國科會專題計畫成果報告

計畫名稱：誘發肺氣栓塞所引發呼吸性反射反應的生理機轉

Mechanisms of respiratory reflexogenic responses induced by pulmonary air embolism.

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一、中文摘要

肺氣栓塞 (Pulmonary air embolism) 會造成呼吸型態的改變 (Breathing pattern change) 和肺組織病理病徵 (Lung tissue injury)。C 纖維 (C fiber nerve endings) 和快適應性受器 (Rapidly adapting receptors) 具有預先偵測肺組織病變徵兆的兩大類肺迷走感覺神經受器，而且刺激這兩類受器皆會產生共同性的淺快呼吸。誘發肺氣栓塞已證實會刺激肺C纖維和快適應性受器。然而到目前為止，肺氣栓塞是否會引發淺快呼吸? 何種肺迷走感覺神經受器在此呼吸型態改變的神經機轉 (Neural pathways) 中扮演重要的角色? 皆仍不清楚。已知肺氣栓塞會導致一些肺介質的釋放，譬如前列腺素及血栓素等環氧化酵素產物 (Cyclooxygenase productors)、以及氫氧自由基 (OH•)。又根據我們最近研究的結果顯示這些肺介質會參與在肺氣栓塞所活化的 C 纖維和快適應性受器之中。然而到目前為止，肺氣栓塞活化的肺迷走神經受器，所產生呼吸型態改變的化學性機轉 (Chemical pathways)，是否藉由這些肺介質的釋放? 亦有待研究。本計劃的目的是去探討： (一). 肺氣栓塞是否會引發呼吸型態的改變? (二). 肺氣栓塞產生呼吸型態改變的神經路徑，是藉由何種迷走感覺神經受器的傳導？ (三). 環氧化酵素的產物和 OH• 等肺介質是否參與在肺氣栓塞引發呼吸型態的改變中？ 本計劃的基礎呼吸型態的長期觀察。

本計劃以成年犬為實驗動物，麻醉後，施以股動脈、股靜脈、氣管插管。其目的分別是測量動脈壓、給予補助麻醉劑、及測量一些呼吸性的參數 (Respiratory parameters)。此些參數分別為潮氣容積 (Tidal volume)、氣流 (Airflow)、氣道內壓 (Airway pressure)。藉這些參數可觀察呼吸型態的變化。以注射空氣進入肺循環來誘發肺氣栓塞。本計劃的實驗設計為研究一 (n=5)，基礎呼吸型態的長期觀察。研究二 (n=8)，觀察肺氣栓塞所引發的呼吸型態。在迷走感覺神經無損的情況下，即給予等張性生理食鹽水，誘發重覆肺氣栓塞。研究三 (n=8) 在阻斷 C-纖維的情況下，即運用兩側頸迷走神經周圍辣椒素處理法，誘發重覆肺氣栓塞。研究四 (n=8)，採用異丁苯丙酸 (Ibuprofen) 處理來抑制環氧化酵素的產物，誘發重覆肺氣栓塞。研究五 (n=8)，採用雙甲基硫尿 (Dimethylthiourea) 處理來清除 OH•，誘發重覆肺氣栓塞。

根據實驗結果顯示，在自發性呼吸的狗上，給予肺氣栓塞後，便引發淺快呼吸反射反應。在辣椒素塗抹頸迷走神經處理後，淺快呼吸的反應被消除。誘發重覆肺氣栓塞可引發加成性的淺快呼吸；相反的，此反應可被異丁苯丙酸、或雙甲基硫尿處理所減弱。綜合先期實驗的結果，我們發現：肺氣栓塞會引發呼吸淺快的反應，其間的機轉可能是藉由環氧化酵素產物以及OH•的釋放來活化 C-纖維，而非快適應性受器，進而引發呼吸型態的改變。另一方面，由於肺氣栓塞會釋放環氧化酵素產物以及 OH•，進而引發肺組織病理病徵。表示肺氣栓塞在出現病徵之前，動物體內都應有 C-纖維傳導訊號至中樞且立即造成淺快呼吸，使動物警覺本身正處於不正常狀態。而本計劃之研究成果可為進一步探討肺氣栓塞發生後，呼吸系統

如何防禦以及此防禦機轉如何失控而造成病理性的傷害的長期計劃的研究基礎。

關鍵詞：肺氣栓塞、呼吸型態改變、辣椒素塗抹神經、氫氧自由基、環氧化酵素產物

ABSTRACT

We investigated the vagal and mediator mechanisms underlying the tachypnea caused by pulmonary air embolism (PAE) in anesthetized and spontaneous breathing dogs. PAE was induced by infusion of air into the right atrium (0.2 ml · kg^{-1} · min^{-1} for 10 min). The first PAE induction caused an increase in respiratory frequency accompanied by a decrease in tidal volume in each of the 30 animals studied. Subsequently, animals were evenly divided into five groups and a second PAE induction was repeated following various experimental interventions. The tachypneic response to PAE was not significantly altered by pretreatment with a saline vehicle, but was largely attenuated by either perivagal capsaicin treatment (a technique that selectively blocks the conduction of unmyelinated C-fibers), pretreatment with ibuprofen (a cyclooxygenase inhibitor), or pretreatment with dimethylthiourea (a hydroxy radical scavenger). Ultimately, the tachypneic response was nearly abolished by a bilateral cervical vagotomy. These results suggest that 1) both lung vagal unmyelinated C-fiber afferents and myelinated afferents are responsible for evoking the reflex tachypneic response to PAE, although the former afferents play a predominant role, and 2) both cyclooxygenase products and hydroxyl readical are important in eliciting this response.

