return. Finally, after shaving the scalp, we drilled two burr holes (0.3 mm diameter) in the skull over the cerebral cortex and inserted temperature tissue probes (CP-004-001, Oxford Optronix) into the right and left hemispheres to record brain temperature.

In the other two animals, we performed similar procedures but, instead of carotid and jugular cannulation, both jugular veins were cannulated to enable retrograde perfusion and return of blood to an extracorporeal perfusion, oxygenation and temperature control circuit.

In all four animals, we applied a cerebral (frontal) oxygen saturation probe to the scalp after shearing to estimate cerebral tissue oxygen saturation using near infrared spectroscopy (NIRS). We used the INVOC in vivo optical spectroscopy system (Somanetics). In both animals, we resected the fourth left rib and applied retractors to enable access to the heart for open-chest cardiac massage.

We constructed the extracorporeal circuit using a Quadrox hollow fibre oxygenator (Maquet) and a roller pump (Stöckert), a 1900 mL soft shell reservoir (MVR venous reservoir, Medtronic), PVC tubing (3/8 inch internal diameter, Medtronic), a gate clamp, pressure transducers (ITL Healthcare) and flow probes (DP38, Medtronic). We primed the circuit with 2.5 L of Hartmann's solution and attached the oxygenator to a heat exchanger to control and lower temperature as desired. In both animals, the cannulae were then connected to an ECMO circuit.

Experimental procedure

Before the induction of CA, we administered heparin (10 000 IU) to all animals to prevent clotting of cannulae or subsequent clotting of the extracorporeal circuit. We induced CA by intravenous administration of potassium chloride (50 mmol bolus). After the onset of electrical asystole and visible cessation of cardiac contraction, we observed the animal for 60 seconds, then applied open-chest cardiac massage at a rate of about 80 contractions per minute. At 10 minutes after CA, the extracorporeal circuit was started and cerebral perfusion maintained while we also continued cardiac massage. Extracorporeal blood flow was set at 200–300 mL/min and the temperature target was set at 10–15°C and applied for about 20–30 minutes. During cardiac massage and cerebral perfusion, we continued mechanical ventilation at Fio_2 of 1.0.

At the end of the experiments, while under anaesthesia, all animals were euthanased by cessation of mechanical support.

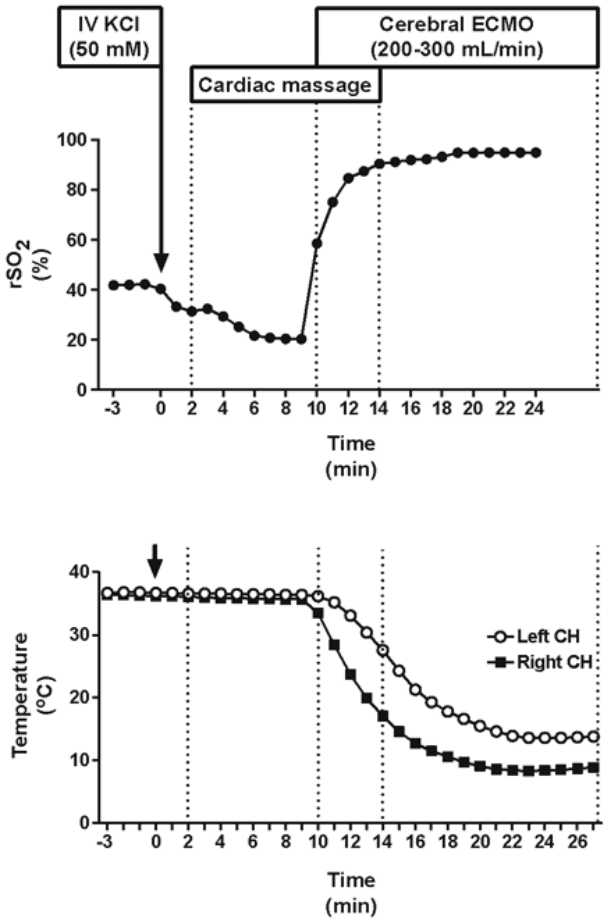
Results

Antegrade perfusion

In the first animal, due to some arterial bleeding related to the insertion of the carotid cannula, there was haemodynamic instability before the induction of CA, leading to a pre-CA cerebral tissue oxygenation ($Scto_2$) level measured by NIRS of just above 40%. After induction of CA, $Scto_2$ decreased to 20% over about 10 minutes, despite the application of open-chest cardiac massage (Figure 1). On induction of ECMO-based cerebral perfusion and cooling, $Scto_2$ levels increased to 60% within 1 minute, then continued to increase further and remained high for the duration of the experiment. This change was associated with visible changes in the appearance of the blood returning to the oxygenating membrane, from poorly oxygenated to highly oxygenated blood.

