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Near-fatal pulmonary embolism in an experimental model: hemodynamic, gasometric and capnographic variables

Embolia pulmonar quase fatal, um modelo experimental: variáveis hemodinâmicas, gasométricas e capnográficas

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Abstract

Introduction: **Experimental studies on pulmonary embolism (PE) are usually performed under mechanical ventilation. Most patients with suspicion of PE enter the Emergency Services in spontaneous breathing and environmental air. Thus, under these conditions, measurements of hemodynamic, gasometric and capnographic variables contribute largely to a more specific comprehension of cardiopulmonary and gasometric alterations in the acute phase of the disease. Studies which evaluated animals under conditions are lacking.**

Objective: **This study aimed to submit animals under spontaneous ventilation and without supplemental oxygen to PE.**

Methods: **PE was induced in six pigs using autologous blood clots, and cardiorespiratory and gasometric records were performed before and after PE. The values of "near fatal" mean pulmonary arterial pressure (MPAP) were previously determined.**

Results: **The presence of obstructive shock could be evidenced by increased MPAP (from 17.8±3.5 to 41.7±3.3 mmHg) (*P*<0.0001) and decreased cardiac output (from 4.9±1.0 to 2.7±1.0 L/min) (*P*<0.003). Consequently, metabolic acidosis occurred (Lac art) (from 2.4±0.6 to 5.7±1.8 mmol/L) (*P*<0.0001). It was observed hypoxemia (from 73.5±12.7 to 40.3±4.6 mmHg) (*P*<0.0001); however, $PaCO_2$ did not vary (from 44.9±4.4 to 48.2±6.0 mmHg) (NS). There were significant increases in both $P(a\text{-}et)CO_2$ (from 4.8±2.8 to 37.2±5.8 mmHg) and $P(A\text{-}a)O_2$ (from 8.2±8.9 to 37.2±10.3 mmHg) (both *P*<0.0001). There was also a significant increase in the total alveolar minute volume (from 4.0±0.9 to 10.6±2.9 L/min) (*P*<0.0001).**

Conclusion: **In this model, the near fatal MPAP was from 2 to 2.5 times the basal MPAP; and the capnographic variables, associated with arterial and venous gasometry, showed effective in discriminating an acute obstructive profile.**

Descriptors: **Pulmonary embolism. Hypertension, pulmonary. Capnography. Models, animal. Swine.**

Resumo

Introdução: **Estudos experimentais de embolia pulmonar (EP) são habitualmente realizados sob ventilação mecânica. A maioria dos pacientes com suspeita de EP adentra os Serviços de Emergência em respiração espontânea e em ar ambiente. Assim, medidas das variáveis hemodinâmicas, gasométricas e capnográficas, nessas condições, em muito**

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contribuiriam para compreensão mais específica das alterações cardiopulmonares e gasométricas na fase aguda da doença. Dessa forma, faltam estudos experimentais que avaliem animais em tais condições.

Objetivo: **O objetivo do presente estudo foi submeter à EP animais sob ventilação espontânea e sem oxigênio suplementar.**

Métodos: **A EP por coágulos autólogos foi induzida em seis porcos e os registros cardiorrespiratórios e gasométricos foram realizados no pré e pós-EP. O valor da pressão média de artéria pulmonar (PMAP) "quase fatal" foi previamente determinada.**

Resultados: **A presença de choque obstrutivo agudo pôde ser evidenciada pelo aumento da PMAP (de 17.8±3.5 para 41.7±3.3 mmHg) (*P*<0.0001) e pela queda do débito cardíaco (de 4.9±1.0 para 2.7±1.0 L/min) (P<0.003). Consequentemente, a presença de acidose metabólica pode ser constatada (de 2.4±0.6 para 5.7±1.8 mmol/L) (*P*<0.0001). Observou-se, ainda, hipoxemia (de 73.5±12.7 para 40.3±4.6 mmHg) (*P*<0.0001), porém, a $PaCO_2$ não variou (de 44.9±4.4 para 48.2±6.0 mmHg) (NS). Houve expressivos aumentos, tanto para $P(a\text{-}et)CO_2$ (de 4.8±2.8 para 37.2±5.8 mmHg) quanto para a $P(A\text{-}a)O_2$ (de 8.2±8.9 para 37.2±10.3 mmHg) (*P*<0.0001). Ocorreu, também, significativo aumento do volume minuto alveolar total (de 4.0±0.9 para 10.6±2.9 L/min) (*P*<0.0001).**

