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CLINICAL INVESTIGATION

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Open chest and pericardium facilitate transpulmonary passage of venous air emboli

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Abstract

Background: Transpulmonary passage of air emboli can lead to fatal brain- and myocardial infarctions. We studied whether pigs with open chest and pericardium had a greater transpulmonary passage of venous air emboli than pigs with closed thorax.

Methods: We allocated pigs with verified closed foramen ovale to venous air infusion with either open chest with sternotomy and opening of the pleura and pericardium (n = 8) or closed thorax (n = 16). All pigs received a five-hour intravenous infusion of ambient air, starting at 4-6 mL/kg/h and increased by 2 mL/kg/h each hour. We assessed transpulmonary air passage by transesophageal M-mode echocardiography and present the results as median with inter-quartile range (IQR).

Results: Transpulmonary air passage occurred in all pigs with open chest and pericardium and in nine pigs with closed thorax (56%). Compared to pigs with closed thorax, pigs with open chest and pericardium had a shorter to air passage (10 minutes (5-16) vs. 120 minutes (44-212), $P < .0001$), a smaller volume of infused air at the time of transpulmonary passage (12 mL (10-23) vs.170 mL (107-494), $P < .0001$), shorter time to death (122 minutes (48-185) vs 263 minutes (248-300, $P = .0005$) and a smaller volume of infused air at the time of death (264 mL (53-466) vs 727 mL (564-968), $P = .001$). In pigs with open chest and, infused air and time to death correlated strongly ($r = 0.95$, $P = .001$).

Conclusion: Open chest and pericardium facilitated the transpulmonary passage of intravenously infused air in pigs.

1 | INTRODUCTION

Venous air emboli frequently complicate surgery, interventional procedures, and trauma.[1] Symptoms range from a transient drop in end-tidal CO_2 concentration, decreased lung compliance, pulmonary edema, cerebral- or myocardial infarction, hemodynamic collapse to death.[2,3] The lungs usually filter emboli, but this filtering capacity is limited and can be overwhelmed, allowing air to traverse the lungs into the systemic circulation, potentially causing embolic infarctions.[4,5] The thorax and pericardium provide a rigid framework for the lungs and heart, limiting overexpansion of the organs.[6] Opening the thorax, including pleura and pericardium, has been shown to reduce air emboli tolerance.[7] However, the effect of open chest and pericardium, including the pleura and pericardial sac, on the lungs' ability to filter venous air embolism has not, to our knowledge, been studied.

Cognitive impairment and micro-infarctions are frequent complications in open-heart surgery. Studies suggest cerebral microemboli of particulate or gaseous matter as a potential mechanism.[8,9] Studies have suggested that systemic air emboli can occur during open-heart surgery or if air enters a cardiopulmonary bypass circuit.[8] Several studies have proposed echocardiography as a sensitive monitor of venous air emboli.[10-13] We hypothesized that opening the chest, including the pleura and pericardial sac, reduces the lung filtering capacity of venous air emboli, potentially leading to systemic egress of air. Thus, we studied the transthoracic passage of venous air emboli in pigs with an open chest and pericardium compared to pigs with closed thorax.

Editorial Comment

In a porcine experimental model to study the transpulmonary passage of air during the intravenous infusion of air, sternotomy with opening of the pleura and pericardium significantly facilitated the egress of air into the systemic circulation compared to animals with a closed chest. The model is conducive to further pathogenetic and pathophysiological research in this area including the impact of airway pressures and the intravascular volume and vascular compliance. Experimental research models remain important to formulate and evaluate hypotheses with clinical relevance.

2 | MATERIALS AND METHODS

The Norwegian Animal Research Authority approved the studies (FOTS ID9466), and we performed the experiments under the Norwegian Laboratory Animal Regulations and the EU directive 2010/63/EU.

2.1 | Experimental animals

In a two-center non-randomized, experimental study using a convenience sample, we allocated Norwegian landrace pigs from two suppliers to undergo an intravenous ambient air infusion either with open chest and pericardium, including open pleura and pericardium or closed thorax, or to serve as sham animals not receiving air. We excluded sick pigs and pigs with open foramen ovale. Finally, 30 pigs were included (Figure 1). Due to laboratory logistics, we retrieved animals allocated to sternotomy from one supplier. We summarize the animal characteristics in Table 1.

