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Prototype airway catheters were developed 1) to allow ventilation with a continuous flow of air into the mainstem bronchi (EI) and 2) to oxygenate by flowing O_2 into the trachea (TRIO). Minimum flows (Vmin) using EI and TRIO were 0.2-0.3 L/kg/min air and 90 ml/min O_2 respectively. Vmin was compatible with $PaO_2 > 50$ mmHg and $PaCO_2 < 60$ mmHg for EI and $PaO_2 > 50$ mmHg for TRIO.

Ventilation for up to 4 hours with Vmin EI was carried out in anesthetized dogs and physiological parameters were measured serially during apnea produced by neuromuscular blockade. Vmin EI was repeated after tetrodotoxin (TTX) was infused to produce apnea. Infusion of about 12 ug/kg TTX over 90 min produced apnea and cardiac depression. 0.4-0.5 L/kg/min EI successfully resuscitated dogs and produced neurologically normal survivors within 2-7 days.

Ventilation with Vmin TRIO produced oxygenation for over 2 hours in some animals, and all could be returned to normality by conventional ventilation. Vmin TRIO after TTX was less successful, but all animals survived at least 40 min before blood pressure dropped below 40 mmHg. High-flow (2 L/min) TRIO successfully resuscitated all TTX-poisoned animals and kept them alive for 4 hours. Generous-flow EI (1 L/kg/min) was equally successful in TTX-poisoned animals. Spontaneous respiration returned between 30 and 60 min after 12 ug/kg of TTX given IV over 90 min.

TTX infusion produces both cardiac and respiratory depression with continuous infusion of 0.15 ug/kg/min. Apnea with TTX is accompanied by loss of train of four and lack of response to tetanic peripheral nerve stimulation.

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List of Acronyms Used

ANOVA	=	analysis of variance
CFV	=	continuous flow ventilation
CMV	=	conventional mechanical ventilation
CPAP	=	continuous positive airway pressure
CI	=	cardiac index
CO	=	cardiac output
ECG	=	electrocardiogram
EI	=	endobronchial insufflation
FIO_2	=	fractional inspired O_2
HFO	=	high frequency oscillation
HFSO	=	high frequency superimposed oscillations
ID	=	internal diameter
MAP	=	mean arterial pressure
OD	=	outer diameter
$PaCO_2$	=	arterial CO_2 tension
PaO_2	=	arterial O_2 tension
Part	=	systemic arterial pressure
Paw	=	airway pressure
Pes	=	esophageal pressure
Ppa	=	pulmonary arterial pressure
PVR	=	pulmonary vascular resistance
QS/QT	=	intrapulmonary shunt
SaO_2	=	arterial saturation O_2
$S\bar{v}O_2$	=	mixed venous saturation O_2
SE	=	standard error
SVR	=	systemic vascular resistance
TRIO	=	tracheal insufflation of O_2
TTX	=	tetrodotoxin
Vmin	=	minimum flow

INTRODUCTION

Nature of work

This laboratory study in dogs is designed to examine the efficacy of continuous-flow ventilation (CFV) techniques for resuscitation from apnea in the field. Two CFV techniques were considered as potential candidates for field use. The first is endobronchial insufflation (EI), which oxygenates and removes CO_2 when room air (21% O_2) is insufflated through catheters placed 2-3 cm down each mainstem bronchus[1]. The second is tracheal insufflation of O_2 (TRIO), which oxygenates (but removes little CO_2) when 100% O_2 is given through a single catheter placed within 1 cm of the carina[2]. This report describes our studies into EI and TRIO during the past 1½ years.

Nature of problem

Although medical treatment of the nerve agent casualty in the front-line battlefield is limited, EI and TRIO appear to have potential as techniques to salvage apneic soldiers when conventional mechanical ventilation (CMV) is not available. Logistically, treatment in the battlefield must require simple equipment; must be easy to apply; and, because of the field limitations of O_2 and fresh gas supplies, must be compact. To address the issue of gas supplies, the studies were designed to develop minimum gas flows (Vmin). For TRIO, Vmin was the lowest flow of 100% O_2 compatible with arterial O_2 tension (PaO_2) greater than 50 mmHg after 30 min TRIO. For EI, Vmin was the lowest flow of air providing PaO_2 of more than 50 mmHg and arterial CO_2 tension ($PaCO_2$) of less than 60 mmHg. Additional studies were planned to see if lowering the O_2 concentration with TRIO or increasing it with EI might enable lower gas flows to be used for longer periods.

Background of previous work

Hirsch in 1905[3] and Volhard in 1908[4] showed that O_2 uptake can take place in the absence of any respiratory movements. They studied curarized rabbits supplied with 100% O_2 at atmospheric pressure at the airway opening. CO_2 elimination was ineffective, but O_2 uptake continued for 1-2 hours before the rabbits died from CO_2 accumulation and acidosis. Draper and Whitehead[5] anesthetized dogs in Denver at atmospheric pressures of 630 mmHg. The animals were denitrogenated with 100% O_2 during spontaneous breathing and then given sodium pentothal overdoses to depress respiration. The animals were connected to an O_2-filled spirometer and O_2 uptake was recorded. Oxygenation was maintained for 25 or more minutes without respirations. Draper and Whitehead realized that the prerequisites for successful diffusion respiration were a) denitrogenation, and b) a patent airway.

Holmdahl[6] used dogs, rabbits, and man in his studies of diffusion respiration. The animals were denitrogenated for 45 min during spontaneous respiration from a Krogh spirometer filled with O_2. Inspiration and expiration were separated by a shunt valve. Apnea was produced by intravenous succinylcholine for periods of an hour or more. Holmdahl studied CO_2 excretion when inspired oxygen was obtained from a spirometer at 1 cm H_2O positive pressure and expired gases were bubbled through $Ba(OH)_2$. Despite alveolar CO_2 concentrations averaging 56% after 1 hour of apnea, the $Ba(OH)_2$ remained clear, indicating no CO_2 excretion, and there was no CO_2 when the sampling catheter was in the trachea. However, when the catheter was passed down one of the bronchi, he encountered CO_2 and noted the concentration fluctuating with the cardiac movements. Holmdahl incorrectly explained two reports in the literature of CO_2 excretion during apneic oxygenation as having occurred because of incomplete apnea. He claimed that the convection stream of O_2 into the lungs prevented CO_2 from being eliminated.

Tracheal insufflation was also noted to be ineffective in eliminating CO_2 in apneic animals by Meltzer and Auer in 1909[7]. However, dogs were kept alive for 4 or more hours. The details of the experimental insufflating flows (except that the tracheal airway pressure was 15-20 mmHg) were not given. Holmdahl repeated these experiments[6] using 5 L/min O_2 and found no CO_2 excretion when the insufflating catheter was placed at the bifurcation of the trachea. He noted that if air replaced oxygen as the insufflating gas, the dog immediately became asphyxiated. Because Holmdahl found complete CO_2 retention during apneic oxygenation and tracheal insufflation, he thought the term "diffusion respiration" as used by Draper and Whitehead was misleading, preferring his term "apneic diffusion oxygenation."

Oxygenation using both apneic oxygen flows of 0.5-1 L/min and tracheal insufflating flows of up to 25 L/min was found to be maintained by all investigators. Draper and Whitehead[5] and Holmdahl[6] believed that a partial pressure gradient built up across the alveolar membrane, causing diffusion of O_2 into the blood. The maintenance of adequate oxygenation was dependant on replacement of O_2 diffusing into the blood with O_2 (not air) and the "hemoglobin-oxygen-pump" flow of deoxygenated blood into the lungs. Holmdahl stresses the importance of maintaining blood pressure to provide sufficient pulmonary blood flow. In 9 human subjects, Holmdahl maintained good oxygenation during 6 min of apneic oxygenation. $PaCO_2$ rose to 74 mmHg and blood pressure rose, on average, from 115/75 to 145/90 mmHg. The techniques employed were the same as those he had described for dogs and rabbits.

Frumin et al.[9] described apneic oxygenation in 8 healthy patients in which respiration was stopped for up to 55 min during surgical anesthesia using succinylcholine or curare. $PaCO_2$ reached up to 250 mmHg, with CO_2 rising at a rate of 2.7-4.9 mmHg/min. All patients made uneventful recoveries. The technique employed denitrogenation with 100% O_2 for 30 min, with manual bag ventilation and CO_2

absorption in a circle system with 8 L/min O_2. Respiratory paralysis was achieved and the patient was left connected to the circle system by means of a cuffed tracheal tube. The fresh-gas flow was turned off and the patient breathed from a filled anesthesia reservoir bag. As the anesthesia bag emptied, it was filled every 15 minutes with 2-3 L of oxygen. No dysrhythmia of consequence occurred, and serum potassium changes were not striking.

Little new information was reported in the literature until 1982, when Lenhert et al.[1] described constant-flow ventilation of apneic dogs, using catheters placed at least 2 cm into the bronchi. With this technique, a room air flow of 1 L/kg/min produced PaO_2 of 65-95 and $PaCO_2$ of 35-55 mmHg in apneic dogs. Smith et al.[10] repeated this study in a larger number of animals and found that they could support normal ventilation (PaO_2 69 $\pm$ 5.9, $PaCO_2$ 35 $\pm$ 2.8, and pH 7.35 $\pm$ 0.1) for 5 hours of continuous flow ventilation.

Babinski et al.[11] studied 5 anesthetized adult humans ventilated at flows of 0.6-0.7 L/kg/min EI. After 30 min, PaO_2 averaged 299 $\pm$ 37 mmHg at these flow rates of 100% O_2. There was a significant rise in $PaCO_2$ from 37 $\pm$ 1.9 mmHg to 54.9 $\pm$ 4.0 mmHg. However, in one patient, no rise in $PaCO_2$ occurred. The mean rise in $PaCO_2$ was 0.6 mmHg/min at these flow rates. Watson et al.[12] investigated the effects of varying flow rates over the range 0.18-1 L/sec and found that $PaCO_2$ was relatively constant at flows above 1 L/sec. EI produced normocapnia at a mean flow in dogs of 0.48 $\pm$ 0.21 L/sec, which is approximately 29 L/min. There was no relationship between body weight and the flow required for normocapnia. In humans, Babinski[11] found that, on average, 54 L/min flows did not produce normocapnia, with one exception. Watson[12] felt their data were consistent with a 2-zone model of gas exchange, where bidirectional convective streaming is the dominant mechanism in the airways closest to the end of the EI catheters. Cardiogenic oscillations were the major mechanism in the most peripheral

airways, and jet-induced turbulence assisted gas mixing between the central and peripheral airways.[8,12]

Slutsky et al.[13] investigated the effect of different catheter positions on gas exchange during EI. They found that up to 3 cm beyond the carina, CO_2 removal is increased by advancing the catheter tip towards the alveoli. Between 3 and 4.5 cm beyond the carina, $PaCO_2$ was not different. As EI catheter tips are advanced beyond 4.5 cm, overventilation of specific lung regions occurs, with a plateau in CO_2 elimination. The relative overventilation of the lower lobes in relation to upper lobes results in ventilation perfusion abnormalities and increased alveolar-to-arterial O_2 differences ($A\text{-}aDO_2$). Differences in mean airway pressures of as much as 9 cm H_2O were found between lung lobes during ventilation with EI at 60 L/min[14]. Change in the physical composition of the insufflating gas during EI from oxygen to Helium/oxygen reduced pressure differences among lung lobes during EI[15] and changed CO_2 excretion[15,16]. $PaCO_2$ was greater with 80% He, 20% O_2 than with air. When SF_6 80%, 20% O_2 was used, $PaCO_2$ was less than that achieved with air.

In the presence of abnormal conditions, such as lung injury induced by oleic acid, EI at 1.2 L/kg/min 50% O_2 still provided adequate oxygenation (PaO_2 av. = 104 mmHg) when there was a 25% shunt. $PaCO_2$ increased slightly, to 46 mmHg, with the lung injury, but EI was able to satisfy gas exchange requirements[17]. Babinski et al. showed that EI was effective at producing gas exchange for 5 hours in dogs with open chests[18]. No significant changes were observed in vascular pressures during EI. $PaCO_2$ was 41.8 $\pm$ 1.9 mmHg after 5 hours EI with open chest, as compared to 40.8 $\pm$ 1.9 during closed-chest spontaneous breathing. Oxygenation of 113 $\pm$ 5.5 mmHg during spontaneous breathing with fractional inspired oxygen concentration (FIO_2) 0.4 and continuous positive airway pressure (CPAP) 5 mmHg was similar to that obtained during open chest EI of 138 $\pm$ 11.7 mmHg. This study[18] and the finding of adequate oxygenation and CO_2 removal despite high shunts induced by oleic acid[17] suggests

that EI may be useful in producing gas exchange even when lung function has considerably deteriorated.

Slutsky et al.[2] showed that tracheal insufflation of oxygen at flows of 2-3 L/min provided adequate oxygenation and sufficient CO_2 elimination to sustain life until more definitive, but more difficult-to-implement measures, such as tracheal intubation, could be applied. No denitrogenation with 100% O_2 was necessary before adequate oxygenation and some CO_2 removal could be achieved. Animals ventilated with room air using CMV were studied. CMV was stopped and a 1 or 5 mm ID catheter was inserted to within 1 cm of the carina. Continuous flows of 0.2-3.0 L/min O_2 were given through the catheter. At all flow rates with both sizes of catheters, PaO_2 and $PaCO_2$ initially increased with time. The rate of increase of PaO_2 was greater and $PaCO_2$ lesser with the higher flows. At flow rates of 2-3 L/min, arterial blood gases reached a plateau after about 2 hours of mean PaO_2 = 363 mmHg, mean $PaCO_2$ = 164 mmHg and mean pH = 6.87. No dogs showed signs of cardiovascular collapse or decompensation after 4-5 hours. Dogs up to 48 kg were successfully ventilated using this technique.

This same group of investigators also examined the contribution of cardiogenic oscillations to the production of gas exchange during TRIO[19]. They found that cardiogenic oscillations increased gas mixing about fourfold. The cardiogenic effect was independent of TRIO flow rates between 0.2 and 10 L/min. It can be concluded, then, that cardiogenic oscillations have a negligible effect during bulk convective tidal volume ventilation, but probably play an important role in conditions in which there is hypoventilation.

The major advantages and disadvantages of the two CFV techniques to be considered in this study are summarized in comparison to those of CMV in Table 1.

Of the CFV techniques, EI has this advantage over TRIO: removal of CO_2. TRIO has these

advantages over EI: a) requires low gas flows, making the logistics of field supplies simpler (but O_2 is needed) and b) does not require quite so precise insufflating catheter placement (although EI may be satisfactory after blind placement of the catheter). All of the CFV techniques have these advantages over CMV: they are simple, inexpensive, and have no breakable parts. Low gas flows can provide adequate oxygenation, and higher flows of EI, CO_2 excretion. No translaryngeal tracheal intubation is required and airway pressures are lower than those generated with CMV.

Purpose

The purpose of the present work is to develop EI and TRIO techniques that provide optimum ventilation of apneic animals with minimum fresh gas supplies in the simplest manner. Optimum ventilation may be achieved by examining different catheter designs for EI and TRIO, by use of different concentrations of air and oxygen, or by consideration of adjuncts that might increase the efficiency of gas exchange. These techniques will be used in animals rendered apneic by infusion of tetrodotoxin (TTX). The goal for the first half of the contract is to examine the survival and physiological changes that occur following TTX and EI and TTX and TRIO at Vmin.

METHODS

Beagle dogs of 8-12 kg were used for all experiments except those that examined the effects of body size on gas exchange during EI and TRIO. Mongrels of 15-25 kg were used to determine whether body weight affected gas exchange during low-flow EI and TRIO. Dogs were anesthetized with 30 mg/kg intravenous pentobarbital and maintained with a continuous infusion of 2-4 mg/kg/hr thiamylal and 0.1 mg/kg/hr of pancuronium. The trachea was intubated with either an EI catheter or a TRIO catheter outside a 9 mm ID HiLo jet endotracheal tube (Mallinckrodt, Glens Falls, NY).

The EI catheters were developed in the early studies (described later), but the final design used in

the studies up to the midterm of the contract was a 35 cm long (1 mm ID, 1.9 mm OD) single-lumen catheter, which had stiff plastic tubing with a forked end composed of two flexible 3 cm long prongs (0.8 mm ID, 1.5 mm OD). The prongs formed a 50° angle when unrestrained, but could be held together for placement through the larynx or through a 4 mm ID cricothyroidotomy cannula. The catheters were manufactured to our specifications by Sheridan Catheter (Argyle, NY), (consultants on this contract). The TRIO catheter was a straight 1.5 mm ID catheter, 40 cm long, although we also used 2.5 mm ID catheters and found no differences with oxygenation or CO_2 excretion.

Conventional mechanical ventilation (CMV) with room air was used at a rate of 12/min and tidal volume sufficient to maintain $PaCO_2$ at 35-40 mmHg. The animals were instrumented with pulmonary artery (PA) and femoral arterial catheters. A pulse oximeter (Nellcor, Hayward, CA) was placed on the tongue to continuously monitor arterial O_2. A fiberoptic cable in the PA catheter gave continuous display of mixed venous saturation (Oximetrics, Abbott, Chicago, IL). Neuromuscular blockade by pancuronium was assessed by means of a peripheral nerve simulator placed on the forepaw.

Systemic arterial pressure (Part), PA pressure (P_{PA}), airway pressure (Paw; monitored through a lumen in the wall of the HiLo jet tracheal tube) and esophageal pressure (Pes, from a balloon placed in the lower third of the esophagus) were monitored by pressure transducers (Statham, Oxnard, CA). Electrocardiogram (ECG), Part, Paw, Pes and arterial saturation (SaO_2) were recorded continuously on an 8 channel ink-jet recorder (Mingograf, Siemens Elema, Sweden). A mass spectrometer (Med Spec II, Allegheny Int., St. Louis, MO), calibrated with room air and factory-calibrated 5.1% CO_2, 30.7% O_2 and 0% N_2, was used to simultaneously analyze airway O_2, N_2, and CO_2 in some EI and TRIO experiments and during CMV.

Full sets of physiological measurements were made serially throughout the experiments and included

arterial and mixed venous blood gases and pH, sampled simultaneously and analyzed with temperature correction (IL 713 Blood Gas Analyzer, Fisher Scientific, Lexington, MA) and cardiac output (Qt, measured by thermodilution). Hemoglobin and arterial and mixed venous saturations were also measured from blood samples with a hemoximeter (OSM2, Radiometer, Copenhagen, Denmark).

Task 1 (1st year, 1st 3 months)

1) Prototype catheters for EI were developed and compared.

2) The effect of dog size on catheter placement.

3) The ease of insertion, complications, and accuracy of naive placement of EI catheters were determined.

Task 1 (1st year, 2nd 3 months)

1) Fourteen dogs were ventilated with EI and TRIO. Different FIO_2 and fresh gas flows were employed to determine PaO_2 and $PaCO_2$ levels. The minimum flows (Vmin) and FIO_2 compatible with PaO_2 greater than 50 mmHg during TRIO was determined. Vmin for EI was the minimum flow and FIO_2 compatible with PaO_2 greater than 50 mmHg and $PaCO_2$ less than 60 mmHg.

2) Gas exchange was compared with and without oscillation (1000 cycles/min) of TRIO or EI and with and without external vibration of the chest or abdomen. Physiological measurements, including blood gases, were made before and after institution of oscillations.

Task 1 (1st year, 3rd 3 months)

1) A canine model of respiratory incapacity was developed by using continuous infusion of TTX at a rate of 14 µg/kg TTX given over 90 min.

