Elevated PaCO2 Levels Increase Arterial Pulmonary Pressures

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Research

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Abstract

Background

The effect of elevated PCO2 in the pulmonary vasculature during mechanical ventilation is not clear. Previous studies in ARDS patients have shown that elevated PaCO2 may be associated with pulmonary hypertension however in models of spontaneously breathing animals results were contradictory.

Results

In this respect, we aimed to investigate the effect of increased PaCO2 on the pulmonary vasculature of rabbits using different levels of tidal volumes during mechanical ventilation. We conducted an experiment using two groups of adult male rabbits (n=30). Animals were randomly allocated in two groups of different tidal volumes either 6 ml/Kgr (LowVt group) or 9 ml/Kgr (HighVt group) and were ventilated with FiO_2 0.3 (Normocapnia-1). Subsequently, animals in each Vt group inhaled an enriched in CO2 gas mixture ($FiCO_2$ 0.10.) in order to develop hypercapnia (Hypercapnia-1) and were then re-ventilated with the same conditions to develop subsequent phases of normocapnia and hypercapnia (Normocapnia-2,Hypercapnia-2). Pulmonary arterial pressures were measured with a catheter introduced in the pulmonary artery connected to piezo pressure transducers integrated in a polygraphic system.

During hypercapnic conditions , both groups showed increase in PAPsyst, PAPdiast and PAPmean compared to their baseline values. PAPmean pressures increased significantly from Normocapnia-2 to Hypercapnia-2 whereas PAPmean at Hypercapnia-2 was found significantly increased compared to Hypercapnia-1.

Conclusions

These findings suggests that hypercapnia may augment the pressures in pulmonary vasculature during mechanical ventilation an effect that was observed either, using low or, higher tidal volumes. An effect of preconditioning of arterial pulmonary vessels in hypercapnia merits further investigation.

Introduction

The effect of elevated PCO2 in the pulmonary vasculature during mechanical ventilation is not clear.[1, 2, 3, 4] Previous studies in ARDS patients have shown that elevated PaCO2 may be associated with pulmonary hypertension.[3] However, those data were derived from studies that evaluated the effect of prone position in cardiac function and were not dedicated to study the effect of increased CO2 in pulmonary arterial pressures. Data in spontaneous breathing subjects are also limited. A previous echographic study suggested that at high $\dot{v}/\dot{q}$ values (> 0.65) as in dead space lung regions due to hyperinflations, the pulmonary vasculature responds to CO2 changes. [5] In models of spontaneously breathing animals, results are contradictory since the overall effect of increased CO2 levels on the

pulmonary vasculature is vasodilatory[6] but this dilator action was not shown in other animal models.[7, 8]

In this experimental study, we aimed to investigate the effect of increased PaCO2 on the pulmonary vasculature of rabbits during mechanical ventilation using different levels of tidal volume.

Materials And Methods

Animal Model

Experiments in two groups of adult white-New Zealand rabbits of 3(0.5)kgr were performed in accordance with the European Community and NIH guidelines for using experimental animals. All procedures were approved by our institution's Animal Studies Committee [EL 42 BIO 04]. The animals were maintained in room air and temperature and after induction of anesthesia with intramuscular administration of 1 ml ketamine 100 mg/ml and 1 ml midazolam 5 mg/ml, a peripheral vein cannula was inserted and administration of N/S 0.9% 20 ml/hour was commenced. Tracheostomy was performed based on previous reports,[9] animals were subsequently endotracheally intubated; animals were subjected to neuro-muscular blocade and were mechanically ventilated to reach stable respiratory conditions with a volume controlled mode (FiO2 = 0.3, frequency 35–40/minute, tidal volume (Vt) = 6 ml/kgr, positive end-expiratory pressure (PEEP) = 2 cm H_2O - Drager Respirator). Animals were subjected to neuro-muscular blocade by administering 1 ml cis-atracurium 2 mg/ml iv and thereafter anesthesia and muscle relaxation were maintained with periodic intravenous infusions of midazolam and cis-atracurium. Subsequently, the femoral artery was exposed and cannulated and the right jugular vein was prepared and the pulmonary artery was cannulated based on a previously described technique.[10, 11] Briefly, an angled polypropylene introducer made from standard tubing 15 cm long, external diameter 3 mm and lumen diameter 2 mm was used. The distal 1.5 cm was heat angled at 90 degrees to the shaft and a marker made to indicate the direction of the angle. The introducer was filled with heparinized saline and a No. 4.5 French gauge right side coronary angiography catheter - which has its tip angled - was inserted so that the tip lied just inside the distal end of the introducer. The catheter was then filled with heparinized saline and connected to a pressure transducer. Following the exposure of the right jugular vein, the introducer-catheter assembly was inserted and passed into the right ventricle through the superior vena cava and the right atrium using the pressure signals for guidance. Correct placement in the right ventricle was confirmed by the pressure signal and then the angled tip was rotated to point anteriorly and slightly to the left and withdrawn until the angle impinges on the tricuspid valve. One ml of cold saline was flushed through the catheter and the catheter was advanced to pass directly into the pulmonary artery. Correct placement was confirmed by the change in the pressure signal.[12]

