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Model of Normothermic Long-term Cardiopulmonary Bypass in Swine Weighing More than Eighty Kilograms

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Purpose: **Swine models have been used to study cardiovascular disease, cardiac physiology, and transplantation, and have been associated with problems, such as friability of certain organs, anesthesia difficulties, ventricular fibrillation, and edema. We describe a stable model of extended cardiopulmonary bypass (up to 22 h) in swine weighing > 80 kg to be used as a research model.**

Methods: **Swine (n = 5, 88 ± 6 kg) had both femoral arteries cannulated and after open sternotomy, a two-stage venous catheter was placed in the right atrium/caudal vena cava. The circuit was primed with four parts blood and one part 0.9% NaCl.**

Results: **Cardiopulmonary bypass was maintained for 10 to 22 h, with the following parameters measured at beginning/middle/end: heart rate, 108 to 134 beats per minute; hematocrit, 30 to 38%; glucose concentration, 4 to 11 mmol/L; lactate concentration 6 to 7 mmol/L; pH 7.4 to 7.5; pCO_2, 35 to 38 mmHg; pO_2, 197-228 mmHg; HCO_3^-, 21 to 25 mmol/L; base excess, -3 to +2; and total urine output, 425 to 1,600 ml.**

Conclusions: **Factors responsible for the success of this model include a higher oxygen concentration on initiation of cardiopulmonary bypass (567 ± 54 mmHg), maintenance of appropriate hematocrit, and use of non-citrated blood-crystalloid prime. The results indicate a stable model of normothermic long-term cardiopulmonary bypass in swine that allows researchers a longer opportunity for further exploration of relevant research issues.**

For several decades, swine models have had acceptance for the study of cardiovascular disease, cardiac physiology, transplantation, and clinical use of cardiopulmonary bypass (CPB). However, the swine models have been associated with problems, such as friability of certain organs, anesthesia difficulties, ventricular fibrillation, and edema (1). Furthermore, most research swine models are not of mature age or body weight, ranging from 6 to 33 kg, which can only be classified as juvenile and not of true adult size (60+ kg) (2). Cardiovascular research has indicated that these smaller-size swine do not have the same responses to stress as do larger more mature swine (3). We describe a model of long-term stable CPB in swine weighing > 80 kg. This model would allow new advancements in the refinement of CPB techniques more applicable to adults, thereby allowing increased success in the outcomes of various research studies using an often difficult but relevant animal model.

Materials and Methods

Animal preparation. All animals used in the study were raised as a closed herd at a government-licensed farm. Once at the research facility, each animal was housed separately and allowed ad libitum access to water and commercial pig chow (LabDiet 5084, Purina Mills Inc., Richmond, Ind.) for at least one week prior to use. Any complications, such as shipping transport shock, disease, or weight loss excluded any animal from this study.

Male adult Yorkshire pigs (n = 5; 88 ± 6.3 kg) were pre-anesthetized with Ketaset (ketamine [100 mg/ml], Ayerst Laboratories, Montreal, Quebec, Canada) and Atrosol (atropine sulfate [1 mg/ml], Ayerst Laboratories) given i.m., followed by Somnotol (sodium pentobarbital, [65 mg/ml], M.T.C. Pharmaceuticals, Cambridge, Ontario, Canada) given, i.v. to maintain a proper plane of anesthesia. After intubation, animals were ventilated, using a Ventometer ventilator (Air-shields Inc., Hatboro, Pa.).

All surgical procedures throughout the CPB model were done aseptically. A catheter was placed, using a cut down procedure, into the right carotid artery to monitor arterial blood pressures and for blood sample collection. The animals themselves were fully heparinized (Hepalean [10,000 IU], Organon Teknika, Toronto, Ontario, Canada) to ensure activated clotting times (ACT) > 1,000 sec. prior to initiation of CPB.