KEYWORDS: lung vagal sensory receptors; microembolism, reflex tachypnea, ibuprofen; dimethylthiourea; cyclooxygenase products; hydroxyl radical

INTRODUCTION

Pulmonary air embolism (PAE) occurs in a number of clinical situations and is known to cause tachypnea (17, 24). The physiological mechanisms underlying the PAE-induced tachypnea is totally abolished by bilateral cervical vagotomy, suggesting that this response is a reflex mediated by lung vagal afferents. Two recent electrophysiological studies in dogs reveal that lung vagal C-fiber nerve endings (7) and pulmonary rapidly adapting receptors (8) are stimulated by PAE. Additionally, both cyclooxygenase products and hydroxyl radical participate in the activation of lung vagal C-fiber nerve endings by PAE (7), whereas the former mediators, but not the latter, contribute to the stimulation of pulmonary rapidly adapting receptors (8). C-fiber nerve endings and rapidly adapting receptors are supplied by lung vagal unmyelinated and myelinated afferents, respectively, and are believed to play an important role in eliciting respiratory reflexes under various pathophysiological conditions (9, 10, 29). Cyclooxygenase products and hydroxyl radical are chemical mediators whose releases in the lungs have been shown to be increased by PAE (13, 22, 27). Thus, questions still remain as to whether one or

both types of lung vagal afferents and chemical mediators are involved in eliciting the tachypneic response to PAE.

To differentiate the role of lung vagal unmyelinated C-fiber afferents and myelinated afferents in evoking respiratory reflexes, previous investigators (15, 18, 21) have employed perivagal capsaicin treatment to produce a differential vagal block. This technique is based upon the fact that application of capsaicin, a chemical extracted from hot peppers, directly to the peripheral nerves blocks the conduction of unmyelinated C fibers, but does not affect the conduction of myelinated fibers (5, 25). Therefore, when capsaicin is applied perineurally to both cervical vagi, it selectively blocks the respiratory reflexes resulting from stimulation of C-fiber nerve endings (15, 18, 21).

The objectives of this study were two-fold:1) to determine the relative contribution of lung vagal unmyelinated C-fiber afferents and myelinated afferents to, and 2) to assess the role of cyclooxygenase products and hydroxyl radical in, the PAE-induced tachypnea in anesthetized dogs, To accomplish our objectives, we compared the ventilatory responses to PAE before and after perivagal capsaicin treatment or bilateral cervical vagotomy, also before and after systemic administration of a saline vehicle, a cyclooxygenase inhibitor (ibuprofen), or a hydroxyl radical scavenger (dimethylthiourea).

METHODS

Dogs (9.2-15.4 kg) of both sex were anesthetized with an intravenous (iv) injection of thiopental sodium (20 mg · kg^{-1} ;Abbott), followed by a combination of chloralose (50 mg · kg $^{-1}$iv; Sigma) and urethan (500 mg· kg^{-1} iv; Sigma). During the experiment, the depth of anesthesia was constantly checked; supplemental doses of chloralose (15 mg· kg^{-1} · hr^{-1}) and urethan (150 mg· kg^{-1}· hr^{-1}) were administered intravenously to maintain abolition of the corneal and withdrawal reflexes. Body temperature was maintained at ~36 ℃ throughout the experiment by means of a servo-controlled heating blanket. Animals used in this study were supplied by the Animal Center of National Yang-Ming University, Taipei, Taiwan, ROC. All protocols were in accordance with the guidelines for the care and use of laboratory animals published by the Committee of National Science Council, Taipei, Taiwan, ROC, and were approved by the University Institutional Animal Care and Use Committee.

Animal preparations. The femoral artery was cannulated for measuring arterial blood pressure. A catheter (PE-240) was inserted into the right atrium via the right jugular vein for administration of pharmacological agents and for induction of PAE. A midline incision was made in the neck and a segment (~3 cm) of each vagus nerve was carefully isolated from the common carotid artery for later use. A short tracheal cannula was inserted just below the larynx via a tracheostomy, through which animals breathed spontaneously in a supine position. Respiratory flow ($\dot{V}_R$) was measured with a pneumoyachograph (Fleisch, No.1) coupled with a differential pressure transducer (Validyne, MP45-12). The flow

signal was integrated to give tidal volume (V_T). Tracheal pressure (P_{tr}) was monitored by another differential pressure transducer (Validyne, MP45-28) via a side tap of the tracheal cannula. All physiological signals were recorded on a chart recorder (Gould, RS3200 or TA240) and a tape recorder (Neurocorder, DR-890) for later analysis.

