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Effects of Elastic Loading and Exercise on Pulmonary Gas Exchange in Dogs

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CHONAN, T., HIDA, W., KIKUCHI, Y., SHINDOH, C., TAGUCHI, O., MIKI, H. and TAKISHIMA, T. *Effects of Elastic Loading and Exercise on Pulmonary Gas Exchange in Dogs.* Tohoku J. Exp. Med., 1991, **164** (2), 157-167, —— We assessed the effects of negative intrathoracic pressure induced by inspiratory elastic loading on pulmonary, gas exchange with and without electrically induced hindlimb exercise in 8 normal, anesthetized dogs. Two elastic loads (EL) were used; one of 81 and one of 140 cmH_2O/liter. These are equivalent to doubling and tripling the normal elastance of the dog's respiratory system, respectively. Elastic loading decreased ventilation and caused hypoxemia and hypercapnia, but it did not affect systemic arterial pressure or heart rate. During exercise, increase in ventilation was limited, whereas increase in cardiac output was not affected by elastic loading. Alveolar-arterial O_2 tension difference ($A\text{-}aDO_2$) was not changed significantly by exercise alone. However, elastic loading accompanied by exercise increased $A\text{-}aDO_2$. Although comparable end-inspiratory pleural pressure was achieved with large EL (-29 ± 2 cmH_2O, mean$\pm$SE) and small EL with exercise (-30 ± 2 cmH_2O), the latter increased $A\text{-}aDO_2$ whereas the former did not. Large negative intrapleural pressure combined with increased cardiac output may have caused transient interstitial edema. ———— loaded breathing; exercise; alveolar-arterial oxygen tension difference; pulmonary gas exchange

External loads have been used to simulate the mechanical disorder caused by airway and pulmonary disease. Although the physiologic abnormalities induced by external loads are not entirely analogous to those seen in diseases, there are some important, features which are common to both: these are loads to respiratory muscles and an increase in swings of intrathoracic negative pressure. Many physiologic disorders observed in airway or lung diseases may be partly due to these effects of loading, rather than to mechanical derangement of the airway or the lung itself.

There is ample literature on the ventilatory and hemodynamic effects of

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external resistive or elastic loading (Cherniack and Altose 1981; Milic-Emili and Zin 1986). However, pulmonary gas exchange during external loading has not been extensively studied. Large swings in intrathoracic pressure occurring in external loading may affect pulmonary gas exchange through hemodynamic and ventilatory changes or could cause pulmonary edema (Loyd et al. 1986) especially when the metabolic demand on the cardiorespiratory system is increased, as in exercise.

In the present experiment we assessed the effects of elastic loading on pulmonary gas exchange with and without electrically induced hindlimb contraction in anesthetized dogs.

Methods

Preparation of animals. Eight mongrel dogs weighing 10.0–13.5 kg were premedicated with intramuscular injections of ketamine hydrochloride (10 mg/kg) and anesthetized by intravenous administration of a chloralose-urethan mixture (60 mg α-chloralose and 40 mg urethan/kg). Light anesthesia was maintained throughout the experiment by intermittently adding a small amount of chloralose-urethan mixture so that corneal reflex was preserved, while at the same time animals did not show any reaction to pinching the skin (Chonan et al. 1984; Hida et al. 1986). Following tracheotomy and intubation (i.d. 10 mm), one catheter was inserted into a brachial vein for addition of anesthetics and infusion of Ringer solution. Bilateral femoral nerves were identified and cut at the iliopsoas muscle just caudal to their points of emergence from the abdominal cavity. Bilateral sciatic nerves were also cut in the upper thigh. The distal cut ends of these nerves were passed through thin rubber tubes (1.2 cm in length) in which bipolar silver stimulating electrodes were placed to induce exercise. The nerves were kept under liquid paraffin and the electrodes were covered with rubber sheets to minimize current spread and drying of the nerves.