Blood pressures were monitored, using pressure transducers (COBE Laboratories Inc., Lakewood, Colo.) connected to a physiologic recorder (BIOPAC Systems Inc., Goleta, Calif.), and blood samples were analyzed, using an ABL30 Acid-Base Analyzer (Radiometer, Copenhagen, Denmark). Body temperature was monitored, using a rectal probe, and myocardial temperatures were monitored, using needle probes placed into the myocardium. These probes were connected to a Shiley temperature unit (Shiley Inc., Irvine, Calif.), which yielded constant read outs. Plasma glucose concentration was measured, using an Accu-Chek blood glucose monitor (Boehringer Mannheim Corporation, Laval, Quebec, Canada). Urine output was measured through a

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catheter placed directly into the urinary bladder through a small intra-abdominal incision and the bladder and catheter contents were allowed to flow freely into a collection cylinder.

All protocols were reviewed and approved by the University of Toronto Animal Care and Use Committee, and all animals received humane care in compliance with the *Guide for the Care and Use of Laboratory Animals*, published by the National Institutes of Health (NIH publication 85-23, revised 1996) and the Canadian Council on Animal Care Guidelines.

Cardiopulmonary bypass prime preparation. The CPB prime solution in the circuit was prepared, using four parts donated adult swine blood and one part 0.9% NaCl (Baxter Corporation, Toronto, Ontario, Canada), and was heated to the proper body temperature (38 ± 0.5°C). The appropriate amount of heparin was added to the prime solution to ensure ACT > 400 sec. prior to the animal being placed on CPB.

Samples from the circuit were taken and analyzed regularly for proper acid-base status, hematocrit (HCT), electrolyte concentrations, and ACT. It was important that all necessary adjustments were made prior to the animal being placed into the circuit to reduce the amount of stress on the CPB circuit and the animal.

Cardiopulmonary bypass design. Following sternotomy, a two-stage venous drainage catheter was inserted into the right atrium and the caudal vena cava and was secured into place. Venous drainage was accomplished via gravity into a venous reservoir where it was then pumped into an oxygenator (CML EXCEL, COBE Laboratories Inc.) and back into the animal. The blood returned through two catheters placed into both femoral arteries to establish retrograde arterial blood flow (Fig. 1). The circuit between the oxygenator and the animal had a temperature probe inserted to measure the temperature of the blood flowing into the animal, ports from which to take samples of blood for measurement or to inject drugs to maintain anesthesia, and an arterial filter to capture microembolytic material, such as clots and air bubbles. A suction line, used to remove free blood from the thorax, was connected to a cardiotomy reservoir. This reservoir served as a collection point for this blood or for the addition of fluids. A heated water circuit from a water bath was connected to the oxygenator to maintain the proper temperature of the blood (Fig. 1). This design closely resembles the systems used in research and clinical settings, and all of the components mentioned are crucial to maintain a stable CPB preparation.

Statistics. Data were analyzed, using one-way analysis of variance (ANOVA) with Tukey's post hoc test. Significance was accepted for $P < 0.05$. Group values are expressed as mean ± SD.

Results

Body weight of these swine ranged from 81 to 94 kg. Duration of CPB for the five animals ranged from 10 to 22 h. Throughout these periods, body temperature was 36.6 ± 0.6°C and myocardial temperature was 38.7 ± 0.1°C from onset of surgery until termination of the study. Pre-CPB ventilatory parameters were taken prior (10 to 20 min) to the animals being placed on CPB. Urine output was measured throughout the entire procedure, and CPB hemodynamic, blood, and blood constituent parameters were taken at regular intervals while the animals were on CPB. The results are shown as pre-CPB and at the beginning, middle and end of CPB.