2.2 | Instrumentation, anesthesia, and surveillance

We anesthetized all pigs with azaperone 40 mg, ketamine 500 mg, and atropine 0.5 mg intramuscularly and maintained the anesthesia with an intravenous infusion of morphine 2 mg/kg/h, midazolam 0.15 mg/kg/h and pentobarbital 4 mg/kg/h. We endotracheally intubated the pigs with a 6 mm outer diameter tube. We mechanically ventilated the pigs with a tidal volume of 10-15 mL/kg, a rate of 20/min, and zero positive end-expiratory pressure. Tidal volume and respiratory rate were adjusted to maintain a pH of 7.35-7.45. Inspiratory oxygen fraction (FiO_2) was adjusted to maintain an arterial pulse oximetry saturation (SpO_2) above 90%. We infused Ringer's acetate to compensate for insensible fluid losses with a rate of 2-3 mL/kg/h in pigs with closed thorax and 10 mL/kg/h in pigs with open chest and pericardium. In situations where MAP dropped below 55 mm Hg, the pigs were resuscitated with repeated boluses of 100 mL Ringer's acetate and infusion of noradrenaline in the range 0.01 to 0.8 μg/kg/min.

We surgically inserted an arterial line in the internal carotid artery, a 7.5 Fr pulmonary artery catheter (Edwards Vigilance Swan-Ganz CCOmbo) through the external jugular vein, a 4 Fr 8 cm PICCO thermodilution catheter (Pulsion/Getinge) in the femoral artery, and a suprapubic catheter with a temperature sensor in the bladder. We placed a pediatric 9T transesophageal echo-probe (General Electric) in an upper-esophageal position and connected it to either a Vivid 7 pro (General Electric) or a Vivid E9 (General Electric) echo machine. We recorded ECG, ST-segment, SpO_2, expired end-tidal CO_2, and continuous invasive arterial-, pulmonary-, and central-venous pressures on either a Solar monitor (General Electric) or SC8000 monitor (Siemens Healthcare). We drew arterial blood gasses hourly throughout the experiments and immediately before death and analyzed these on the ABL Flex 80 (Radiometer).

Pigs allocated to open chest and pericardium had a sternotomy with an opening of the pleural sac and pericardium. We saw M-mode sensors (Imasonic SAS) onto the left and right ventricle, and a combined six-axis gyroscope and accelerometer MPU6050 (Invensense Inc) onto the right ventricle of the heart (Supporting Information 1A). We retrieved recordings from the M-mode sensors using a custom-built computer and software (The Intervention Centre, Oslo University Hospital).

Before the start of the experiment, we performed a transesophageal echocardiogram (TEE) in all pigs, including an agitated saline test to examine for patent foramen ovale, and we then positioned the