Electrically induced hindlimb exercise. The dog exercise model employed in the present experiment has been previously reported (Chonan et al. 1984; Hida et al. 1986). The

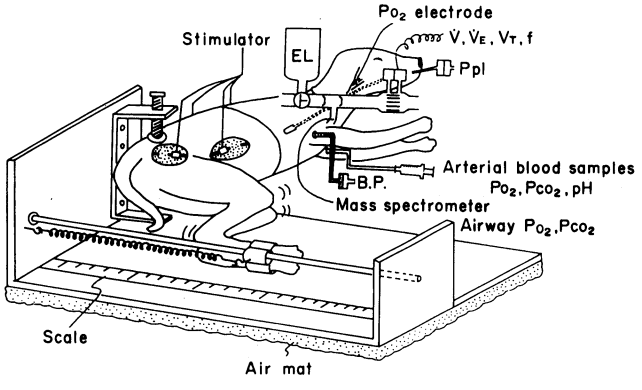

Fig. 1. Experimental preparation. Dogs were placed in the lateral decubitus position. Elastic load (EL) was applied to the inspiratory side of the unidirectional valve. Phasic hindlimb exercise was induced by electrically stimulating bilateral femoral and sciatic nerves. $\dot{V}$, expiratory flow; $\dot{V}_E$, minute ventilation; V_T, tidal volume; f, breathing frequency; Ppl, pleural pressure; B.P., blood pressure.

apparatus employed in the present study was designed to maintain the work done by the legs almost constant during exercise (Fig. 1). It consists of a spring and a foot holder to which the feet are tightly fixed. The foot holder runs parallel to a steel bar 55 cm in length. The foot holder is attached to a spring which can be stretched parallel to the steel bar. The elastic modulus of the spring is 7.8×10^4 dyn/cm which is appropriate to maintain constant work for several minutes with nerve stimulation. The resting length of the spring is 20 cm which corresponds to the length of the legs in the resting flexion position. Both sides of the sacral portion were fixed with a clamp and the whole apparatus was put on an air mat in order to minimize transmission of leg movement to the animal's abdomen, chest and head. When electrical stimulation was started, the legs extended along the steel bar against the force of the spring, and when the stimulation stopped the legs were returned to the resting position by the retraction of the spring. Leg movement was kept maximum (18–20 cm) and constant by manually varying the voltage of the electrical pulses. Thus, we could induce constant work during exercise with back and forth movement of the legs. Phasic contraction of hindlimb muscles was evoked by stimulating the bilateral femoral and sciatic nerves with pulse trains of 50 msec duration, delivered at a frequency of 1 train/sec using an electronic stimulator (SEN-3201, Nihonkohden, Tokyo) and isolator (SS-302J, Nihonkohden, Tokyo) triggered by a function generator. Within each stimulus train, square-wave pulses of 1–4 V and 1 msec duration were delivered at a rate of 100 pulses/sec. The work of the legs was kept almost constant, as described above.

Elastic loading. A three-way cock was attached to the inspired side of the two way valve. One side of the three-way cock was attached to one of two rigid containers of different size and the other side was open to the atmosphere. The elastances of these containers were 81 (small elastic load) and 140 (large elastic load) cmH_2O/liter which are equivalent to doubling and tripling the normal elastance of the dog's respiratory system, respectively (Zin et al. 1986). Elastic loads were applied by occlusion of the free side of three-way cock manually during inspiration. The resistance of the inspiratory circuit, including the tracheal tube, was 2.6 cmH_2O/liter/sec.

Measured variables. Oxygen tension (Po_2) and carbon dioxide tension (Pco_2) in the inspired and expired gases were monitored with a mass spectrometer (200 MGA, Centronic, New Addington, England) by continuous sampling from the tracheal tube. The tracheal tube was connected to a low resistance Hans-Rudolph two way non-rebreathing valve (dead space 15 ml). Expired airflow was measured with a heated (38°C) pneumotachograph (Fleisch No. 1) and a Validyne differential pressure transducer at the expired side of the two way valve. Tidal volume (V_T) and minute ventilation ($\dot{V}_E$) were obtained by integration of the expired flow signal. A polyethylene catheter with a 5-cm-long latex balloon was inserted in the lower esophagus and connected to a Validyne differential pressure transducer to measure pleural pressure (Ppl). Blood pressure and heart rate were measured continuously with an indwelling intra-arterial catheter which was inserted into a brachial artery and connected to a strain-gauge pressure transducer (MPU 0.5, Toyo Sokki, Tokyo). From the arterial catheter two milliliter blood samples were drawn slowly (30–60 sec) and anaerobically during steady states using a heparinized glass syringe. A sample of blood was taken to flush the catheter before the normal sample was taken. Blood gases and pH were analyzed within 2 min after sampling using a pH/blood gas analyzer (IL 1303, Instrumentation Laboratory, Milano, Italy) and corrected to rectal temperature which was monitored with a thermistor (MGA-3, Shibaura electronics, Tokyo). Rectal temperature was maintained at 38 ± 0.5°C by using a heating pad and lamps.

