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Acute hemodynamic, respiratory and metabolic alterations after blood contact with a volume priming and extracorporeal life support circuit: an experimental study

Alterações hemodinâmicas respiratórias e metabólicas agudas após o contato do sangue com o circuito extracorpóreo da ECMO: estudo experimental

ABSTRACT

Objective: To investigate the hemodynamic, respiratory and metabolic impact of blood contact with a priming volume and extracorporeal membrane oxygenation circuit, before the initiation of oxygenation and ventilation

Methods: Five animals were instrumented and submitted to extracorporeal membrane oxygenation. Data were collected at the baseline and 30 minutes after starting extracorporeal circulation, without membrane ventilatory (sweeper) flow.

Results: After starting extracorporeal membrane oxygenation, there was a non-significant elevation in pulmonary vascular resistance from 235 (178,303) to 379 (353,508) dyn.seg.$(cm^5)^{-1}$ (P=0.065), associated with an elevation in the alveolar arterial oxygen gradient from 235 (178,303) to 379 (353,508) mmHg (P=0.063). We also observed a reduction in the left ventricle stroke work from 102 (94,105) to 78 (71,87) (mL.mmHg)/beat (P=0.064), in addition to a reduction in cardiac output from 7.2 (6.8,7.6) to 5.9 (5.8,6.3) L/min (P=0.188). The right ventricle stroke work was counterbalanced between the pulmonary vascular resistance increment and the cardiac output reduction, maintaining a similar value.

Conclusions: We presented an experimental model that is feasible and safe. Blood contact with the priming volume and extracorporeal membrane oxygenation circuit resulted in non-significant systemic or metabolic changes.

Keywords: Acute respiratory distress syndrome; Respiration, artificial; Extracorporeal membrane oxygenation; Multiple organ failure; Swine

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) has been used to support patients with severe respiratory and/or cardiovascular failure.[1] Despite increasing clinical experience and success,[2-5] there are currently few reports in the literature about the physiology and about acute patients' experienced with ECMO use.[6]

In animal studies, the use of polypropylene ECMO is associated with an acute elevation of plasmatic interleukins and with intestinal and pulmonary edema.[7] Accordingly, gut barrier dysfunction associated with polypropylene ECMO use can be an important contributor to ECMO-related systemic inflammation.[8] In human beings, respiratory support using polymethylpentene ECMO membranes is also associated with early, new, radiographic pulmonary infiltrates, a phenomenon known as white-out.[9] The development of bioactive and biopassive coated extracorporeal

This study was conducted at the Instituto de Ensino e Educação do Hospital Sírio Libanês - São Paulo (SP), Brazil.

Conflicts of interest: The authors received a donation of PLS systems from Maquet Cardiopulmonary from Brazil, to conduct an experimental research study and for patient support.

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circuits reduced inflammatory and pro-coagulant pathway activation in a simulated model.[10]

Routine priming using calcium salts can prevent severe hypocalcemia in neonates;[11] however, the effects of priming with normal saline have not been characterized. Thus, the aim of this study was to describe the acute hemodynamic, respiratory and metabolic effects of blood-extracorporeal circuit contact and priming with normal saline in an animal model.

METHODS

This study received approval from the Institutional Animal Research Ethics Committee and was performed according to National Institutes of Health guidelines for the use of experimental animals. The instrumentation and surgical preparation were performed as previously described.[12-14]