Perivagal Capsaicin Treatment. The technique of perivagal capsaicin treatment was modified fgrom that employed by previous investigators (15, 16, 18). In brief, a segment (~ 4 mm) of each cervical vagus nerve was wrapped in a cotton strip which was presoaked in capsaicin solution (6 mg · ml^{-1}). After 20 min, when the reflex apneic responses to the right atrial injection of capsaicin (5 μg · kg^{-1}) had been abolished, the cotton strips were removed; this dose of capsaicin injection is known to stimulate pulmonary vagal C-fiber nerve endings and to evoke resultant pulmonary reflexes in dogs (9, 10, 11). Solutions of capsaicin were made daily from a refrigerated stock solution (5 mg · ml^{-1}, Sigma) which was prepared by dissolving capsaicin into a solvent containing 10% ethanol, 10% Tween 80, and 80% saline. To determine whether this treatment affected conduction in myelinated fibers, the reflex apneic response induced by inflating the lungs to a unique value of P_{tr} (20 cmH_2O) was also compared before and 20 min after perivAgal capsaicin treatment.

Induction of PAE. PAE was induced by a constant infusion of air (0.2 ml · kg^{-1} · min^{-1}) into the right atrial catheter by an infusion pump (Nan Jou 101) for a 10-min period. The infusion rate thus ranged from 1.8 to 3.1 ml · min^{-1}, depending on the body weight of each individual animal. Each study of PAE challenge consisted of a 5-min baseline period, a 10-min period during PAE induction, followed by a 15-min recovery period after the end of air infusion.

Experimental Procedures. Thirty dogs werte first studied for their control responses to PAE. Subsequently, these animals were randomly and evenly divided into five groups and the challenge of PAE was repeated after the following experimental interventions: *Group 1*, pretreatment with saline vehicle; *Group 2*, perivagal capsaicin; *Group 3*, pretreatment with ibuprofen (20 mg · kg^{-1}, Sigma); *Group 4*, pretreatment with dimethylthiourea (50 mg · kg^{-1}, Sigma); *Group 5*, bilateral cervical vagotomy. Ibuprofen and dimethylthiourea, dissolved in isotonic saline, were slowly injected into the right atrium over a 2-min period. Perivagal capsaicin treatment, vagotomy, and pretreatment with a saline vehicle or drugs were made 30 min before the onset of the second PAE induction. In *Gropus 1-4*, the reflex apneic responses induced by right atrial injection of capsaicin (5 μg · kg^{-1}) and by hyperinflation the lungs (P_{tr} = 20 cmH_2O) were studied 10 min before the first PAE induction and 15 min after the end of the second PAE induction. Six min before each PAE challenge, the animal's lungs were hyperinflated (4 × V_T) to establish a constasnt volume history. Since air emboli lasts for less than 5 min (26), 35 min were allowed to elapse between two challenges of PAE.

Data analysis and statistics. Inspiratory duration, respiratory frequency (f), $\dot{V}_R$ and V_T were all analyzed on a breath-by breath basis

and were measured in 30-s intervals. Mean arterial blood pressure was measured in 1-s intervals. Baseline data of these physiological parameters were calculated as the average values over ten consecutive 30-s periods immediately preceding the PAE induction. Peak responses in f or V_T were measured as the maximal or minimal values averaged over six consecutive 30-s periods following the PAE induction and expressed as percentage of baseline values. These physiological parameters were analyzed using a computer equipped with an analog/digital convertor (Gould DASA 4600) and software (BioCybernatics, 1.0). Results obtained from the computer analysis were routinely checked with those obtained by manual calculation for accuracy. Results were analyzed by a paired *t* test. $P < 0.05$ was considered significant. All data are presented as mean ± SE.

RESULTS

During control, induction of PAE caused a tachypneic response (Fig. 1A and 1B), which atarted within 2.1 ± 0.1 min (n = 30) after the onset of air infusion. On average (n = 30), the f progressively and significantly increased from a baseline of 21.4 ± 0.8 breaths min to a peak of 52.8 ± 2.9 breaths min^{-1} during the period from 1 min before to 3 min after the termination of PAE induction (Figs. 1D, 2, and 3). The f then gradually declined to its baseline value within 8-14 min after the termination of PAE induction (Fig. 1C). In a similar time course, the V_T significantly decreased from a baseline of 140.8 ± 5.4 ml to a maximal reduction of 117.7 ±7.0 ml before it gradually returned to its baseline value (Fig. 1E, 2, and 3).