2) The dose of TTX to produce apnea was determined. An apnea test was developed that included the following criteria: a) lack of movement detected by magnetometers placed across the rib cage

and abdomen, b) no changes in airway or esophageal pressure, c) no evidence of breathing shown on a CO_2 wave form analyzed from the tip of the tracheal tube, d) no volume change detected by a pneumotachograph attached to the HiLo tracheal tube. The dose producing apnea was closely associated with the loss of response to a train of four (T4) and loss of response to tetanic stimulation from a peripheral nerve stimulator placed on the radial nerve of a forepaw. The method of producing apnea and judging when the infusion was nearly complete was greatly simplified by this process and enabled us to titrate the dose to produce apnea very accurately. Rarely in the later studies did we have to repeat an apnea test.

Task 2 (1st year, 4th 3 months)

1) Fourteen dogs were given TTX sufficient to produce apnea as described above. Generous flows of room air EI (1 L/kg/min) and generous flows of TRIO (2 L/min, 100% O_2) were then given. Baseline physiological measurements were made and repeated at 10 min intervals for 30 min after starting EI or TRIO, then at 15 min intervals for an additional 3½ hours.

2) Sacrificed dogs had veterinary pathology performed and pertinent gross and microscopic autopsy findings recorded.

3) Surviving dogs had neurological deficits assessed within 24 hours of finishing the study. These examinations included assessment of gait, mental status, postural reactions, spinal reflexes, and cranial nerves. The examinations were repeated, if a deficit was found. In one animal, $NaHCO_3$ was given after blood pressure dropped on reinstitution of CMV after 4 hours of TRIO.

Task 3 (2nd year, 1st 6 months)

1) Fourteen dogs were ventilated using Vmin EI and TRIO following dosing with TTX sufficient to produce apnea as defined above. Vmin for EI was 0.4-0.5 L/kg/min of room air when TTX was

used. Vmin for TRIO was 90 ml/min, 100% O_2. Physiological measurements were made for 30 min during CMV. During TTX infusion, serial physiological measurements were made until apnea was induced. TRIO or EI then began at Vmin. Measurements were repeated serially every 10 min for 30 min, then every 15 min thereafter for a further 3½ hours. In one animal during recovery from TTX when spontaneous breathing was returning after ventilation with EI, spontaneous ventricular dysrhythmias appeared. Lidocaine reversed them uneventfully.

Data in all experiments were analyzed using paired and unpaired t-tests. Bonferroni corrections were applied when serial measurements were compared. When appropriate, repeated- measures ANOVA techniques were employed.

RESULTS

Task 1

Prototype EI catheters were developed by Sheridan Catheter. The EI catheters used up to the midterm of the contract are described in the Methods. We have recently made a further adaptation to the catheter which will be tested in the next 3 months. The adaptation is to improve the joint between the two prongs that sit astride the carina, and to increase the ID of the prongs from 0.8 mm to 1.0 mm. We had noted that at very low flows (100 ml/min), disparate amounts of gas went down the prongs of the EI catheters. The disparity occurred because of differences in resistance in the two prongs. The improved junction and change in ID of the prongs should equalize flows into each lung. Because the TRIO catheter is straight, no adaptations were necessary.

The catheters are easy to insert. TRIO catheters are placed blindly until resistance is felt, and then withdrawn 4 cm. EI catheters are similarly placed; they, however, are not withdrawn. Fiberoptic bronchoscopy confirms correct placement. In about 80% of the animals, no adjustment is required.

When cricothyroidotomy was used, the complications included perforation of the posterior membrane of the trachea, insertion of the cricothyroidotomy cannula into the paratracheal tissues, insertion of the EI and TRIO catheters into the esophagus (through the posterior wall of the trachea), and blood in the trachea. The ability to pass EI and TRIO catheters blindly and to perform cricothyroidotomies will be assessed more rigorously later in the contract (under Task 5).

The data from the dogs in which different FIO_2 and fresh gas flows were employed are summarized in Figs. 1-8 for TRIO. PaO_2 is flow-dependent in all animals. A higher flow of O_2 gives a higher PaO_2. If PaO_2 fell, then increasing the flow rate of TRIO from 100 to 150 ml increased PaO_2 (Fig. 2). Sampling by mass spectrometry (a continous removal of 150 ml/min of airway gas) reduced PaO_2 at the same TRIO flow (Fig. 3), and the mass spectrometer was not used in subsequent low-flow EI and TRIO studies. None of the animals in Figs. 1-8 were ventilated with less than 80 ml/min TRIO. If FIO_2 less than 1.0 was employed, the arterial O_2 saturation, monitored by pulse oximetry, fell immediately. At low-flow TRIO, no animals maintained adequate oxygenation long enough to obtain a 5 min arterial blood gas when FIO_2 was less than 1.0.

Typical changes in vital signs of a 12 kg animal ventilated at TRIO Vmin are shown in Fig. 9. Fig. 9 shows that mean arterial pressure and cardiac output (MAP and CO, respectively) rose to a peak of about 160 mm Hg and 2.9 L/min after about 45 min of TRIO at 80 ml/min, thereafter declining exponentially to about 60 mmHg and less than 1 L/min after 2 hours. $PaCO_2$ rose non-linearly from about 37-97 mmHg during the first 40 min of TRIO (a rate of 1.5 mm Hg/min). After 40 min, the PaO_2 rise became linear and increased to about 152 mmHg after 120 min (a rise of 0.7 mmHg/min). PaO_2 remained within the range 60-90 mmHg throughout the 2 hours, while pH fell from 7.36 to 6.5 after 100 min. This indicates that cardiac impairment, NOT hypoxemia, causes the study to be stopped at 140

min. We suspect that profound acidosis caused the cardiac impairment. It was usually the case that, during minimum-flow TRIO, acidosis and mypcardial depression, not hypoxemia, limited the duration of TRIO. One animal required $NaHCO_3$ to reverse a fall in blood pressure on reinstitution of CMV after 4 hours TRIO.

The data for EI at different flows with and without superimposing oscillations (HFO) are shown in Figs. 10-15. Generally, external HFO using a vest was more effective at reducing CO_2 but also produced lower PO_2 levels than internal HFO. Internal HFO was the term used for superimposition of HFO (HFSO) onto the fresh gas flow in the EI catheter. In addition, these figures show a variety of gas exchange with different flows and FIO_2. The lowest flow rates at which these 6 animals could be ventilated within the criteria was 0.4 L/kg/min. Higher flows were generally required for larger animals. No difficulties were encounted in catheter placement due to dog size. For internal HFO, a piston pump driven by a linear motor was used. For external HFO, a vest that was inflated over the upper abdomen and then oscillated with the same pump at 1000 cycles/min was employed. The chest was not oscillated because of the foreseen difficulty of creating atelectasis by the tight binding of the vest.

The effects of different catheter sizes on gas exchange are shown in Figs. 15 (A and B), 16, and 17. Fig. 15 compares 3 catheters, a 2.5 mm ID, a 2 mm ID catheter with 1 mm, ID prongs, and a catheter of 1 mm ID throughout at flow rates of 0.6 L/kg/min. The smaller the catheter the better the oxygenation and CO_2 removal. A 1 mm catheter at flows of 0.4 L/kg/min produced better CO_2 removal than the 2.5 mm ID catheter at 0.6 L/kg/min. Figs. 16 and 17 also confirmed these findings using a 3.2 mm ID catheter.

The mean $\pm$ SE of cardiorespiratory variables during 30 min of Vmin TRIO are shown in Table 2. Cardiac index (CI) and Ppa rose, and there was pronounced respiratory acidosis. Arterial and mixed

venous blood gases and cardiorespiratory variables during 2 hours of Vmin TRIO are plotted in Figs. 18 and 19. The effects of superimposed HFO on airway gases during Vmin TRIO are shown in Fig. 20. Blood gases with and without HFO are shown in Table 4. In Fig. 20, Sites 1-4 refer to the airway-gas sampling sites. Site 1 was in a subsegmental bronchus, Site 2 a segmental bronchus; Site 3 in the mainstem bronchus, and Site 4, 5 cm above the carina. Addition of HFO to TRIO decreased O_2 and lowered ($p<0.05$) the concentrations of O_2 at all 4 sampling sites after 5 min (Fig. 20). At Sites 1-4, there were increases in N_2 concentration ($p<0.05$) at 5 min with the addition of HFO. Arterial and airway CO_2 at sites 1-3 fell ($p<0.05$) with HFO at both time points. The 10 min data is similiar to the 5 min data. During TRIO without HFO, O_2 concentration at 5 min was greater at Sites 2 and 3 than at Site 4. This difference was lost with addition of HFO. Similarly the differences in CO_2 concentrations among the various sites present during TRIO were disrupted by the addition of HFSO at both time points. O_2 and CO_2 removed from the airways with HFO was replaced by N_2 found in similiar quantities at each airway sampling site.

Fig. 21 shows the average $\pm$ SE blood gases and cardiovascular variables of 6 anesthetized, paralyzed dogs during CMV (time=o) and 2 hours of endobronchial insufflation at 0.2 or 0.3 L/kg/min of air. The characteristics of the animals and ventilation parameters obtained during CMV and 2 hours Vmin EI with room air are shown in Table 3.

Measurements of cardiorespiratory function during dosing with TTX are shown in Figs. 22 and 23. The serial measurements were made during constant infusion of 0.15 µg/kg/min of TTX and CMV until apnea occurred.

Task 2

Endobronchial insufflation

Serial measurements of physiological parameters were made in the animals rendered apneic by TTX. EI using generous flows (1 L/kg/min) of room air began at a time 0. Baseline measurements at time 0 were made on conventional ventilation before institution of EI. Measurements made during 4 hours of EI are shown in Figs. 24 and 25.

As can be seen from Fig. 24, PaO_2 was significantly less at 10, 20, and 30 min than PaO_2 was at 120 min. PaO_2 was not significantly different at 10 min, compared to time=0 throughout the 4 hours of EI. Spontaneous respiratory efforts began between 45 and 60 min after apnea was produced by TTX. The instigation of respiratory efforts was accompanied by an increase in PaO_2 and a decrease in $PaCO_2$ (though this was not statistically significant). Heart rate rose after 180 min, and cardiac index rose (though this was not statistically significant). Intrapulmonary shunt ($\dot{Q}s/\dot{Q}t$) fell after 2 hours from values obtained after 10 and 20 min EI. Intravascular pressures and resistances were not significantly changed by EI. One animal spontaneously developed ventricular dysrhythmias on recovery from TTX. These were reversed with lidocaine IV.

Tracheal insufflation of O_2

Measurements made during TRIO using generous flows (2 L/min 100% O_2) are shown in Figs. 26 and 27. Baseline measurements were made on conventional ventilation at time=0 after TTX infusion had rendered the animals apneic.

The differences in PaO_2, $P\bar{v}O_2$, mixed venous saturation O_2 ($S\bar{v}O_2$), and pH during TRIO are shown in Fig. 26. $PaCO_2$ progressively rose to about 94 mmHg after 30 min of TRIO. Spontaneous respiration efforts were just detectable at 45 min and increased in volume progressively. After 90 min, $PaCO_2$

remained within the physiological range of normality (around 40 mmHg) for the remaining 2½ hours of the experiment. PaO_2 was instantly elevated by TRIO compared to room air CMV. pH values followed the changes in arterial CO_2. Intrapulmonary shunt (Qs/Qt) was not changed by TRIO or by resumption of spontaneous respiration. Vascular pressures (MAP, MPA), resistances (SVR, PVR) and cardiac index (CI) were unchanged compared to baseline throughout the 4 hour experiment.

Task 3

Endobronchial insufflation

Minimum flows for EI were established as 0.2-0.3 L/kg air (see Table 1 attached). After TTX, we generally found that the dogs given EI required greater than minimum flow to allow survival. If we had continued ventilating with Vmin of 0.3 L/kg, only 1 of our initial 5 dogs ventilated at Vmin would have survived more than 20 min. Therefore, we ventilated the animals at 0.4-0.5 L/kg/min of air (actual flows, 3.4-5.2 L/min). All animals survived 4 hours of Vmin ventilation, and by the end of 4 hours all were breathing spontaneously and did not require mechanical ventilation. Continuous-infusion thiamylal anesthesia was turned off and the animals allowed to waken before extubation of the trachea. All EI Vmin animals were described as depressed by the veterinarian on day 1 after TTX. By day 2, all had improved. By 1 week, all had returned to normal neurological function. The finding of neurological depression on day 1 and the somewhat prolonged recovery is in contrast to the pancuronium low-flow EI animals that were all neurologically normal on day 1. This suggests the depression was due to TTX, since both groups of animals had the same continuous infusion anesthetic given.

Physiological data (mean $\pm$ SE) measured during EI in 5 dogs at 0.4-0.5 L/kg are shown in Figs. 28 and 29, together with statistical differences.

Tracheal insufflation of O_2

TRIO Vmin was 90 ml/min O_2. It was apparent from the first study that these animals would not survive for 4 hours. No spontaneous respiratory efforts were seen in any animals ventilated with Vmin TRIO after TTX. In contrast, when generous flows of 1 L/min O_2 were used with TRIO, spontaneous respiratory efforts returned progressively after 45 min and normocarbia was established after 90 min of TRIO. When Vmin TRIO was employed, despite some animals surviving as long as 105 min, we saw neither spontaneous respiration nor return of any response to T4 or to tetanic peripheral nerve stimuli.

All animals survived at least 40 min of Vmin TRIO. Physiological data are graphed in Figs. 30 and 31. $PaCO_2$ and $P\bar{v}CO_2$ rose and pH fell significantly. Blood pressure, both systemic and pulmonary, fell--though this was not significant. The data shown in Figs. 30 and 31 should be interpreted bearing in mind that the number of animals surviving beyond 40 min progressively declined, as shown in the n values.

We re-instituted conventional ventilation when systolic BP fell below 40 mmHg. In early studies, we had found that the animals tolerated persistent systolic BP of 42-62 mmHg. Immediately after systolic BP fell below 40 mmHg, the animals rapidly deteriorated and died--even though PaO_2 remained above 200 mmHg. By re-instituting conventional ventilation, we could determine whether the more sophisticated equipment that might be available in a field hospital could resuscitate these moribund animals. The field scenario would be the soldier who was evacuated to a more medically sophisticated environment, in which CMV would be available. In all of these animals, room air CMV restored normal physiological function.

The animals were awakened and assessed by the veterinarian. Most dogs were depressed neurologically for 2 days, some for 3 days. All were recovered and were considered neurologically

normal as determined by systematic examination within 1 week. Signs of neurological deficits included hyperreflexia and inactive hindlegs, sluggish eye reflexes, and not eating.

SUMMARY AND IMPLICATION OF RESULTS

TRACHEAL INSUFFLATION OF (Vmin) O_2 (TRIO)

1. Minimum fresh gas flow for TRIO is 90 ml/min for 10-12 kg animals.
2. Requirements for Vmin increase as animal size increases. A 20 kg animal had a Vmin of 125 ml/min.
3. On the basis of volume of airways from the carina to air alveolus in humans, a 70 kg adult would require about 300 ml/min TRIO for it to be efficacious.
4. Acidosis and myocardial depression, not hypoxemia, usually limit the duration of TRIO at minimum flow.
5. Apparent return of physiological function occurs within 20-30 mins of hyperventilation with room air conventional mechanical ventilation after prolonged TRIO.
6. Both internal and external HFO impair gas-exchange TRIO by increasing gas mixing. Other maneuvers that would produce a similiar effect include mass spectrometer sampling and external chest compression such as may be used during cardiopulmonary resuscitation.
7. Lowering FIO_2 with TRIO severely impairs gas exchange and requires greatly increased Vmin to produce a PaO_2 >50 mmHg.
8. Using pancuronium to produce apnea during Vmin TRIO gave an average survival in 6 dogs of 97 min (range 45-140 min) before decompensation occurred.
9. When TTX was employed to produce apnea, survival of 3 dogs ventilated at Vmin TRIO was 40,

43, and 105 min, respectively. There was, therefore, generally shorter survival probably due to the additional cardiac depression produced by TTX.

10. All Vmin-TRIO-ventilated dogs, whether given pancuronium or TTX to produce apnea, could be resuscitated to near normal physiological values by room air CMV as long as CMV was instituted immediately when systotic BP fell below 40 mmHg. The implication is that in a field scenario, where a soldier is evacuated to a more medically sophisticated environment, CMV would be effective resuscitation, even when profound cardiac depression occurs.

11. Neurological recovery to normal function occurred in all generous-flow and Vmin-TRIO animals given pancuronium. Animals who received TTX and generous-flow TRIO generally had mild neurologic dysfunction (sluggish reflexes) which recovered within 36-48 hours. Animals receiving Vmin TRIO had more marked neurological dysfunction (inability to move back legs) which fully recovered in 36-72 hours.

12. When Vmin TRIO and TTX was used, no animals had any signs (detected by magnetometers on the rib cage and abdomen) of respiratory efforts or return of neuromuscular transmission (identified by peripheral nerve stimulation). All other animals, except the low-flow TRIO group, had evidence of respiratory efforts and return of T4 or tetanic stimulation within 30-90 min of the TTX infusion ceasing. Since the anesthetic and TTX infusion techniques were identical in the other animals, this data implicates respiratory acidosis as the cause of the impaired neuromuscular transmission.

13. All three TTX dogs that received Vmin TRIO had low blood pressures, but maintained cardiac output. This suggests that systemic vascular resistance fell.

Endobronchial insufflation (EI)

1. Minimum flow (Vmin) for EI with pancuronium producing apnea varies from 0.2 - 0.3 L/kg in later studies performed using the small catheters.
2. The smallest catheter among 3.2, 2.5, 2.0, and 1.0 mm catheters produced the most favorable gas exchange.
3. Larger animals generally require higher flows to meet the ventilatory criteria of PaO_2 greater than 50 and $PaCO_2$ less than 60 mm Hg. We ~~applied~~ implied a Vmin for a 70 kg adult of 0.6 L/kg equivalent to 42 L/min. In studies not supported by this contract, we have successfully ventilated 7 humans for 20-40 min using an endobronchial flow of 40 L/min. Two humans (one weighing over 100 kg) were hyperventilated with $PaCO_2$ less than 40 mm Hg. We implicate the combined insult of cardiac depression and respiratory impairement as the cause of the higher flow requirements.
4. Increasing FIO_2 of EI to 0.25 in some animals enabled successful reduction of Vmin. However, ventilating with anything other than ambient air makes the important assumption that oxygen can logistically be obtained in the mass-casualty scenario.
5. High pressures are required to deliver the necessary flow rates through 1 mm ID catheters. Ideally the flow should be humidified. In short-term use this may not be necessary.
6. EI at 0.3 L/kg for 2 hours after pancuronium produced neurologically normal survivors. In animals ventilated for 4 hours, we achieved the same outcome.
7. The physiological changes that occur with EI after pancuronium include an increase in cardiac index, mean arterial and pulmonary artery pressures. These changes may be due to hypercapnia. Other blood gas and cardiovascular parameters remain stable.
8. Superimposed HFO onto EI usually impairs gas exchange in dogs ventilated using Vmin.

9. When TTX, not pancuronium, was used to produce apnea, Vmin for room air EI increased to 0.4-0.5 L/kg/min. We implicate the combined insult of cardiac depression and respiratory impairment as the cause of the higher flow requirements.

10. If minimum-flow EI obtained with pancuronium had continued in the dogs given TTX, only one of the five would have survival more than 20 min as systolic blood pressure fell below 50 mm Hg and gas exchange was poor.

11. Conventional mechanical ventilation restored normal physiological parameters and gas exchange when min flow EI failed after TTX dosing.