Instrumentation and surgical preparation

The room temperature was set at 24ºC. Five domestic female Agroceres pigs (80±3 kg) were anesthetized with thionembutal (10 mg/kg, Tiopental, Abbott, Brazil) and pancuronium bromide (0.1 mg/kg, Pavulon, AKZO Nobel, Brazil) and were connected to a mechanical ventilator (Evita XL Dräger, Dräger, Luebeck, Germany) with the following parameters: tidal volume 8 mL/kg; end-expiratory pressure 5 cm H_2O; FIO_2 initially set at 100% and subsequently adjusted to maintain arterial saturation between 94% and 96%; and respiratory rate titrated to maintain $PaCO_2$ between 35 and 45 mm Hg or end-tidal CO_2 (NICO, Dixtal Biomedica Ind. Com, Sao Paulo, Brazil) between 30 and 40 mm Hg. The electrocardiogram, heart rate, oxygen saturation, and pressures of the animals were monitored with a multiparametric monitor (Infinity Delta XL, Dräger, Luebeck, Germany). Anesthesia was maintained during the study with midazolam (1- 5 $mg.kg^{-1}.h^{-1}$) and fentanyl (5-10 $mcg.kg^{-1}.h^{-1}$, Fentanyl; Janssen-Cilag, Brazil), and muscular relaxation was maintained with pancuronium bromide (0.2 $mg.kg^{-1}.h^{-1}$). The adequate depth of anesthesia during the surgical period was evaluated with the maintenance of physiological variables (heart rate and arterial pressure) and the absence of reflexes (corneal and hind limb flexion response), as well as unresponsiveness to stimuli during manipulation. Supplementary boluses of 3 - 5 mcg/kg fentanyl and 0.1 – 0.5 mg/kg midazolam were administered as necessary.

The left external jugular vein was cannulated (guided by ultrasonography) to introduce a pulmonary artery catheter, and the right external jugular vein was cannulated to introduce a 25-cm ECMO devolution cannula (Edwards Lifesciences, Irvine, CA, USA). The right femoral vein was punctured for the insertion of a 55-cm ECMO drainage cannula (Edwards Lifesciences, Irvine, CA, USA), which was positioned close to the right atrium with the aid of trans-hepatic ultrasonographic visualization. Only the guidewires were kept in place after the first baseline measurements during the stabilization period; the guidewires were then replaced by the cannulas. After the insertion of the guidewires, an infusion of 1000 IU per hour of heparin was started. A central venous catheter and an invasive arterial blood pressure catheter were placed in the left femoral vein and artery, respectively.

Through a midline laparotomy, a cistostomy was performed, and a bladder catheter was inserted. During the surgical interventions, 15 $mL.kg^{-1}.h^{-1}$ of lactated Ringer's was continuously infused, and boluses of 250 mL were administered to maintain a systemic mean arterial blood pressure (ABPm) of 65 mm Hg or greater, a central venous pressure (CVP) of 8 mm Hg or greater, and SvO_2 greater than 65% until the end of instrumentation.

Stabilization and support of the animals

After the end of the instrumentation, the animals were allowed to stabilize for 1 h. At the beginning of the stabilization period, a continuous infusion of 3 $mL.kg^{-1}.h^{-1}$ of lactated Ringer's was started and maintained throughout the entire experiment.

When the animals became hypotensive (ABPm<65 mm Hg), a bolus of 500 mL of lactated Ringer's was infused. If the ABPm failed to rise above 65 mmHg after the bolus, an infusion of norepinephrine 0.1 $mcg.kg^{-1}.min^{-1}$ (Norepine, Opem Pharmaceuticals, São Paulo, Brazil) was started and titrated to an ABPm≥65 and <80 mmHg.

ECMO priming, starting, and maintenance

The ECMO system (Permanent life support system - PLS, Jostra – Quadrox D, Maquet Cardiopulmonary, Hirrlingen, Germany) was primed with a 37ºC normal saline solution and connected to a centrifugal pump (Rotaflow, Jostra, Maquet Cardiopulmonary, Hirrlingen, Germany). With the circuit filled, 1000 IU of heparin were injected in the circulating fluid.

The PLS uses a polymethylpentene membrane; the tubes are coated with a bioactive and biopassive system (Bioline, Maquet Cardiopulmonary, Hirrlingen, Germany).[10] Two Luer locks were connected, respectively, to the pre- and post-membrane ports,

to allow for the measurement of pressures and for the collection of blood samples. Pressure lines were connected to the ports in the drainage tube (before the centrifugal pump), before and after the ECMO membrane; pressure measurements were performed in real time with a multiparametric monitor (Dx 2020, Dixtal Biomedical Ind. Com, Sao Paulo, Brazil).