Twenty five min after perivagal capsaicin treatment or intravenous injection of saline vehicle, ibuprofen, or dimethylthiourea, the baseline f and V_T did not significantly ($P > 0.05$) change in these groups of animals (Figs. 1, 2, and 3A). However, 25 min after bilateral cervical vagotomy, animals displayed a slow and deep respiration so that the baseline f decreased and the baseline V_T increased (Fig. 3B). In animals pretreated with saline vehicle, a repeated challenge of PAE induced ventilatory responses of a very similar amplitude and time course as compared to PAE induced ventilatory responses of a very similar amplitude and time course as compared to their control responses (Fig. 1D and 1E). In contrast, the ventilatory responses to the second PAE induction were markedly suppressed in animals pretreated with perivagal capsaicin (Fig. 2A), ibuprofen (Fig. 2B), or dimethylthiourea (Fig. 3A). Additionally, the tachypneic response to the second PAE in induction was prevented in vagotomized animals (Fig. 3B). Instead, these animals responded to the PAE induction with an increase in V_T (Fig.3B).

Since the time at which peak responses occurred varied among the animals, the peak increase or decrease in f or V_T was measured in each animal and the average data is shown in figure 4. Statistical analysis revealed that the peak increase in f produced by PAE was not significantly affected by pretreatment with saline vehicle, but was significantly attenuated by pretreatment with perivagal capsaicin, ibuprofen, or dimethylthiourea, and was nearly abolished by vagotomy

(Fig.4). Furthermore, the maximal reduction in V_T produced by PAE was not significantly affected by pretreatment with saline vehicle, perivagal capsaicin, or dimethylthiourea, but was prevented by pretreatment with ibuprofen, and was converted into a significant increase by vagotomy (Fig.4).

In the perivagal capsaicin-treated group, the reflex apneic response induced by right atrial injection of capsaicin, which had been totally abolished 20 min after the treatment, remained absent at the end of the observation period for the second PAE challenge (Table 1). Conversely, this reflex apneic response was not significantly affected by pretreatment with saline vehicle, ibuprofen, or dimethylthiourea (Table 1). Furthermore, the reflex apneic response induced by hyperinflation of the lungs was not significantly changed by any of these four experimental interventions (Table 1).

Induction of PAE did not significantly alter the mean arterial blood pressure (before vs. 10 min after the onset of PAE induction, 110.9 ± 2.6 vs. 114.5 ± 2.7 mmHg; n = 30; $P > 0.05$).

DISCUSSION

Results of this study semonstrated that PAE caused an increased an increase in f accompanied by a decrease in V_T in anesthetized dogs. These results are in general agreement with those reported by previous investigators using air emboli (20) or other emboli such as starch particles, plastic spheres, or glass beads (2, 3, 14, 22, 28). In addition, we demonstrated that when two challenges of PAE separated by 35 min were induced, ventilatory responses similar in both amplitude and time course were produced in the same animals (Fig. 1D and 1E). The reproducibility of the ventilatory responses to PAE, therefore, allowed us to investigate the effects of vagotomy, perivagal capsaicin treatment, ibuprofen, or dimethylthiourea on the PAE-induced tachypnea.

In this study, the PAE-induced tachypnea was prevented by bilateral cervical vagotomy (Fig. 2A), confirming that this response was mediated through lung vagal afferents as suggested by other investigators (20). Additionally, we showed that perivagal capsaicin treatment largely reduced the tachypneic response to PAE (Fig. 2B). This capsaicin treatment also selectively abolished the reflex apnea resulting from stimulation of lung vagal C-fiber afferents by capsaicin injection, but did not affect the reflex apnea orginating from activation of lung vagal myelinated afferents (pulmonary stretch receptors) by hyperinflation (Table 1). These results suggest that lung vagal C-fiber afferents play a primary role in eliciting the PAE-induced tachypnea. This notion is supported by our recent observation (7) that these lung unmyelinated sensory nerve endings are actived by a same method of PAE induction Two previous studies investigated the C-fiber mechanism in the tachypnea induced by other emboli. Whitteridge (28) reported that the tachypneic response to starch emboli persisted when vagal myelinated fibers were differentially blocked by low temperature, suggesting the involvement of vagal C-fiber afferents. Guz and Trenchard (14) showed that the tachypneic response to microsphere emboli

in rabbits was unaffected by anodal polarization block of vagal myelinated fibers, indicating the exclusive role of vagal C-fiber afferents. Whether the difference in the C-fiber contribution between ours and Guz and Trenchar's study (14) was due to the dissimilarity in the embolic or animal model is not known. However, it is clear that lung vagal C-fiber afferents are important in eliciting tachypnea during various types of pulmonary microembolism. On the other hand, the small and residual PAE-induced tachypneic response after perivagal capsaicin treatment (Fig. 2B) presumably orignated from the participation of lung vagal myelinated afferents. In fact, PAE has been shown to stimulate pulmonary rapidly adapting receptors (8) and inhibit pulmonary stretch receptors (19), both of which have been postulated to contribute to the elicitation of tachypnea during various types of pulmonary microembolism (1, 19, 23).

