Determinants of mortality after hypothermic circulatory arrest in a chronic porcine model

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Abstract

Objective: Beside neurological morbidity, mortality is a relevant end-point of experimental porcine model of hypothermic circulatory arrest (HCA) and this study was conducted to identify the determinants for postoperative death. Methods: One hundred and thirty-five pigs underwent a 75-min period of HCA at 20°C to evaluate the efficacy of different methods of cerebral protection. Results: Survival rate at 7-day follow-up was 52%. Lower oxygen extraction, oxygen consumption/kg, and venous lactate at the end of cooling and higher oxygen delivery rates were significantly associated with better outcome. Logistic regression showed that the oxygen consumption/kg at the end of cooling was the only predictor of mortality (P = 0.046). Animals with an oxygen consumption/kg rate less than 1.43 ml/min per kg at the end of cooling had a mortality rate of 28%, whereas it was 50% among animals with an oxygen consumption/kg rate higher or equal to 1.43 ml/min per kg (P = 0.020). The latter had even an increased 1-day mortality rate (40% vs. 26%) (P not significant). The mortality rate after anesthesia induction with ketamine plus 100% of oxygen was 38%, 45% after anesthesia induction with ketamine plus 35% oxygen, and 53% after anesthesia with medetomidine plus 35% oxygen (P not significant). Conclusions: Parameters of oxyhemodynamics should be monitored especially from the induction of anesthesia to the end of cooling before a 75-min period of HCA. The use of medetomidine and/or 35% of oxygen at induction of anesthesia should be avoided in favor of ketamine plus 100% of oxygen. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Hypothermic circulatory arrest; Neuroprotection; Oxygen extraction; Oxygen consumption; Oxygen delivery; Oxygen saturation

1. Introduction

The management of aneurysms of the aortic arch remains a challenge for cardiac surgeons, cerebral protection being of major concern during aortic arch replacement. Hypothermic circulatory arrest (HCA) provides adequate cerebral protection and an optimal operative field, but it is associated with important time limitations. Several technical and pharmacological strategies are currently under evaluation whether they may mitigate ischemic brain injury and improve the safety of HCA. Our experience in the experimental porcine model of 75-min period of HCA at 20°C provided interesting results on the efficacy of different adjuvant methods in cerebral protection [1–5], but the postoperative mortality rate after the experiments was not irrelevant. This observation led us to a critical analysis of the results of a consecutive series of 135 pigs, including those animals that died just after the operation and, therefore, were not eligible for original studies, in order to identify the risk factors affecting the survival after a 75-min period of HCA.

2. Material and methods

From January 1998 to November 2000, 135 female pigs (8–10 weeks old) of a native stock, with a median weight of 27.2 kg (21.0–38.2), underwent a 75-min period of HCA at 20°C according to different study protocols [1–5]. The present series includes even those animals that died during day of operation and that, therefore, were not the subjects of our previously published studies [1–5]. Sixty-five pigs underwent experimental protocol as controls, whereas seven pigs underwent intermittent retrograde cerebral perfusion and HCA, eight underwent continuous retrograde cerebral perfusion and HCA, 22 received lamotrigine (20 mg/kg intravenously over a period of 20 min) 2 h before the operation, ten
received memantine (5 mg/kg intravenously over a period of 20 min) 75 min before HCA, ten underwent HCA with leukocyte filtration (Leukoguard LG6, Pall Biomedical, Portsmouth, UK) during cardiopulmonary bypass (CPB) and 13 underwent HCA with leukocyte filtration plus lamotrigine.

2.1. Preoperative management

All animals received humane care in accordance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Researches and published by the National Institutes of Health publication No. 85-23, revised 1985). The study was approved by the Research Animal Care and Use Committee of the University of Oulu.

2.2. Anesthesia and hemodynamic monitoring

In 42 animals (31%), anesthesia was induced with ketamine hydrochloride (10 mg/kg administered intramuscularly) and midazolam (1 mg/kg administered intramuscularly), and muscular paralysis was maintained with pancuronium (0.1 mg/kg administered intravenously) plus positive-pressure ventilation with 100% of oxygen. In 24 animals (24%), ketamine hydrochloride (10 mg/kg administered intramuscularly), midazolam (1 mg/kg administered intramuscularly), pancuronium (0.1 mg/kg administered intravenously) and positive-pressure ventilation with 35% of oxygen were used. Anesthesia was maintained in all animals with isoflurane.