After the baseline measurements, the extracorporeal circulation was initiated with blood flow of 1.5 L/minute and with the gas (sweeper) flow turned off. After a stabilization period of 30 min, a second baseline was measured with blood, but no gas flow, through the membrane, i.e., without gas exchange, with the aim of assessing the isolated effects of blood contact with the ECMO circuit.

Study procedures

The following data were collected: heart rate (HR); mean arterial blood pressure (ABPm); central venous pressure (CVP); mean pulmonary artery pressure (PAPm); pulmonary artery occluded pressure (PAOP); cardiac output (CO); core temperature; peripheral oxygen saturation; end-tidal CO_2 ($EtCO_2$) and mixed venous oxygen saturation (SvO_2); PEEP; FiO_2; auto-PEEP measured with 4 seconds of expiratory pause; plateau pressure with 2 seconds of static inspiratory pause; and peak pressure. Blood samples from the pulmonary and femoral arteries were collected and analyzed in a standard ABL 600 radiometer (Radiometer, Copenhagen, Denmark). The samples from the femoral artery were used for the biochemical analysis.

Calculations

The calculations were performed using standard formulas as follows.[13-16] Static respiratory compliance (mL/mmHg): *Cst = tidal volume/(plateau pressure – PEEP); d*ynamic respiratory compliance (mL/mmHg):*Cdyn = tidal volume/(peak pressure – PEEP); a*irway resistance (mmHg.L-1.s-1): *Cst = (peak pressure – plateau pressure)/ inspiratory airway flow; a*lveolar arterial oxygen gradient (mmHg): $D\ (A-a)\ O_2 = [FiO_2 \bullet 643 - (PaCO_2 / 0.8) - PaO_2]$; *s*ystemic vascular resistance (dyn.seg.cm-5): SVR = *(ABPm – CVP) • 80/ cardiac output; p*ulmonary vascular resistance (dyn.seg.cm-5): PVR = *(PAPm – PAOP) • 80/ cardiac output;* right ventricle stroke work (mL.mmHg/beat): *RVSW = (PAPm – PAOP) • stroke volume 0.136; l*eft ventricle stroke work (mL.mmHg/beat): *LVSW = (ABPm – CVP) • stroke volume 0.136; s*tandard base excess (mEq/L): $SBE = 0.9287 \bullet (HCO3^- - 24.4 + 14.83 \bullet (pH - 7.4))$.

Statistical analysis

The data were predominantly non-parametrical as assessed using a Shapiro-Wilk goodness-of-fit model. Consequently, the data are shown as medians and 25th and 75th percentiles. Paired data were analyzed with Wilcoxon's test. The R free source statistical package and comprehensive-R archive network (CRAN)-specific libraries were used to build the graphics and to perform all of the statistical analyses.[17]

RESULTS

Table 1 and figure 1 show the hemodynamic, respiratory and metabolic consequences of priming and blood-ECMO membrane contact. Despite the absence of statistical significance, it is interesting to note the elevation of mean pulmonary artery blood pressure, resulting in higher pulmonary vascular resistance, in addition to lower cardiac output and a reduced left ventricle stroke work index. It is also interesting to note

Table 1 - Hemodynamic, respiratory and metabolic data of animals' before and thirty minutes after ECMO, beginning without sweeper flow