We further demonstrated that pretreatment with either ibuprofen or dimethylthiourea markedly suppressed the tachypneic response to PAE (Fig. 3), suggesting that both cyclooxygenase product and hydroxyl radical may play important roles in eliciting this reflex response. The exact sources of these two chemical mediators are not well understood. However, it is known that the lung are a rich source of arachidonate are not well understood. However, it is known that the lungs are a rich source of arachidonate products and the enzymes necessary for their metabolism (4, 6, 22). Furthermore, circulating leukocytes and possibly lung cells have been suggested to be possible sources for the production of oxygen radicals following pulmonary microembolism (12, 22, 27). In deed, both in vivo and in vitro studies have demonstrated activation of the cyclooxygenase pathway and leukocytes following PAE (13, 22, 27). The diminished tachypneic response we observed was unlikely due to the possible nonspecific effects of ibuprofen or dimethylthiourea on the reflex neural pathways because capsaicin injection and lung hyperinflation could still evoke reflex apneic responses originating from the stimulation of lung vagal unmyelinated and myelinated afferents, respectively, in these animals (Table 1). Quite parallel to these findings, our recent studies (7, 8) demonstrated that either ibuprofen or dimethylthiourea suppressed the stimulation of lung vagal C-fiber nerve endings by PAE, whereas ibuprofen inhibited the activation of pulmonary rapidly adapting receptors by PAE. These observations indicate the important contributions of cyclooxygenase products and/or hydroxyl radical to the PAE-induced afferent stimulation, although the mechanisms of their involvements are not completely known. It is therefore conceivable that the attenuation of the PAE-induced tachypnea by a cyclooxygenase blockade or by scavenging hydroxyl radical observed in this study may be due to the suppression of afferent responses of these two types of lung vagal sensory receptors to PAE. Two previous studies have investigated the mediator mechanism in the tachypnea induced by other emboli. Armstrong and coworkers showed that the reflex tachypnea response to glass-bead microembolism in rabbits was totally prevented by platelet

depletion (3) and partially attenuated by a serotonin receptor antagonist (2), suggesting that the response was mediated in part by the effects of serotonin associated with platelet aggregation. Although not specifically identified as (the) mediator(s) involved in their study (3), many mediators including cyclooxygenase products, oxygen radicals, and serotonin could be released as a consequence of platelet aggregation (22). In this study, no attempt was made to investigate the involvement of serotonin because lung lung vagal C-fiber afferents, the major type of pulmonary receptors mediating the PAE-induced tachypnea, are relatively insensitive to serotonin in dogs (10). However, these finding (2, 3) that indomethacin or aspirin (two other cyclooxygenase inhibitors) completely abolished the reflex tachypneic response to glass-bead microembolism also reflect the importance of the cyclooxygenase products in eliciting the tachypnea in their embolic model.

When their tachypneic response was prevented, vagotomized animals conversely responded to PAE with a large increase in V_T (Fig. 3B), a result similar to the finding reported by Armstrong and Kay (2) who used glass beads as the emboli. The mechanism responsible for this nonvagal response is not known at present. Armstrong and Kay (2) postulated that arterial chemoreceptors might be a possible origin. It is interesting to note that this large increase in V_T was not seen in intact animals in this study, despite the fact that most of them had suppressed tachypneic response to PAE following experimental interventions. It appears that there were different controls for f and V_T during PAE and lung vagal afferents might provide a dominant and inhibitory influence on V_T during PAE in intact animals. Thus, this nonvagal response of V_T to PAE might be revealed after removing the inhibitory influence by vagotomy. If this be the case, lung vagal C-fiber afferents were unlikely to be the candidate to exert the inhibitory influence because perivagal capsaicin-treated animals did not display such an increase in V_T following PAE (Fig. 2A).

In summary, both lung vagal unmyelinated C-fiber afferents and myelinated afferents are responsible for evoking the reflex tachypneic response to PAE, although the former afferents play a predominant role. Additionally, both cyclooxygenase preoducts and hydroxyl radical are important in eliciting the reflex tachypneic response to PAE.