Expired gas was collected for 1 min in a 12 liter meteorological balloon during the steady states. From the O_2 and CO_2 content and $\dot{V}_E$ we calculated $\dot{V}o_2$ using standard formulas (Otis 1964). Ideal alveolar oxygen tension (P_AO_2) was calculated from the alveolar gas equation and A-aDO_2 was obtained as the difference between P_AO_2 and PaO_2. Calibration of the blood gas analyzer was performed with tonometered blood. The pH electrode was calibrated with two IL precision pH buffers (pH 6.840 and pH 7.384).

Experimental protocol. Three experiments were performed in each dog: 1) exercise alone; 2) exercise with small elastic load; 3) exercise with large elastic load. The order of the three experiments was selected at random. The duration of exercise was 3.5 min and the duration of loaded breathing before starting the exercise was also 3.5 min. Respiratory and cardiovascular parameters were taken for 30–60 sec of the control period and the last 30–60 sec of loaded breathing or exercise in the steady state. As an additional experiment a Swan-Ganz catheter was inserted into the pulmonary artery and cardiac output was measured by the thermodilution method in four dogs in the three experiments described above.

Data analysis. Values for grouped data are presented as means±S.E. Since $\dot{V}_E$ reached a plateau 2–3 min after beginning elastic loading or electrical stimulation of the nerves, values during the last minute of the experimental run were defined as steady state. Statistical significance was evaluated using the paired student's *t*-test. Significance was accepted at $p<0.05$.

Results

Table 1 shows the mean values of end-inspiratory pleural pressure (Ppl) in each state. Swings in Ppl increased with elastic load (EL) and increased further during exercise with loading. The negativity of end-inspiratory Ppl was greater in trials with large EL than in those with small EL.

Table 2 shows the mean values of respiratory and cardiovascular parameters in each state. Tidal volume decreased and breathing frequency increased significantly with elastic loading. Therefore, the breathing pattern became rapid and shallow and this tendency was more marked when the load was large. With elastic loading, minute ventilation ($\dot{V}_E$) decreased and, during exercise, its increase was limited. The mean values of $\dot{V}_E$ during steady-state exercise were 21% (with small elastic load) and 26% (with large elastic load) smaller than without elastic loads ($p<0.05$). Oxygen consumption ($\dot{V}o_2$) increased to about twice the control level during exercise, whether the elastic load was present or not. $\dot{V}o_2$ did not change significantly with elastic loading alone, suggesting that the oxygen cost of breathing was relatively small, compared with the metabolic rate of the whole body. However, the O_2 cost of breathing may have contributed to the slight increase in average $\dot{V}o_2$ during exercise with loads since the level of respiratory motor output was accentuated significantly during exercise, compared to the

Table 1. *Magnitude of end-inspiratory pressure (cmH_2O)*

	C[a]	ELs	ELs+Ex	C	ELl	ELl+Ex	C	Ex
Means	9.7	21.4**	29.6**	9.5	28.8**	38.4**	8.9	11.6**
±S.E.	±0.8	±1.2	±2.4	±0.8	±2.0	±3.1	±1.0	±1.2

[a]C, control state; ELs, small elastic load; ELs+Ex, small elastic load with exercise; ELl, large elastic load; ELl+Ex, large elastic load with exercise; Ex, exercise.