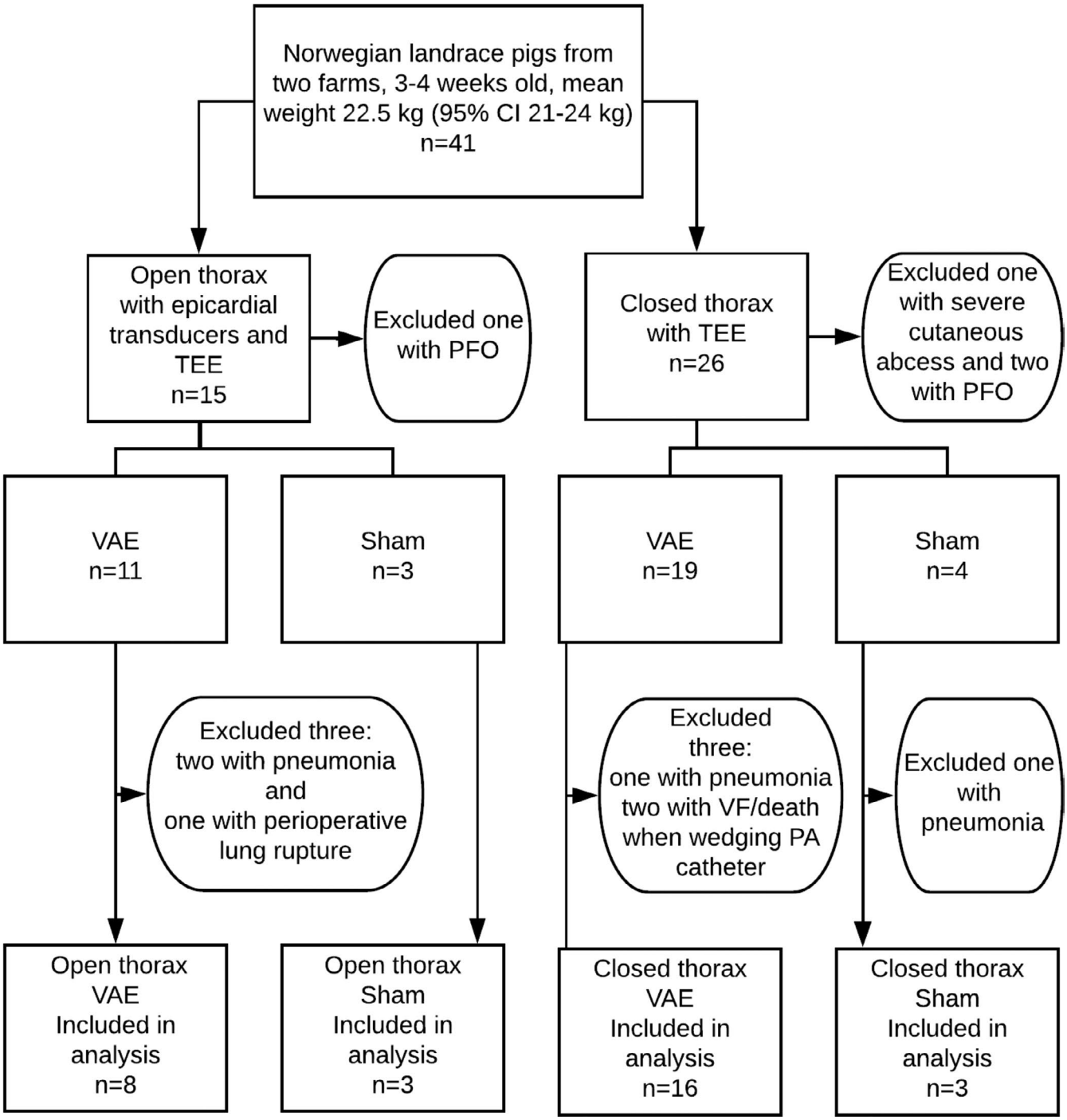

FIGURE 1 Inclusion of animals. We allocated forty-one pigs to receive infusion with either open chest and pericardium or closed thorax or serve as sham animals. We excluded animals with PFO, pneumonia, perioperative lung injury, or ventricular fibrillation related to wedging of the PA catheter. TEE, transesophageal echocardiogram; PFO, patent foramen ovale; VAE, venous air emboli; VF, ventricle fibrillation; PA, pulmonary artery

transesophageal echo probe as described by Vik,[13] to visualize the aorta and the right ventricular outlet tract (RVOT) or the pulmonary artery or the left atrium and the RVOT. We repeatedly assessed right and left ventricular dimension and function throughout the experiments.

We recorded cardiac output by hourly thermodilution (average of three injections of 5 mL ice-cold Ringer's Acetate) by the Edwards Vigilance II (Edwards) and Pulsion PICCO2 (Pulsion/Getinge).

2.3 | Air infusion and data collection

All pigs, except sham animals, received an infusion of ambient air through an ear vein, initially at a rate of 4-6 mL/kg/h, and increased by 2 mL/kg/h every hour until the pigs died or until the end of the experiment after 300 minutes. The air infusion was titrated based on previous studies,[4,7,13] aiming to cause hemodynamic instability, but

TABLE 1 Animal characteristics after instrumentation, before air infusion

	Open thorax		Closed thorax	
	VAE (n = 8)	Sham (n = 3)	VAE (n = 16)	Sham (n = 3)
Weight (kg)	24 (2.1)[a]	23 (0.3)	22 (4.2)	21 (2.3)
Sex male/female	4/4	1/2	11/5	0/3
MAP (mm Hg)	80 (20)	71 (7)	82 (11)	74 (6)
MPAP (mm Hg)	24 (8)	25 (7)	21 (2)	18 (2)
MPAP/MAP	0.27 (0.08)	0.36 (0.08)	0.26 (0.04)	0.24 (0.04)
CVP mm Hg	13.2 (7.5)[b]	8.5 (0.7)[c]	8 (4.1)[d]	5.7 (1.5)
PVR (dynes*sec/cm^5)	295 (108)[e]	141 (26)	304 (65)[f]	149 (76)
PaO_2 (kPa)	14.1 (3.9)	11 (2.3)	10.6 (1.8)	12 (2.9)
PaO_2 (kPa)/FiO_2	40.7 (7.9)	43.2 (22.5)	41.2 (10.3)	44.1 (11.5)
SpO_2/FiO_2	2.7 (0.6)	3.7 (1.3)	3.7 (1.1)	4.1 (0.7)
$EtCO_2$ (kPa)	5.6 (1.2)	5.4 (0.4)	5.3 (0.6)	4.9 (0.5)
Pinsp (cmH_2O)	17 (5.0)	16 (4.7)	20 (4.2)	21 (1.0)