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LEGENDS FOR FIGURES

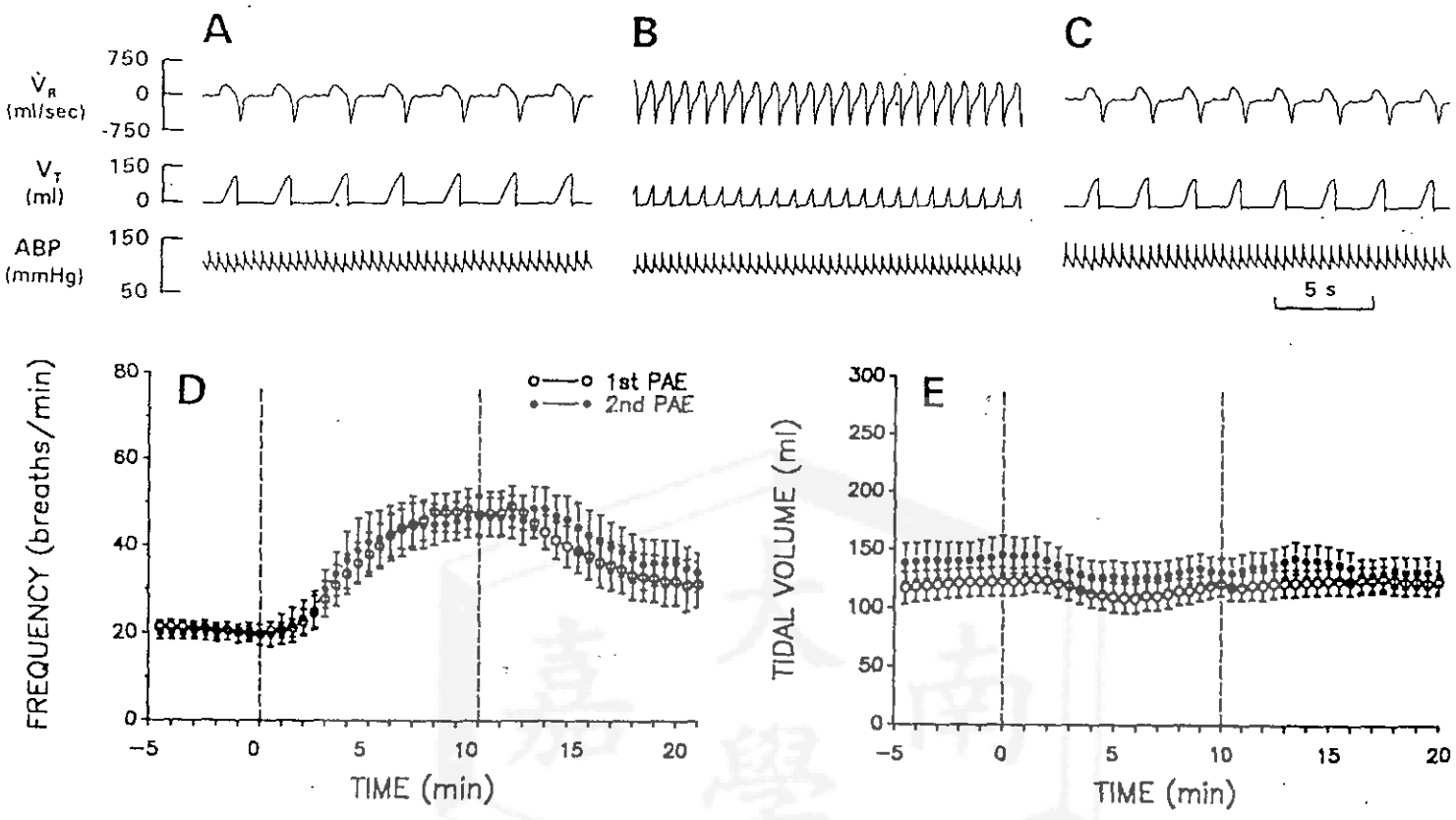
Fig.1. Ventilatory responses to pulmonary air embolism (PAE). A: baseline recorded 1 min before PAE induction; B: responses recorded 10 min after onset of PAE induction; C: recovery of responses recorded 15 min after termination of PAE induction. PAE was induced by infusion of air (0.2 ml kg^{-1} min^{-1} for 10 min) into right atrium. V_R respiratory flow; V_T, tidal volume; ABP, arterial blood pressure. Panels D and E are mean ventilatory responses to two consecutive inductions of PAE separated by 35 min in one group of animals pretreated with saline vehicle before the second PAE induction. Period of PAE induction is indicated between two dashed lines. Data are means ± SE of six dogs.

Fig.2. Mean ventilatory responses to two consecutive inductions of pulmonary air embolism (PAE) separated by 35 min in two groups of dogs. Animals received

pretreatment with dimethylthiourea (A) or pretreatment with ibuprofen (B) before the second PAE induction. Period of PAE induction is indicated between two dashed lines. Data in each group are means ± SE of six dogs.

Fig. 3. Mean ventilatory responses to two consecutive inductions of pulmonary air embolism (PAE) separated by 35 min in two groups of dogs. Animals received pretreatment with dimethylthiourea (A) or bilateral cervical vagotomy (B) before the second PAE induction. Period of PAE induction is indicated between two dashed lines. Data in each group are means ± SE of six dogs.

Fig. 4. Averaged peak increase in respiratory frequency and maximal decrease in tidal volume produced by two consecutive inductions of pulmonary air embolism (PAE) in five groups of dogs. A: saline-treated group; B: perivagal capsaicin-treated group; C: ibuprofen-treated group; D: dimethylthiourea-treated group; E: vagotomy group. Data in each group are means ± SE of six dogs. *, significantly different from responses produced by first PAE induction. Dashed lines were added to indicate the 100% level.