The introduction in our experiments of medetomidine for anesthesia induction coincided with the need to avoid any potential interaction between ketamine and memantine [4], the latter having been suggested to offer effective neuroprotection [6], since both are N-methyl-D-aspartate receptor antagonists and may contribute to central nervous system protection [7]. Thus, in the subsequent studies involving 69 pigs (51%), anesthesia was routinely induced with medetomidine hydrochloride (0.4 mg/kg) and muscular paralysis was maintained with pancuronium bromide (0.1 mg/kg intravenously) plus positive-pressure ventilation with 35% of oxygen.

An arterial catheter was positioned in the left femoral artery. A thermodilution catheter (Criticath, 7 F, Ohmeda GmbH, Erlangen, Germany) was placed through the femoral vein to allow blood sampling, pressure monitoring in the pulmonary artery, and recording of cardiac output. The intracranial temperature probe was placed in the epidural space through a drill hole 1 cm to the right of the sagittal joint above a parietal line. The probe was then isolated with bone wax. Other probes were placed into the esophagus and rectum. A 10-F Nelaton catheter was placed into the urinary bladder to monitor urine output.

2.3. Cardiopulmonary bypass

The heart and great vessels were exposed through a right thoracotomy. A membrane oxygenator (Midiflow D 705, Dideco, Mirandola, Italy) was primed with 1–1.5 l of Ring-er’s acetate and heparin (5000 IU). After heparinization (300–400 IU/kg), the ascending aorta was cannulated with a 16-F arterial cannula, and the right atrial appendage was cannulated with a single 24-F atrial cannula. Non-pulsatile CPB was initiated at a flow rate of 100 ml/kg per minute, and afterward, the flow was adjusted to maintain a perfusion pressure of 50 mmHg. A 12-F intracardiac sump cannula was positioned in the left ventricle for decompression of the left heart during CPB. A heat exchanger was used for core cooling. The pH was maintained with alpha-stat principles at 7.40 ± 0.05 with an arterial PCO 2 of 3.5–5.0 kPa, uncorrected for temperature. All measurements were performed at 37°C.

The cooling period of 60 min was carried out to attain a rectal temperature of 20°C. Cardiac arrest was induced by injecting potassium chloride (1 mEq/kg) into the aortic cannula, and topical cardiac cooling was then maintained throughout the aortic cross-clamp period. The ascending aorta was cross-clamped just proximally to the aortic cannula.

2.4. Experimental protocol

After cooling to a rectal temperature of 20°C and cross-clamping the aorta, the animals underwent a 75-min period of HCA with the head packed in ice. For other technical details, see Refs. [1–5]. After a 75-min period, antegrade CPB rewarming was initiated. The left ventricular cannula was removed. Weaning from CPB occurred approximately 60 min after the start of rewarming with administration of 40 mg of furosemide, 15.0 g of mannitol, 80 mg of methylprednisolone, and 40–150 mg of lidocaine, depending on cardiac arrhythmias. Cardiac support was provided with dopamine. The animals were kept in isoflurane anesthesia until the following morning, extubated, and moved into a recovery room.

During the experiment, hemodynamic and metabolic measurements were recorded at baseline, at the end of cooling (at 20°C, immediately before HCA), during rewarming (at 30°C), and 2 and 4 h after the start of rewarming, respectively. Systemic arterial and venous blood samples were obtained to determine pH, oxygen tension, carbon dioxide tension, oxygen saturation, oxygen content, hematocrit, hemoglobin, and glucose concentrations (Ciba-Corning, 288, Blood Gas System; Ciba-Corning Diagnostic Corp., Medfield, MA). Lactate concentrations were measured by means of a YSI 1500 analyzer (Yellow Spring Instruments Co., Yellow Springs, OH). Leukocyte count was done with a Cell-Dyn analyzer (Abbott, Santa Clara, CA). Temperatures were recorded at intervals throughout the study. Hemodynamics, temperatures, and respiratory gases were monitored...
by Datex AS/3 anesthesia monitor (Datex Inc., Espoo, Finland).

Each surviving animal was electively put to death on day 7 after the operation. The entire brain was immediately harvested, weighed and immersed in 10% neutral formalin. Histopathological examination was done in 106 cases.