**Significantly different from the control value at $p<0.01$.

TABLE 2. *Respiratory and cardiovascular variables*

		C[a]	ELs	Ls+Ex	C	ELl	ELl+Ex	C	Ex
$\dot{V}_E$	(liter • min^{-1})	3.28±0.27[b]	3.19±0.17**	5.53±0.72*	3.90±0.33	2.94±0.28**	5.22±0.44*	3.57±0.30	7.02±0.68**
V_T	(liter)	0.25±0.02	0.16±0.01**	0.21±0.02*	0.22±0.01	0.13±0.01**	0.17±0.01**	0.22±0.01	0.30±0.03**
f	(min^{-1})	16.1±1.8	20.4±1.8*	26.8±2.1**	18.4±2.0	23.5±2.4*	31.0±2.0**	16.8±1.0	23.9±1.7**
pH		7.37±0.02	7.34±0.02*	7.33±0.02**	7.39±0.02	7.35±0.02**	7.32±0.02**	7.40±0.02	7.39±0.02
$\dot{V}_{O_2}$	(ml • min^{-1})	108±8	114±6	198±29**	105±10	106±11	204±25**	101±8	183±16**
$\dot{V}_{CO_2}$	(ml • min^{-1})	78±5	75±3	155±24*	81±6	71±7	161±22**	77±5	155±9**
RQ		0.73±0.04	0.66±0.03*	0.79±0.02	0.79±0.04	0.67±0.02**	0.79±0.02	0.77±0.03	0.87±0.04*
MAP	(torr)	121±10	122±11	114±11	124±11	122±8	111±8*	132±8	122±10*
HR	(min^{-1})	159±7	156±8	174±10*	157±14	150±14	171±12	143±10	170±7**

[a]C, control state; ELs, small elastic load; ELs+Ex, small elastic load with exercise; ELl, large elastic load; ELl+Ex, large elastic load with exercise; Ex, exercise; $\dot{V}_E$, minute ventilation; V_T, tidal volume; f, breathing frequency; pH, arterial pH; $\dot{V}_{O_2}$, O_2 uptake; $\dot{V}_{CO_2}$, carbon dioxide output; RQ, respiratory quotient; MAP, mean arterial pressure; HR, heart rate.

[b]Values are means±S.E.

Significantly different from the corresponding control value at $^*p<0.05$ and $^{**}p<0.01$.

resting condition. Mean arterial pressure (MAP) and heart rate (HR) did not change significantly with elastic loading alone. MAP decreased slightly and HR rose by 20-30/min with exercise whether the elastic load was present or not.

When the elastic load was small, P_AO_2 fell significantly with elastic loading, but it recovered to the control value with exercise. The value of PaO_2 also fell significantly with elastic loading, however it did not recover with exercise. This tendency was almost the same when the elastic load was large. Neither P_AO_2 nor PaO_2 showed a significant change during exercise alone. $PaCO_2$ increased significantly due to alveolar hypoventilation when the large elastic load was introduced (Fig. 2).

Table 3 shows the values of alveolar-arterial O_2 tension difference ($A\text{-}aDO_2$) in each state. $A\text{-}aDO_2$ did not change significantly either by elastic loading or exercise alone. However, $A\text{-}aDO_2$ widened during loading with exercise in both loading conditions.

Table 4 shows cardiac output measured with the thermodilution method in four additional dogs. Cardiac output tended to increase slightly with elastic

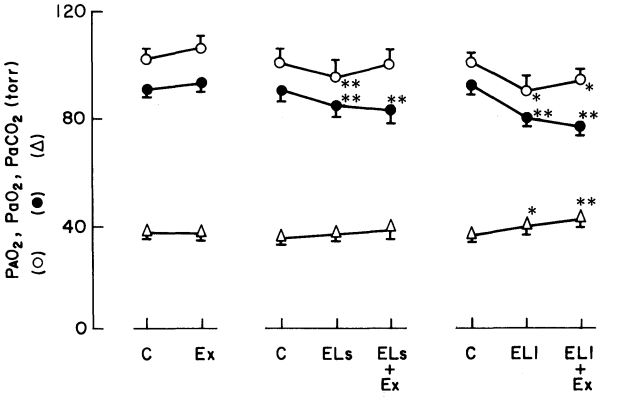

Fig. 2. Mean values of ideal alveolar PO_2 (P_AO_2), arterial PO_2 (PaO_2) and arterial PCO_2 ($PaCO_2$) in each state. P_AO_2 was calculated from the alveolar equation. C, control; Ex, exercise; ELs, small elastic load; ELl, large elastic load. Asterisk indicates a statistically significant change from the control state at $*p<0.05$ and $**p<0.01$. Data points are plotted as means ± S.E. See also Table 1.