Samples of arterial blood were obtained from the femoral artery. End expiratory carbon dioxide (EtPCO2) was continuously monitored using a capnograph (RESPIRONICS CO2SMO MONITOR, USA) adapted to the endotracheal tube.

Animals were ventilated with the aforementioned baseline settings to obtain stable physiological conditions and were then exposed to different experimental conditions in terms of ventilation settings and inhaled gas mixtures. Initially, animals were randomly allocated in two groups of different tidal volumes either 6 ml/Kgr (LowVt group) or 9 ml/Kgr (HighVt group) and were ventilated with FiO_2 0.3 (Normocapnic Phase (NP1)). Subsequently, animals in each Vt group inhaled an enriched in CO2 gas mixture (FiO_2 0.3, $FiCO_2$ 0.10.) in order to develop hypercapnia (PCO2 was targeted between 70–90 mmHg - Hypercapnic Phase-1(HP1)). Animals were then re-ventilated with FiO_2 0.3 (Normocapnic Phase-2 (NP2)) and then re-exposed to enriched in CO2 gas mixture (FiO_2 0.3, $FiCO_2$ 0.10.) (Hypercapnic Phase-2 (HP2) to assess the impact of hypercapnic preconditioning in pulmonary pressures. All animals were exposed to each setting for 30 minutes to obtain stable condition before measurements and between different conditions were ventilated with the baseline settings for 30 min (Fig. 1). At the end of the experiments, animals were sacrificed by administering potassium chloride 5% iv while under anesthesia.

Ancillary studies

In order to assess the impact of hypoxic conditions to pulmonary pressures, six animals under mechanical ventilation inhaled a gas mixture with low O2 concentration (FiO_2 0.15, $FiCO_2$ 0.0) whereas in three of them, heart and lungs were exposed for macroscopic inspection of the placement of the catheter and for measurements of the mechanical properties of the exposed lungs.

Pulmonary arterial pressures were recorded at expiration; pressure signal was recorded with a commercially available polygraphic system (NIHON KOHDEN POLYGRAPH SYSTEM RM-6000, Japan) and simultaneously displayed on the screen of the recording system. Pressures were measured with piezo pressure transducers integrated in the polygraphic system. Pressure transducer was calibrated immediately before, after, and when necessary, during each procedure.

Outcome

Mean pulmonary arterial pressure changes (PAPmean – mmHg) was the primary outcome of this investigation.

Statistics

Results are expressed as mean (SD). Data were analyzed for normality with the Shapiro-Wilk test and by the paired T-test or the Wilcoxon matched pair test as appropriate. The statistical tests were 2-sided. A result was considered statistically significant when $p < 0.05$. Analysis was performed using statistical software, SPSS v.15 for Windows.

Results

Overall, thirty-three rabbits were used in the experiments; two of them died during procedures leaving 31 animals for data evaluation. Deaths were attributed to anesthesia induction or to pneumoperitoneum in one case and occurred early during experiments before the application of any experimental condition. Baseline hemodynamics at different tidal volumes are shown in Table 1. Animals ventilated with high tidal volumes (HVt) – 9 ml/Kgr - (n = 12) had similar PO2 and PCO2 values with animals ventilated with lower tidal volumes (LVt) – 6 ml/Kgr - (n = 13) but Pairway, PAPsyst, PAPdiast, PAPmean values were increased in HVt compared to LVt group.

Pulmonary Arterial Pressures At Different Pco2 Levels

During hypercapnic conditions (HP-1), animals in LVt and HVt group presented similar Pairway but increased PAPsyst, PAPdias and PAPmean values compared to NP-1 (Fig. 2).