Ventilatory parameters before CPB. The pre-CPB values

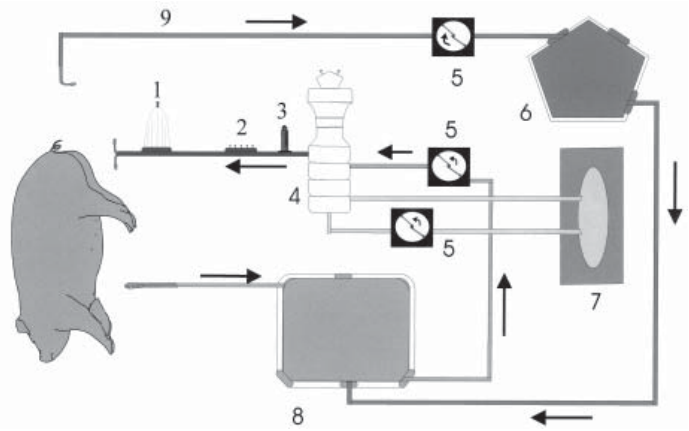

Figure 1. Diagram of general adult cardiopulmonary bypass circuit. The arterial line (in black) containing an arterial filter (1), sampling ports (2), and temperature probe (3) brings blood from the membrane oxygenator (4) to the animal. The venous line (in grey) brings blood back from the animal into the venous reservoir (8), from which the blood is pumped into the membrane oxygenator (4) by a pump head (5). A suction line (9) removes blood from the thorax and the blood is pumped via another pump head (5) into a cardiotomy reservoir (6) and into the venous reservoir (8), then back into the animal via the membrane oxygenator (4). A separate pump head (5) moves water from a heated water bath (7) to and from the membrane oxygenator (4). Arrows indicate direction of flow (■ arterial side, □ venous side, □ water, and ◘ suction/recirculation).

Table 1. Urine output during cardiopulmonary bypass (CPB)

Animal	Duration of CPB (h)	Body weight (kg)	Total urine output (ml)	Calculated urine output per hour (ml)	Estimated urine output per hour (ml)
1	10.25	94	800	78	20-118
2	22	81	425	19	17-101
3	12.5	86	1600	128	18-108
4	12	94	500	42	20-118

Total urine output, calculated urine output per hour, and estimated urine output per hour for adult animals (n = 4) while on CPB for variable duration (10 to 22 h). Data are expressed as mean ± SD.

were within normal physiologic parameters except for the pO_2, which were kept artificially high (pO_2, 567 ± 54 mmHg) to help transition of the animal onto CPB. The pre CPB pO_2 was significantly ($P < 0.05$) different from all the other CPB values. Heart rate (HR, 131 ± 14 beats per minute [bpm]), blood pressure (BP, 116 ± 14/75 ± 26 mmHg), mean arterial pressure (MAP, 90 ± 27 mmHg), HCT, 40 ± 5%, and acid-base status (pH 7.56 ± 0.16; pCO_2, 30 ± 10 mmHg; pO_2, 567 ± 54 mmHg; HCO_3^-, 26 ± 4 mmol/L, O_2 saturation [SAT], 99.9 ± 0%, and base excess [BE], 5.7 ± 6) values were taken prior to initiation of CPB.

Urine output during CPB. Table 1 shows the duration of CPB for four animals (column 2), their body weight (column 3), and the total urine output for each animal while on bypass (column 4). The total amount of urine was divided by the CPB time to calculated how much urine was produced per hour for each animal (column 5). The estimated hourly urine output for each animal (column 6) was calculated on the basis of the weight of each animal, using the formula:

0.21 – 1.25 ml/kg/h (2).

For each animal, actual urine volume produced per hour was within estimated urine output.

Hemodynamic parameters during CPB. Table 2 shows

Table 2. Hemodynamic parameters during CPB

Interval	HR (bpm)	MAP (mmHg)	Line pressure (mmHg)
Beginning	128 ± 14	65 ± 7	200 ± 67
Middle	134 ± 20	71 ± 16	193 ± 42
End	110 ± 30	67 ± 11	215 ± 21

Heart rate (HR), mean arterial pressure (MAP), and line pressures for animals (n = 5) while on CPB.
There were no significant differences between pre-CPB and the beginning, middle, or end of the CPB time intervals or among the CPB time intervals themselves.
bpm = beats per minute.
Data are expressed as mean ± SD.

the CPB hemodynamic parameters for HR, MAP, and line pressures at the beginning, middle, and end points of CPB. There was no significant difference in HR between the pre-CPB values and the CPB time points or between the CPB time points themselves. The MAPs of the pre-CPB values were not significantly different from those of the CPB time points. The CPB MAPs themselves were artificially maintained by use of the CPB pump, and the line pressures reflected values that would keep each animal at its appropriate MAP values.

Blood parameters during CPB. Table 3 shows the CPB blood parameters for the circuit at the beginning, middle, and end of the bypass period. Hematocrit was not significantly different from that of the pre-CPB or during the CPB period or within the CPB period itself. Activated clotting time was maintained > 1,000 sec. for each animal prior to initiation of CPB and throughout the entire CPB procedure.