2.5. Statistical analysis

Values are expressed as the median with interquartile ranges (25th and 75th percentiles). Statistical analysis was performed using an SPSS software (SPSS version 9.0.1., SPSS Inc., Chicago, IL). Kaplan–Meier curves were constructed to evaluate the survival rates of pigs. Fisher’s exact test was used to compare categorical variables. Differences between survivors and deaths were determined by means of the t-test or the Mann–Whitney test. One-way analysis of variance and the Kruskal–Wallis tests were used to compare continuous variables between different anesthesia protocols. Logistic regression was used to analyze the data, and the baseline mixed venous oxygen saturation, and oxygen extraction and oxygen consumption/kg at the end of cooling, were used as independent variables. A P value of less than 0.05 was considered as statistically significant.

3. Results

The median weight of pigs was 27.0 kg (24.5–30.0) in the group of deaths and 27.4 kg (24.5–30.0) in the group of survivors (P = not significant [NS]). The median CPB cooling time was 61 min (60–65) in the group of survivors and 61 min (60–64) in the group of deaths (P = NS). The median CPB rewarming time was 65 min (60–73) in the group of survivors and 68 min (60–74) in the group of deaths (P = NS). The median CPB time was 129 min (125–138) in the group of deaths and 128 min (120–138) in the group of survivors (P = 0.04). Sixty–four animals died during the early postoperative period. Survival rates at 1-, 2- and 7-day follow-up were 89, 59 and 52%, respectively.

The mean weight of harvested brains in the group of survivors was 72.5 g (69.2–77.2), whereas it was 76.5 g (72.9–80.2) in the group of deaths (P = 0.003). Histopathological examination of 106 harvested brains showed areas of infarction in 8% of pigs in the group of deaths and in 67% of pigs in the group of survivors (P < 0.0001).

Univariate analysis showed that oxygen kinetics parameters and cardiac output were significantly impaired in the animals that died postoperatively (Table 1 and Fig. 1). The most relevant differences in oxygen parameters were observed during the first two perioperative intervals, i.e., at baseline and at the end of cooling intervals. Lower oxygen extraction and oxygen consumption/kg rates, and venous lactate level at the end of cooling were significantly associated with better outcome (Table 1 and Fig. 1).

These findings led us to observe that, although without statistical significance, the anesthesia induction protocol was associated with marked differences in the mortality rates. The mortality rate among animals that underwent anesthesia with ketamine and 100% of oxygen was 38%, in those that underwent anesthesia with ketamine and 35% oxygen was 45%, and it rise to 53% in those in whom medetomidine and 35% oxygen were used (P = NS). Twelve animals (28%) that underwent anesthesia with ketamine and 100% of oxygen died during the same day of operation or on the first postoperative day, whereas immediate death occurred in 33 animals (47%) after anesthesia with medetomidine and 35% of oxygen, and in 10 animals (42%) after anesthesia with ketamine and 35% of oxygen (P = NS). The mortality rates during the same day of operation were 7, 13 and 12%, respectively (P = NS).

The use of different anesthesia protocols was associated with marked differences in the perioperative oxyhemodynamic parameters (Fig. 2). It is worth of noting that, according to the Kruskal–Wallis test, the animals that underwent anesthesia with ketamine and 100% of oxygen had significantly lower oxygen consumption/kg and oxygen extraction rates at the end of cooling (Fig. 2e,d). The use of medetomidine plus 35% of oxygen was associated with lower cardiac output during all the perioperative intervals (P < 0.0001) (Fig. 2a) with clear reflections on the oxygen delivery rate (Fig. 2b). The same trend was observed among the animals that underwent anesthesia with ketamine and 35% of oxygen (Fig. 2a,b).

The animals that underwent anesthesia induction with medetomidine plus 35% of oxygen had statistically significant differences in the mean arterial pressure during all the intervals from the baseline to the 4-h after start of rewarming measurements. Among the animals that underwent anesthesia with ketamine, those that underwent positive-pressure ventilation with 35% of oxygen had higher mean arterial pressure values than those that had 100% of oxygen during the anesthesia induction. Such differences were statistically significant during rewarming (at 30°C) (P < 0.0001) and 2 h after the start of rewarming (P = 0.01).

The heart rate was decreased in pigs that underwent anesthesia with medetomidine as well (P = 0.005). This anesthesia protocol resulted even in marked lower percentages of mixed venous oxygen saturation at the baseline measurements (Fig. 2e), a parameter that tended to be significantly associated with postoperative mortality (P = 0.056) (Fig. 1e).