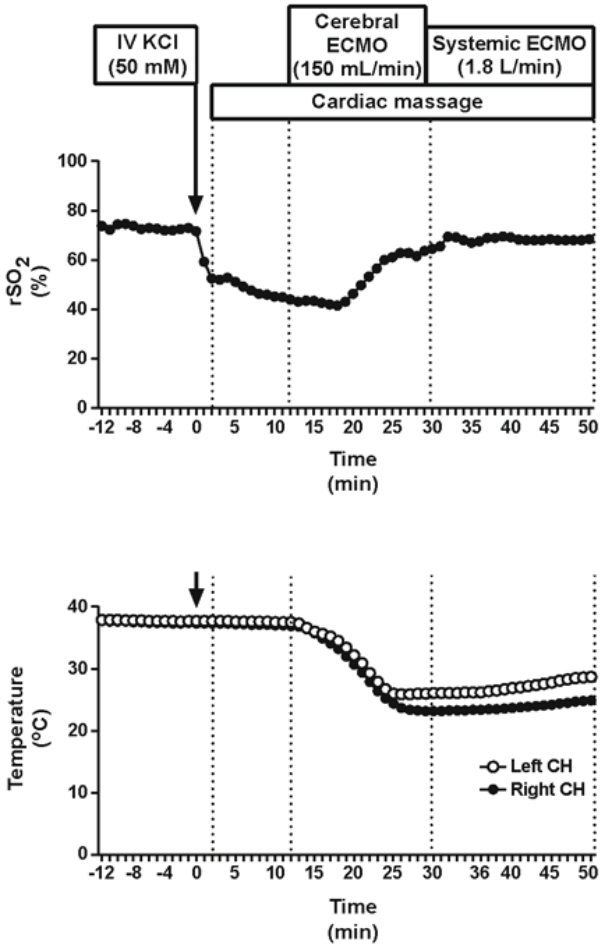
Simultaneously, the cerebral temperature on the carotid perfusion side decreased from 37°C to 25°C in about 3 minutes, and to below 10°C within about 12 minutes. The temperature on the non-perfusion side also decreased, but less efficiently, reaching 25°C in about 9 minutes and a nadir of about 14°C at 12 minutes.

Figure 1. Cerebral tissue oxygenation (measured by near infrared spectroscopy) and temperature before, during and after cardiac arrest, with treatment using antegrade perfusion and cooling in an anaesthetised sheep



rSo_2 = cerebral tissue oxygenation. IV = intravenous. ECMO = extracorporeal membrane oxygenation. CH = cerebral hemisphere.

Figure 2. Cerebral tissue oxygenation (measured by near infrared spectroscopy) and temperature before, during and after cardiac arrest, with treatment using antegrade perfusion and cooling in an anaesthetised sheep*



rSo_2 = cerebral tissue oxygenation. IV = intravenous. ECMO = extracorporeal membrane oxygenation. CH = cerebral hemisphere. * Low-flow systemic ECMO was initiated after cerebral ECMO, as an additional experiment after the initial cerebral perfusion experiment was completed, as part of an additional assessment of low-flow ECMO on cerebral blood flow.