There was no significant differences between any of the acid-base parameters from the pre-CPB period until the end of the CPB procedure except for pO_2 and O_2 SAT. The pre-CPB oxygen values were significantly ($P < 0.05$) different from the other CPB values, and O_2 SAT values were significantly different from the pre-CPB values at the middle point of CPB, with a trend toward significance at the end point of CPB.

Blood constituents during CPB. Table 4 shows the CPB blood concentrations of potassium, sodium, calcium, glucose, and lactate taken at the beginning, middle, and end of CPB. There was no significant differences between any of the CPB points for any of the constituents during CPB, and all were within physiologic ranges for adult pigs.

Discussion

Most CPB research studies normally use a time line that matches what is found in a clinical setting (two to three hours) and which can be extended to four hours with use of hypothermia (3-5). However, recent studies have indicated that use of CPB at various temperatures, which affects how long CPB can be maintained, may have a role in factors, such as blood transfusion requirements, heparin doses, and complement activation (6-8). It has been documented that duration on CPB and the temperatures maintained during the procedure may affect individual organs differently (9, 10). For example, increased time of CPB has been associated with an increase in cerebral microemboli (11). Other specific problems associated with CPB are caused by "post-perfusion syndrome," which is associated with pulmonary dysfunction, renal dysfunction, increased interstitial fluids, and/or hemolysis (12). These serious problems further complicate research efforts to understand the effects of time on CPB, and a model to study these issues would be extremely valuable.

Although swine are the ideal animal model to study cardiovascular issues in humans, it is well known that swine can be problematic when used for cardiovascular procedures and they can be especially technically challenging when used as a CPB model (1). Interestingly, our normothermic CPB adult model did not develop any of the aforementioned problems usually associated with animals being on extended CPB, which in our study, was from 10 to 22 h.

The amount of urine produced by each animal per hour was within the calculated range of normal estimated urine output. This would indicate that the kidneys were functioning appropriately and were not clinically stressed. If hemolysis had occurred, or proper perfusion pressures and oxygen delivery had not been maintained throughout entire the CPB procedure, organs such as the kidney would have shown signs of failure and urine output would have decreased significantly (13).

The HR of the animals at the beginning, middle, and end of CPB were slightly increased from normal values (2). However, they were well within the normal range seen in swine under pen-

Table 3. Blood parameters during CPB

Interval	HCT (%)	ACT (seconds)	pH	pCO_2 (mmHg)	pO_2 (mmHg)	HCO_3^- mmol/L	SAT (%)	BE
Beginning	38 ± 6	> 1,000	7.40 ± 0.16	40 ± 9	184 ± 153*	25 ± 7	97 ± 4	0.2 ± 9
Middle	32 ± 7	> 1,000	7.47 ± 0.05	36 ± 6	199 ± 92*	25 ± 3	99 ± 1	2.1 ± 2
End	30 ± 10	> 1,000	7.38 ± 0.13	35 ± 4	197 ± 82*	21 ± 7	99 ± 1	-3.2 ± 9

*Significantly different versus pre-CPB values ($P < 0.05$).
Values for hematocrit (HCT), activated clotting time (ACT), and blood gas and acid base status for animals (n = 5) while on CPB bypass.
There were no other significant differences between the beginning, middle and end time intervals of CPB.
Data are expressed as mean ± SD.

Table 4. Blood constituents during CPB

Interval	Potassium (mmol/L)	Sodium) (mmol/L)	Calcium (mmol/L)	Glucose (mmol/L)	Lactate (mmol/L)
Pre-CPB	4.3 ± 1.7	142.0 ± 5.3	2.5 ± 0.2	6.3 ± 0.3	4.5 ± 1.6
Beginning	5.3 ± 2.0	148.9 ± 10.4	1.9 ± 1.1	5.9 ± 0.6	7.1 ± 4.6
Middle	5.8 ± 1.5	145.0 ± 2.6	2.5 ± 0.2	3.9 ± 0.9	8.3 ± 4.1
End	5.4 ± 1.4	147.0 ± 7.2	2.0 ± 0.5	4.5 ± 2.1	6.6 ± 5.9