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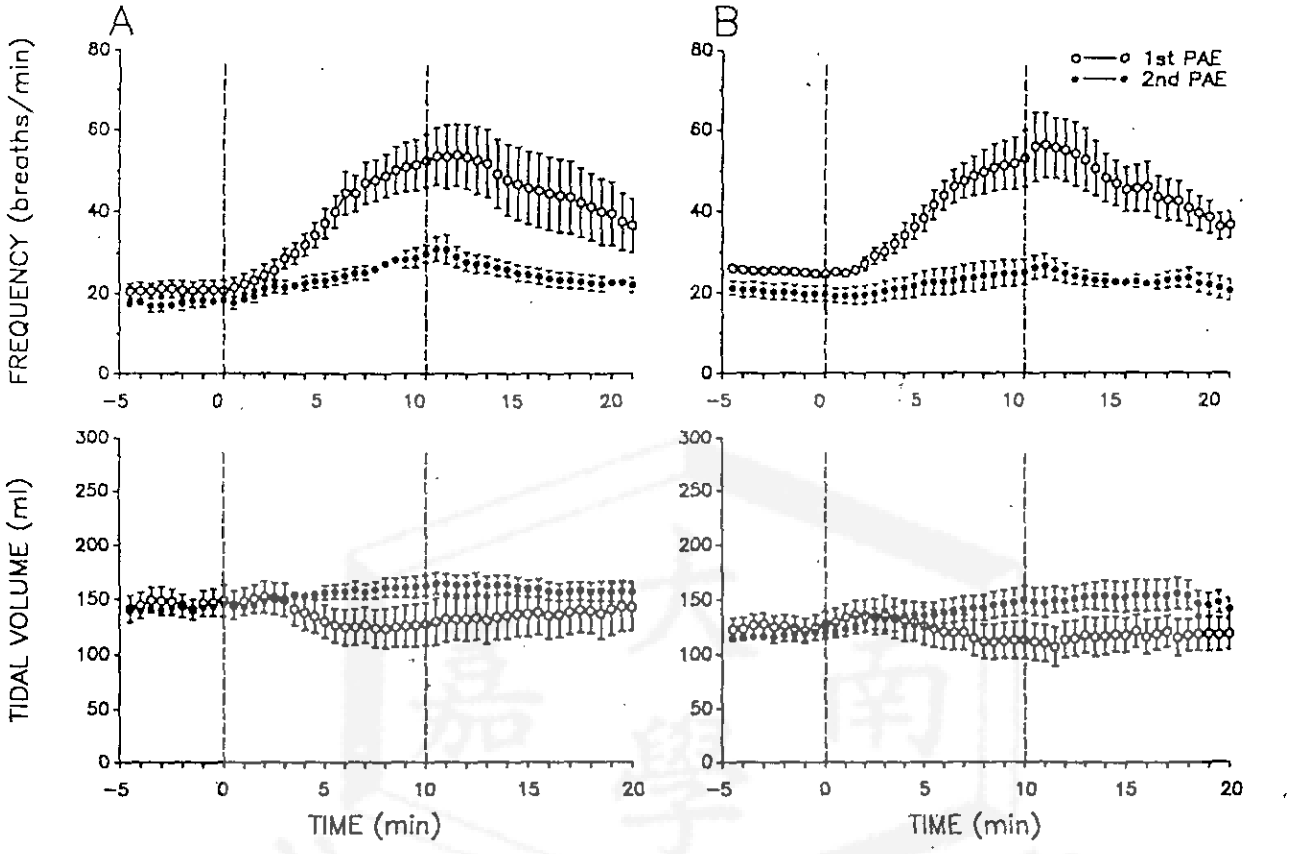
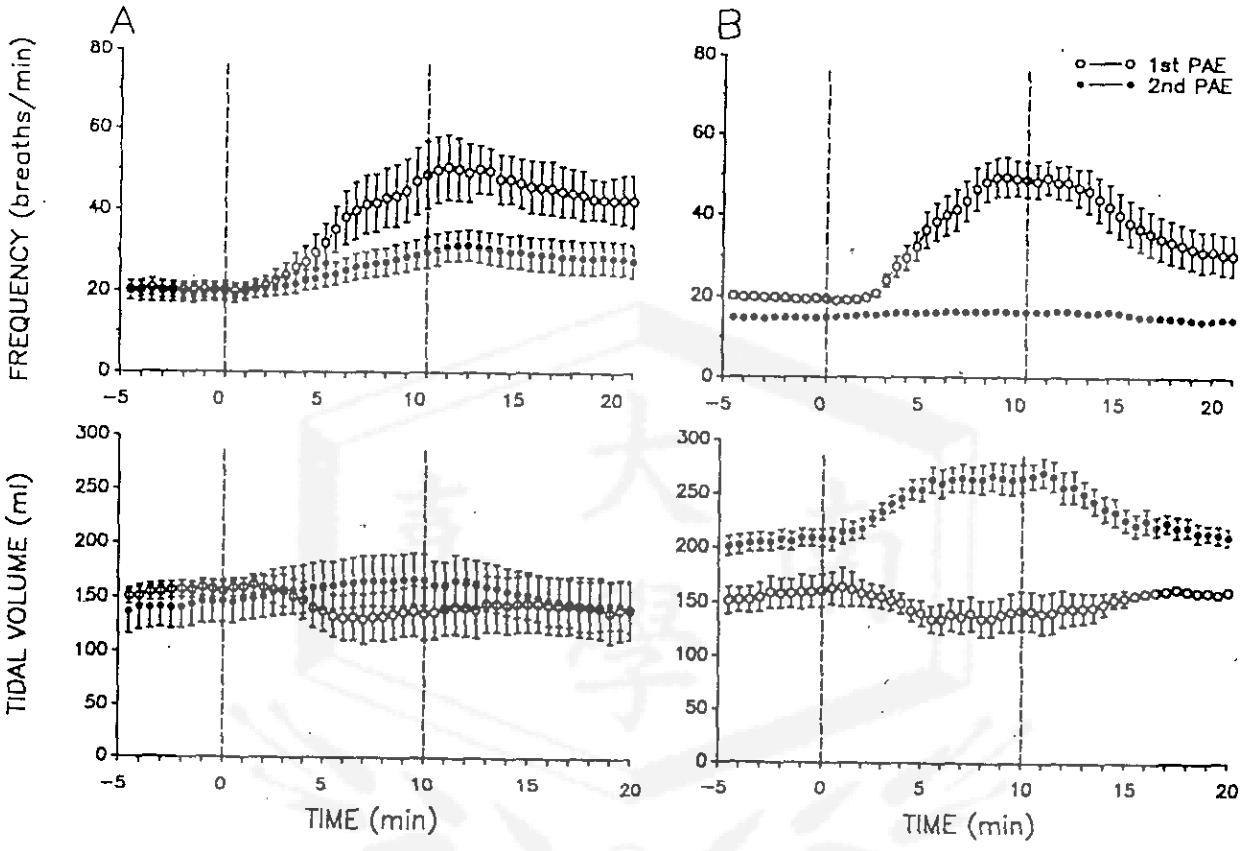