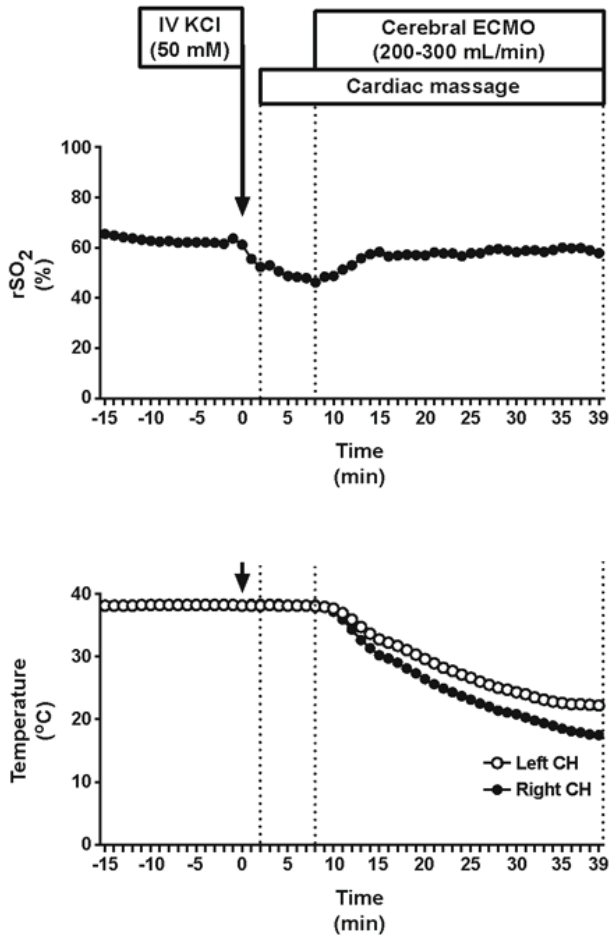
In the second animal, using slightly lower perfusion flows similar improvements in $Scto_2$ were achieved, as well as rapid falls in temperature (Figure 2).

Retrograde perfusion

In the first animal, before the induction of CA, the $Scto_2$ (measured by NIRS) was consistently above 60%. After the induction of CA, the $Scto_2$ decreased to 48% over about 10 minutes, despite the application of open-chest cardiac massage. On induction of ECMO-based cerebral perfusion and cooling, the $Scto_2$ levels slowly increased to 56%–58% within 5 to 6 minutes and remained at 58%–60% for the duration of the experiment (Figure 3). This change was associated with visible changes in the appearance of the blood returning to the oxygenation membrane, from poorly oxygenated to highly oxygenated blood. Simultaneously, the cerebral temperature on the retrograde perfusion side decreased from 37°C to 30°C in about 12 minutes and to about 20°C within about 22 minutes. The temperature on the non-perfusion side also decreased, but less efficiently, reaching 33°C in about 12 minutes and dropping to a nadir of about 22°C at 25 minutes.

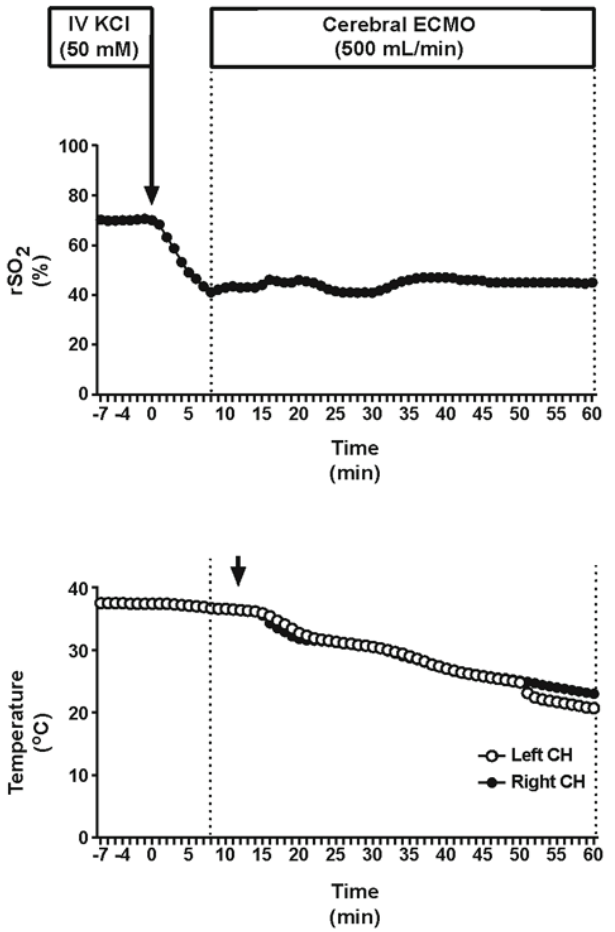
In the second animal, despite higher perfusion flows, the improvements in $Scto_2$ were similar and were also achieved slowly. Similarly, the decrease in temperature was less than that seen with antegrade perfusion and also occurred slowly (Figure 4).

Figure 3. Cerebral tissue oxygenation (measured by near infrared spectroscopy) and temperature before, during and after cardiac arrest, with treatment using retrograde perfusion and cooling in an anaesthetised sheep



rSo_2 = cerebral tissue oxygenation. IV = intravenous. ECMO = extracorporeal membrane oxygenation. CH = cerebral hemisphere.