12. EI flows 0.1-0.2 L/kg higher than Vmin were required to ventilate dogs after dosing with TTX.

13. Neurological outcome with EI flows 0.1-0.2 L/kg above Vmin was more favorable than with Vmin TRIO. The dogs were in a similiar neurological state to those given TTX and generous-flow TRIO. The EI TTX animals were depressed, but showed recovery of the reflex depression by day 2, and all were considered to have normal reflexes and be neurologically normal by day 5.

DISCUSSION

On a L/min basis, the EI flows used in these studies were considerably less than half those used by Watson et al.[12] and Smith et al.[10] Our lower Vmin could be attributed to the use of catheters whose inner diameter (0.8 mm) was smaller than that of the catheters used by Watson and Smith. Decreasing catheter diameter has the same effect on turbulence generated at the catheter exit as increasing the flow rate[20] does.

Our data in Fig. 21 suggest that the period of EI ventilated at Vmin may be extended to more than 2 hours since, except for Part and P_{PA}, blood gases and cardiovascular variables were stable after 90 min. How long low-flow EI will be compatible with survival in an emergency situation is dependent

on many factors, including the time course and magnitude of recovery of spontaneous breathing. In TTX-dosed animals, where apnea was produced with a standardized infusion, EI allowed survival for 4 hours (Figs. 24-25 and 28-29). However, spontaneous respiration returned in about 40-60 min in all animals.

It is difficult to extrapolate from these results the flows compatible with survival in human subjects under similar conditions since, in addition to scaling factors for body size, the differences in canine and human airway geometries must be considered. In clinical studies (not covered under this contract), we have used a 2 mm ID EI catheter and flows of 45 L/min 100% O_2. In 7 patients, PaO_2 values have been in excess of 300 mmHg for 20-40, min and $PaCO_2$ values have varied between 35 and 60 mmHg. The patients have been given EI during harvesting of the internal mammary artery for coronary artery bypass grafting. In all instances, the chest was open by median sternotomy during EI. Patient weight varied from 54 to 110 kg. In all instances, adequate oxygenation was achieved. In 2 patients, one 54 kg and the other 96 kg, hyperventilation ($PaCO_2$ less than 40 mmHg) occurred for as long as 20 min. We think, therefore, that using the catheters we have developed, a clinical EI technique could be developed that is superior to other techniques described in the literature. There are three reports of clinical use of EI using 50-100% O_2 at flows from 0.5 L/kg/min[21,22] to 1.6 L/kg/min[23]. $PaCO_2$ ranged from 55 to 69 mmHg after 8-30 min of EI.

From our EI studies, we demonstrated the efficacy of low-flow EI with air. EI may have a place for emergency use in the field when other techniques may not be feasible or available. Low-flow EI may be able to maintain ventilation and life until more comprehensive life support equipment is obtained.

The results of TRIO are quite different from those of EI because TRIO is a model of respiration in which oxygenation is adequate but CO_2 excretion is extremely limited. In EI, $PaCO_2$--even at Vmin--was

less than 60 mmHg. In the first 10 min of Vmin, TRIO $PaCO_2$ rose rapidly from about 40 to 100 mmHg and then rose to about 170 mmHg in the next 20 min (Fig. 18). We observed, without exception in 9 dogs, that $PaCO_2$ was consistently higher than $PvCO_2$ for all measurements made after starting Vmin TRIO (Table 2). We attributed this to the Haldane Effect. As TRIO progressed, significant CO_2 excretion occurred during Vmin TRIO (Fig. 18), probably assisted by the increased gas mixing due to cardiogenic oscillations. Cardiogenic oscillations are especially important as gas mixing mechanisms during conditions of extreme hypoventilation[24,25]. Another factor causing CO_2 excretion may be the large increase (about sevenfold in 1 hour) in the diffusion gradient for CO_2 from the alveoli to the mouth.

Addition of HFO to TRIO decreased PaO_2 (Table 3) and lowered ($p<0.05$) the concentration of O_2 analyzed at all 4 sampling sites after 5 min (Fig. 20). At Sites 1-4, there were increases in N_2 concentration ($p<0.05$) at 5 min with addition of HFO. Arterial and airway CO_2 at Sites 1-3 fell ($p<0.05$) with HFO after 5 min of HFO (Fig. 20). The 10 min data with addition of HFO were similar to the 5 min data. During TRIO without HFO, O_2 concentration at 5 min was greater at Sites 2 and 3 than at Site 4. This difference was lost with the addition of HFO. Similarly, the differences in CO_2 concentrations among the various sites present during TRIO were disrupted by addition of HFO at both time points. O_2 and CO_2 removed from the airways with HFO was replaced by N_2 found in similar quantities at each airway sampling site. Oxygenation with TRIO occurs because a high concentration of O_2 is rapidly established in the peripheral airways, facilitated by fresh gas flow entry within 1 cm of the carina. Enhanced gas mixing produced by HFO causes ambient gas to dilute the O_2 gradient established between the carina and the alveoli. As a result, N_2 dilutes the O_2 concentration in the peripheral airways so that alveolar O_2 and, ultimately, PaO_2 is lowered.

In light of our finding that increased gas mixing with HFO decreases oxygenation during low-flow

TRIO, and the observation that oxygenation was impaired if neuromuscular block was insufficient and slight respiration efforts occurred, we do not think Vmin TRIO would be useful for ventilation of patients involved in mass casualties. If slight respiratory efforts were made by the casualty victim, then Vmin TRIO would not oxygenate well. However, continuous higher flows of O_2 are beneficial when spontaneous respiratory efforts are present. Our data from experiments using generous-flow TRIO after apnea produced by TTX show that higher flows are efficacious. This is confirmed by Long et al.[26], who found that tracheal oxygen insufflation of 5-20 L/min, 2 cm above the carina through a single catheter, was efficacious in reducing CO_2 and improving oxygenation in an animal model of ventilatory failure produced by partial neuromuscular blockade. Similar efficacy has been shown in humans with CO_2 retention from chronic respiratory failure[27].

To determine whether it might be feasible to use TRIO if upper airway resistance was particularly high, if flow of expired gases was limited by secretions, or if there were even complete upper airway obstruction, we developed a model. The model consisted of a 11.5 cm-long cricothyroidotomy cannula (Portex Minitracheostomy) of 4 mm ID connected to a pair of model lungs. A TRIO catheter (OD, 1.9 mm) was passed down the cricothyroidotomy cannula and pressure was measured in the model lungs during TRIO at various flows. The only exit for gas was the space between the TRIO cannula and the lumen of the 4 mm ID cricothyroidotomy cannula. The highest pressure recorded during 3 L/min TRIO was 3 cm H_2O, suggesting that, with complete airway obstruction, TRIO up to these flows through a cricothyroidotomy may be a well-tolerated event. If a smaller TRIO cannula were used, presumably even higher flows could be employed.

Our studies of Vmin TRIO show that 91 ml $\pm$ SE 5 ml/min of O_2 can sustain life in apneic dogs weighing mean 12 kg for over 2 hours without denitrogenation or preoxygenation. Conventional

ventilation with room air restored baseline blood pressures and arterial CO_2 and returned pH and cardiac output to-near baseline values within 30-60 min in 4 of 6 animals given Vmin TRIO for more than 30 min. In one animal, after 30 min TRIO, arterial pressure fell dramatically to 35 mmHg on institution of positive-pressure ventilation. The hypotension was reversed by intravenous $NaHCO_3$ (50 mEq). In the sixth animal, after 90 min Vmin TRIO, systolic arterial pressure was restored, but cardiac output remained low, at 0.8 L/min compared to a baseline of 1.8 L/min. No inotropic support or supplementary O_2 was given during CMV to any animals in these studies. The limitation to the duration of TRIO, when not caused by hypoxemia, appeared to be due to cardiovascular depression secondary to hypercarbia and acidosis. Humans would require greater Vmin flows because their oxygen consumption is higher than that of anesthetized dogs and their functional residual capacity and physiological dead space are greater. Both Vmin TRIO and EI were roughly correlated with body weight in animals.

TTX appears to be a good model of respiratory and cardiovascular depression. Therefore, it simulates the physiological dysfunction found with organophosphorus poisoning. The TTX dosing produced falls in heart rate, mean arterial pressure, and cardiac index. In early dosing studies, we found that in 3 non-surviving animals, infusion of 13.5 µg/kg over 97 min produced death. In the 5 animals studied subsequently, a dose of 12.3 µg/kg over 87 min produced cardiac depression and apnea, but resuscitation using generous-flow EI at 1 L/kg/min was successful. These observations indicate that a narrow margin exists between the dose that produces apnea and that causing cardiovascular collapse and death. During complete apnea after TTX dosing, PaO_2 and $PaCO_2$ were 73 $\pm$ SE 4.4 mmHg and 55 $\pm$ SE 5.1 mmHg, respectively. Animals started to breathe at a mean time of 50 min, which produced rapid improvement in PaO_2, $PaCO_2$, pH, SaO_2, and SvO_2. In summary, TTX infusion depressed the

cardiovascular system before producing apnea. However, EI with flows of 1 L/kg/min of room air sustained life unless cardiovascular depression was too great. In those circumstances of depression from TTX where systolic BP was less than 50 mmHg and cardiac output under 1 L/min, even conventional ventilation was ineffective in preventing death.

For animals dosed with 12 µg/kg TTX to produce apnea, cardiovascular and respiratory measurements show marked normalization of physiological parameters after 60 min EI (Figs. 24 and 25). This improvement was related to return of spontaneous respiration. Respiration returned with synchronous rib cage and chest wall movements just detectable by the magnetometers. By the time tetanic stimuli and train of four peripheral nerve stimuli had returned, abdominal movements were greater than rib cage. As recovery progressed, rib cage movement increased. There were episodes in which tonic contractions occurred in the abdominal muscles. Periods of intense activity of the musculature of the rib cage and chest wall are associated with a fall in blood pressure and slowing of the heart rate. In one instance during EI and recovery from TTX, when the animal was breathing well, with nearly normal vital signs and blood gas, ventricular dysrhythmias spontaneously appeared and required lidocaine for reversal. At the end of EI, no animals required mechanical ventilation. We measured tidal volumes of 125 ml or more, with rib cage movement predominating.

TABLE 1: Advantages and disadvantages of different ventilation techniques.

	Advantages	Disadvantages
CFV	Simple, no breakable parts. Techniques Gas flows 1 L/kg can provide in general oxygenation and/or CO_2 removal. No translaryngeal tracheal intubation required.	CO_2 excretion not good at low flows. Drying mucosa and heat loss at high flows. Precise catheter positioning in some circumstances.
TRIO	Flow of 2-3 L/min oxygenates and removes some CO_2. No prior denitrogenation required. Normal animals survive at least 5 hrs with no adverse cardio-pulmonary effects. Useable when upper airway obstruction occurs	CO_2 excretion is decreased and $PaCO_2$ oflevels 160 mmHg after 1 hour may cause adverse effects. Precise positioning of cannula difficult though can be achieved blindly. Gas must be supplied at a point 1 cm proximal or up to 1 cm beyond the carina. Unknown effectiveness with abnormal lung pathology. Low airway pressures.
EI	Flow of 0.8-1 L/kg/min oxygenates and removes CO_2. No prior denitrogenation required. Can be used immediately. Less than 100% O_2 effective. Room air ventilates well. Useable with upper airway obstruction if a double ended connector is employed. Lower airway pressures than CMV. Model may be developed to assist blind positioning.	High flows dry mucosa. Large gas supplies required, though one supply could serve several individuals Requirements for catheter position essential for gas exchange.
CMV	CO_2 and O_2 controlled. Positive airway pressure can be applied.	Bulky, complex to operate and requires expensive machines. Requires translaryngeal intubation to be effective. High airway pressure may depress cardiac function.

TABLE 2: Mean ± SE of cardiorespiratory variables during Vmin TRIO in 9 dogs for 30 min.

Variable	BL	10 min	20 min	30 min
HR (min^{-1})	171 ± 9.2	129 ± 11.7	140 ± 12.9	143 ± 12.4
Part (mmHg)	137 ± 6.4	128 ± 6.7	143 ± 6.6	148 ± 6.9
Ppa (mmHg)	17 ± 0.7	23 ± 1.5*	26 ± 1.0*	28 ± 1.9*
PaO_2(mmHg)	103 ± 2.1	94 ± 8.3	96 ± 9.6	89 ± 9.1
PvO_2(mmHg)	50 ± 1.3	63 ± 3.5	70 ± 4.5	68 ± 5.2
pHa	7.3 ± 0.01	7.0 ± 0.01*	6.9 ± 0.01^{*+}	6.8 ± 0.01^{*+o}
pHv	7.3 ± 0.01	7.0 ± 0.01*	6.9 ± 0.01^{*+}	6.9 ± 0.01^{*+o}
$PaCO_2$(mmHg)	35 ± 1.1	104 ± 7.9*	140 ± 13.6*	172 ± 20.8^{*+}
$PvCO_2$(mmHg)	40 ± 1.6	94 ± 7.5^{x*}	128 ± 10.8^{x*}	153 ± 15.1^{x*+}
CI ($L.min^{-1}.M^2$)	3.5 ± 0.2	4.4 ± 0.4	4.6 ± 0.3*	4.6 ± 0.4

*	$p < 0.05$	compared to BL
$^{+}$	$p < 0.05$	compared to 10 min data
^{o}	$p < 0.05$	compared to 20 min data
^{x}	$p < 0.05$	compared to arterial value at same time

TABLE 3: Description of animals and ventilation parameters obtained during conventional mechanical ventilation (CMV) and during 120 min of endobronchial insufflation with room air (EI). V = delivered minute ventilation during CMV. Vmin = minimum EI flows compatible with PaO_2 > 45 mmHg and $PaCO_2$ < 65 mmHg after 30 min. Min-EI PaO_2 = minimum value for PaO_2 during EI; the time after onset of EI that it occurred, t, is in parentheses. Max-EI $PaCO_2$ = maximum value for $PaCO_2$ during EI (time after onset in parentheses).

Dog #	Wt kg	CMV V $L.kg^{-1}.min^{-1}$	EI Vmin $L.kg^{-1}.min^{-1}$	CMV PaO_2 mmHg	CMV $PaCO_2$ mmHg	Min-EI PaO_2(t) mmHg(min)	Max-EI $PaCO_2$(t) mmHg(min)
1	10.5	0.4	0.2	111	36	51 (90)	72 (105)
2	9.5	0.3	0.2	107	34	60 (105)	65 (105)
3	8.0	0.4	0.3	107	36	62 (105)	61 (120)
4	9.5	0.3	0.3	103	37	56 (120)	68 (120)
5	10.0	0.3	0.3	97	34	43 (90)	71 (90)
6	10.0	0.3	0.3	109	32	38 (120)	80 (120)
Mean	9.6	0.33	0.27	106	35	51 (105)	69 (110)
±SE	0.4	0.02	0.02	5	1	4 (6)	3 (5)

TABLE 4: Arterial blood O_2 (PaO_2) and CO_2 (PaO_2) after 5 and 10 min of TRIO or TRIO + HFSO in six dogs.

TIME	5 MINUTE		10 MINUTE	
INTERVENTION	TRIO	TRIO + HFSO	TRIO	TRIO + HFSO
PaO_2 (mmHg)	75 ± 5.2	39 ± 3.0*	77 ± 6.9	35 ± 3.8*
$PaCO_2$ (mmHg)	80 ± 5.2	63 ± 3.0*	101 ± 6.0+	74 ± 4.8*+

* P<0.01 TRIO vs TRIO + HFSO

\+ p<0.005 different from 5 min value

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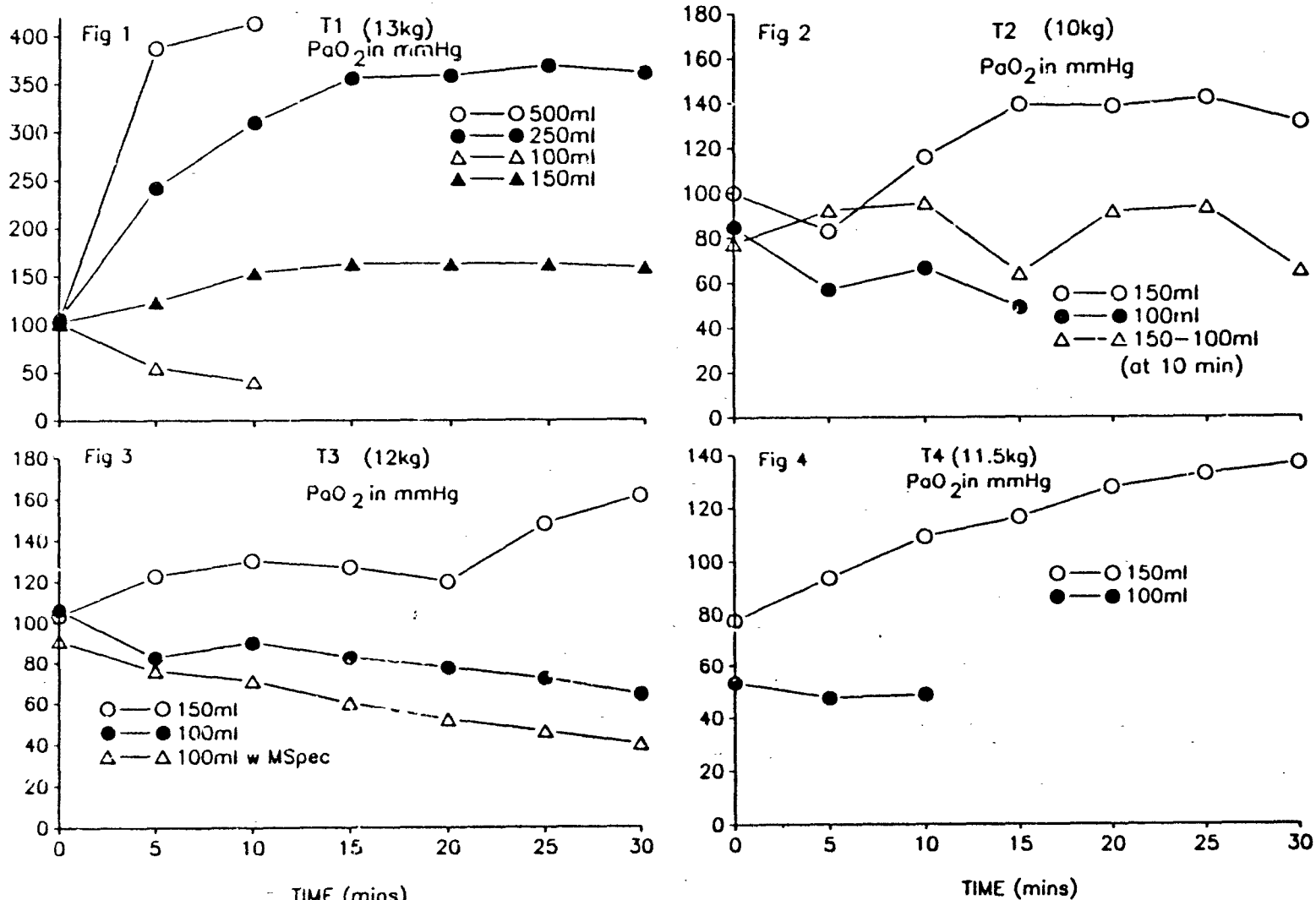
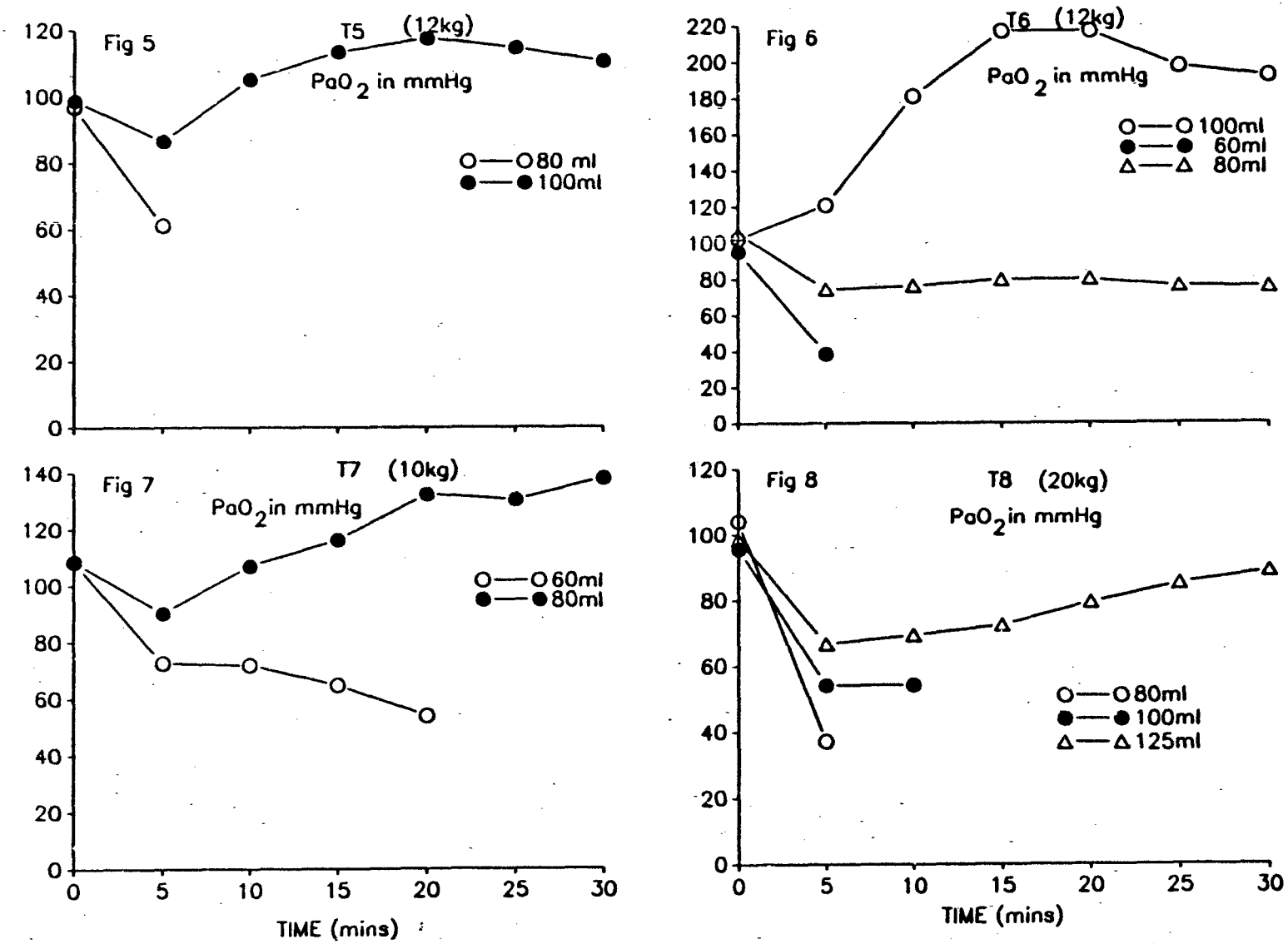