Following the second induction of hypercapnia (assessment of preconditioning), animals in both tidal volume groups presented again similar Pairway but increased PAPsyst, PAPdias and PAPmean values compared to NP-2 (Table 1). It was observed that during HP-2, PAPmean and PAPdias increased significantly compared to HP-1 (Fig. 3).

Discussion

- In this study hypercapnic conditions were associated with a statistically significant increase in PAPmean in mechanically ventilated rabbits. Notably, animals were subjected to different PCO2 levels achieved by the inhalation of a gas mixture rich in PCO2 (10% CO2) at two different tidal volumes (6 ml/kg and 9 ml/kg) and it was found that PAPmean increased following the induction of hypercapnia in both conditions. Furthermore, it was observed that PAPmean increased significantly between two subsequent hypercapnic phases in the high tidal volume group, whereas there was an indication towards increased PAPmean values in the low tidal group, suggesting that there was an effect of preconditioning in PAPmean and potentially in pulmonary vasculature.
- PAPmean elevation following hypercapnia possibly suggest that increased PCO2 may increase the resistance of the pulmonary vasculature denoting a vasoconstrictive effect. This hypothesis is supported by previous animal or in vitro studies which evaluated elastic vascular properties and found that hypercapnia can cause vasoconstriction in mammal lungs.[6, 13, 14] Von Euler and Liljestrand showed in cats that pulmonary hypertension ensued when the concentration of carbon dioxide in the inspired air was increased. They described that the addition of CO2 to the inspired gas elevated PPa by 11 mmHg (8–17 mnHg) and PVR by 56% (14–170%)[15]. Another investigation[16] suggested that this effect of hypercapnic acidosis in pulmonary vasculature may be beneficial to lung gas exchange as a compensatory mechanism by improving ventilation-perfusion matching during hypoxic conditions. Other investigators suggested that the over-all effect of CO_2 on the pulmonary vasculature depends on a balance between a vasoconstrictor action caused by carbonic acid and vasodilatation, caused by some other property of the molecule, an action which was more

evident in isolated rat lungs.[6] Our findings are in line with the aforementioned data but they furthermore suggest that the effect of hypercapnia in pulmonary vasculature may be present during mechanical ventilation and in different tidal volumes.

- In the present study we assessed arterial pulmonary pressures using different tidal volumes (low or, high, set at 6 or 9 ml/Kg respectively) aiming to simulate a clinical scenario in humans where low or, high tidal volumes may produce different stress in the pulmonary vasculature.[4, 17] At baseline, we observed that both, airway and pulmonary pressures, were significantly increased when higher tidal volumes were used during mechanical ventilation. This suggests that the increased pressures observed could be the effect of increased lung stress and strain in the pulmonary circulation. On the other hand, during hypercapnic conditions we observed that pulmonary pressures were increased within each group of animals ventilated with the same tidal volume whereas airway pressures remained similar. This suggests that the effect of hypercapnia in pulmonary vasculature may be independent from the tidal volume used during mechanical ventilation.

In this experimental study we also sought to assess whether hypercapnic preconditioning has an impact in the pulmonary vasculature. Hence, following the first induction of hypercapnia (HP1) normocapnic conditions were achieved (NP2) and then, hypercapnic conditions (HP2) was re-induced. We found that PAPmean pressures increased significantly in HP2 compared to HP1 in the high tidal volume group whereas there was an indication towards increased values in the low tidal group as well (Fig. 3). This suggest an effect of preconditioning in pulmonary vasculature and we might speculate that following hypercapnia pulmonary arterial vessels might present increased susceptibility to vasoconstriction that merits further investigation.

Conclusions

- Unfortunately neither we, nor others, have evaluated blood flow and cardiac function in the pulmonary circulation which could have provided more insight in the effect of PO2 levels in the pulmonary vasculature. In this study no cardiac output measurements were performed and in this respect local pulmonary pressures fails to draw a complete picture; the study would greatly benefit from cardiac output data. One might assume that since systemic blood pressure (MAP) and heart rate changes did not significantly change during the various CO2 conditions (Table 1), cardiac output might have remained relatively stable and therefore pulmonary artery changes should have followed changes in the resistance of the pulmonary vasculature. However, this hypothesis needs further clarification in a future study since it is well known that acute hypercapnia does have several effects on the cardiovascular system in various animal models.
- It should also be underlined here that the results of the present investigation should be interpreted taking into account certain points. First, hypercapnia induction induced also hypercapnic acidosis which was not reversed by infusion of agents that could counterbalance acidosis by producing metabolic alkalosis whereas experiments were relatively short to observe any compensatory metabolic alkalosis by the animals. However, experiments followed the clinical scenario where

correction of hypercapnia during mechanical ventilation is not advised but only in cases where acidosis is associated with clinical instability that was not observed in our experiments. Secondly, we have not assessed directly lung stress and strain and therefore we cannot exclude that the choice of specific tidal volumes (i.e. 6 ml/Kg and 9 ml/Kg) used in our study have not produced significantly different stress in the lungs since it is known that lung stress may be variable and not linearly related with the tidal volume used.[17]