Abbreviations: CVP, central venous pressure; $EtCO_2$, end-expired CO_2 concentration; FiO_2, Inspired O_2 fraction; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PaO_2, Partial arterial O_2 pressure; Pinsp, inspiratory airway pressure;
PVR, pulmonary vascular resistance; VAE, venous air embolism.

[a]Data are given as mean (SD).

[b]n = 6.

[c]n = 2.

[d]n = 14.

[e]n = 6.

[f]n = 9.

not death. We euthanized pigs still alive 300 minutes after start of the air infusion by injection of potassium chloride.

We used continuous M-mode and intermittent 2D echocardiography to detect air in the left and right heart (Supporting Information 1B. Examples of TEE recordings in Supporting Information Video S1 and S2). The same researcher performed all echo examinations. Additionally, in pigs with open chest and pericardium, continuous epicardial M-mode ultrasound was used to monitor for air in the myocardium and ventricles (Supporting Information 1C and 1D). The experimental setup is shown schematically in Figure 2.

We registered elapsed time and amount of air at the first transpulmonary passage and at the time of death. Postmortem, we examined the heart and lungs, focusing on foam or clots in the cardiac chambers, air in the coronary vessels, and verified a closed foramen ovale.

2.4 | Power calculation

We expected to find systemic egress of intravenously infused air in 50% of pigs with closed thorax and 99.9% of pigs with open chest and pericardium based on pilot studies. Using an online sample calculator[14] with a 2:1 enrolment ratio, alpha of 5%, and power of 80%, we calculated the groups' necessary sizes to be 14 pigs with closed and seven pigs with open chest and pericardium. To minimize the sacrifice of pigs, we chose to include in the study only three sham animals with open chest and pericardium and three sham animals with closed thorax.

2.5 | Statistics

We used Prism for Mac 8.4.2 (Graphpad Software) for statistical calculations and used the Mantel-Cox log-rank test to compare Kaplan-Mayer survival curves and Spearman's test for correlations. We considered a $P < .05$ significant.

3 | RESULTS

3.1 | Transpulmonary passage of air

By TEE we detected air in the aorta in all eight pigs with open chest and pericardium and nine of sixteen pigs with closed thorax. In pigs with open chest and pericardium, we detected air in the aorta after a median infusion of 12 mL (IQR:10-23) of air vs 170 mL (IQR:107-494) of air in pigs with closed thorax ($P < .0001$). (Figure 3A). We detected air in the aorta after a median of 10 minutes (IQR:5-16) in pigs with open chest and pericardium, compared to 120 minutes (IQR:44-212) in pigs with closed thorax ($P < .0001$). In all pigs with open chest and pericardium receiving air infusion, we detected intraventricular air in the left ventricle by epicardial M-mode ultrasound.