Figures 1-4. Data identifying PaO_2 with different TRIO flows, ranging between 100 and 500 ml/mm O_2. Animal weight and legends identifying flow rates used are shown in each graph. In Fig. 3, the effect of continuous gas sampling by mass spectrometer (MSpec) is shown. In Fig. 2, 150-100 ml at 10 min means that flow was reduced from 150-100 ml after 10 min.



Figures 5-8. Data identifying PaO_2 with different TRIO flows, ranging between 60 and 125 ml/min O_2. Animal weight and legends showing flow rates used are on each figure.

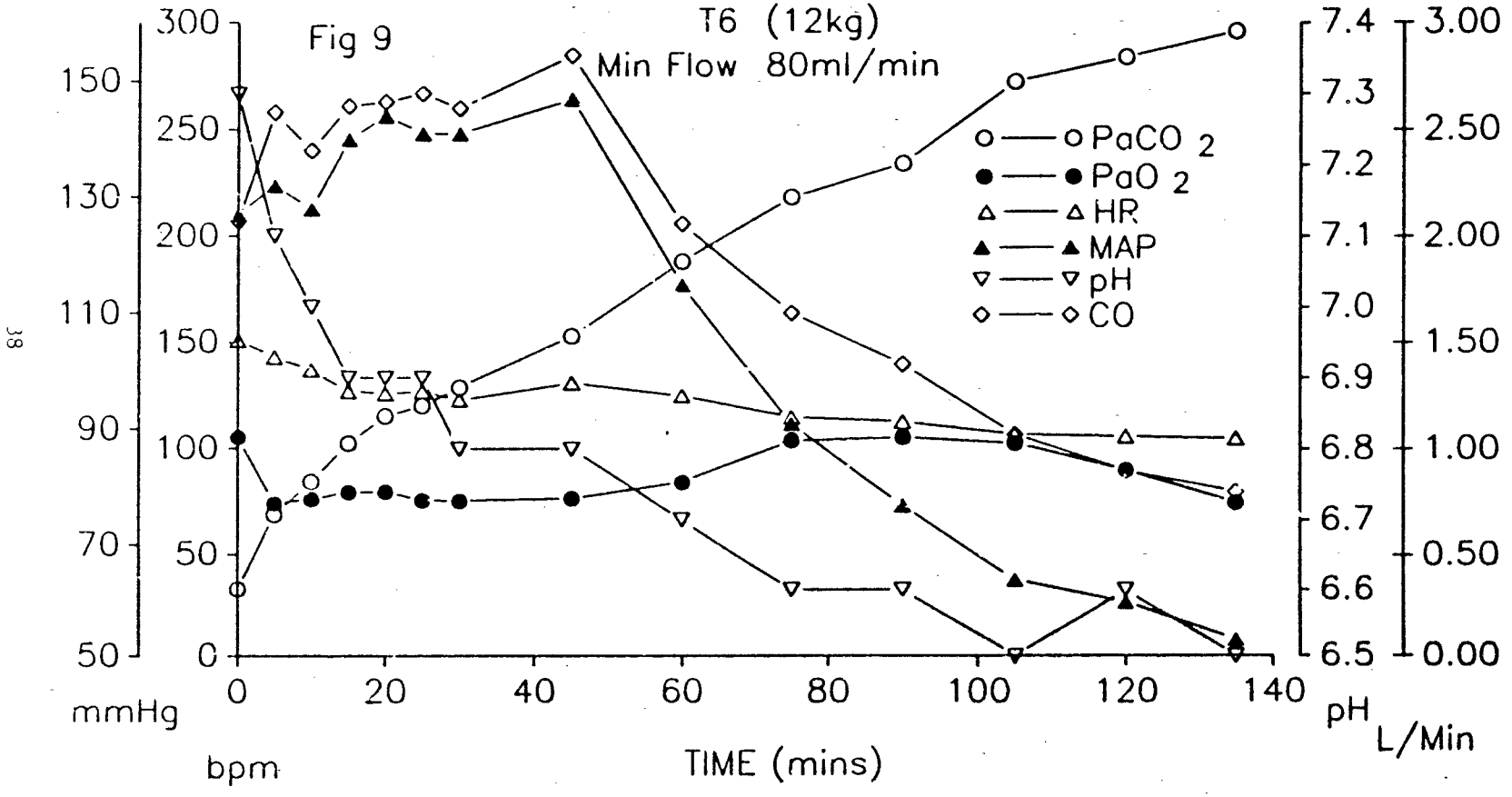
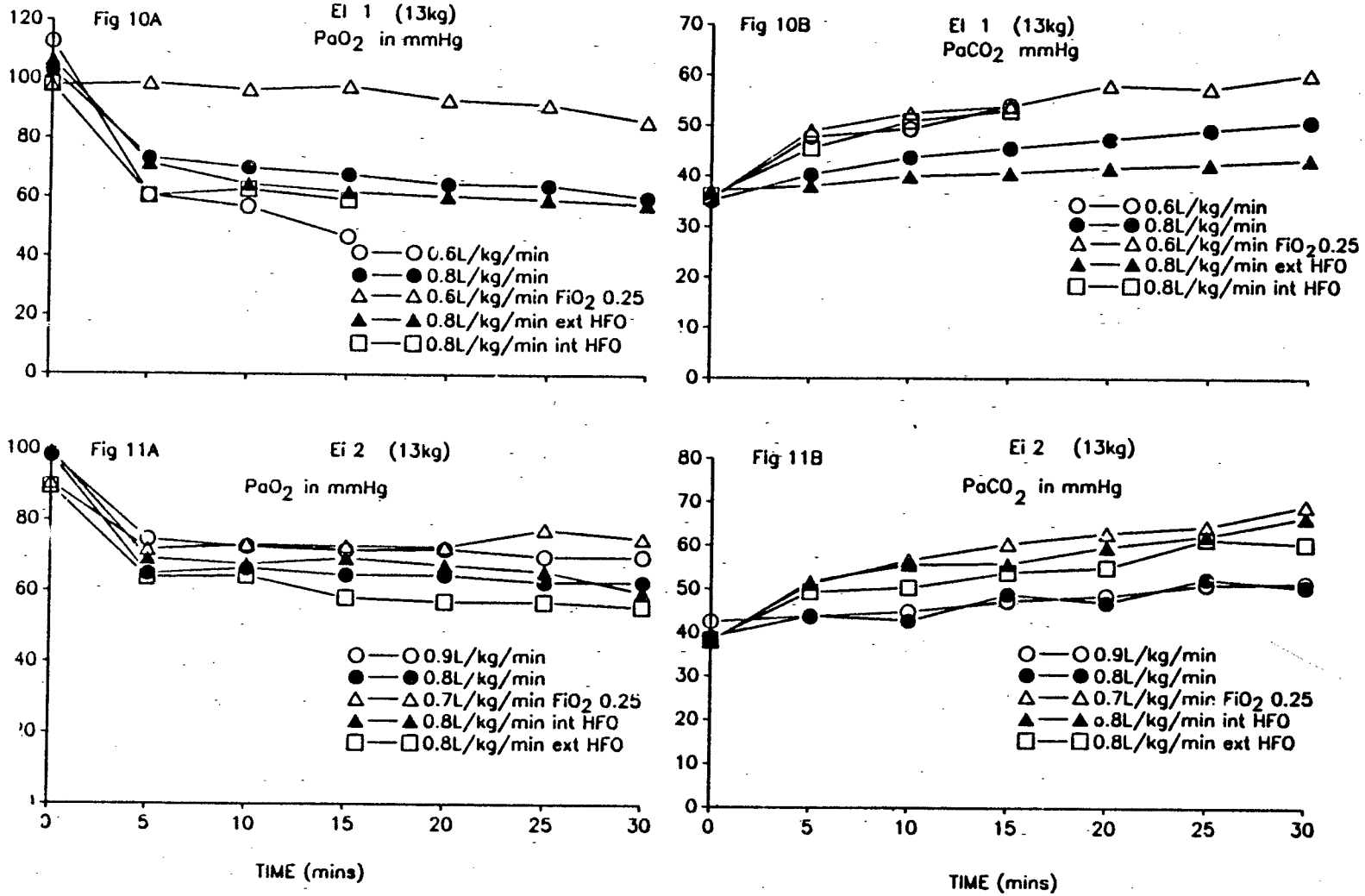
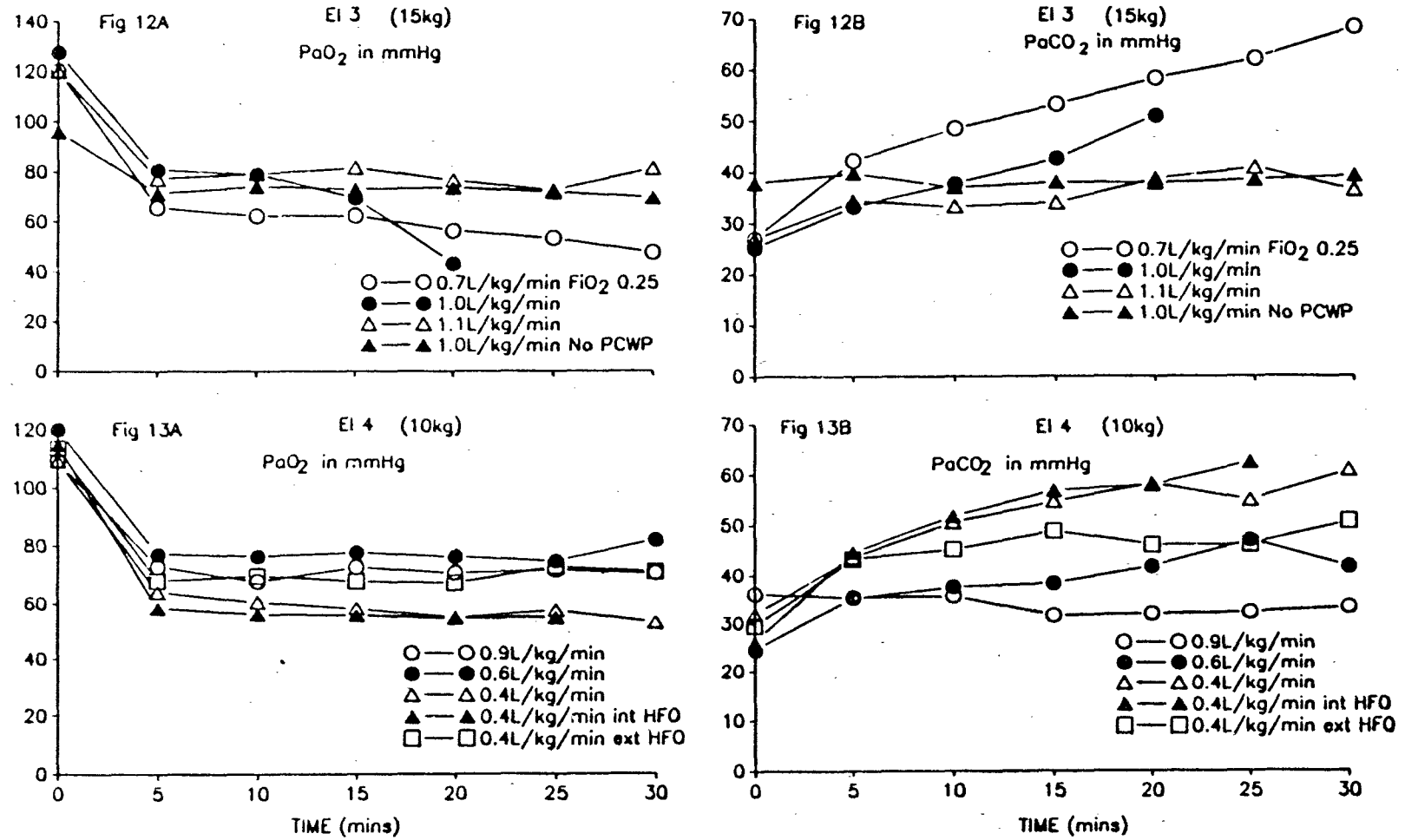


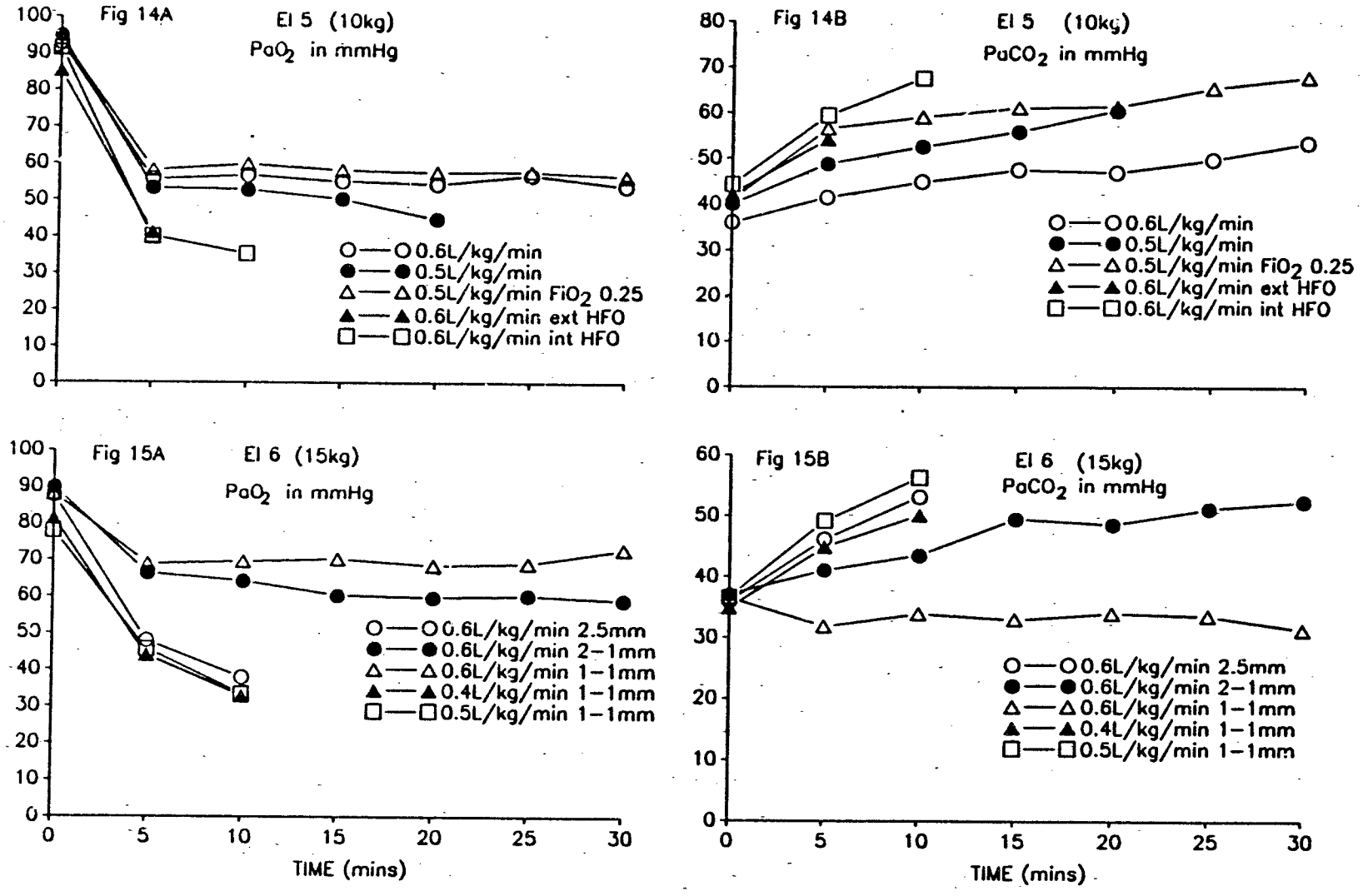
Figure 9. Typical changes in physiological parameters of a 12 kg dog ventilated at TRIO 80 ml/min for 130 min. Note the 4 axes.