Logistic regression showed that the oxygen consumption/kg at the end of cooling was the only predictor of mortality (P = 0.046). Animals with an oxygen consumption/kg rate less than 1.43 ml/min per kg at the end of cooling had a mortality rate of 28%, whereas it was 50% among animals with an oxygen consumption/kg rate higher or equal to 1.43 ml/min per kg (P = 0.022). The latter had even an increased 1-day postoperative mortality rate (40% vs. 26%) (P = NS).
Table 1
Metabolic data on 71 animals that survived and on 64 animals that died during the early postoperative period after 75-min hypothermic circulatory arrest*

<table>
<thead>
<tr>
<th>Cardiac output (l/min)</th>
<th>Baseline</th>
<th>End of CPB cooling</th>
<th>30°C</th>
<th>Time after start of rewarming</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deaths</strong></td>
<td>2.79 (2.39–3.51)</td>
<td>–</td>
<td>–</td>
<td>3.04 (2.40–3.65)*</td>
</tr>
<tr>
<td><strong>Survivors</strong></td>
<td>3.10 (2.62–3.53)</td>
<td>–</td>
<td>–</td>
<td>3.41 (2.85–4.03)*</td>
</tr>
<tr>
<td><strong>Rectal temperature (°C)</strong></td>
<td>37.3 (36.7–37.6)</td>
<td>20.2 (20.0–20.5)</td>
<td>28.8 (26.8–30.0)</td>
<td>34.5 (33.7–34.8)</td>
</tr>
<tr>
<td><strong>Blood temperature (°C)</strong></td>
<td>37.1 (36.6–37.6)</td>
<td>20.1 (20.0–20.5)</td>
<td>28.9 (26.9–30.0)</td>
<td>34.5 (33.8–35.0)</td>
</tr>
<tr>
<td><strong>Epidural temperature (°C)</strong></td>
<td>37.2 (36.4–37.6)</td>
<td>19.4 (19.1–19.8)</td>
<td>35.5 (33.9–35.5)</td>
<td>34.1 (33.2–34.9)</td>
</tr>
<tr>
<td><strong>Hemoglobin (g/l)</strong></td>
<td>36.9 (36.4–37.5)</td>
<td>19.4 (19.1–19.6)</td>
<td>34.5 (32.8–35.7)</td>
<td>34.4 (33.5–34.9)</td>
</tr>
<tr>
<td><strong>Arterial pH</strong></td>
<td>37.2 (36.5–37.5)*</td>
<td>19.5 (18.5–20.0)</td>
<td>32.5 (30.4–34.2)</td>
<td>34.6 (33.2–34.9)</td>
</tr>
<tr>
<td><strong>Venous pH</strong></td>
<td>36.9 (36.5–37.6)*</td>
<td>19.2 (18.1–19.9)</td>
<td>31.9 (29.3–34.1)</td>
<td>34.4 (33.8–34.9)</td>
</tr>
<tr>
<td><strong>Epidermal temperature (°C)</strong></td>
<td>35.3 (34.4–36.1)</td>
<td>19.3 (18.9–19.8)</td>
<td>30.6 (29.0–32.5)</td>
<td>32.6 (31.6–33.4)</td>
</tr>
<tr>
<td><strong>Survivors</strong></td>
<td>34.9 (33.6–36.0)</td>
<td>19.2 (18.8–19.7)</td>
<td>31.1 (28.6–32.4)</td>
<td>32.6 (30.2–33.6)</td>
</tr>
<tr>
<td><strong>Hematocrit (%)</strong></td>
<td>7.45 (7.43–7.47)</td>
<td>7.37 (7.31–7.44)</td>
<td>7.44 (7.40–7.49)</td>
<td>7.39 (7.34–7.43)</td>