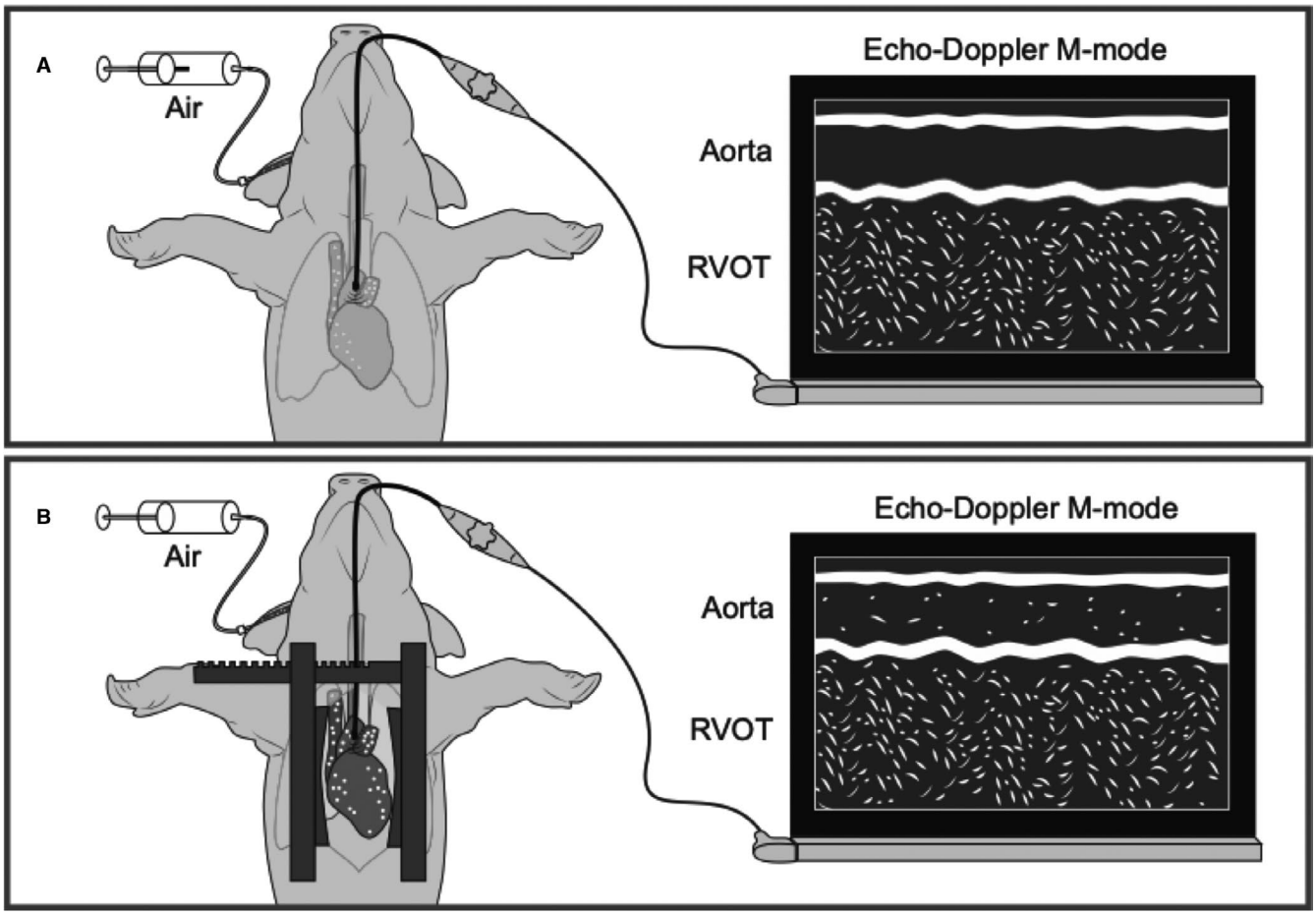

FIGURE 2 Experimental setup. In pigs with closed thorax (A) or pigs with sternotomy with open pleura and pericardium (B), We infused ambient air using a syringe driver through an ear vein. We detected air in the right ventricular outlet tract (RVOT) and the aorta by continuous transesophageal M-mode echocardiography

3.2 | Time to death after air infusion

All pigs with open chest and pericardium, except sham animals, had a median time to death of 122 minutes (IQR:48-185) (Figure 3B). Five pigs with closed thorax and all sham animals were still alive after 300 minutes (Figure 3B). Pigs with closed thorax, including pigs euthanized after 300 minutes, died after a median time of 263 minutes (IQR:248-300) (P =.0005 between the groups). At death, pigs with open chest and pericardium had received a median infusion of 264 mL air (IQR:53-466), compared to 727 mL air (IQR:564-968) in pigs with closed thorax (P =.001) (Figure 3C). There was a strong correlation for pigs with open chest and pericardium (r = 0.95 P =.001) between infused air and time to death (Figure 3D).

3.3 | Cardiovascular effects of infused air

Air infusion triggered an immediate rise in the mean pulmonary artery pressure and reduced systemic arterial pressure resulting in an increase in the mean pulmonary artery to mean arterial pressure ratio (MPAP/MAP) in all pigs receiving air infusion. The MPAP/MAP ratio remained constant in the sham animals (Figure 4A,B). Air infusion also led to reduced gas exchange and increased airway compliance, and triggered a tachycardia, as described in Supporting Information 2.