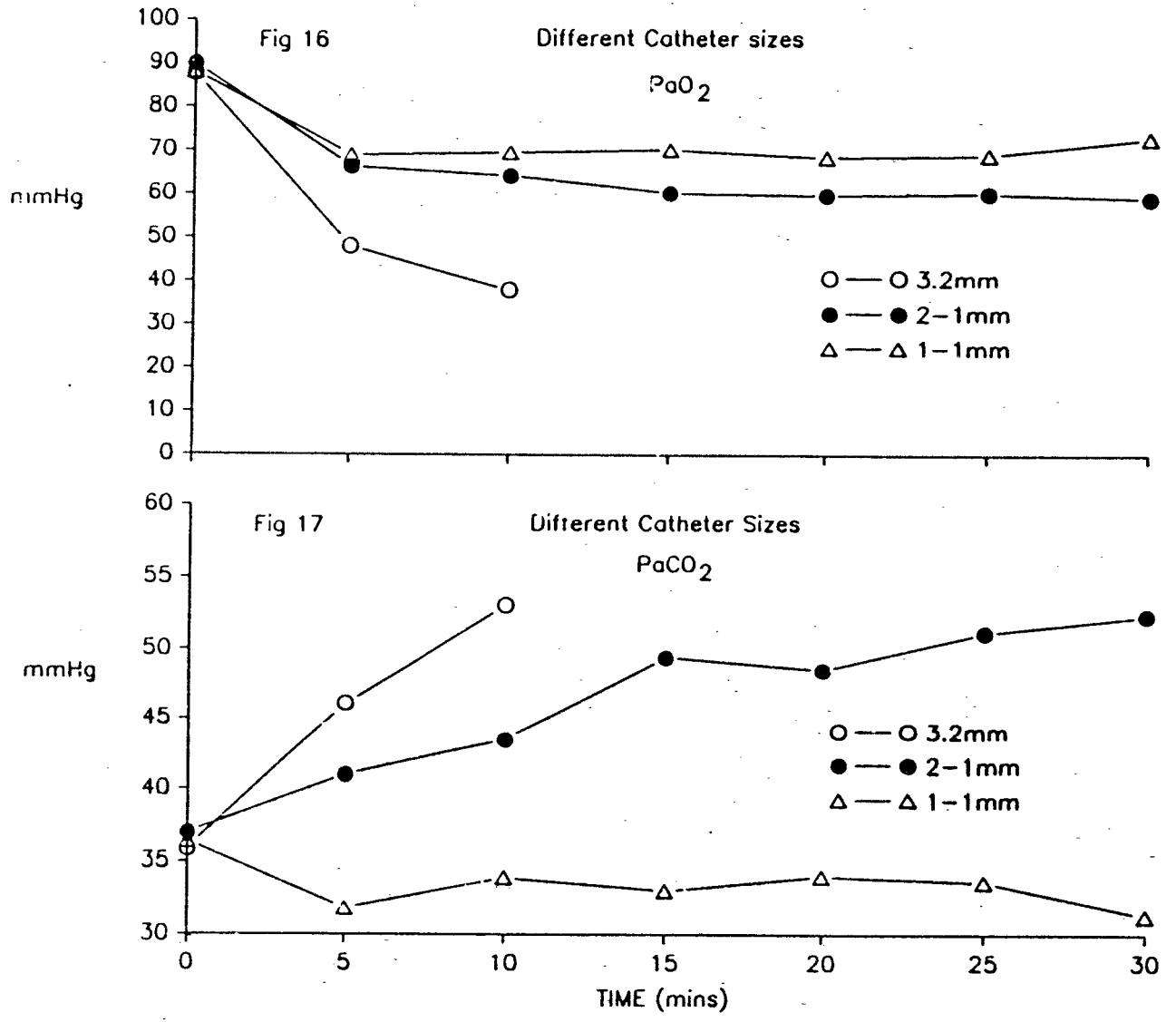
.es 10 and 11 (A,B). PaO_2 (left-side graphs) and $PaCO_2$ (right-side graphs) during different flows of EI. The legends show the symbol used for each flow. Ext HFO refers to oscillation of an abdominal binder at 1000/min. Int HFO refers to superimposed HFO onto the EI flow at Vmin.



Figures 12 and 13 (A,B). PaO_2 (left-side graphs) and $PaCO_2$ (right-side graphs) during different flows of EI in dogs of different weights. The legends show the symbol used for each flow. Ext HFO refers to oscillation of an abdominal binder at 1000/min. Int HFO refers to superimposed HFO onto the EI flow at Vmin.



Figures 14 (A,B) and 15 (A,B). Show PaO_2 (on left) and $PaCO_2$ (on right) with different EI catheters and flow rates. 2.5 mm = 2.5 mm ID, 2-1 = 2 mm single catheter with 1 mm ID prongs. 1-1 = 1 mm ID catheter with 1 mm ID prongs. HFO int and ext refer to internal HFO to EI Vmin and external oscillation with abdominal binder.



Figures 16 and 17 show the effects of different catheter sizes on PaO_2 (Fig. 16) and $PaCO_2$ (Fig. 17)

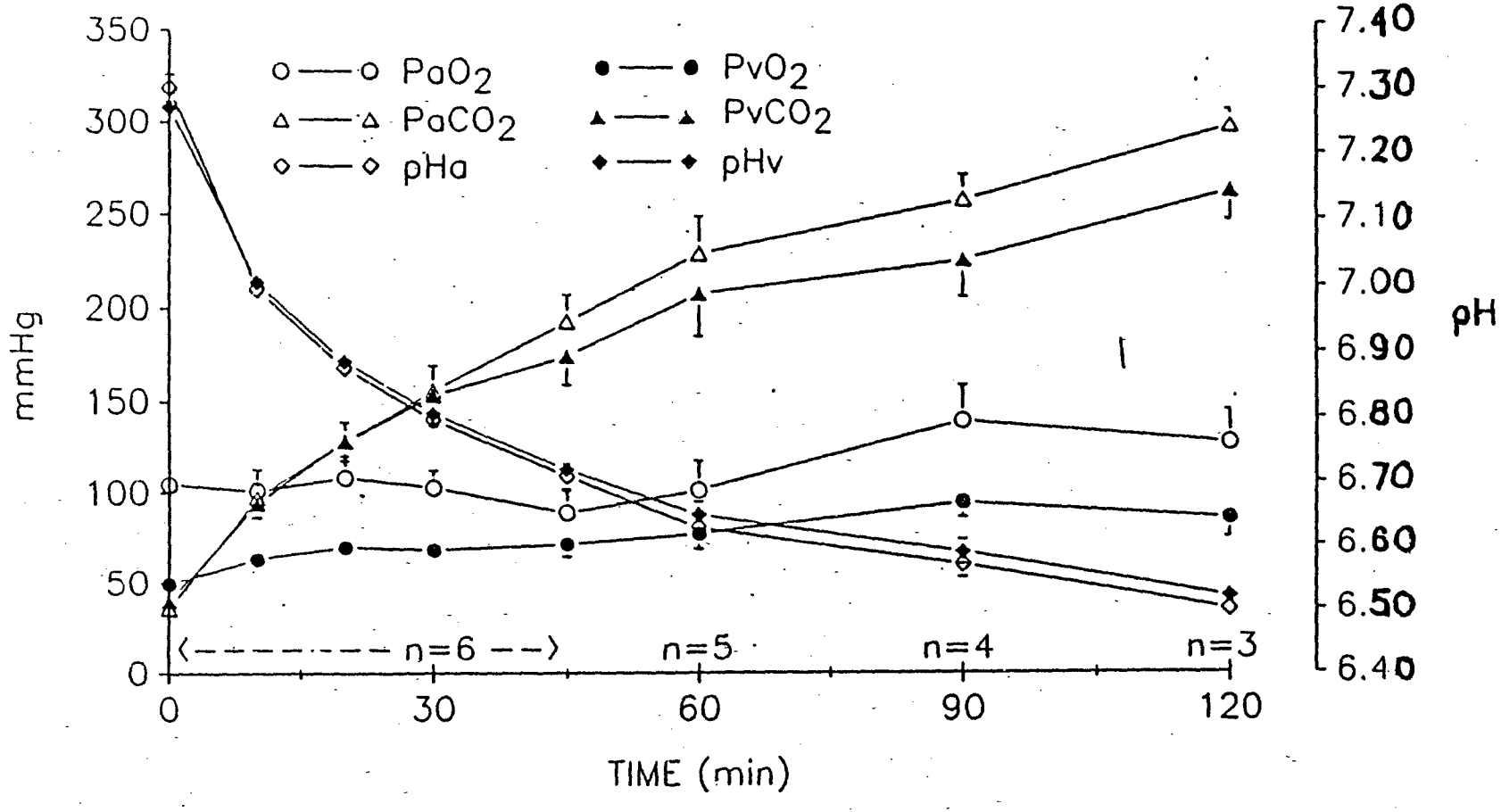


Figure 18. Mean ± SE of PaO_2, $PaCO_2$ and pH during prolonged minimum-flow TRIO of 91 ± SE 5 ml/min.

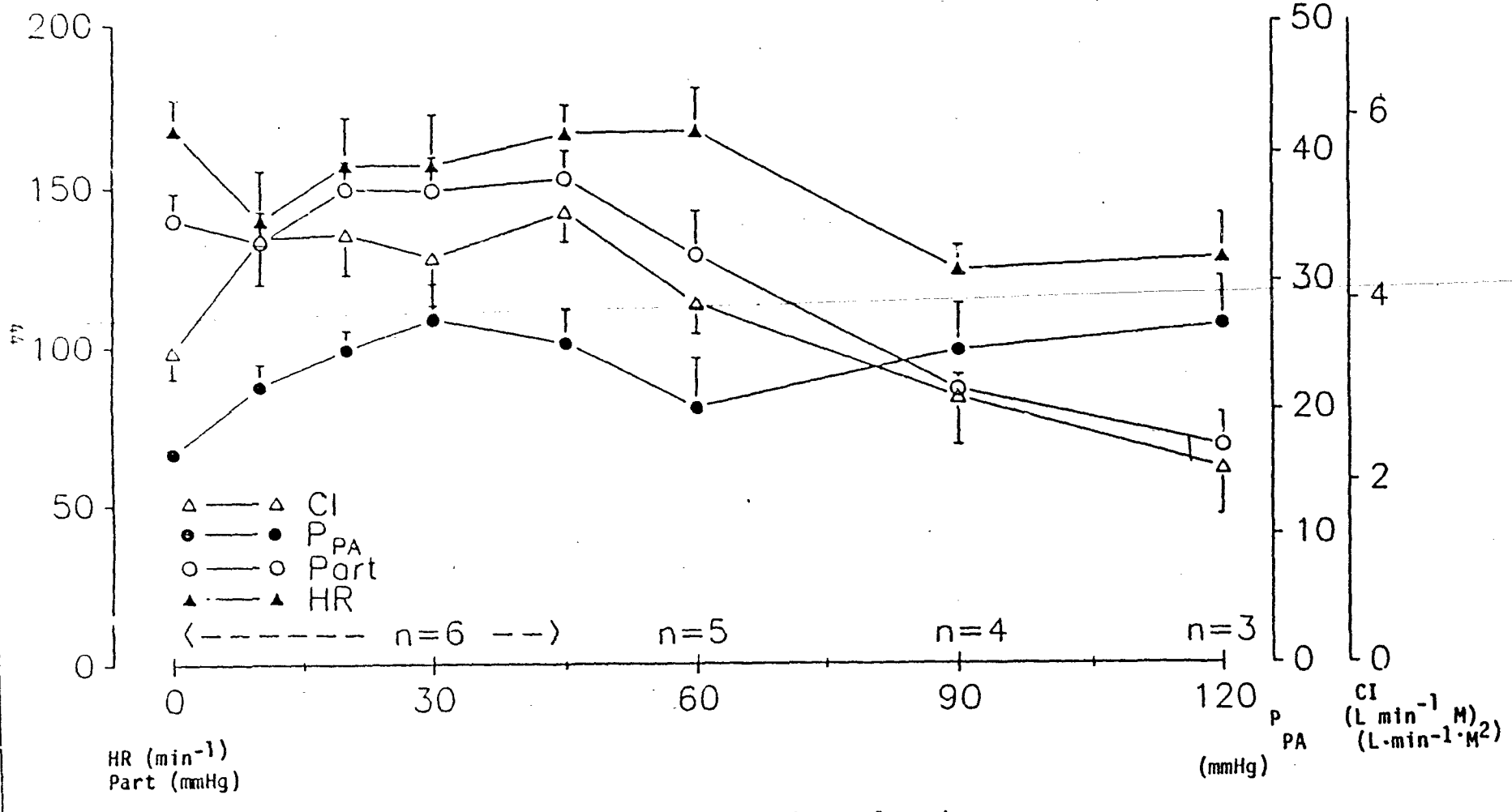


Figure 19. Mean ± SE of cardiorespiratory variables during prolonged minimum-flow TRIO of 91 ± SE 5 ml/min. n= # dogs in displayed data.

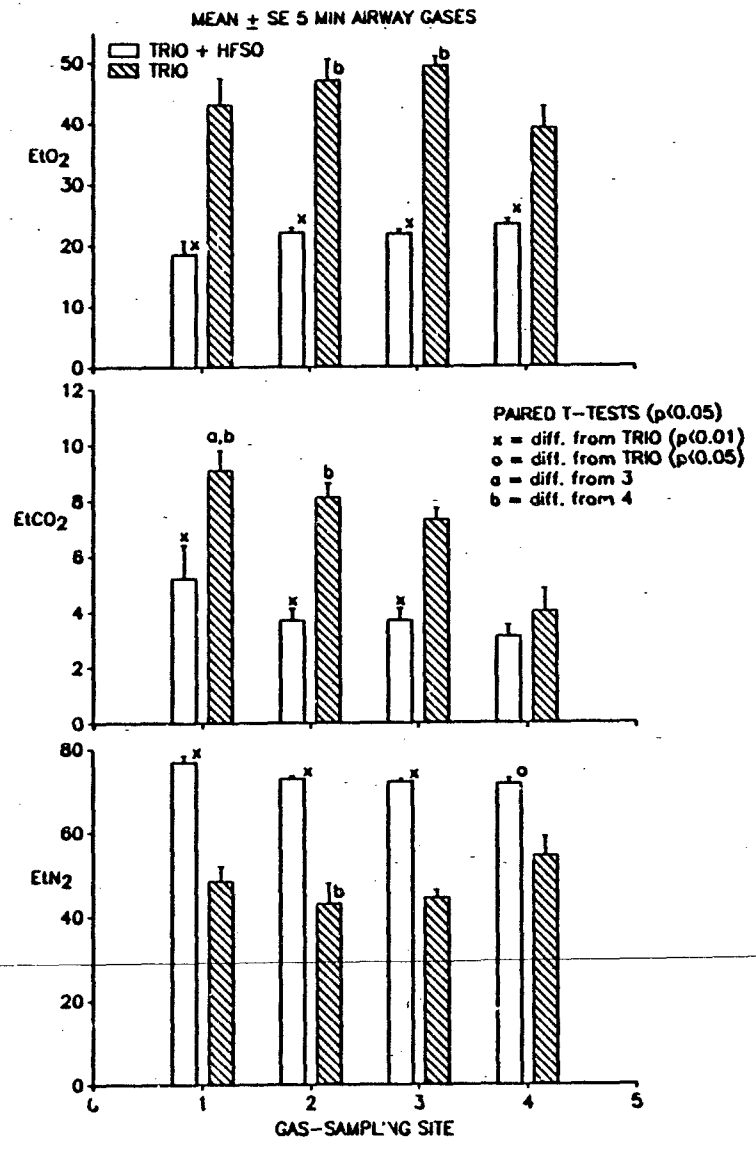


Figure 20. O_2, CO_2 and N_2 concentrations (%) simultaneously sampled from sites 1-4 (see text) with TRIO and TRIO + HFSO.

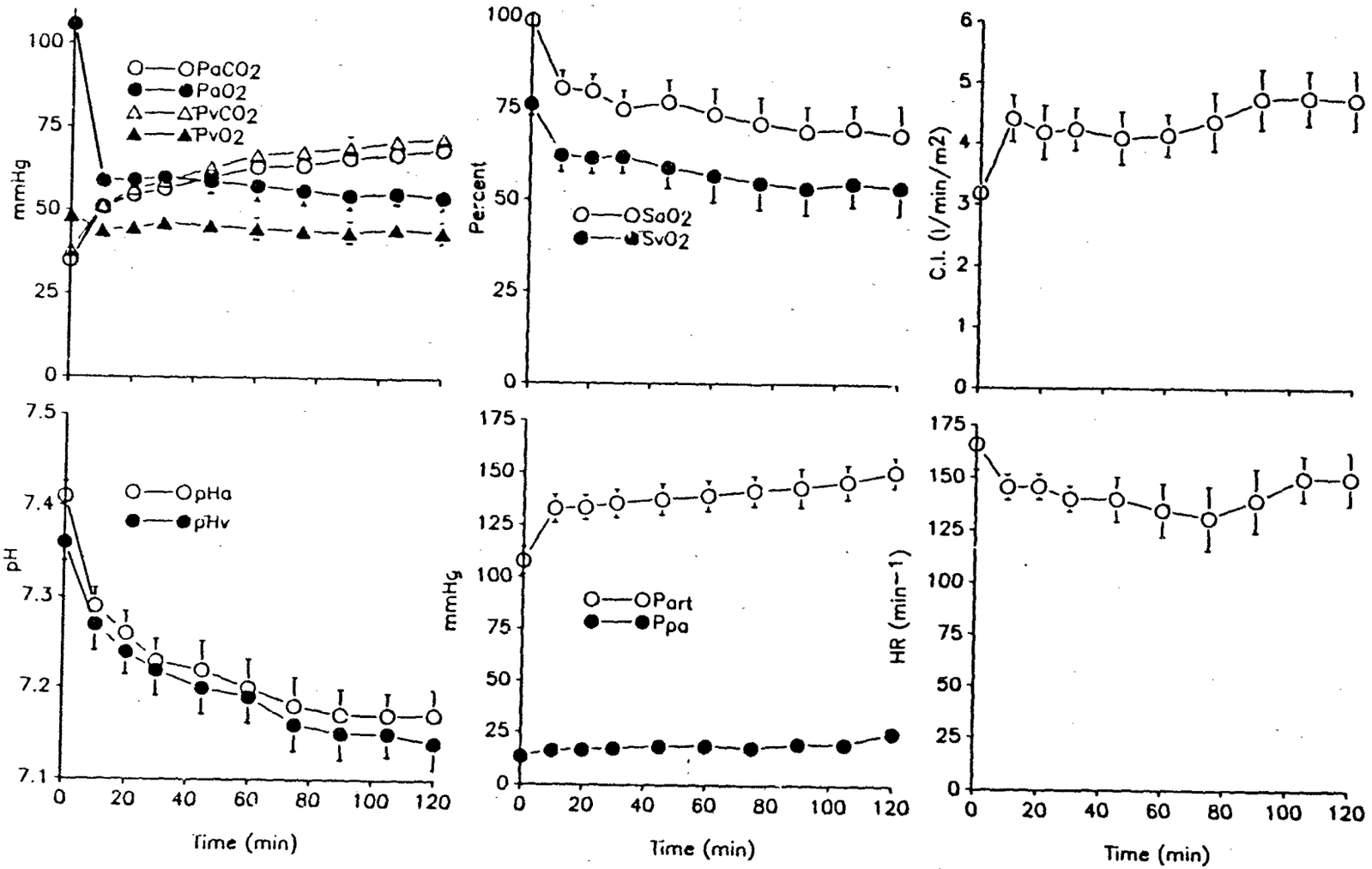


Figure 21. Mean ± SE blood gases, intravascular pressures, Part (mean arterial), PPA (mean pulmonary artery), heart rate (HR) and cardiac index (CI) in 6 anesthetized and paralyzed dogs during CMV (time = 0) and 2 hours EI at 0.2 or 0.3 L/kg/min air.