Conclusão: **Nesse modelo, a PMAP quase fatal foi de 2 a 2,5 vezes a PMAP basal e as variáveis capnográficas, associadas a gasometria arterial e venosa, mostraram-se eficazes em discriminar um quadro obstrutivo agudo.**

Descritores: **Embolia pulmonar. Hipertensão pulmonar. Capnografia. Modelos animais. Suínos.**

INTRODUCTION

Cardiopulmonary and gasometric alterations originated from massive pulmonary embolism (PE) in experimental models that use autologous clots are not totally clarified due to scarcity of some data and models.

It is known that the factors that precede PE in humans, i.e. the formation of venous thromboembolism, favor venous thrombogenesis (Virchow's Triad), venous flow stasis, endothelial lesion or inflammation and hypercoagulable states [1]. The impact of embolus on pulmonary artery will lead to hemodynamic, gasometric and respiratory repercussions. Hemodynamicaly, we can observe increased right chamber pressure [2]; while from the respiratory point of view, the presence of emboli within the pulmonary arteries will promote an increase in the alveolar dead space [3,4] – which is defined by preserved ventilation areas and partial or total reduction in pulmonary blood flow, depending on the degree of vascular obstruction. Other alterations may still be verified, such as the incoordinations alveolar ventilation/pulmonary perfusion (V_A/Q) and vessel constriction/reflex bronchoconstriction. From a ventilatory point of view, the blood flow deviation for nonembolized but bronchoconstrictor areas may generate a "shunt effect". Alveolar volume losses may lead to lung volume reduction and consequent elevation of hemidiaphragm and atelectasis [5].

These alterations (V_A/Q) have direct implication for pulmonary gas exchange, which immediately reflect on arterial gasometry. A classic finding is the presence of arterial hypoxemia is observed [6], there is also an increase in the alveolar-arterial oxygen gradient [$P(A\text{-}a)O_2$] [7], and there is a drop in end-expiratory pressure of carbon dioxide ($PetCO_2$) when using volumetric capnography [8]. These alterations will be larger or smaller, depending on the extent of the abnormalities caused by PE.

PE should be considered a disease of extreme severity, especially if it is not treated within the first hours after the initial event [9]. Given the real difficulty in performing immediate comprobatory diagnostic exams, capnography may be an auxiliary exam of great value [4,8,10-12]. When associated with arterial gasometry, more specifically with partial pressure of CO_2 in arterial blood ($PaCO_2$), among other variables, it allows calculating the alveolar dead space fraction [4,8,10-12]. Although it is a simple examination, capnography is not less important than others. It consists of a continuous record of $PetCO_2$ each respiratory cycle, in addition to being a noninvasive study of low cost and of easy performance.

Since most patients with diagnostic suspicion of PE use hospital emergency services in spontaneous breathing and environmental air [10], bibliographic data, especially experimental ones, which could provide values of hemodynamic, gasometric and capnographic variables under these conditions (spontaneous breathing and environmental air), contributed greatly to a more specific and detailed comprehension of cardiopulmonary and gasometric alterations in the acute phase of the disease, leading to possible interventions.

After a bibliographic research by indexed sources (Medline, Embase), it was found that experimental studies evaluating animals under spontaneous breathing and environmental air are lacking.

Thus, the objective of this study was to submit midsize pigs breathing spontaneously and without supplemental oxygen supply to PE by using autologous clots, aiming to verify the value of "near fatal" mean pulmonary arterial

pressure (MPAP), i.e. the MPAP value to be acutely elevated without causing death; at that time, hemodynamic, gasometric and capnographic data of animals were recorded.

