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EXPERIMENTAL PAPER

Hyperbaric oxygen improves rate of return of spontaneous circulation after prolonged normothermic porcine cardiopulmonary arrest☆

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Epinephrine (adrenaline)

Summary
Aim: This controlled, prospective, randomized porcine study tests the hypothesis that high-dose hyperbaric oxygen ($HDHBO_2$) compared with normobaric oxygen (NBO_2) or standard-dose hyperbaric oxygen ($SDHBO_2$), improves return of sustained spontaneous circulation (ROSC) after a normothermic, normobaric, 25-min, non-intervened-upon cardiopulmonary arrest. The study incorporated a direct mechanical ventricular assist device (DMVAD) for open chest continuous cardiac compressions (OCCC) to assist advanced cardiac life support (ACLS). The experiment demonstrates a dose response to oxygen concentration in the breathing mix used in resuscitative ventilation.
Materials and methods: Male pigs (average 30 kg weight) underwent a 25-min, normothermic, non-intervened-upon cardiopulmonary arrest. Following arrest all animals were ventilated with 100% oxygen and were subjected to OCCC, incorporating DMVAD-aided ACLS. The animals so treated were randomized to be in one of three groups, with six animals in each group. The NBO_2 group remained at 1.0 atmosphere absolute (ATA), while the $SDHBO_2$ and $HDHBO_2$ groups were initially placed at 1.9 and 4.0 ATA, respectively. Uniform, but not American Heart Association (AHA) protocol, ACLS was maintained as needed over the ensuing 2 h for all animals in all groups. At the end of 2 h, the animals were euthanized.

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Results: Continuously sustained ROSC (mean arterial pressure $\geq$50 mmHg at all times), without the need of the pump assist over the 2-h resuscitation attempt that followed the 25-min arrest, occurred in four out of six animals in the $HDHBO_2$ group, and in none of the animals in the NBO_2 or $SBHBO_2$ groups ($p \leq 0.001$).

Conclusions: Our results show significantly sustained ROSC using $HDHBO_2$ to resuscitate swine after a 25-min, non-intervened-upon, normothermic cardiopulmonary arrest. These results could not be achieved using NBO_2 or $SDHBO_2$.

Early advances in resuscitation of patients in cardiopulmonary arrest resulted from technological improvements in airway management,[1] breathing,[2] circulation,[3] defibrillation,[4] epinephrine,[5] and hyperbaric oxygenation[6] (A, B, C, D, E, O_2). As a consequence, ''A, B, C, D, Es'' during cardiopulmonary resuscitation/advanced cardiac life support (CPR/ACLS) became codified by the American Heart Association (AHA).[7] Despite major reworking of the AHA CPR/ACLS algorithmic approach over the years, clinical outcomes today remain similar to those achieved several decades ago. Despite extensive AHA efforts for uniformity of approach, skills, and equipment in CPR/ACLS education, the M. Eisenberg prediction grid for survival after cardiopulmonary arrest from 1979 is still largely applicable today. If CPR coupled with ACLS is not initiated within 16 min of a normothermic cardiopulmonary arrest, the probability of achieving survival is zero[8] (Table 1). Thus, the estimated probability of a person who has suffered a pre-hospital cardiopulmonary arrest to be resuscitated and to leave the hospital neurologically unimpaired is 1—5%.[9–11]

Perhaps return of sustained spontaneous circulation (ROSC) after normothermic arrest is under-reported. We published a report of a 35-year-old who underwent a *normothermic* cardiopulmonary arrest about 25 min before CPR/ACLS was begun. This case involved the resuscitative use of six atmospheres of oxygen in a hyperbaric environment. A 22-year follow-up confirmed an excellent neurologic outcome.[12] Normothermic, isolated, in vitro, central nervous system (CNS) tissue[13–17] and myocardial tissue[18–21] remain viable for up to 20 min after cessation of tissue oxygen supply.

Here we tested the hypothesis that after a prolonged, normothermic, unattended cardiopulmonary arrest of 25 min in a porcine model, ventilation with oxygen in a hyperbaric environment during CPR/ACLS makes ROSC possible. Before the attempt to resuscitate normothermic cardiopulmonary arrest victims, the chance of sustained ROSC becomes less as the time of non-intervention increases. Our literature search (incorporating use of Ovid, Medline, and PubMed searching from 1950 to present) of human case reports and animal trials confirms this point. The longest controlled trial that was found for swine undergoing non-intervened-upon normothermic arrest that resulted in successful ROSC was 15 min.[22–25] Using the same search instruments and time frame, no human case reports of ROSC in a non-intervened-upon, normothermic cardiopulmonary arrest of more than 16 min could be found.[26]

Materials and methods

Animals

All 18 animals in this study were male pigs of a land-raised breed crossed with Yorkshire or Hampshire breed from a single-source herd. This study was approved by the Institutional Animal Care and Use Committees (IACUC) of the Louisiana State University Health Sciences Center in New Orleans and of the Baromedical Research Institute, New Orleans. After uniform acclimatization of the animals in a temperature-controlled, Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC)-approved, climate-controlled, vivarium and laboratory, food but not water was withheld overnight from the animal to be used in the experiment. On the day of the experiment, the animal was assigned by computer-generated randomization (www.randomize.net) to one of three groups: (1) 1.0 atmosphere absolute (ATA) or 100% surface equivalent fraction inspired oxygen ($SEFIO_2$) for 2 h ($n = 6$); (2) 1.9 ATA or 190% $SEFIO_2$ for 2 h ($n = 6$); or (3) 4.0 ATA or 400% $SEFIO_2$ for 15 min, then 2.8 ATA for 45 min, 1.9 ATA for 60 min ($n = 6$). The hyperbaric chamber was highly controlled and operationally arranged to be identical for all animal groups; however, it was not possible to blind members of a seasoned diving research crew to sham pressurization for the surface control group. Further, the difference in diving profiles for the pressure groups were easily distinguishable by the diving research crew. Lastly, safety considerations for defibrillation in the hyperbaric environment required procedural contingency that required the diving research crew to need to know at what depth they were.

On the day of the experiment, atropine (0.02 mg/kg) and ketamine (20 mg/kg) were injected intramuscularly. Animals were washed, dried, and transferred from the vivarium to the operating room. Continuous ear oximetry and three-lead electrocardiogram (EKG) monitoring were initiated. After a 2-s spray of the epiglottic vallecula with 20% benzocaine spray, animals were endotracheally intubated and placed on a ventilator with 95% oxygen and 5% isofluorane. The isofluorane was reduced over 10 min to a 1% concentration. A rectal thermistry probe continuously monitored temperature. Animals were placed in supine position on top of a water-circulated warming blanket to maintain rectal temperature at 37 °C. Using direct cutdown, catheters were placed in the femoral artery and the internal jugular vein for arterial manometry and for central venous/pulmonary artery manometry, oximetry and thermistry. Cardiac out-