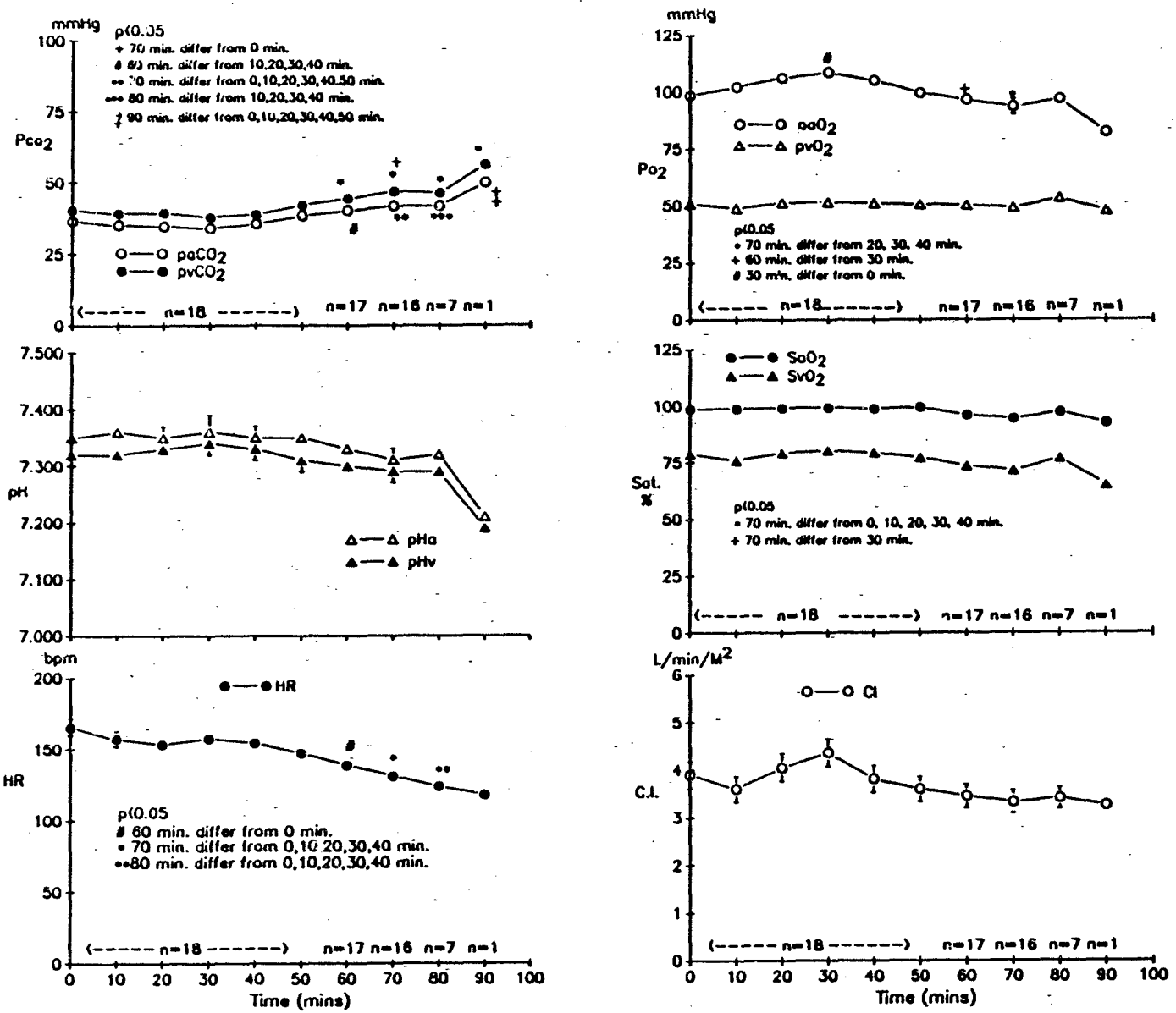


Figure 22. Cardiorespiratory variables of 18 dogs during infusion of 0.15 ug/kg/min TTX until apnea occured.

Tetrodotoxin Dosing

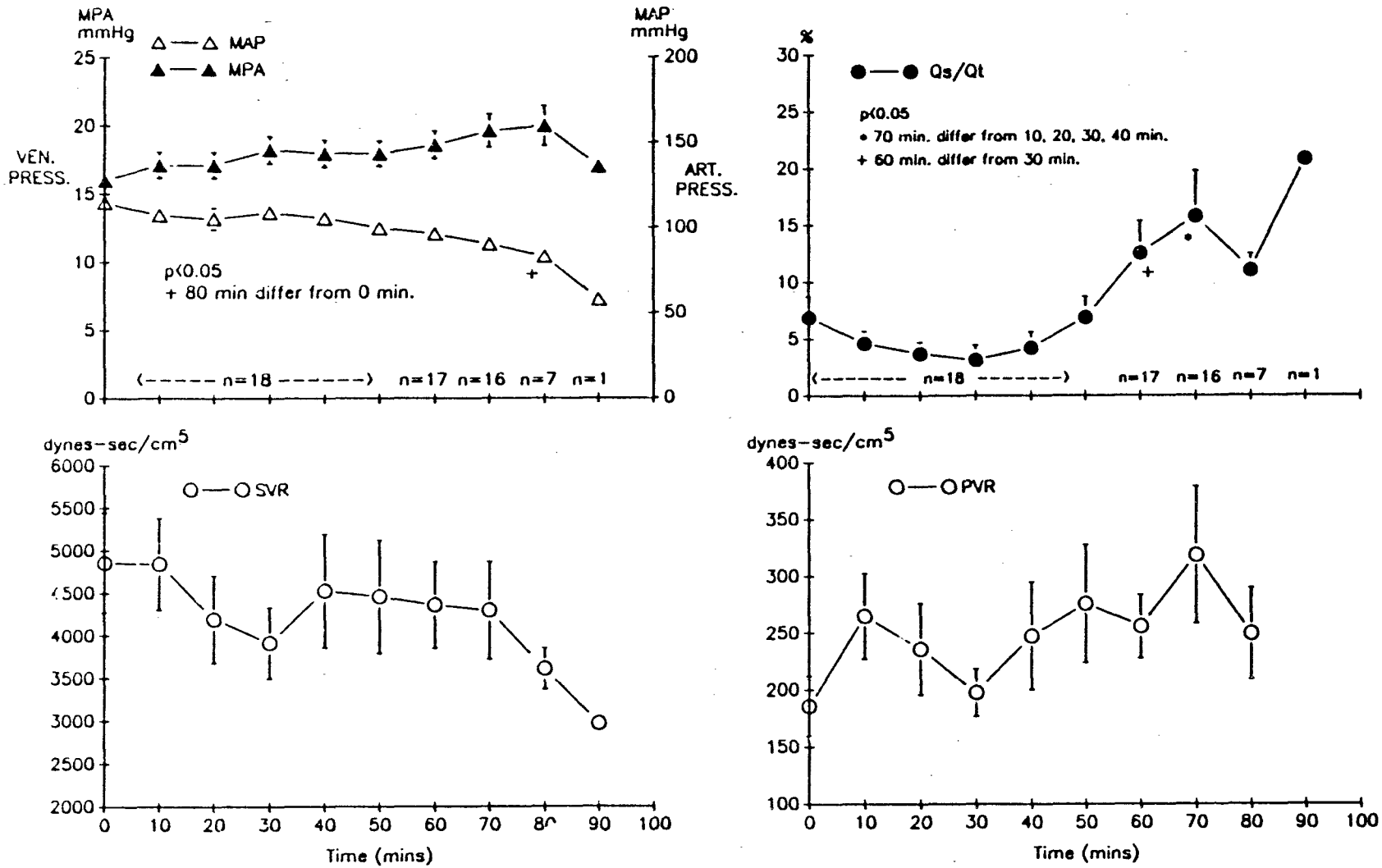


Figure 23. Cardiorespiratory variables of 18 dogs during infusion of 0.15 ug/kg/min TTX until apnea occurred. MAP = mean arterial pressure; MPA = mean pulmonary artery pressure; Qs/Qt = intrapulmonary shunt; SVR = systemic; and PVR = pulmonary vascular resistances.

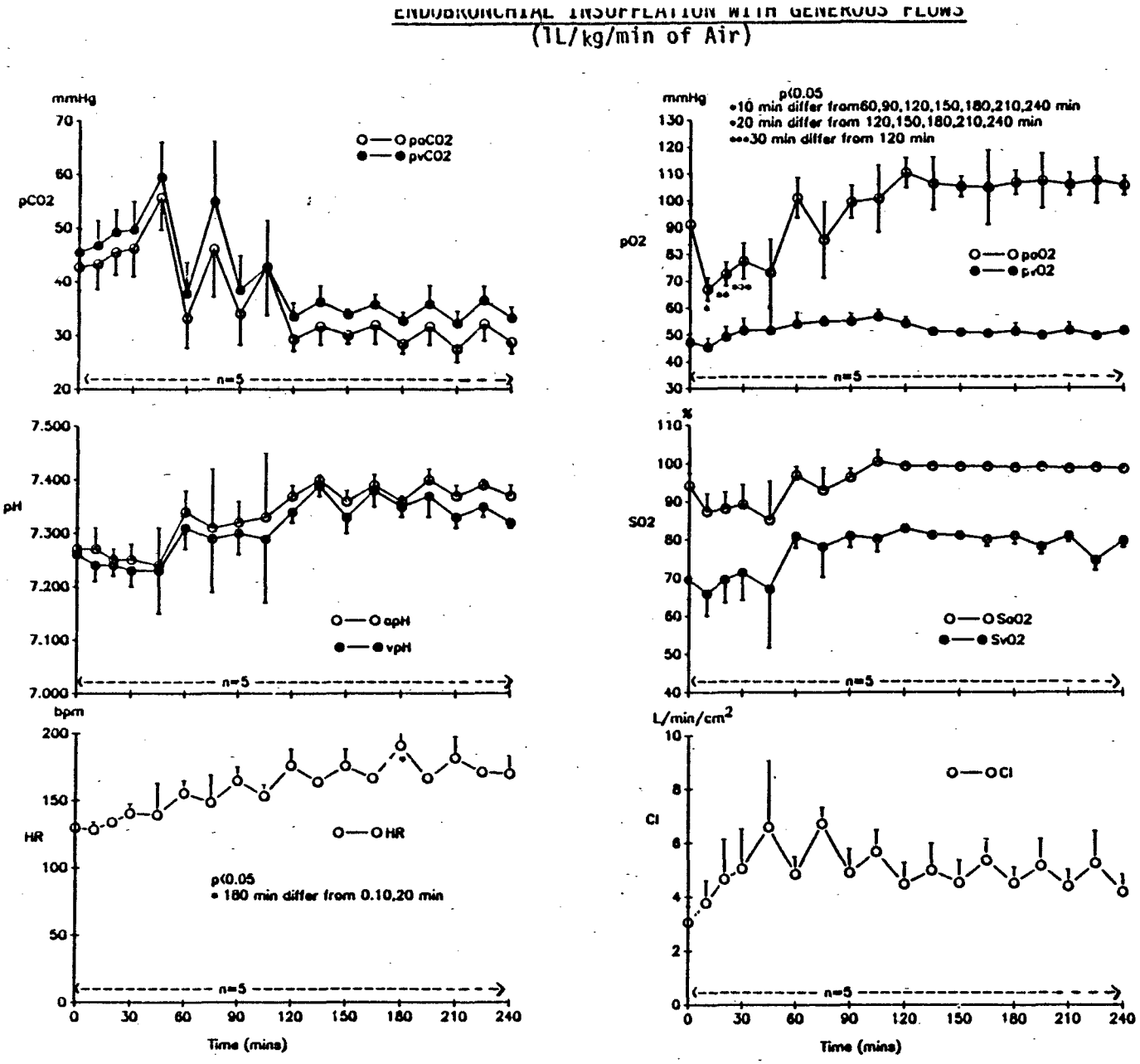


Figure 24. Physiological parameters on CMV (time = 0) and during endobronchial insufflation with generous flows of room air during 4 hours of 1L/kg/min EI.

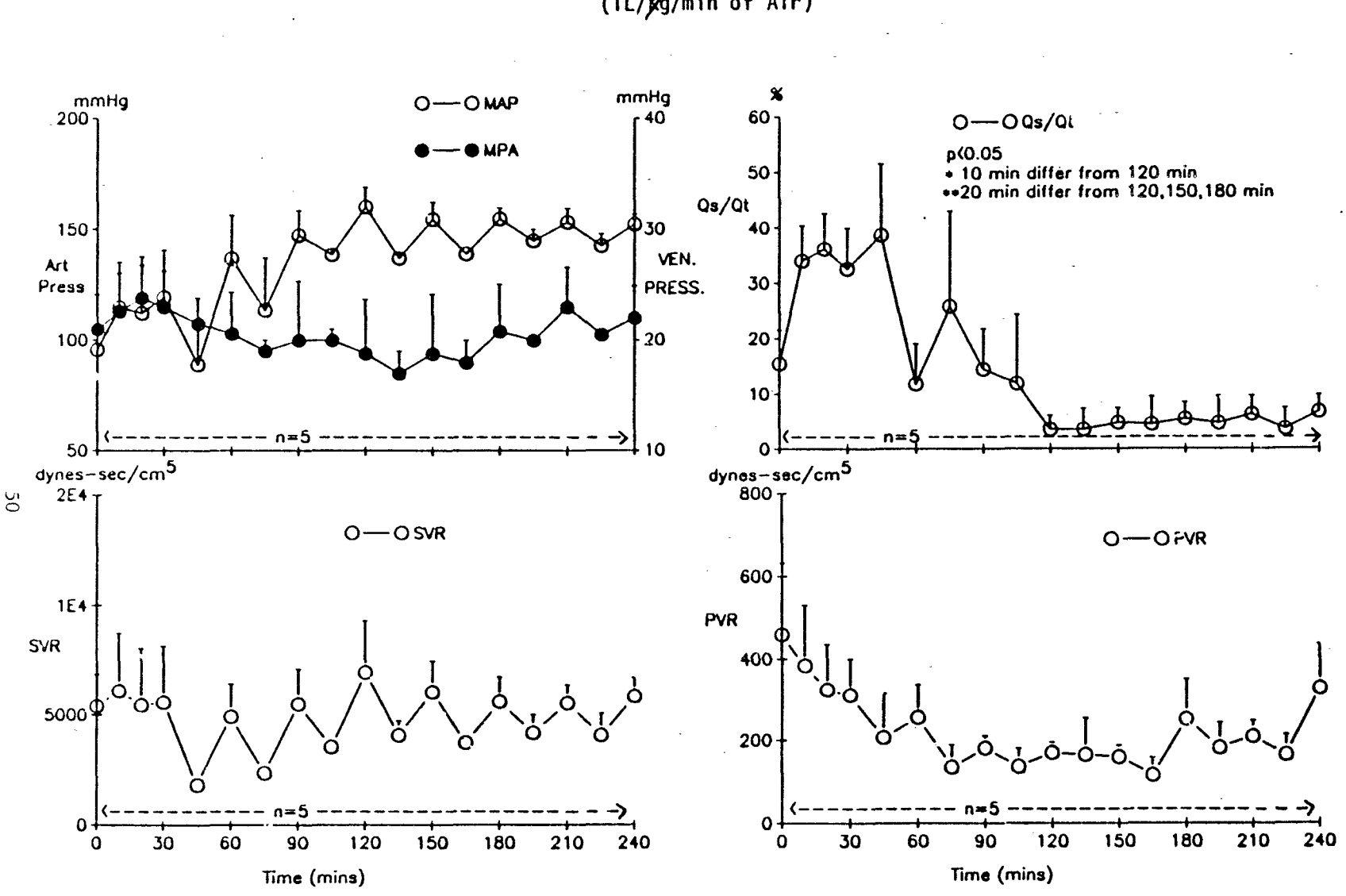


Figure 25. Physiological parameters on CMV (time = 0) and during 4 hours EI, using generous flow.

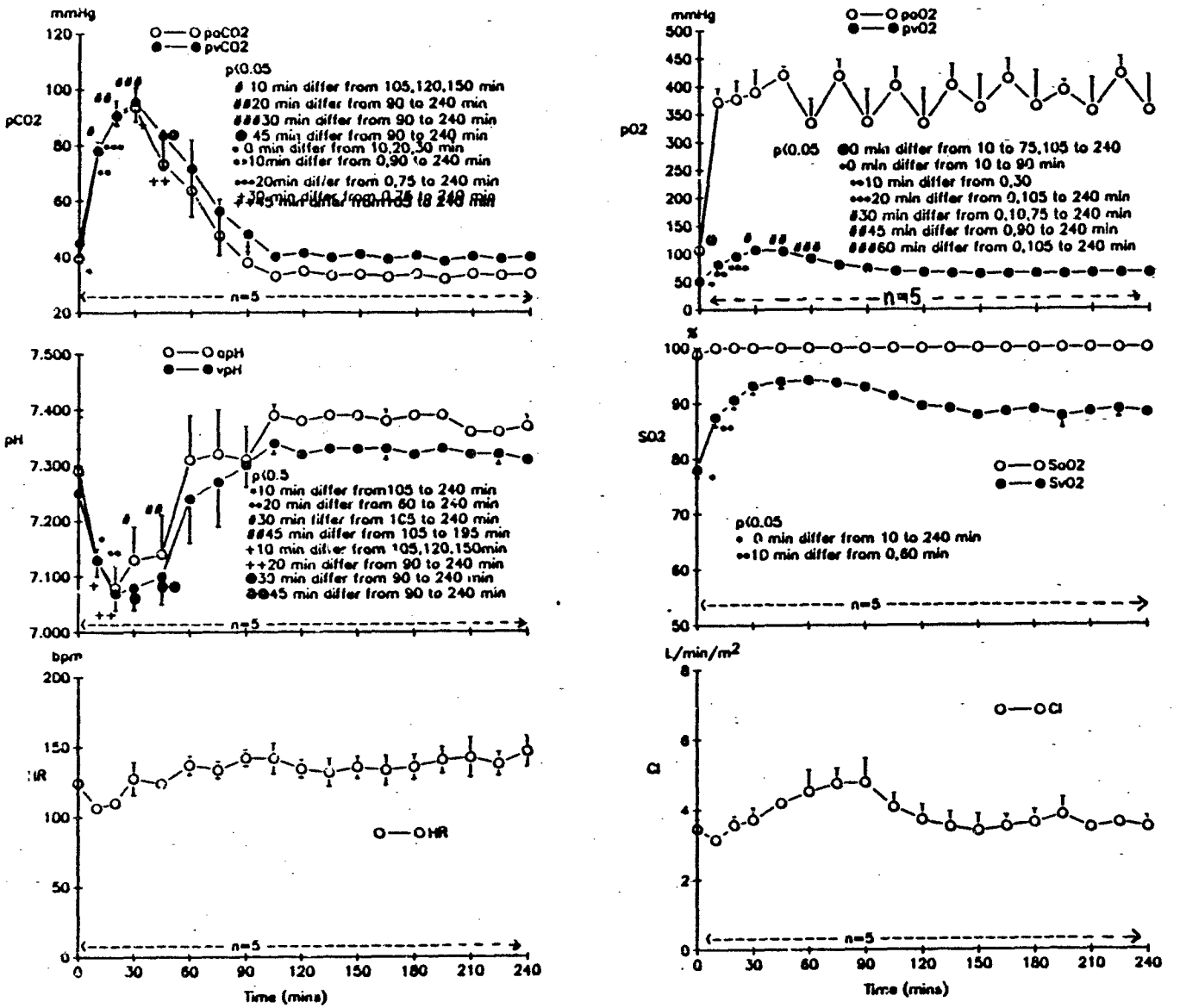


Figure 26. Mean ± SE physiological parameters during TRIO, using generous flow (2 L/min O_2).