In most of the pigs receiving air infusion, we observed by echocardiography, a progressive right ventricular dilatation and subsequent ventricular failure with concomitant normo- or hypovolemic left ventricle. In the inferior ECG leads II, III, and aVF, we noted ST-segment changes greater than ±2 mm in six of eight pigs with open chest and pericardium and six of sixteen pigs with closed thorax. We detected air in the aorta before the occurrence of ST-segment changes in six of eight pigs with open chest and pericardium and five of sixteen pigs with closed thorax. Two of eight pigs with open chest and pericardium and four of sixteen pigs with closed thorax had ST-segment changes without air detected in the aorta (Table 2).

At postmortem autopsy, all pigs with open chest and pericardium and ten of sixteen pigs with closed thorax had markedly dilated right ventricle (Table 2). We found air in the great cardiac vein (illustrated in Supporting Information 3A) in five of 16 pigs with closed thorax, but in no pigs with open chest and pericardium. We found foam clots (illustrated in Supporting Information 3B) in the right ventricle in four of eight pigs with open chest and pericardium, seven of sixteen pigs with closed thorax, and no sham animals (Table 2).

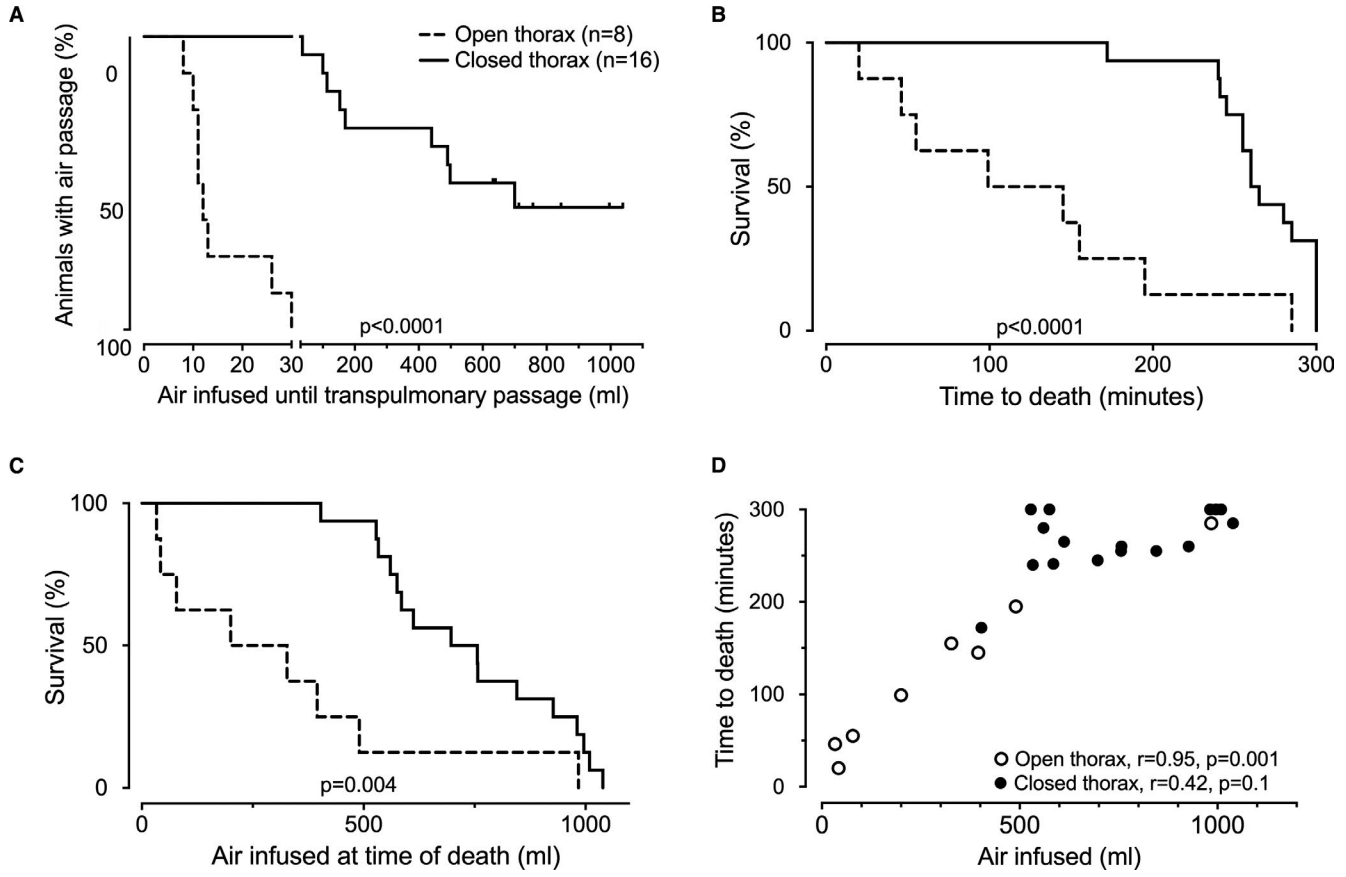

FIGURE 3 Transpulmonary passage of air and time to death after infusion. A, Amount of air infused when transpulmonary air was detected. Note, the *X*-axis is split. B, Time to death during air infusion. C, Amount of air infused at death. D, Correlation between the amount of air infused and the time of death for pigs with open chest and pericardium and pigs with closed thorax. We compared the groups using the Mantel-Cox log-rank test, and examined the correlations using Spearman r

4 | DISCUSSION

In a porcine model of venous air embolism, we have shown that an open chest and pericardium facilitates the transpulmonary passage of venous air infusion. Our findings showed that transpulmonary passage of air occurs in a dose-dependent manner, suggesting that the lungs' filtering capacity is limited, in accordance with other studies.