- In conclusion, the present study suggests that hypercapnia may augment the pressures in pulmonary vasculature during mechanical ventilation an effect that was observed either, using low or, higher tidal volumes. An effect of preconditioning of arterial pulmonary vessels in hypercapnia merits further investigation.

Table 1. Hemodynamic data of mechanically ventilated animals with low (6 ml/Kgr) or higher tidal volumes (9 ml/Kgr) during different experimental PCO2 conditions

	Normocapnia-1	Hypercapnia-1	Normocapnia-2	Hypercapnia-2
T (C°)	39.1(0.3)	39.2(0.2)	39.4(0.4)	39.5(0.5)
HR (bpm)	136.5(6.2)	140.5(7.0)	139.0(4.4)	142(6.4)
LVt	138.3(7.1)	147.7(5.3)	148.2(5.7)	149(7.8)
HVt				
MAP mmHg	138.2(6.8)	137.4(8.2)	139.1(7.4)	137.4(4.8)
LVt	140.5(5.4)	138.6(8.3)	140.8(6.4)	138.2(5.4)
HVt				
pH	7.38(2.6)	7.22(4.2)	7.31(4.6)	7.12(8.7)
LVt	7.36(8.4)	7.20(6.1)	7.29(6.8)	7.08(5.2)
HVt				
PO2 mmHg	221(92)	221(92)	221(92)	221(92)
LVt	253(99)	253(99)	253(99)	253(99)
HVt				
PCO2 mmHg	40.8(6.0)	80.8(8.2)	43.5(5.1)	87.7(9.0)
LVt	47.5(6.0)	81.8(7.4)	43.5(5.2)	84.0(10.3)
HVt				
Pairw cmH2O	10.3(1.6)	11.3(1.5)	10.8(1.2)	11.2(1.1)
LVt	11.6(0.5)	12.7(3.2)	11.2(0.8)	12.4(2.0)
HVt				
PAPmean mmHg	17.8(5.1)	24.5(2.4)*	22.2(5.0)	28.2(3.6)*
LVt	17.8(6.2)	26.9(3.8)*	25.4(3.1)	33.2(5.7)*,#
HVt				
PAPdias mmHg	12.5(6.6)	20.4(6.5)*	19.5(5.1)	21.5(1.2)*
LVt	14.7(4.8)	22.5(3.1)*	16.8(4.9)	28.4(6.0)*
HVt				
PAPsys mmHg	21.4(5.9)	31.0(5.4)*	24.0(4.5)	37.6(4.3)*
LVt	26.7(5.3)	34.5(4.3)*	27.5(3.1)	43.4(5.1)*
HVt				

	Normocapnia-1	Hypercapnia-1	Normocapnia-2	Hypercapnia-2

Data are presented as mean(SD)

T = Temperature, HR = Heart Rate, LVt = low tidal volume (6 ml/kgr), HVt = high tidal volume (9 ml/kgr), MAP = Mean Arterial Pressure, Pairw = Mean Airway Pressure (Pplateau), PAPmean = Mean Pulmonary Arterial Pressure, PAPdias = Diastolic Pulmonary Arterial Pressure, PAPsys = Systolic Pulmonary Arterial Pressure

*p < 0.05 between normocapnia and hypercapnia within the same experimental condition of tidal volume

#p < 0.05 between HP-1 and HP-2 within the same experimental condition of tidal volume

Declarations

Ethical Approval and Consent to participate

All procedures were approved by our institution's Animal Studies Committee [EL 42 BIO 04]. All authors have consented to participate in the study.

Consent for publication

All authors consent to the publication of this study.

Availability of data and materials

All the data and materials of the study are available and at your disposal for further examination.

Competing interests

There is no conflict of interest regarding this study.

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Authors' contributions

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Authors' information

Not applicable.