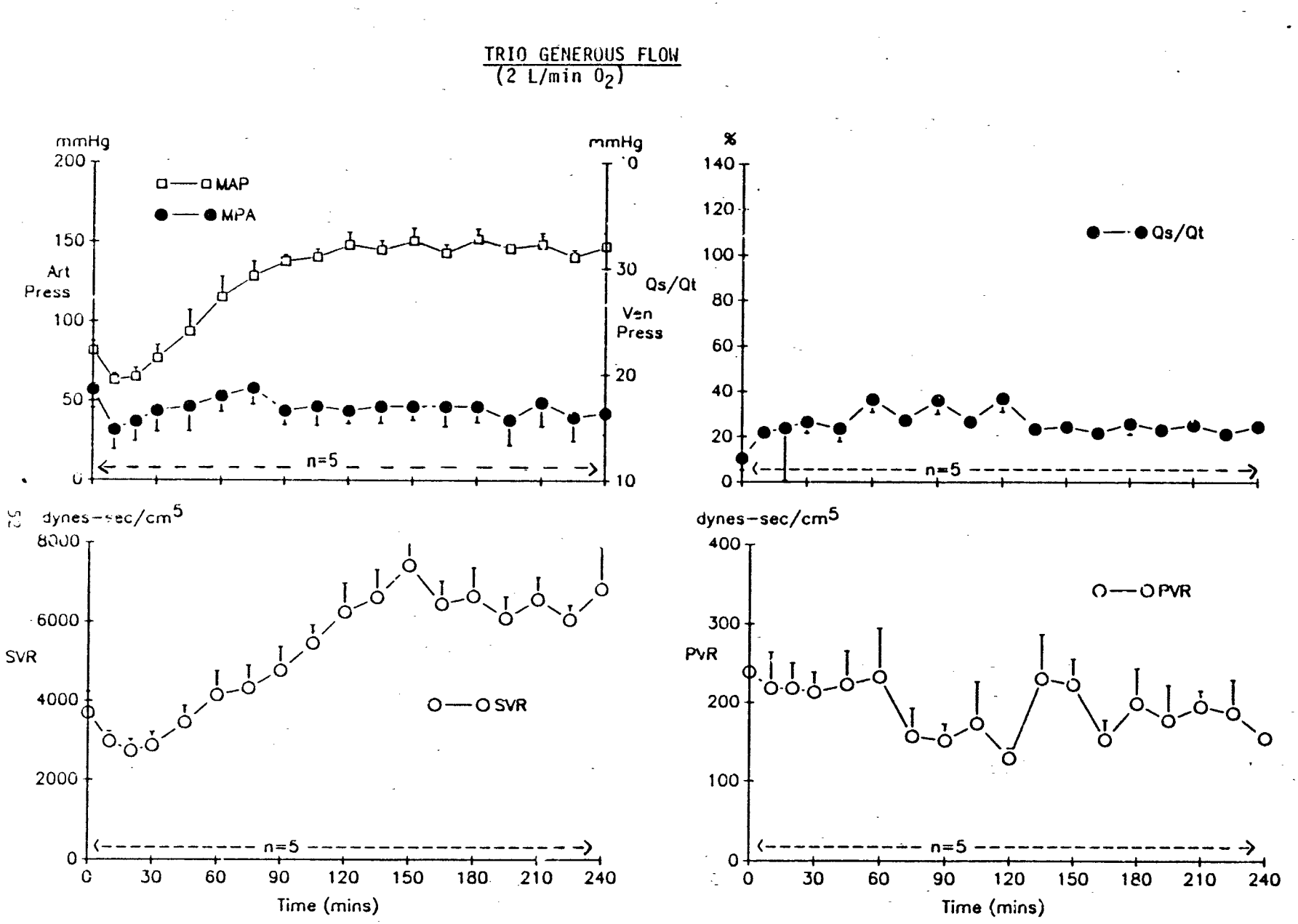


Figure 27. Mean ± SE physiological parameters during TRIO, using generous flow (2 L/min O_2).

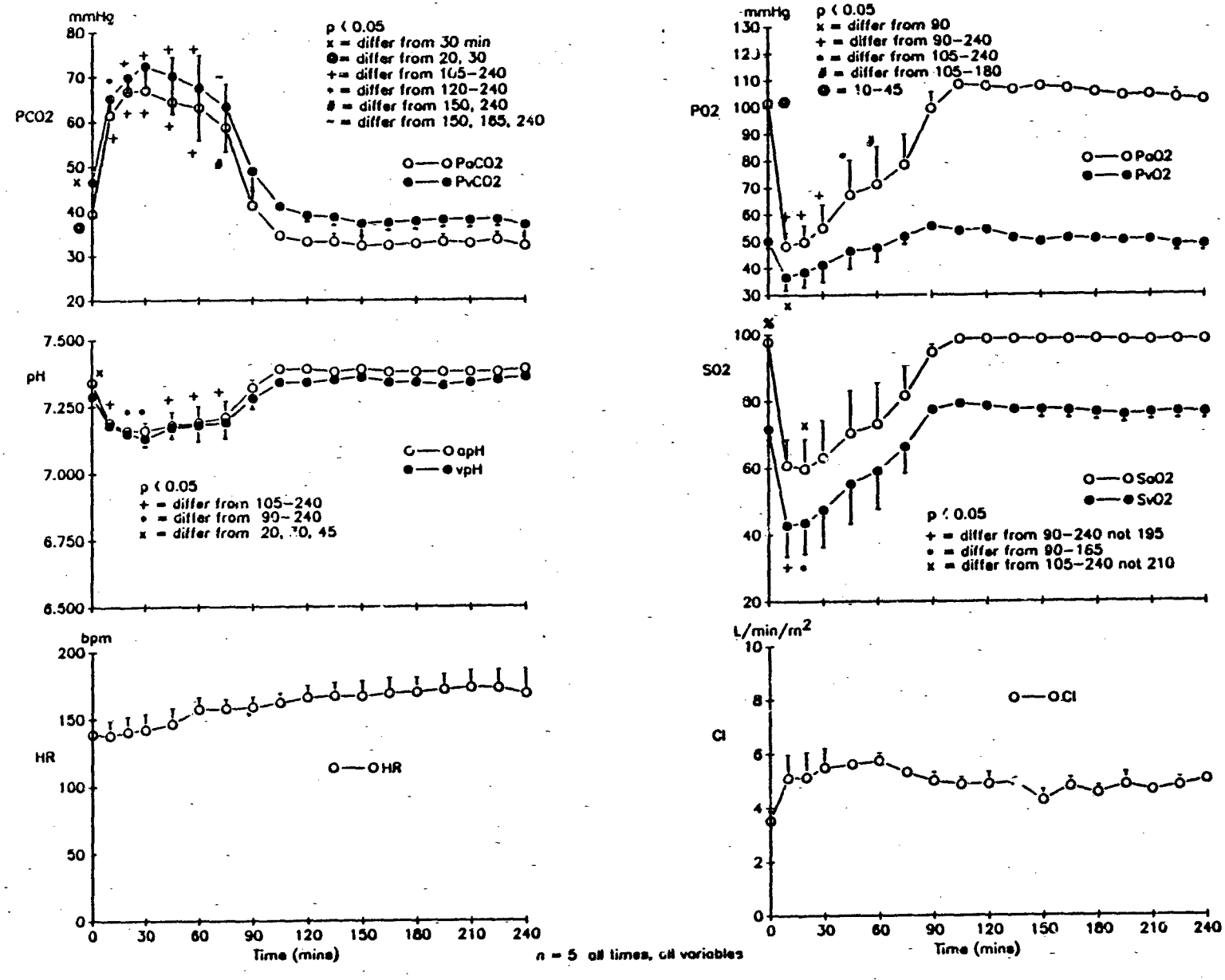


Figure 28. Physiological changes (mean ± SE) during EI at 0.5 - 0.4 L/kg/min after TTX.

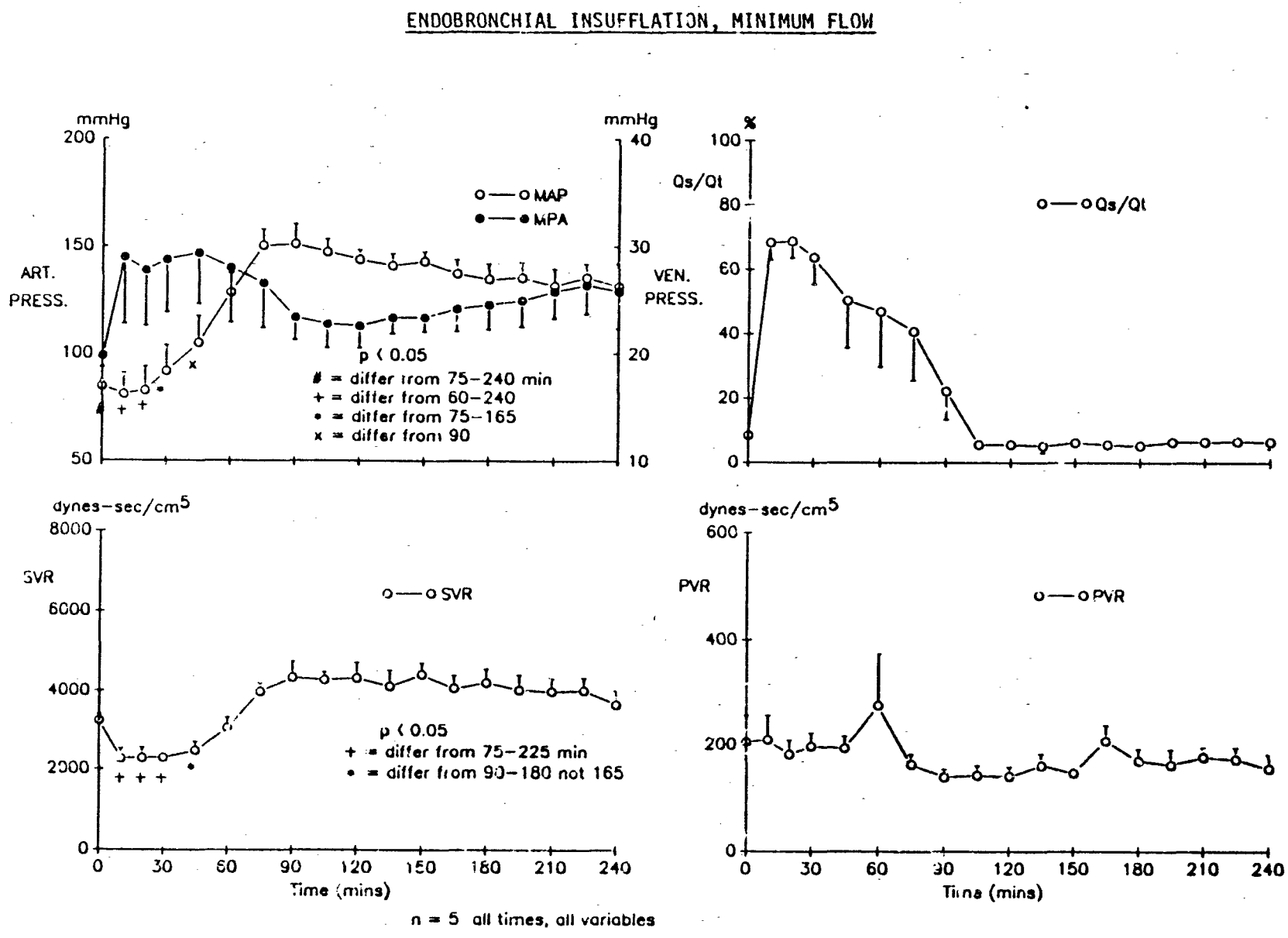


Figure 29. Physiological changes (mean ± SE) during EI at 0.4 - 0.5 l/Kg/min after TTX.

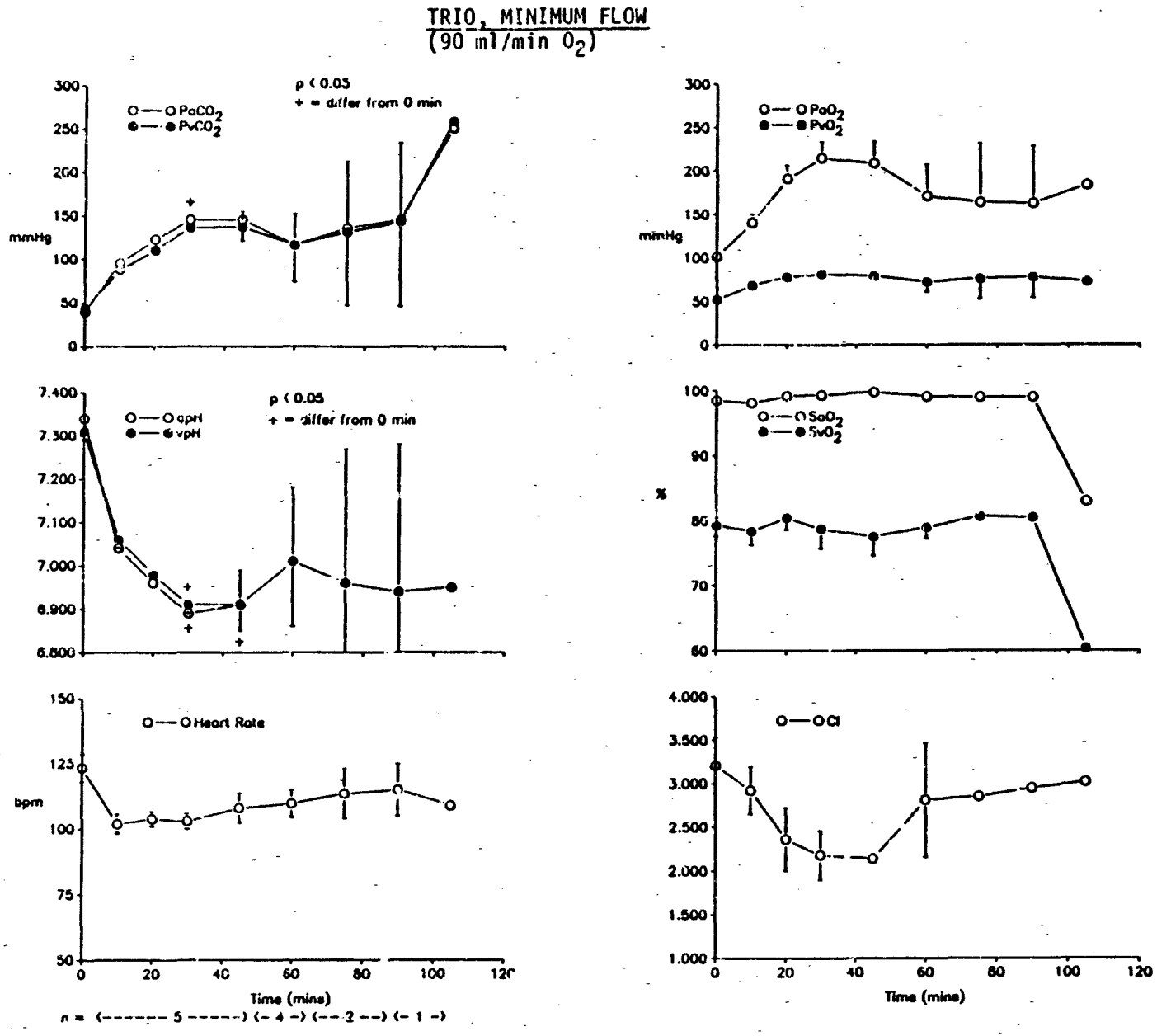


Figure 30. Mean ± SE physiological changes during 90 ml/min TRIO. n = number of animals.

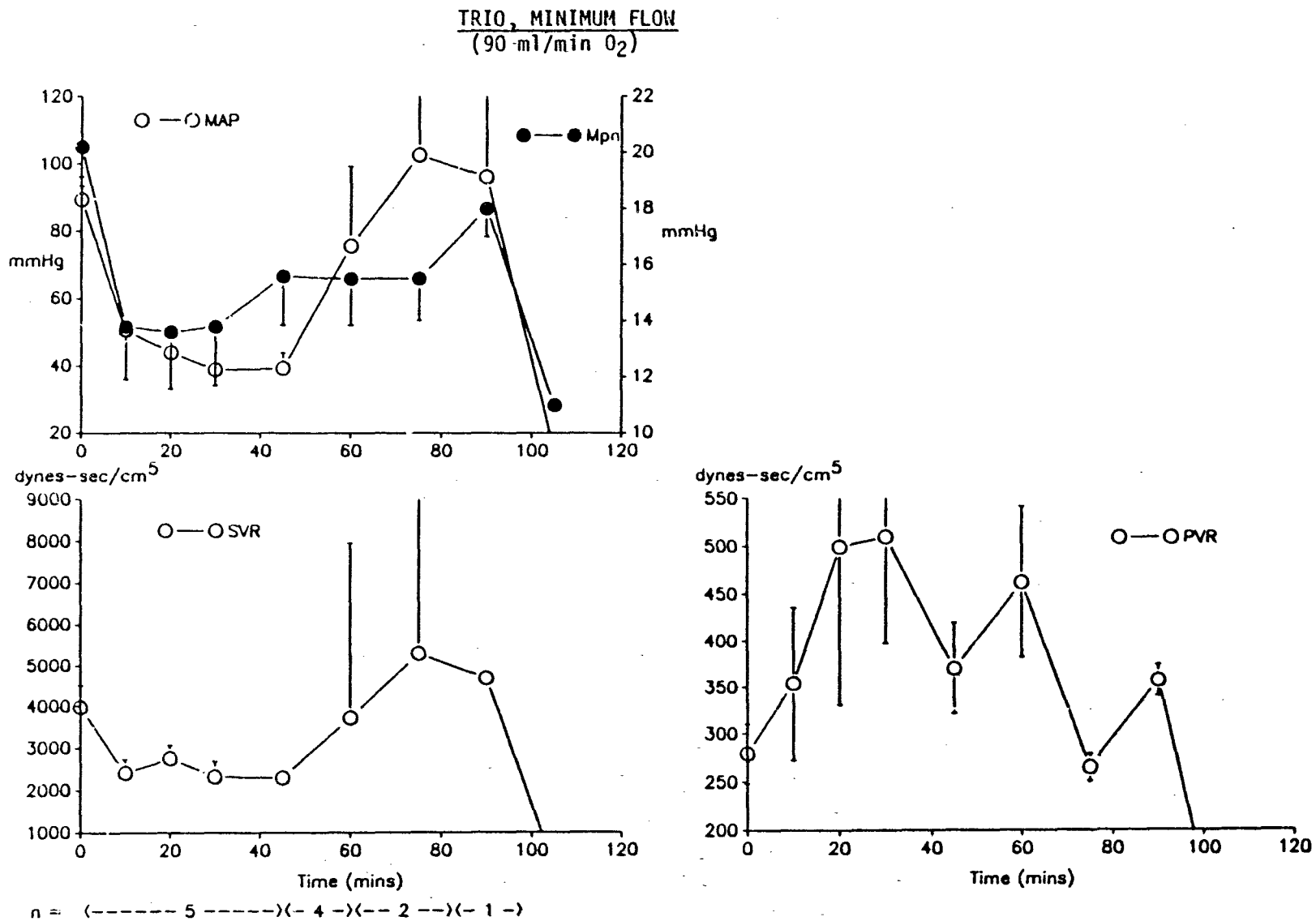


Figure 31. Mean ± SE physiological changes during 90 ml/min TRIO. n = number of animals.