	Pre-ECMO	Post-ECMO	Difference#	p value*
Hemodynamic				
Heart rate (beats / minute)	133 (110,135)	130 (129,135)	2 (-6,14)	0.625
ABPm (mmHg)	145 (132,153)	140 (123,146)	-9 (-15,-5)	0.136
CVP (mmHg)	7 (4,9)	7 (5,8)	0 (0,1)	0.774
PAOP (mmHg)	10 (9,16)	13 (10,13)	2 (1,3)	0.438
RVSW ((mL.mmHg) / beat)	22 (20,24)	27 (19,29)	9.1 (-4.9,9.8)	0.816
SVR (dyn.seg.$(cm^5)^{-1}$)	1505 (1344,1754)	1765 (1310,1871)	369 (-150,473)	0.313
Respiratory				
PaO_2 (mmHg)	99 (92,103)	82 (64,94)	-11 (-18,0)	0.201
Sat O_2 (%)	97 (95,97)	94 (88,96)	-3 (-6,-0)	0.188
$PaCO_2$ (mmHg)	38 (37,39)	39 (32,40)	-0.5 (-1.2,0.7)	0.814
FiO_2	0.3 (0.3,0.3)	0.3 (0.3,0.4)	0.0 (0.0,0.1)	0.371
Resp. rate (breaths/min)	18 (14,30)	20 (18,30)	0 (0,0)	1.000
$D(A\text{-}a)O_2$ (mmHg)	235 (178,303)	379 (353,508)	201(37,205)	0.063
P/F ratio	340 (331,368)	286 (204,370)	-54 (-127,0)	0.201
P_{peak} (cm H_2O)	30 (28,30)	31(28,39)	1 (0,8)	0.269
$P_{plateau}$ (cm H_2O)	22 (18,24)	22 (17,30)	-1 (-2,0)	0.584
PEEP (cm H_2O)	5 (5,5)	5 (5,5)	0 (0,0)	1.000
R_{aw} (mmHg/L/seg)	17 (13,19)	12 (12,17)	-1 (-2,0)	0.584
C_{st} (mL/ m Hg)	38 (33,49)	33 (15,43)	-4 (-8,9)	0.715
C_{dyn} (mL/mm Hg)	26 (24,26)	22 (18,26)	-1 (-6,0)	0.361

Continues...

Table 1 - Continuation

	Pre-ECMO	Post-ECMO	Difference#	p value*
Metabolic				
Core temperature (ºC)	38.2 (37.8,38.7)	37.5 (37.2,38.1)	-0.6 (-0.6,-0.2)	0.058
pH	7.49 (7.47,7.52)	7.48 (7.45,7.54)	-0.014 (-0.038,-0.014)	0.588
SBE (mEq/L)	4.1 (3.8,5.8)	3.2 (3.2,5.7)	-1.9 (-2.1,-0.6)	0.188
Lactate (mEq/L)	1.8 (1.0,1.9)	1.6 (1.3,2.1)	-0.2 (-0.7,0.4)	0.814
Na (mEq/L)	138 (138,140)	139 (138,141)	1 (-1,1)	0.766
K (mEq/L)	3.6 (3.5,3.6)	3.6 (3.6,3.6)	0 (-0.1,0.0)	1.000
Ca (mEq/L)	1.34 (1.32,1.36)	1.34 (1.30,1.39)	0.03 (-0.02,0.03)	0.787
Cl (mEq/L)	102 (101,104)	104 (103,105)	2 (1,2)	0.057
Hemoglobin (g/dL)	11.8 (11.3,13.2)	11.2 (10.7,12.0)	-0.9 (-1.1,-0.1)	0.188
Glucose (mg/dL)	121 (111,129)	119 (105,133)	-6 (-12,-2)	0.187

ECMO - extracorporeal membrane oxygenation; ABPm - mean arterial blood pressure; CVP - central venous pressure; PAOP - pulmonary artery oxygen in arterial blood; RVSW - right ventricle stroke work; SVR - systemic vascular resistance; PaO_2 - partial pressure of carbon dioxide; $SatO_2$ - oxygen arterial saturation; $PaCO_2$ - partial pressure of carbon dioxide in arterial blood; FiO_2 - fraction of inspired oxygen ; Resp. rate - respiratory rate; $D(A\text{-}a)O_2$ – alveolar arterial oxygen. P/F ratio - ratio of arterial oxygen concentration; P_{peak} - peak pressure; $P_{plateau}$ - plateau pressure; PEEP - positive end expiratory pressure; R_{aw} - airway resistance; C_{st} - respiratory static compliance; C_{dyn} - respiratory dynamic compliance; SBE - standard base excess. # Difference = Post-ECMO - Pre-ECMO. * p value of the comparison before and after ECMO.

the trend toward elevation of the alveolo-arterial oxygen gradient. There were trends toward the reduction of the core temperature and chloride elevation.