Blood constituents are the electrolyte, glucose, and lactate concentrations for the animals (n = 3) while on CPB.
There were no significant differences between the pre-CPB and the beginning, middle, or end of the CPB time intervals or among the CPB time intervals themselves. Data are expressed as mean ± SD.

tobarbital anesthesia, where it is more difficult to maintain a sufficiently deep stage of anesthesia to abolish all reflexes, including increase in HR, without putting the animal at risk (14). Once CPB was initiated, the proper plane of anesthesia and stabilization of the animal were made easier and, generally, the hemodynamic parameters were within acceptable ranges. The MAPs and line pressures were kept at the necessary values to maintain proper perfusion for each animal's requirements and were not significantly different from the beginning to the end of CPB.

With the exception of ACT and pO_2, the blood parameters of the animals throughout the CPB procedure remained within normal values and were not significantly different from each other from beginning to end of CPB. The ACT was high in response to heparin administration and was kept so throughout CPB. The pO_2 also was kept artificially high throughout CPB, which may explain why our long-term model was successful in swine. In 1999, Parolari and co-workers (15) reported that, in 101 patients undergoing hypothermic CPB, there was a direct linear relationship between oxygen consumption and oxygen delivery during the various phases of bypass (cooling, hypothermia, re-warming). They speculated that an increase in oxygen metabolism resulted in a chronic underperfusion of body capillary beds. This capillary hypoperfusion might not allow complete tissue perfusion with the current perfusion protocols used during CPB, and that this was especially true while patients were being rewarmed and weaned off of CPB. In patients on ventilators, a condition known as pathologic oxygen supply dependency results in diminished ability to either extract oxygen in tissue or an increased tissue oxygen demand, or both (15). With initiation of normothermic CPB, there may be a phenomenon of lowered blood flow resulting in venous desaturation differences to certain organs such as the brain (16). In our CPB model that was normothermic throughout the entire bypass procedure (which could lead to higher demand of oxygen) the increased oxygen values, prior to and during would keep the animals from experiencing any oxygen deficiencies that may be initiated by placing the animals on CPB.

Other problems commonly associated with CPB in patients and swine are hemolysis and accumulation of interstitial fluids (12). Hematocrit was maintained in each animal from the beginning to end of the CPB procedure despite the long duration of CPB. The increase in interstitial fluid accumulation was not significant at these hematocrit values, and this was confirmed by the water content of the right ventricle from three representative animals (77 ± 5%). These numbers are within literature values for animals of this age (78 ± 1%) range (17). Priming the CPB circuit with a combination of more adult blood than crystalloid solution possibly prevented the tissue edema often seen in such procedures (1). Blood samples taken throughout the CPB procedure remained clear and free of hemolysis as well.

The electrolyte values from pre-CBP, beginning, middle, and end of the procedure (Table 4) were not different from each other throughout the procedure. All of these values were within accepted literature values and confirm the absence of cellular disruption usually caused by the action of the pump heads (2). Table 4 also shows plasma glucose and lactate values for the same time intervals. These values are within normal ranges, and are not significantly different from each other, with the singular exception that one animal had a sudden increase in glucose concentration on initiation of CPB, but normal glucose values returned by the middle of the procedure (18).

This model of CPB may also allow further studies exploring a number of ongoing controversies, including which temperature is best for the patient during CPB. With the advent of normothermic CPB, many institutions have had better post-CPB results, but this may in part be due to improved technology, allowing better blood flow to organs or lessened damage to blood cells (19). However it also has been reported that the benefits of hypothermia may not become apparent unless longer periods of ischemia are imposed (four to six hours) (5).

In conclusion, this CPB model clearly documents the successful use of swine weighing > 80 kg undergoing a long and complicated procedure, which previously was not thought possible. Modifications to the procedure, including a higher blood-to-crystalloid ratio in the priming solution, slightly higher oxygen concentration in the circuit, and maintaining acid base status, seemed to contribute to the success of this model. Therefore, this CPB model, which exceeds the time normally seen in a research or clinical settings and remains stable throughout the procedure, could be used to explore new research procedures and allow optimal benefit from a wider range of CPB procedures.

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