Abbreviations

T= Temperature, HR= Heart Rate, LVt= low tidal volume (6ml/kgr), HVt = high tidal volume (9ml/kgr), MAP= Mean Arterial Pressure, Pairw= Mean Airway Pressure (Pplateau), PAPmean= Mean Pulmonary Arterial Pressure, PAPdias= Diastolic Pulmonary Arterial Pressure, PAPsys= Systolic Pulmonary Arterial Pressure

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Figures

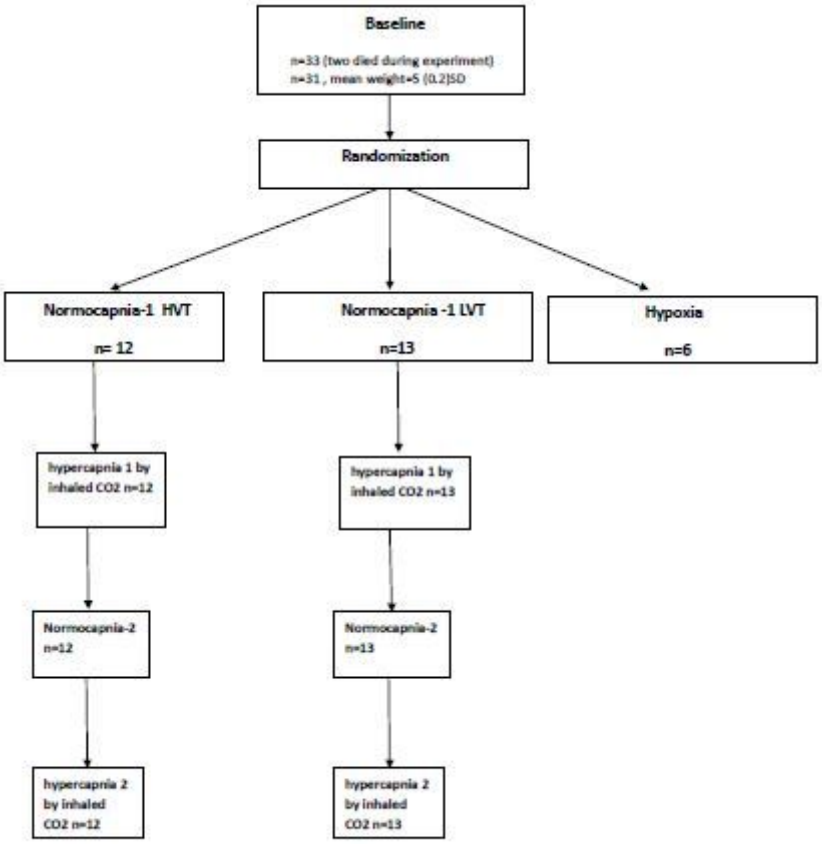

Figure 1

Flowchart of the study.