METHODS

This study was approved by the Animal Use Ethics Committee (CEUA) of University of Campinas (UNICAMP).

Six Large-White pigs weighting 24.0±0.6 kg received 11mg/kg of ketamine (Ketalar, Parke-Davis & Co., Guarulhos, SP, Brazil) and 0.5 mg of atropine (Ariston, SP, Brazil) intramuscularly. Afterwards, they were intubated with orotracheal tube and sedated using 0.5% halothane (Zeneca Farmacêutica do Brasil Ltda., Cotia, SP, Brazil) under environmental air and spontaneous breathing.

A pediatric Swan-Ganz catheter n.5F was introduced by the right femoral vein. Another catheter – of polyethylene, n.6F – was introduced by the right femoral vein and its extremity was guided up to the abdominal aorta, while the other catheter (n.8F) was introduced by the right jugular vein and located in the superior vena cava.

The femoral and Swan-Ganz catheters were connected to Medex electro-manometers (Hilliard, Ohio, USA). The cardiac output (CO) and the arterial pressure were obtained by using a cardiac monitor (BESE, Belo Horizonte, Brazil). All pressure measurements were performed with the animal set on drip, in the supine position, having zero reference point to the animal's mid-thoracic line.

After discarding the fluid occupying the catheter dead space, the mixed venous blood and arterial blood were collected into heparinized syringes for gasometry, hemoxymetry and determination of arterial lactate. The arterial lactate was measured using the equipment Accusport® (Boehringer Mannheim, Asta Médica, São Paulo, SP, Brazil).

The assessment of respiratory mechanics and capnography was performed by the monitor of respiratory profile (DX-8100 CO_2SMO® PLUS Dixtal/Novametrix) attached to the computer, where data were stored on the software Analysis Plus®, which allows the calculation of respiratory physiological variables and respiratory mechanics online and offline. From the records of flow signals and capnography, data of the last 40-45 respiratory cycles that preceded blood collection and hemodynamic records were late compiled in an offline sequence, in spreadsheet.

The determination of arterial-alveolar gradient of carbon dioxide was performed according to the following equation: $P(a\text{-}et)CO_2$ [13]; while the calculation of alveolar dead space fraction was made according to the equation: $AVDSf = P(a\text{-}et)CO_2 / PaCO_2$ [11], where: $PaCO_2$ is the partial pressure of carbon dioxide in arterial blood, and $PetCO_2$ is the final pressure of carbon dioxide in the exhaled air.

The calculation of alveolar-arterial oxygen difference [$P(A\text{-}a)O_2$] was performed using the classic equation:

$P_AO_2 = [(BP – PH_2O) \times FiO_2] – (PaCO_2/0.8)$, where:

BP: barometric pressure (703±3 mmHg – values recorded by capnograph);

PH_2O: vapor pressure of water (47 mmHg);

FiO_2: the oxygen fraction in inspired air (21%);

$PaCO_2$: the partial pressure of carbon dioxide in arterial blood;

R: respiratory coefficient (0.8);

$P(A\text{-}a)O_2$ normal < 10mmHg [7].

The clots were previously prepared removing 200 ml of blood. The amount of 100 UI of lyophilized bovine thrombin diluted in 2ml of distilled water was added to blood placed in sterile kidney cuba. After a 45 minutes period of stagnant blood, the clot was fragmented in a manual processor to obtain a uniform set of thrombi with approximately 3.0 mm in diameter. These thrombi were filtered and suspended in physiological serum and placed in a syringe with a large opening tip, allowing their connection with the proximal end of a probe 8F inserted into the right jugular vein of the animal.

Before the infusion of blood clots, the records of variables at basal period (T_0) were performed.