[4,5] We found that opening the thorax, pleura, and pericardium greatly reduced the threshold for when air reached the systemic circulation through the lungs. We had not designed our study to elaborate on the anatomical mechanisms underlying these findings. However, we suggest that recruitment of extra-alveolar shunt vessels by the following mechanism played an important role: Opening of the chest and pericardium resulted in reduced transmural lung pressure and allowed for over-expansion of the lungs with increased parenchymal traction. In line with the mechanisms described by Cortes-Puentes et al,[15] the increased parenchymal traction could, in conjunction with positive pressure ventilation, have resulted in compressions of alveolar vessels and recruitment of extra-alveolar shunt vessels, facilitating the transpulmonary air emboli passage.

As in previous studies by Durant et al,[7] we found that venous air emboli caused right ventricular ischemia and failure, and that opening of the thorax and pericardium substantially reduced the amount of air required to cause circulatory collapse. Several findings in our study coincide with findings by Durant, suggesting that right ventricular failure played an important role in the cause of death; First, all pigs with open chest and pericardium and ten of sixteen pigs with closed thorax had massive right ventricle enlargement postmortem. As suggested by Durant, the dilation of the right ventricle could have hindered muscular blood flow through the Thebesian veins. Second, in nearly half of the pigs we observed a foam-clot in the RVOT. As suggested by Durant, foam in the RVOT could have obstructed blood from the right ventricle. Third, in our study, nearly a third of pigs with closed thorax had air emboli in the great cardiac vein, which might have obstructed blood flow from the myocardium. Fourth, all pigs in our study developed a pronounced tachycardia, increasing myocardial workload and reducing diastolic time. Fifth, in many animals, systemic air emboli were noted before ST-segment changes were detected. Thus ST-segment changes might represent acute coronary ischemia with right and left ventricular failure due to coronary air emboli.