VETERINARY PATHOLOGY FINAL REPORT
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
VETERINARY RESOURCES

Accession No.:	89-377
Date Submitted:	5/16/89
Date Phone Report:	
Date Written Report:	5/19/89
Investigator:	Dr. C. Mackenzie
Department:	Anesthesiology
School:	Medicine
Phone:	3418
Species:	Dog
Strain/Stock:	Beagle
Source:	Quaker Farms
Sex:	F
Age:	
Animal I.D.:	
Location:	
Time/Manner of Death:	

This dog died approximately one hour after the start of the experiment. The animal was dosed with tetrodotoxin at 16 mg/Kg.

Necropsy was performed at 5:00 pm.

Body wt. - 10 Kg
Spleen - 147 g
Liver - 493 g

GROSS FINDINGS

1. Right ventricle dilated
2. Liver congested
3. Spleen enlarged and very congested
4. Lungs were inflated. Areas very reddened, both lungs but one side, presumably dependent, was diffuse.

HISTOLOGY

1. Heart - LV and RV unremarkable
2. Liver - siunsoids congested. Also extensive areas in which lack of blood in sinusoids. Maybe indicative of cardiovascular abnormal physiology ie. acute hypoxic necrosis.
3. Spleen - marked congestion
4. Lung - left (dependant) congestion, diffuse. Also some hemorrhage into alveclar spaces and airways.
   - right lobe congestion,edema

5. Lung - Bouin's fixative: congestion, edema. Also hemorrhage into alveolar spaces.The edema is more pronounced than was appreciated from the H&E.

6. Kidney - marked congestion, especially at the cortico-medullary junction.

CONCLUSIONS

The dilated right ventricle, pulmonary congestion and edema; and visceral congestion seen on gross and histology are indicative of cardio-vascular insufficiency. This was the probable cause of death.

Robert G Russell
Chief, Veterinary Pathology
Program of Comparative Medicine/Veterinary Resources

COMMENTS: Animal # 6446 - Used for TTX dosing and EI. Respiratory efforts during EI after 12 ug/Kg TTX, a further 3 ug/Kg was given to produce apnea but the animal died.

1

VETERINARY PATHOLOGY FINAL REPORT
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
VETERINARY RESOURCES

Accession No.: 89-417

Date Submitted: 5/23/89
Date Phone Report:
Date Written Report: 5/25/89

Investigator: Dr. C. Mackenzie
Department: Anesthesiology
School: Medicine
Phone: 3418

Species: Dog
Strain/Stock: Beagle
Source: Quaker Farms
Sex:
Age:
Animal I.D.:
Location:
Time/Manner of Death:

Dog submitted for necropsy at 5:00

Liver 413 g
Spleen 65 g
Urine 350 ml

Histopathology

1. Lung marked congestion and pulmonary edema.
2. Liver unremarkable
3. Kidney cortex congested

Conclusion: acute pulmonary edema

COMMENTS:
Animal # 6453 - Used to determine the correct TTX dosage of 16 ug/Kg over 45 minutes. Animal finally died when we tried to wake it up.

VETERINARY PATHOLOGY FINAL REPORT
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
VETERINARY RESOURCES

Accession No.: 89-430

Date Submitted: 5/30/89
Date Phone Report:
Date Written Report: 6/1/89

Investigator: Dr. C. Mackenzie
Department: Anesthesiology
School: Medicine
Phone: 3418

Species: Dog
Strain/Stock: Beagle
Source: Quaker Farms
Sex:
Age:
Animal I.D.:
Location:
Time/Manner of Death:

This animal died approximately two hours prior to necropsy.

Body weight 9 Kg
Liver 470 g
Spleen 114 g

Spleen enlarged. Liver congested. Heart dilated - right ventricle.

Histopathology

1. Lung pre-existing pneumonia.Also evidence of aspiration.
2. Liver very congested, areas of acute hypoxic necrosis, sometimes extensive.
3. Heart unremarkable
4. Spleen very congested
5. kidneys possible - acute tubular degeneration

Conclusion: Cardiovascular insufficiency

COMMENTS:

Animal # 6445 - Used for TTX dosing and EI (died). Animal was given 15 ug/Kg TTX over 90 minutes. Leaking humidifier in EI circuit and animal died within 10 minutes of EI.

VETERINARY PATHOLOGY FINAL REPORT
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
VETERINARY RESOURCES

Accession No.: 89-483

Date Submitted: 6/6/89
Date Phone Report:
Date Written Report: 6/12/89

Investigator: Dr. C. Mackenzie
Department: Anesthesiology
School: Medicine
Phone: 3418

Species: Dog
Strain/Stock: Beagle
Source: Quaker Farms
Sex:
Age:
Animal I.D.:
Location:
Time/Manner of Death:

Animal submitted for necropsy at 5:00 pm.
Tetrodotoxin administered at 16 mg/Kg.

Body wt	10.5 Kg
Liver	667 g
Spleen	142 g

Liver congested. Spleen very enlarged and congested.

Histopathology

1. Lung possible partial atelectasis.Numerous PMN's.
2. Liver very congested, extensive areas of hypoxic necrosis.
3. Spleen very congested.
4. Kidney congested.

Robert G Russell
Chief, Veterinary Pathology
Program of Comparative Medicine

COMMENTS:
Animal # 6451 - Used for TTX dosing and EI 1.0 L/Kg (died). Animal was dosed with 16 ug/Kg TTX over 90 minutes. Developed low cardiac output (0.54L). After 70 minutes of EI we tried airway occlusion but animal died.

VETERINARY PATHOLOGY FINAL REPORT
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
VETERINARY RESOURCES

Accession No.: 89-558

Date Submitted: 6/15/89
Date Phone Report:
Date Written Report: 6/16/89

Investigator: Dr. C. Mackenzie
Department: Anesthesiology
School: Medicine
Phone: 3418

Species: Dog
Strain/Stock: Beagle
Source: Quaker Farms
Sex:
Age:
Animal I.D.:
Location:
Time/Manner of Death:

Animal died 9:00 pm 6/14 and was necropsied the following morning 10:00 am 6/15.

Liver 622 g
Spleen 155 g
Urine 100 ml

Gross examination

spleen enlarged. Right ventricle dilated. Partial atelectasis of the right lungs (trachea was not completely tied off before opening the thorax). Dorsal diaphragmatic lobe and left lung had passive congestion.

Histologic Findings

lung, liver, kidney, spleen congested.
diaphragm, thyroid, parathyroid unremarkable.
trachea, superficial erosion of the epithelium

Robert G Russell
Chief, Veterinary Pathology
Program of Comparative Medicine

L DETOLLA
Director
Veterinary Resources

COMMENTS: Animal #6450 - 14.8 ug/Kg TTX given over 90 minutes. EI for 4 hours but animal died later on in the evening. (EI flow was 1.0 L/Kg)

PATHOLOGY REPORT - SUMMARY

Necropsy conducted on five dogs. Histopathology completed on four of them. All dogs had enlarged congested livers (413 to 667 gram). Four of the five dogs had a very enlarged spleen (114 to 155 gram), the other dog was 65 gram. The first two dogs had pulmonary congestion and edema. In this dog and three of four dogs histology showed liver congestion and evidence of hypoxic hepatocellular necrosis. All dogs had right ventricular dilatation. Some also had left heart dilatation.

One dog had pre-existing pneumonitis with bronchitis. Another dog had aspiration into the lung.

VETERINARY PATHOLOGY FINAL REPORT
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
VETERINARY RESOURCES

Accession No.: 89-595

Date Submitted: 6/28/89
Date Phone Report:
Date Written Report: 6/30/89

Investigator: Dr. C. Mackenzie
Department: Anesthesiology
School: Medicine
Phone: 3418

Species: Dog
Strain/Stock: Beagle
Source: Quaker Farms
Sex:
Age:
Animal I.D.:
Location:
Time/Manner of Death:

COMMENTS: Animal# 6454 - 16 ug/Kg TTX given over 90 minutes. Animal survived 4 hours of EI (1 L/Kg). We elected to terminate at 7:14pm.

Liver 528 g
Spleen 95 g
Urine 100 ml

Froth in trachea at necropsy. Heart, liver and spleen appeared normal.

Histopathology

Liver congested - marked
Spleen congested - marked
Kidneys proteinuria in the glomeruli, and tubules
Heart OK
Tongue OK
Diaphragm OK
Larynx, Trachea, Major bronchi loss of luminal epithelium - may be post-mortem change. Also see lung
Lungs marked congestion of vessels. Pulmonary edema. Evidence of acute aspiration pneumonia by bacterial colonies and bacilli in parenchyma and in the airways with PMN's in some sites.

Robert G. Russell
Chief, Veterinary Pathology

Dr L DeTolla
Director, Veterinary Resources
Program of Comparative Medicine

VETERINARY PATHOLOGY FINAL REPORT
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
VETERINARY RESOURCES

Accession No.: 89-663

Date Submitted: 7/18/89
Date Phone Report:
Date Written Report: 7/21/89

Investigator: Dr. C. Mackenzie
Department: Anesthesiology
School: Medicine
Phone: 3418

Species: Dog
Strain/Stock: Beagle
Source: Quaker Farms
Sex:
Age:
Animal I.D.:
Location:
Time/Manner of Death:

COMMENTS: Animal# 6445 - Weighed 8Kg and needed only 11.75 ug/Kg TTX to produce apnea. Died after 50 mins EI (1 L/Kg).

Spleen 158 g
Liver 542 g

Histopathology

Spleen	congested
Liver	hepatocytes swollen and have vacuolation. Diffuse throughout the sections.
Heart	OK
Kidneys	OK
Diaphragm	OK
Intercostals	OK
Tongue	OK
Lungs	OK

Robert G. Russell
Chief, Veterinary Pathology

Dr. L DeTolla
Director, Veterinary Resources
Program of Comparative Medicine

VETERINARY PATHOLOGY FINAL REPORT
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
VETERINARY RESOURCES

Accession No.: 89-765

Date Submitted: 8/8/89
Date Phone Report:
Date Written Report: 9/17/89

Investigator: Dr. C. Mackenzie
Department: Anesthesiology
School: Medicine
Phone: 3418

Species: Dog
Strain/Stock: Beagle
Source: Quaker Farms
Sex:
Age:
Animal I.D.:
Location:
Time/Manner of Death:

COMMENTS: Animal# 6444 - Needed 10 ug/Kg TTX to produce apnea. After 18 mins TRIO (1 L/min) Part was 38 mmHg. Animal resuscitated with CMV. Subsequent efforts with EI and TRIO failed and animal died.

This dog was necropsied on 8/9/89.

Gross Examination

Liver 612 g
Spleen 140 g
Urine 130 ml

Right ventricle and left ventricle were dilated.
Spleen congested
Lungs O.K. - no froth in trachea

Histology

no significant pathologic changes in the lung, adrenal,

spleen, liver, kidney congested

L DeTolla
Director
Veterinary Resources

Robert G Russell
Chief, Veterinary Pathology
Program of Comparative Medicine

VETERINARY PATHOLOGY FINAL REPORT
UNIVERSITY OF MARYLAND SCHOOL O. MEDICINE
VETERINARY RESOURCES

Accession No.: 89-948

Date Submitted: 9/27/89
Date Phone Report:
Date Written Report:

Investigator: Dr. C. Mackenzie
Department: Anesthesiology
School: Medicine
Phone: 3418

Species: Dog
Strain/Stock: Beagle
Source: Quaker Farms
Sex:
Age:
Animal I.D.:
Location:
Time/Manner of Death:

COMMENTS: Animal# 6448 - TRIO (80 ml/min) for 120 mins

TTx experiment survivor

Spleen	123 g
Liver	541 g
Urine	130 ml

Histology

Trachea at bifurcation and at origin of right bronchus there was superficial erosion of epithelium. Left bronchus and 1,2 cm right bronchus OK.

Robert G Russell
Chief, Veterinary Pathology
Program of Comparative Medicine

Dr. L DeTolla L. DeTolla
Director, Veterinary Resources
Program of Comparative Medicine

VETERINARY PATHOLOGY FINAL REPORT
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
VETERINARY RESOURCES

Accession No.: 89-977

Date Submitted: 10/3/89
Date Phone Report:
Date Written Report:

Investigator: Dr. C. Mackenzie
Department: Anesthesiology
School: Medicine
Phone: 3418

Species: Dog
Strain/Stock: Beagle
Source: Quaker Farms
Sex:
Age:
Animal I.D.:
Location:
Time/Manner of Death:

COMMENTS: Animal# 6447 - EI (0.3 L/Kg) for 120 mins. Also used 9/11/89 for TRIO 30 ml/min for 70 minutes.

TTx experiment survivor

Spleen	54 g
Liver	510 g
Urine	180 ml

Histology

trachea at bifurcation mild erosion of the luminal epithelium. Mild blood accummulation in the left and right bronchi.

Robert G Russell
Chief, Veterinary Pathology
Program of Comparative Medicine

Dr. L Detolla L. Detolla
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VETERINARY PATHOLOGY FINAL REPORT
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
VETERINARY RESOURCES

Accession No.:	89-992
Date Submitted:	10/11/89
Date Phone Report:	
Date Written Report:	
Investigator:	Dr. C. Mackenzie
Department:	Anesthesiology
School:	Medicine
Phone:	3418
Species:	Dog
Strain/Stock:	Beagle
Source:	Quaker Farms
Sex:	
Age:	
Animal I.D.:	6455
Location:	
Time/Manner of Death:	

TTx experiment survivor

Spleen	66 g
Liver	598 g

Histology Trachea and bronchi showed autolysis of the epithelium

Robert G Russell
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Dr. L DeTolla L. DeTolla
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COMMENTS: Animal# 6455 - EI (0.3 L/Kg) for 120 mins.

VETERINARY PATHOLOGY FINAL REPORT
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
VETERINARY RESOURCES

Accession No.:	89-1104
Date Submitted:	11/21/89
Date Phone Report:	
Date Written Report:	
Investigator:	Dr. C. Mackenzie
Department:	Anesthesiology
School:	Medicine
Phone:	3418
Species:	Dog
Strain/Stock:	Beagle
Source:	Quaker Farms
Sex:	
Age:	
Animal I.D.:	6535
Location:	
Time/Manner of Death:	

Spleen 80 g
Liver 376 g

Histology
epithelial changes in the trachea and bronchus attributed to autolysis

Robert G Russell
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COMMENTS: Animal# 6535 - EI of 0.3 L/Kg failed at 20 mins but animal survived EI of 0.4 L/Kg for 4 hours. Animal was slow and depressed 2 days after experiment and was fully recovered by 5 days.

VETERINARY PATHOLOGY FINAL REPORT
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
VETERINARY RESOURCES

Accession No.: 89-1115

Date Submitted: 12/5/89
Date Phone Report:
Date Written Report:

Investigator: Dr. C. Mackenzie
Department: Anesthesiology
School: Medicine
Phone: 3418

Species: Dog
Strain/Stock: Beagle
Source: Quaker Farms
Sex:
Age:
Animal I.D.: 6538
Location:
Time/Manner of Death:

Spleen 99 g
Liver 464 g

Histology Trachea and both bronchi from the bifurcation to 2 cm along each bronchus shows mild to moderate subepithelial infiltration of inflammatory cells which is diffuse around the perimeter. It is suggested that this may have been experimentally induced by the catheter equipment inserted into the airway

Robert G Russell
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COMMENT: Animal# 6538 - Used 11/21/89 for EI/TTX 0.5 L/Kg for 4 hours.

VETERINARY PATHOLOGY FINAL REPORT
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
VETERINARY RESOURCES

Accession No.: 89-1147

Date Submitted: 12/14/89
Date Phone Report:
Date Written Report:

Investigator: Dr. C. Mackenzie
Department: Anesthesiology
School: Medicine
Phone: 3418

Species: Dog
Strain/Stock: Beagle
Source: Quaker Farms
Sex:
Age:
Animal I.D.:
Location:
Time/Manner of Death:

Histology trachea and bronchi unremarkable

Spleen 41 g
Liver 299 g

Robert G Russell
Chief, Veterinary Pathology
Program of Comparative Medicine

Dr. L DeTolla L. DeTolla
Director, Veterinary Resources
Program of Comparative Medicine

COMMENTS: Animal# 6561 - After 43 minutes of TRIO (90 ml/min) Part fell to 40 mmHg. TRIO was stopped and CMV resumed. Dog was fully recovered by 2nd day after experiment.

VETERINARY PATHOLOGY FINAL REPORT
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
VETERINARY RESOURCES

Accession No.:	90-12
Date Submitted:	1/12/90
Date Phone Report:	
Date Written Report:	
Investigator:	Dr. C. Mackenzie
Department:	Anesthesiology
School:	Medicine
Phone:	3418
Species:	Dog
Strain/Stock:	Beagle
Source:	Quaker Farms
Sex:	
Age:	
Animal I.D.:	6537
Location:	
Time/Manner of Death:	

TTx experiment survivor

Spleen	104 g
Liver	631 g

Lungs congested

re TGI

Histology trachea and bronchi unremarkable

Robert G Russell
Chief, Veterinary Pathology
Program of Comparative Medicine

L. DeTolla

Dr. L DeTolla
Director, Veterinary Resources
Program of Comparative Medicine

COMMENTS: Animal# 6537 - Used for EI/TTX/low flow 11/13/89. EI of 0.3 L/Kg failed at at 10 mins and the animal survived 0.4 L/Kg to 4 hours.

VETERINARY PATHOLOGY FINAL REPORT
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
VETERINARY RESOURCES

Accession No.: 90-13

Date Submitted: 1/12/90
Date Phone Report:
Date Written Report:

Investigator: Dr. C. Mackenzie
Department: Anesthesiology
School: Medicine
Phone: 3418

Species: Dog
Strain/Stock: Beagle
Source: Quaker Farms
Sex:
Age:
Animal I.D.: 6533
Location:
Time/Manner of Death:

TTx experiment survivor

Spleen 44 g
Liver 434 g

Bladder full

No abnormalities
Looks as if died spontaneously

Histology trachea and bronchi unremarkable

Robert G Russell
Chief, Veterinary Pathology
Program of Comparative Medicine

Dr. L DeTolla L. DeTolla
Director, Veterinary Resources
Program of Comparative Medicine

COMMENTS: Animal# 6533 - Used twice 10/23/89 for EI of 0.3 L/Kg for 2 hours
11/20/89 for EI/TTX/0.4 L/Kg for 4 hours.

VETERINARY PATHOLOGY FINAL REPORT
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
VETERINARY RESOURCES

Accession No.: 90-14

Date Submitted: 1/18/90
Date Phone Report:
Date Written Report:

Investigator: Dr. C. Mackenzie
Department: Anesthesiology
School: Medicine
Phone: 3418

Species: Dog
Strain/Stock: Beagle
Source: Quaker Farms
Sex:
Age:
Animal I.D.: 6559
Location:
Time/Manner of Death:

TTx experiment survivor

Spleen 66 g
Liver 450 g

Histology autolytic changes to the airway epithelium of the trachea and bronchi

Robert G Russell
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Dr. L DeTolla L. DeTolla
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Program of Comparative Medicine

COMMENT: Animal# 6559 - Used 12/5/89 for low flow TRIO/TTX (90 ml/min)