The clots were injected 5ml each time until reaching borderline, i.e. "near fatal" MPAP (endpoint). The amount of injected clots was 24.7±4.3 ml, and the mean time of clot injection was 45 minutes. T_0 corresponde to baseline. Other three records, T_1 (endpoint), T_2 (30 minutes after T_1) and T_3 (one hour after T_1) of hemodynamic and respiratory variables and the collection of arterial and venous blood samples were successively performed. In a previous study, it was demonstrated that animals which MPAP reached, in an acute way, values exceeding three times the basal value did not survive. Therefore, a "near fatal" value was defined as a MPAP from 2 to 2.5 times the basal value.

There was no intervention during the experiment. At the end of the study, the animals were kept under observation for 24 hours and all of them survived.

Statistical analysis

Comparisons between respiratory and hemodynamic variables at T_0, T_1, T_2 and T_3 were done by Anova for repeated measurements (Winstat 3.1).

RESULTS

Autologous clot embolization led to a significant reduction in $PetCO_2$ levels at time T_1 (endpoint), showing recovery in times T_2 and T_3 after embolization. There was a slight hypercapnia, although this increase has not been significant.

The increases in P(a-et)CO_2 and AVSDf, which denote increase in alveolar dead space, a characteristic profile of PE, was significant in their times as well.

Hypoxemia may be confirmed by the significant decrease in PaO_2 at time T_1, with a tendency toward a recovery in times T_2 and T_3, while the alveolar-arterial oxygen gradient [P(A-a)O_2] presented a significant increase at time T_1, although practically it has not changed in the other times.

The presence of hyperpnea may be observed by the significant increase in the following respiratory variables: total minute volume (VM tot), anatomical dead space minute volume (VM an tot) and alveolar minute volume (VM alv tot); however, despite this profile, there was not a significant increase in respiratory rate (RR).

The Tables 1 and 2 present the values obtained.

Concerning the hemodynamic alterations, there was a significant increase in the mean pulmonary arterial pressure (MPAP). Conversely, there was a reduction in the mean arterial pressure (MAP) during embolization, even though this drop has not been significant. The near fatal model of PE led to a significant reduction in cardiac output (CO), with recovery trend over subsequent times; however, without reaching the basal values. An acute obstructive shock was also observed by a significant increase in arteriovenous saturation gradient [Ä (art-ven) Sat. (%)], arterial lactate (art Lac) and pulmonary vascular resistance (PVR). It was observed a significant drop in venous partial pressure of oxygen (PvO_2), as well as the differences in arterial base (BE art) and arterial oxygenation index (PaO_2/FiO_2).

Table 1. Gasometric and capnographic variables.

Variables	T_0	T_1	T_2	T_3	*P*
$PetCO_2$	40.1±2.0	11.0±2.7	16.9±5.5	19.7±4.6	<0.0001
$PaCO_2$	44.9±4.4	48.2±6.0	45.4±5.8	43.5±6.2	0.158
P(a-et)CO_2	4.8±2.8	37.2±5.8	28.5±4.5	23.8±3.5	<0.0001
AVDSf	0.09±0.05	0.59±0.06	0.51±0.06	0.47±0.05	<0.0001
PaO_2	73.5±12.7	40.3±4.6	42.5±6.1	45.8±7.3	<0.0001
P(A-a)O_2	8.2±8.9	37.2±10.3	38.6±9.4	37.6±7.7	<0.0001
RR	47±9	48±8	53±11	54±12	0.061
VM tot	6.4±1.4	14.7±3.6	14.0±5.3	11.5±2.6	<0.0001
VM an tot	2.4±0.6	4.0±0.8	4.1±1.4	3.8±1.1	<0.0001
VM alv tot	4.0±0.9	10.6±2.9	9.9±3.8	7.8±1.6	<0.0001

$PetCO_2$: end-tidal pressure of CO_2; $PaCO_2$: partial pressure of CO_2 in arterial blood; P(a-et)CO_2: difference between arterial and end-tidal pressure of CO_2; AVDSf: alveolar dead space fraction end-tidal; PaO_2: partial pressure of O_2 in arterial blood; P(A-a)O_2: difference between alveolar and arterial pressure of O_2; RR: respiratory rate; VM tot: tidal volume per minute (liters); VM an tot: volume of anatomic dead space per minute (liters); VM alv tot: alveolar tidal volume per minute (liters);T_0: baseline; T_1: endpoint; T_2: 30 minutes after T_1; T_3: one hour after T_1

Table 2. Hemodynamic and metabolic variables.