Figure 4. Cerebral tissue oxygenation (measured by near infrared spectroscopy) and temperature before, during and after cardiac arrest, with treatment using retrograde perfusion and cooling in an anaesthetised sheep*



rSo_2 = cerebral tissue oxygenation. IV = intravenous. ECMO = extracorporeal membrane oxygenation. CH = cerebral hemisphere. * No cardiac massage was attempted to assess whether cardiac massage might interfere with retrograde perfusion.

Discussion

Key findings

We performed four proof-of-concept animal experiments to test the hypothesis that it would be possible to provide rapid cerebral perfusion and cooling by delivering oxygenated blood directly to the brain by means of an ECMO circuit. The circuit was connected to the cerebral circulation via cannulae inserted into either the carotid artery (antegrade perfusion) or the jugular vein (retrograde perfusion). We found evidence that such direct perfusion and cooling appeared possible with direct antegrade and retrograde perfusion, as suggested by coherent and logical changes in $Scto_2$ level and cerebral temperature. However, we also found that the recovery of $Scto_2$ to baseline or above baseline levels, and the speed and degree of cooling, were markedly more pronounced with antegrade perfusion.

Relationship to previous findings

To our knowledge, our findings provide the first experimental evidence on the effect of antegrade or retrograde perfusion on cerebral oxygenation (assessed by $Scto_2$) and cerebral temperature (assessed by direct tissue measurements) during CA and open-chest cardiac massage. However, both antegrade and retrograde cerebral perfusion techniques have been applied for many years to achieve cerebral protection during complex aortic arch surgery.[16] In such settings, unilateral antegrade or retrograde perfusion of the anterior circulation, accompanied by whole-body

hypothermia to temperatures of about 18–20°C for periods of close to 30 minutes, has been reported to provide sufficient cerebral protection for patients such that there is a return to apparently normal cerebral function after the operation.[16] In addition, anecdotal cases of patients surviving prolonged CA by drowning in icy water and rapidly reaching profound hypothermia[17] further support the notion that rapidly reaching low cerebral temperatures can provide protection to the brain, even in the absence of cardiac output for periods lasting at least 30 minutes.

Study implications

Our experimental findings imply that, in the setting of CA, restoration of $Scto_2$ and rapid cerebral hypothermia can be achieved with direct antegrade perfusion (and more slowly with retrograde perfusion) of the anterior cerebral circulation by appropriate cannulation and delivery of blood flow using an ECMO circuit. Our preliminary findings also suggest that further investigation of the quality and extent of such perfusion, possibly by magnetic resonance techniques, may be justified. Finally, if such perfusion were found to be sufficient, they suggest the need for further experimental investigations of this approach, including animal recovery and functional evaluation.

Strengths and limitations

Our study has several strengths. We describe a novel approach to cerebral cooling and perfusion. We showed clear changes in temperature and NIRS-derived cerebral oxygenation compared with standard approaches. Finally, we showed clear differences between antegrade and retrograde perfusion, in terms of time to cooling and levels of cerebral oxygenation, thus providing strong support for the preferential choice of antegrade perfusion.

Our study also has several limitations. It was not a randomised controlled trial, but each animal served as its own control by showing cerebral desaturation with conventional treatment or no treatment and resolution of cerebral hypoxia with direct perfusion. We did not measure markers of cerebral metabolism, such as lactate or glucose, by microdialysis or measurement of concentrations in venous jugular bulb blood. Such measurements will be important additional assessments in future studies. Whether extracorporeal perfusion is sufficient to maintain organ function remains untested. However, similar isolated organ perfusion involving the liver has been reported to be successful.[18-20] Finally, the accuracy of NIRS-derived oxygen saturation in describing cerebral perfusion in this setting remains unclear. It may be that in these experiments, the NIRS-derived signal mostly reflects extracranial perfusion rather than cerebral perfusion. For this reason, we plan to undertake more sophisticated measurements of cerebral perfusion using magnetic resonance technology in future studies.

Conclusions

We performed two proof-of-concept animal experiments and were able to provide rapid cerebral perfusion and cooling by delivering oxygenated blood directly to the brain by means of an ECMO circuit connected to the anterior cerebral circulation. Such perfusion delivered coherent and logical changes in $Scto_2$ and cerebral temperature. Our preliminary findings support further investigations of this approach to cerebral protection during experimental CA.

Competing interests

None declared.

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