</tr>
<tr>
<td><strong>Survivors</strong></td>
<td>7.49 (7.46–7.52)</td>
<td>7.35 (7.30–7.43)</td>
<td>7.43 (7.39–7.50)</td>
<td>7.39 (7.31–7.43)</td>
</tr>
<tr>
<td><strong>Venous lactate (mmol/l)</strong></td>
<td>7.45 (7.43–7.48)</td>
<td>7.33 (7.28–7.40)</td>
<td>7.33 (7.29–7.37)</td>
<td>7.34 (7.30–7.37)</td>
</tr>
<tr>
<td><strong>Survivors</strong></td>
<td>7.45 (7.42–7.47)</td>
<td>7.33 (7.27–7.39)</td>
<td>7.32 (7.28–7.32)</td>
<td>7.35 (7.28–7.39)</td>
</tr>
<tr>
<td><strong>Survivors</strong></td>
<td>1.15 (0.98–1.51)</td>
<td>2.12 (1.77–2.35)*</td>
<td>5.72 (5.13–6.24)</td>
<td>4.51 (4.07–5.60)*</td>
</tr>
<tr>
<td><strong>Survivors</strong></td>
<td>1.16 (0.85–1.48)</td>
<td>1.85 (1.44–2.18)*</td>
<td>5.61 (4.83–6.57)</td>
<td>4.11 (3.27–5.30)*</td>
</tr>
<tr>
<td><strong>Hemoglobin (g/l)</strong></td>
<td>90.4 (88.0–101.5)</td>
<td>60.0 (55.0–66.0)</td>
<td>70.0 (62.0–76.0)</td>
<td>86.0 (80.0–94.7)</td>
</tr>
<tr>
<td><strong>Survivors</strong></td>
<td>97.0 (91.0–103.0)</td>
<td>61.2 (56.0–66.1)</td>
<td>68.0 (61.0–76.0)</td>
<td>87.0 (80.7–94.2)</td>
</tr>
<tr>
<td><strong>Survivors</strong></td>
<td>27.6 (25.7–29.8)</td>
<td>17.9 (16.2–19.4)</td>
<td>20.6 (17.9–22.1)</td>
<td>25.1 (22.8–27.7)</td>
</tr>
<tr>
<td><strong>Survivors</strong></td>
<td>28.7 (26.7–30.0)</td>
<td>18.1 (16.5–19.4)</td>
<td>19.7 (18.0–22.0)</td>
<td>25.6 (23.7–26.7)</td>
</tr>
<tr>
<td><strong>Survivors</strong></td>
<td>76.7 (69.5–84.4)</td>
<td>99.5 (99.1–99.6)</td>
<td>76.7 (71.7–79.4)</td>
<td>77.7 (71.0–83.2)</td>
</tr>
<tr>
<td><strong>Survivors</strong></td>
<td>80.4 (74.3–84.3)</td>
<td>99.6 (98.9–99.7)</td>
<td>77.8 (73.3–81.6)</td>
<td>80.3 (72.1–85.3)</td>
</tr>
<tr>
<td><strong>O2 extraction (ml/dl)</strong></td>
<td>3.5 (2.5–4.2)</td>
<td>3.6 (2.6–3.8)</td>
<td>1.7 (1.5–1.9)*</td>
<td>3.0 (2.7–3.6)</td>
</tr>
<tr>
<td><strong>O2 consumption/kg (ml/min/kg)</strong></td>
<td>3.68 (3.24–4.10)</td>
<td>1.65 (1.38–1.86)*</td>
<td>3.17 (2.78–3.49)</td>
<td>3.64 (3.12–4.33)</td>
</tr>
<tr>
<td><strong>O2 delivery (ml/min/kg)</strong></td>
<td>3.64 (3.17–3.84)</td>
<td>1.43 (1.27–1.72)*</td>
<td>3.13 (2.83–3.49)</td>
<td>3.74 (3.34–4.40)</td>
</tr>
<tr>
<td><strong>Survivors</strong></td>
<td>107 (98–118)*</td>
<td>–</td>
<td>125 (113–141)</td>
<td>126 (109–137)</td>
</tr>
<tr>
<td><strong>Survivors</strong></td>
<td>113 (105–128)*</td>
<td>–</td>
<td>132 (118–151)</td>
<td>128 (111–142)</td>
</tr>
</tbody>
</table>