Variables	T_0	T_1	T_2	T_3	*P*
MPAP	17.8±3.5	41.7±3.3	37.0±3.6	34.3±5.3	<0.0001
MAP	78.5±7.1	65.8±12.8	73.8±12.6	75.3±15.7	0.340
CO	4.9±1.0	2.7±1.0	3.6±1.1	3.9±1.3	<0.003
Art Lac	2.4±0.6	5.7±1.8	5.3±2.1	5.2±2.4	<0.0001
Art BE	4.6±1.7	-0.3±3.2	-0.8±3.6	0.3±3.8	<0.0001
Ä (art-ven) Sat. (%)	17.4±6.0	38.8±5.4	29.9±11.2	26.2±8.9	<0.0001
PvO_2	45.0±6.0	23.5±4.3	27.7±5.9	31.0±6.8	<0.0001
PaO_2/FiO_2	350.0±60.3	192.1±22.1	202.4±28.8	218.3±34.7	<0.0001
PVR	3.8±1.1	16.8±5.7	11.2±3.5	9.8±3.9	<0.0001

MPAP: mean pulmonary arterial pressure; MAP: mean arterial pressure; CO: cardiac output; Art Lac: arterial lactate; Art BE: arterial base excess; Ä (art-ven) Sat. (%): arterial saturation less venous saturation (percentage); PvO_2: venous pressure of O_2; PaO_2/FiO_2: relation between partial pressure of O_2 in arterial blood on inspired fraction of O_2; PVR: pulmonary vascular resistance;T_0: baseline; T_1: endpoint; T_2: 30 minutes after T_1; T_3: one hour after T_1

DISCUSSION

The study of hemodynamic, gasometric and capnographic data in the present model of pulmonary embolism (PE) by autologous blood clots allowed physiological responses closer to the real ones, since the animals were under spontaneous ventilation and environmental air.

There is practically no report of such model in the literature. However, there are studies on animals under mechanical ventilation, either using autologous clots or inert elements and with different endpoints for mean pulmonary arterial pressure (MPAP).

Hypoxemia is one of the classic findings of PE. Some hypotheses are suggested, aiming to explain hypoxemia during PE. Santolicandro et al. [14] declare that one of the causes may be the inadequate ventilation/perfusion ratio (V_A/Q), which leads to a reduction in PvO_2; hypothesis also defended by D'Alonzo et al. [15].

Levy et al. [16] declare that the increase in the alveolar dead space contributes to hypoxemia. While right-left shunt was the factor described by Wilson et al. [17] and D'Alonzo et al. [18], inadequacy of V_A/Q was also the factor attributed by Manier et al. [19] and Huet et al. [20].

Both situations could be found in the present study: significant drop in PvO_2 in practically 50% of the basal value (from 45.0±6.0 to 23.5±4.3 mmHg) and, regarding the inadequacy of V_A/Q, from the ventilatory point of view, it was found that the significant increase in the alveolar dead space fraction (AVDSf) (from 0.09±0.05 to 0.59±0.06), in anatomical dead space minute volume (VM an tot) (from 2.4±0.6 to 4.0±0.8 L/min), associated with the increase also significant in $P(A\text{-}a)O_2$ (from 8.2±8.9 to 37.2±10.3 mmHg), would explain the hypoxemia profile. The reduction in PaO_2 may also be verified by the significant drop (P<0.0001) in PaO_2/FiO_2, [from 350.0±60.3 (T_0) to 192.1±22.1 (T_1)]. Although the MAP has not presented significant variation, the drop (P<0.0001) in CO reduced from 4.9±1.0 (T_0) to 2.7±1.0 L/min (T_1); this profile led to a significant variation in Art Lac and Art BE. In addition, the obstructive profile caused by PE led to a significant increase in PVR (from 3.8±1.1 to 16.8±5.7 mmHg/L), contributing to a decreased blood pulmonary flow, which added to extensive areas of alveolar dead space fatally culminated in acute hypoxemia.