DISCUSSION

In this study, there were no significant differences in the measured respiratory, hemodynamic and metabolic variables before or after blood contact with an ECMO circuit and fluid priming.

The core temperature decrease and chloride elevation could be explained by the system's normal saline priming, not necessarily reflecting the contact of blood with the ECMO circuit. We cannot exclude the possibility of chloride elevation due to systemic inflammation, as described with endotoxemia.[18] One could expect more metabolic alterations due to the sudden increase in intravascular distribution volume; however, in this model using large animals, those

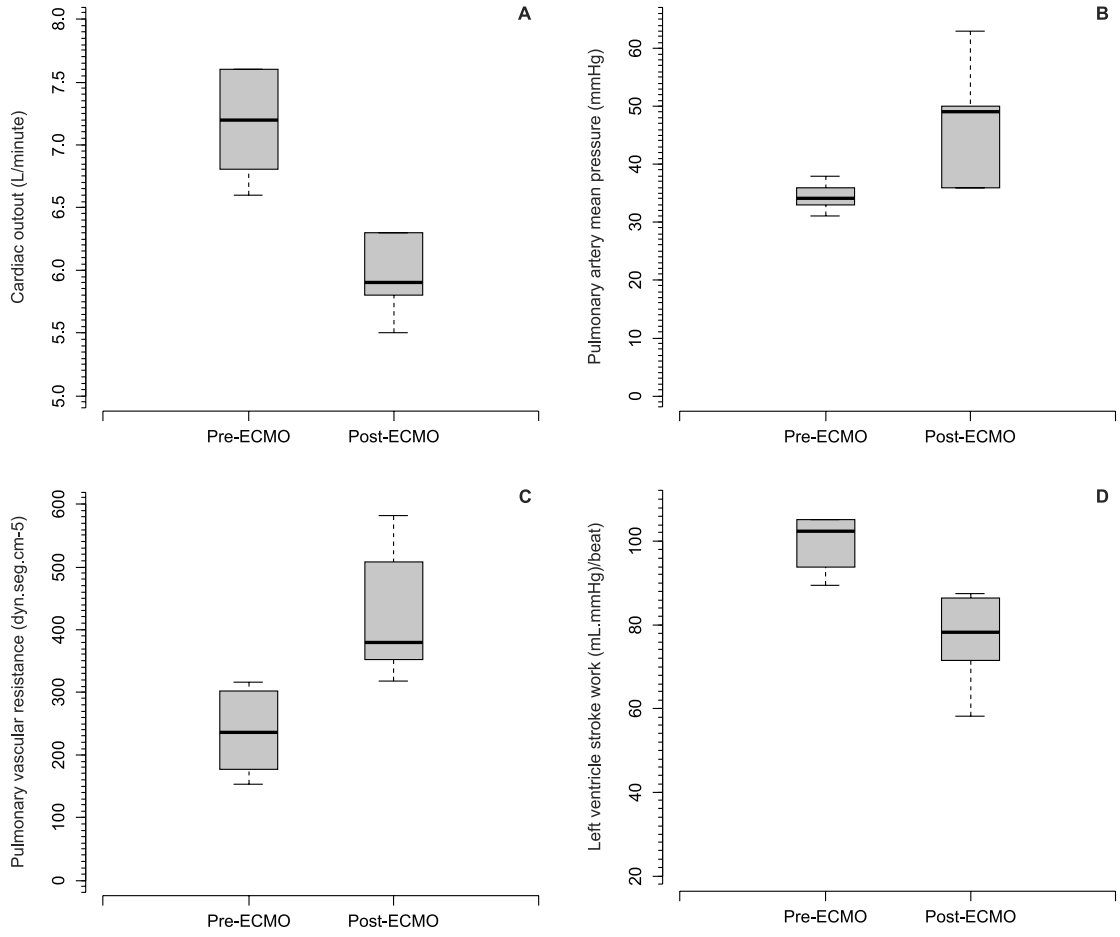

Figure 1 - Hemodynamic variables before and after extracorporeal circulation without sweeper flow initiation. Panel A shows the cardiac output (P=0.188), Panel B shows the pulmonary artery pressure (P=0.279), Panel C shows the pulmonary vascular resistance (P=0.065), and Panel D shows the left ventricle stroke work (P=0.064). ECMO - extracorporeal membrane oxygenation. The Wilcoxon's U test was used for the pre-post comparisons.

expected alterations did not occur.