Fig.2. Mean ventilatory responses to two consecutive inductions of pulmonary air embolism (PAE) separated by 35 min in two groups of dogs. Animals received perivagal capsaicin treatment (A) or pretreatment with ibuprofen (B) before the second PAE induction. Period of PAE induction is indicated between two dashed lines. Data in each group are means ± SE of six dogs.



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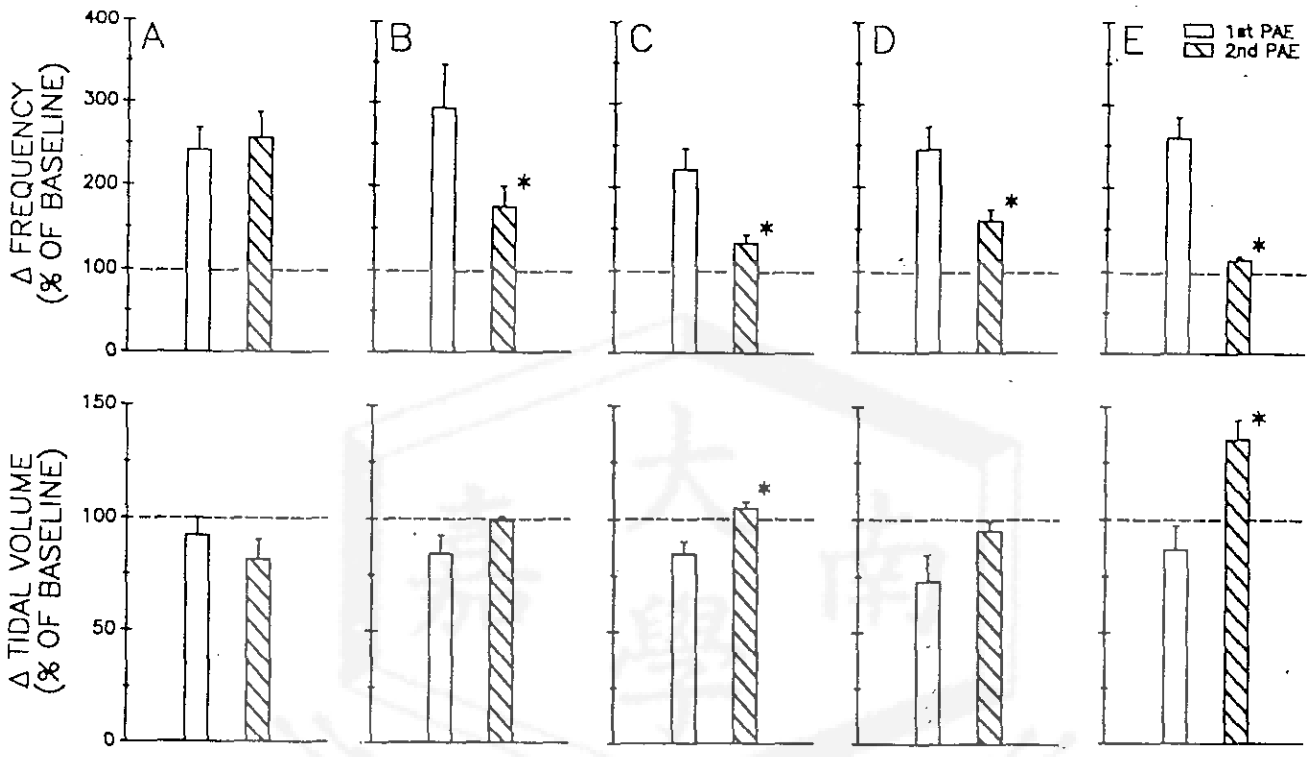

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