In addition to the anatomical dead space, there is another dead space represented by a pulmonary perfusion deficiency that may be total or partial. This dead space is denominated alveolar dead space and is little expressive under normal conditions, as well as may occur by V_A/Q heterogeneous distribution. In contrast, the alveolar dead space, specifically, will present an increase when occurring during PE. Either in experimental studies [21-25], or in clinical studies [2,4,8,10-12], this is a real finding. In the present study, the $P(a\text{-}et)CO_2$ and AVDSf variables indicated the significant increase in this space, from 4.8±2.8 (T_0) to 37.2±5.8 mmHg (T_1) and from 0.09±0.05 (T_0) to 0.59±0.06 (T_1), respectively.

The $PaCO_2$ variable in the present study showed a different pattern from the findings of the literature. Using animal models of similar weights and with autologous clots, Ferreira et al. [21], Vidal Melo et al. [22] and Maggiorini et al. [23] found a significant increase in this variable, although this variable in these studies tended to reduce with time (pulmonary fibrinolysis). The same pattern may be observed in the models in which inert elements (microespheres) were used, as for example that by Schreiner et al. [24]. However, in all these studies, the animals were under mechanical ventilation (with respiratory rate and fixed volumes). Conversely, in this work, the fact that the animals are under spontaneous ventilation led them to react with a significant increase in the total alveolar minute volume (from 4.0±0.9 to 10.6±2.9 L/min), a fact that prevented a significant increase in $PaCO_2$. Furthermore, the $PetCO_2$ presented a significant drop, varying from 40.1±2.0 to 11.0±2.7 mmHg, i.e. a reduction of approximately 70%; while in the study by Ferreira et al. [21] where the animals were under mechanical ventilation and with FiO_2=0.21, the variation was also significant (from 35.6±1.2 to 23.2±8.2 mmHg); however, in percentage terms, a drop of 35%. Fatally, this percentage difference is because the present model allowed physiological responses, being manifested by the increase in VM alv tot, which practically doubled in relation to the basal value, in an attempt to compensate the metabolic acidosis caused by a state of low CO.

The increase in MPAP is proportional to the amount of emboli in the pulmonary vasculature. The surgery (thromboendarterectomy) is indicated in a specific situations [2,12]. In the present study, this pressure increased significantly from 17.8±3.5 to 41.7±3.3 mmHg. In addition to this factor, Delcroix et al. [25] and Maggiorini et al. [23] reported that a sudden drop of P_AO_2 contributes to the increase in MPAP by hypoxemic pulmonary vasoconstriction.

Clinically, it is known that PE is an event of repercussions usually proportional to the degree of commitment to the pulmonary vasculature. Hence, as soon as it is identified and diagnosed, the reduction in morbidity and mortality can be achieved, and unnecessary deaths can be avoided, especially with the early recognition of the patient "near fatal" state.

Surgically, the capnographies variables associated with gasometry may give important and useful data about effectiveness of thromboendarterectomy [12].

The present study did not intend to exhaust the PE pathophysiology in experimental models that are under spontaneous ventilation and environmental air; however,

it has the merit to present evidences that, added to those of other studies using the same line, may greatly contribute to a more clear understanding of near fatal states of PE.

CONCLUSION

The current experimental model of PE seems more closely resembling a real embolic event. For this experimental model, the "near fatal" MPAP was 2 to 2.5 times the basal MPAP. At the endpoint, the capnographic variables, when associated with venous and arterial gasometry, evidenced a massive obstructive profile in a noninvasive, simple, fast and safe form before and after embolic event.

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