The remaining alterations were likely related directly or indirectly to blood contact with the membrane. The increase in the alveolar-arterial oxygen gradient and the increase in the pulmonary vascular resistance were in line with the pulmonary injury and systemic inflammation in animals supported by a polypropylene-based ECMO device,[7] added to the pulmonary white-out of patients supported by polymethylpentene-based ECMO systems.[9] The increase in the pulmonary vascular resistance could *per se* explain the reductions in cardiac output and in left ventricle stroke work. The right ventricle stroke work did not increase, most likely due to the counterbalance between the higher pulmonary arterial pressure and the reduced cardiac output. Although more biocompatible than polypropylene-based membranes, contact of the blood with polymethylpentene-based ECMO circuits still induces changes noticeable at the bedside with potential clinical importance.[9] In other words, the contact of blood with the priming volume and the ECMO circuit could be responsible for left ventricle dysfunction, likely via an inflammatory pathway,[19] causing pulmonary hypertension and the elevation of the alveolar-arterial gradient of oxygen. Another point to consider is the temperature decrease, which could be at least partially responsible for the alterations measured.

Weighting our findings, the non-significant alterations in respiratory physiology and hemodynamics, the advantage of using protective or ultra-protective mechanical ventilation will likely be greater than the lung injury in this

The strength of this study is its first characterization of immediate systemic alterations due to blood contact with the priming volume and the circuit in the ECMO at the beginning, without the influence of oxygenation. However, the study has several limitations: 1) the small number of animals rendered the power of the study poor and was likely responsible for the non-significant findings; and 2) the absence of measurements of inflammatory markers precluded an adequate conclusion correlating the study findings with a systemic inflammatory process.

CONCLUSIONS

In this study, the safety and feasibility of the model were demonstrated. Given the low number of animals studied, blood contact with the priming volume and ECMO circuit resulted in non-significant systemic and metabolic alterations.

RESUMO

Objetivo: Investigar o impacto hemodinâmico, respiratório e metabólico do contato do sangue suíno com o volume do *primming* e com o circuito extracorpóreo da oxigenação por membrana extracorpórea, antes do início da ventilação e da oxigenação da membrana.

Métodos: Cinco animais foram instrumentados e submetidos a oxigenação por membrana extracorpórea. Os dados foram coletados no basal e 30 minutos depois do início da circulação extracorpórea, ainda sem o fluxo de ventilação da membrana.

Resultados: Depois do início da circulação pela membrana, houve elevação não significativa da resistência vascular pulmonar de 235 (178,303) para 379 (353,508) dyn.seg.$(cm^5)^{-1}$ (p=0,065), associada a uma elevação no gradiente alveolo arterial de oxigênio de 235 (178,303) para 379 (353,508) mmHg (p=0,063). Foi observada também uma queda no trabalho sistólico do ventrículo esquerdo de 102 (94,105) para 78 (71,87) (mL.mmHg)/batimento (p=0,064), em paralelo a uma redução do débito cardíaco de 7,2 (6,8-7,6) para 5,9 (5,8-6,3) L/min (p=0,188). O trabalho sistólico do ventrículo direito foi contrabalanceado entre o aumento da resistência vascular pulmonar e a queda do débito cardíaco, mantendo-se estável.

Conclusões: O modelo é seguro e factível. O contato do sangue dos animais com o *primming* e o circuito extracorpóreo resultou em alterações sistêmicas e metabólicas não significativas.

Descritores: Síndrome do desconforto respiratório do adulto; Respiração artificial; Oxigenação por membrana extracorpórea; Insuficiência de múltiplos órgãos; Suínos

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