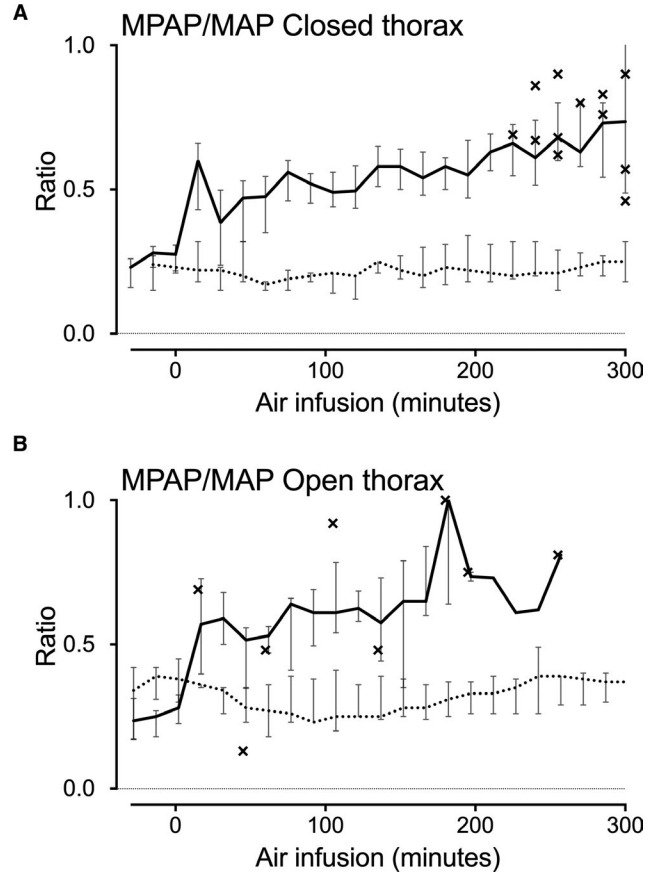

FIGURE 4 Pulmonary arterial and systemic arterial pressure. Mean pulmonary artery to mean arterial pressure ratio (MPAP/MAP) in pigs with closed thorax (panel A) and open chest and pericardium (panel B). *Solid line* = Pigs receiving air infusion, *Dotted lines* = Sham animals. *X* = Time of death and corresponding MPAP/MAP. Data presented as median; error bars span the IQR

Importantly, and not described by Durant, we found that the time of death coincided with the detection of systemic air emboli in several animals, pointing to the danger that emboli represent not only to the heart but also to other vital supply-dependent organs such as the brain and the medulla. The echocardiographic technique used to detect pulmonary air passage is an important extension of Durant's seminal experiments. In this regard, the TEE short-axis M-mode through RVOT and aorta or RVOT and LA easily enabled detection of venous air emboli and transpulmonary passage of air. Our experiments are easily replicable, and further testing is possible to challenge and explore in greater detail how the opening of the chest, pleura, and pericardium facilitates the systemic egress of venous air through the pulmonary circulation.

Our study has a number of limitations. We conducted the experiments at two laboratories. However, the same researchers performed the experiments, and the animals were of the same race and were bred from the same national insemination stock and supplier. We based the intervention on convenience sampling. Data collection from monitors and ventilators had intermittent glitches, creating some missing data points. Since air partly obscured the echocardiographic views, conventional estimates of ventricular dimensions and function were challenging to obtain; we based the echocardiographic estimates of right ventricular function on visual impressions of ventricular dilatation and reduced wall contraction. Furthermore, in pigs with open chest and pericardium, we directly inspected the heart for dilatation and contractility. Finally, we examined hearts from all pigs postmortem for dilatation, clots, and emboli.

In conclusion, in a porcine model of venous air emboli, we have shown that thoracotomy with pericardiotomy facilitated the transpulmonary passage of intravenously infused air.

TABLE 2 ST-segment changes and findings at autopsy

	Open thorax (8 pigs) N (%)	Closed thorax (16 pigs) N (%)	Sham (6 pigs) N (%)
Perioperative ST-segment changes exceeding ± 2.0 mm.	6 (75%)	6 (38%)	
Air detected in aorta[a]	6 (100%)[b]	5 (83%)[b]	0
No air detected in aorta[a]	0	1 (17%)[b]	0
No ST-segment change	2 (25%)	10 (63%)	6 (100%)
Air detected in aorta[a]	2 (100%)[c]	4 (40%)[c]	0
No air detected in aorta[a]	0	6 (60%)[c]	6 (100%)
Findings at autopsy			
Dillated right ventricle	8 (100%)	10 (63%)	0
Right ventricle not dillated	0	6 (37%)	6 (100%)
Air in great cardiac vein	0	5 (31%)	0
No air in great cardiac vein	8 (100%)	11 (69%)	6 (100%)
Foam-clot in right ventricle	4 (50%)	7 (44%)	0
No foram-clot in right ventricle	4 (50%)	9 (56%)	6 (100%)

[a]Air was detected by continuous transesophageal M-mode echocardiography of the aorta.

[b]Of pigs with ST-segment changes with open or closed thorax, respectively.

[c]Of pigs with no ST-segment changes with open or closed thorax, respectively.

CONFLICTS OF INTEREST

None of the authors declare any conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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