* Values are shown as medians with interquartile range in parentheses. SvO2, mixed venous oxygen saturation; CPB, cardiopulmonary bypass. *P < 0.05, deaths vs. survivors; **P < 0.01, deaths vs. survivors.

In a subanalysis of animals that underwent a 75-min period of HCA as controls, the median oxygen consumption/kg at the end of cooling was 1.46 ml/min per kg among survivors and it was 1.65 ml/min per kg among animals that died postoperatively (P = 0.044). This parameter was clearly affected by the higher oxygen extraction rates as observed among the animals that died compared with survivors (1.81 vs. 1.57 ml/dl, P = NS).

4. Discussion

Most of studies dealing with HCA have focused their attention to improve the results in terms of neurological morbidity after operations on the aortic arch. The porcine HCA model represents a valid model to assess the efficacy of different HCA adjuvant strategies and it provided major insights on cerebral metabolism during cardiac surgery.
However, neurological outcome does not represent the only end-point both in the experimental field and in clinical practice. Furthermore, poor outcome in pigs undergoing experimental HCA cannot be related solely to ischemic brain injury.

The present study was done in order to optimize our chronic porcine model by identifying the risk factors impairing the survival outcome of pigs undergoing 75-min HCA. The large number of pigs included in this study provided a unique series for an adequate statistical analysis, the latter not being considered for validation of any protocol of cerebral protection over the others previously tested. In fact, the efficacy of each adjuvant method for cerebral protection during 75-min HCA cannot be evaluated other than within a homogeneous randomized protocol study whose results are, therefore, not comparable with the results from different

Fig. 1. (a–e) Oxyhemodynamic parameters during the experiment between survivors (■) and deaths (○) (★P < 0.05; **P < 0.01). SvO₂, mixed venous oxygen saturation. Number of animals in each subgroup are given.
experimental protocols, i.e. anesthesia management. Nevertheless, we believe that a critical review of the survival outcome of those animals that were eligible for the final studies as well as of those that did not survive immediately after the HCA and that, therefore, were excluded from further analysis, is worthwhile to better understand the metabolic derangements undermining postoperative survival.

The analysis of the results of our series provided evidence that impairments in oxygen metabolism are of major importance in predicting the outcome of these animals. Imbalance in oxygen consumption and delivery has been subject of extensive studies in critically ill patients and it has been suggested as a mechanism leading to anaerobic metabolism, multiorgan failure and death [8,9]. Such observations have
been confirmed in patients with acute myocardial infarction [10–13] and after cardiac surgery [14,15], mixed venous blood oxygen saturation, oxygen consumption, oxygen extraction, oxygen delivery and cardiac output being the most relevant predictors of outcome and valid parameters for therapeutic intervention. Increased level of lactate is also a potential predictor of outcome, but its increase is often associated with nonspecific conditions or it may signal significant critical derangement in oxygen metabolism when it might be too late for any intervention to avoid irreversible organ injury [14].

In this regard, the period from anesthesia induction to the end of cooling seems to be of critical importance for any imbalance of oxygen metabolism. The increased oxygen extraction and consumption/kg rates at the end of cooling observed among the animals that died postoperatively suggest that during the period from the beginning of the experiment to the end of cooling these animals were subjected to unfavorable metabolic conditions. These may be due to different individual tolerability, but as shown in Fig. 2, anesthesia protocol might have had a great impact on oxyhemodynamics since the beginning of the experiment. It is worth noting the major impact of medetomidine on cardiac output and mean arterial pressures during all the intervals of the experiment resulting in a suboptimal oxygen delivery.

Medetomidine is a potent α₂-adrenoceptor agonist, which stimulates receptors centrally producing dose-dependent sedation and analgesia, and receptors peripherally resulting in a decreased cardiac output and heart rate and increased systemic vascular resistance [16]. In the study by Talke et al. [16], administration of medetomidine in sheep was associated with increased systemic and pulmonary vascular resistance and decreased peripheral blood flow, but in the hepatic artery. After administration of atipamezole, a competitive α₂ antagonist, systemic vascular resistance, mean arterial pressure and cardiac output returned to baseline and heart rate increased above baseline, but cerebral cortex, left ventricle and renal blood flow remained below baseline. Furthermore, medetomidine decreased arterial oxygenation, oxygen consumption and venous oxygen saturation, and increased arterial and venous CO₂ and shunt fraction [16].

Such unfavorable conditions which posed the animals under an increased debt of oxygen have been paid back after rewarming with derangement in cardiac performance and oxygen metabolism. Although the differences in terms of mortality between different anesthesia protocols were not statistically significant, it seems that the use of medetomidine and/or 35% of oxygen is a suboptimal method for anesthesia induction in this chronic porcine model and is associated with a markedly higher risk of postoperative death.

5. Conclusion

These observations led us to conclude that the parameters of oxyhemodynamics should be closely monitored, especially from the induction of anesthesia to the end of cooling, as increased oxygen consumption, extraction and delivery rates during this period are associated with poor survival rates in an experimental porcine model of 75-min HCA. It is likely that monitoring and correction of oxyhemodynamic parameters during the period preceding the start of HCA can be of benefit in the clinical setting as well. Medetomidine and/or 35% of oxygen should not be administered at induction of anesthesia before HCA, since their use is associated with poorer results as compared with ketamine plus 100% of oxygen.

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References

[8] Shoemaker WC. Oxygen transport and oxygen metabolism in shock