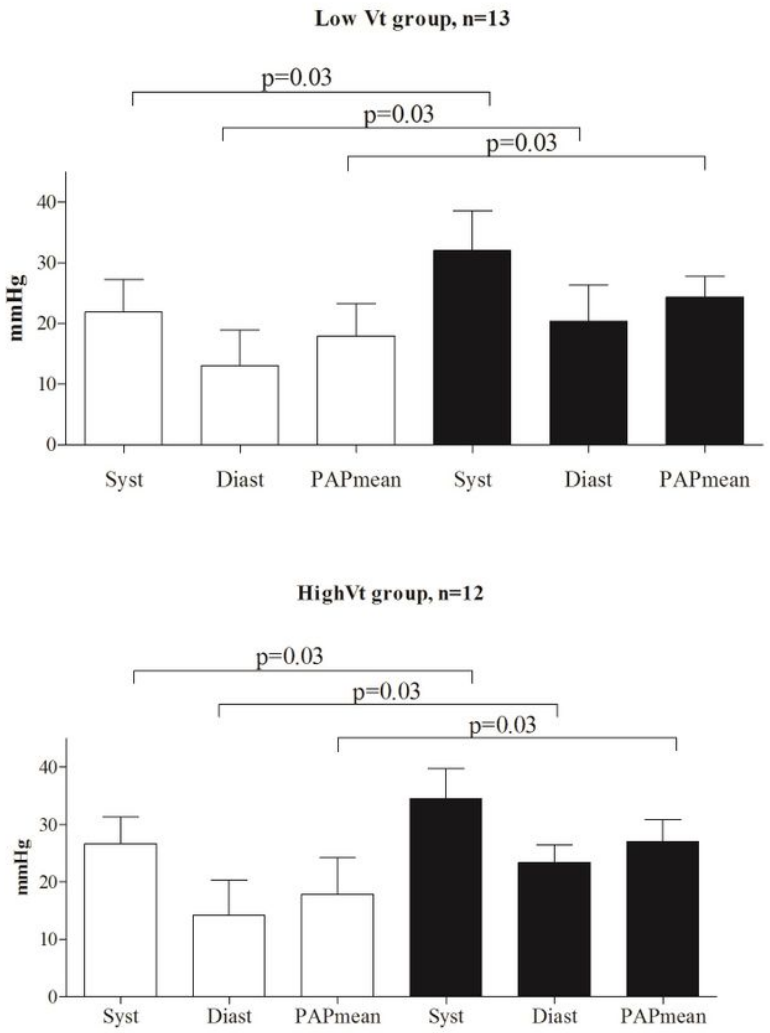

Figure 2

Pulmonary arterial pressures - Systolic (Syst), Diastolic (Dias), and mean (PAPmean) - in animals mechanically ventilated with two different tidal volumes (Low Vt group and High Vt group - 6 and 9 ml/Kg respectively) during normocapnia (Normocapnia-1) and hypercapnia induced using inhaled gas rich in CO2 (Hypercapnia-1). White bars and black bars represent mean(SD) values in normocapnia and hypercapnia, respectively.

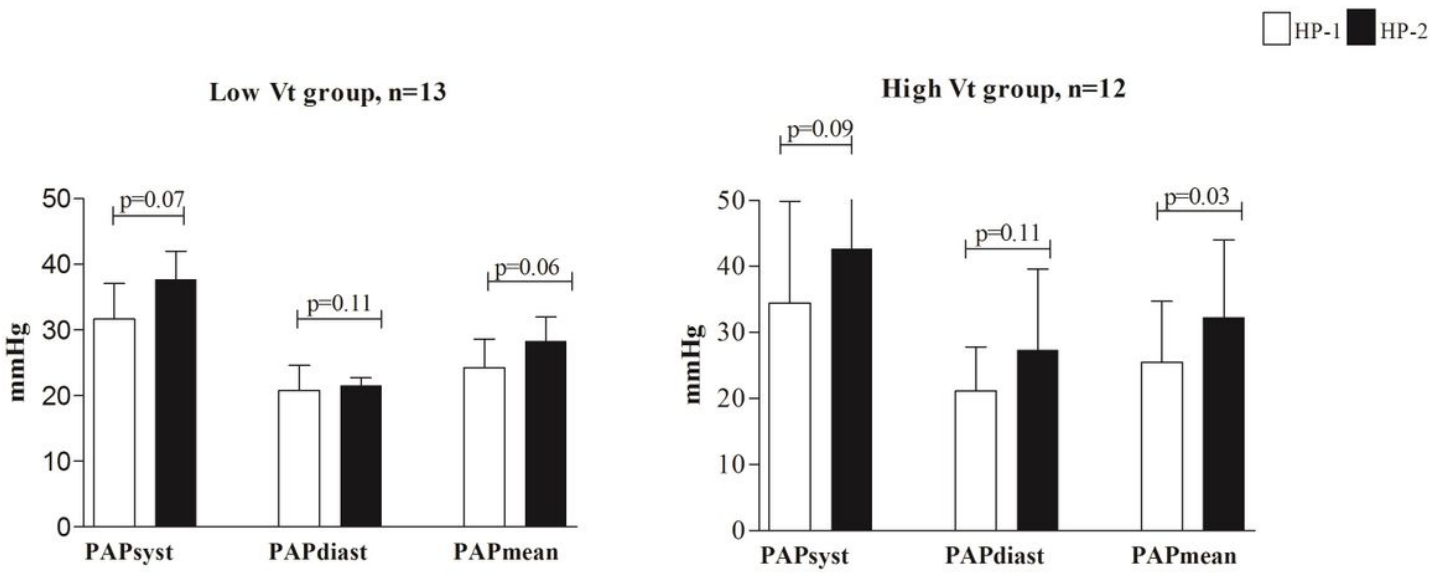

Figure 3

Pulmonary arterial pressures - Systolic (Syst), Diastolic (Dias), and mean (PAPmean) - in animals mechanically ventilated with two different tidal volumes (Low Vt group and High Vt group - 6 and 9 ml/Kg respectively) during the two subsequent phases of hypercapnia (HP-1 and HP-2). White bars and black bars represent mean(SD) values in HP-1 and HP-2, respectively.