TABLE 3. *Alveolar-arterial O_2 tension difference (torr)*

	C[a]	ELs	ELs+Ex	C	ELl	ELl+Ex	C	Ex
Means	11.1	13.3	18.2*	11.6	12.0	18.5*	12.4	14.7
±S.E.	±4.1	±3.3	±4.6	±3.0	±3.5	±4.2	±4.0	±3.9

[a]Abbreviations are the same as in Table 1. Asterisk indicates a significant change from the control state ($p<0.05$).

TABLE 4. *Cardiac outputs (liter/min) in four dogs*

Dog No.	C[a]	ELs	ELs+Ex	C	ELl	ELl+Ex	C	Ex
1	2.24	2.48	4.20	2.24	2.44	4.16	2.26	3.88
2	2.82	3.04	4.16	2.63	3.02	4.24	2.32	3.54
3	2.65	2.74	4.22	2.62	2.69	3.65	2.29	3.36
4	1.34	1.38	2.40	2.09	2.13	4.06	1.53	2.75
Means	2.26	2.41	3.75**	2.40	2.57	4.03**	2.10	3.38**
±S.E.	±0.33	±0.36	±0.45	±0.14	±0.19	±0.13	±0.19	±0.24

[a]Abbreviations are the same as in Table 1.
**Significantly different from the corresponding control value at $p<0.01$.

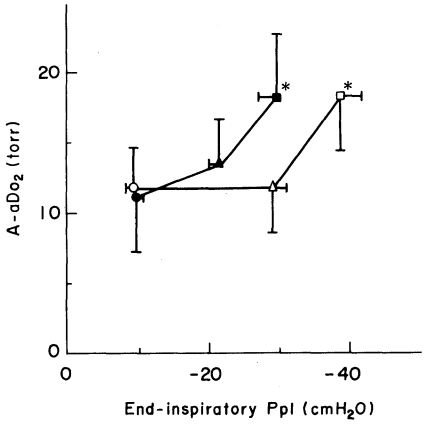

Fig. 3. Relationship between end-inspiratory pleural pressure (Ppl) and alveolar-arterial O_2 tension difference (A-aDo_2) in trials with small elastic load (filled symbols) and large elastic load (open symbols). Circles, triangles and squares indicate control, elastic load, and elastic load with exercise, respectively. Values are means±S.E. Asterisk indicates a statistically significant change from the control state ($p<0.05$).

loading. Cardiac output increased by 40–90% (mean 60%) from rest to exercise regardless of the presence or absence of elastic load.

Fig. 3 shows the relationship between end-inspiratory Ppl and A-aDO_2 trials with small EL and with large EL. The end-inspiratory Ppl induced by large EL alone was comparable to that observed during exercise with small EL. Loading alone, if it was large, did not cause a widening of A-aDO_2, whereas loading accompanied by exercise increased A-aDO_2.

DISCUSSION

In the present experiment we investigated the effects on pulmonary gas exchange of external elastic loading which double or triple the elastance of the

normal respiratory system with and without electrically induced hindlimb exercise in anesthetized dogs. Elastic loading decreased ventilation through reduction of tidal volume, resulting in hypoxemia and hypercapnia. Systemic arterial pressure and heart rate were unchanged by elastic loading, and during exercise the increase in cardiac output was not affected by elastic loading. Alveolar-arterial oxygen tension difference ($A\text{-}aDO_2$) was not changed by elastic loading or exercise alone. However, the elastic loading accompanied by exercise widened $A\text{-}aDO_2$.

Anesthetics have been reported to increase intrapulmonary shunt through airway closure (Bendixen et al. 1964). Although we cannot completely rule out this possibility, the resting values of PaO_2, $PaCO_2$ and pH were within normal limits of awake dogs (Feigl and D'alecy 1972). Therefore we think this possibility is minimal, in the resting state, in this study. Anesthetics are thought to abolish or depress respiratory load compensation mechanisms, especially those through the higher brain centers (Cherniack and Altose 1981), which may have caused underventilation against loads.

In the present study elastic loading restricted the increase in ventilation during exercise (Table 2), but it did not affect the increase in cardiac output during exercise. Therefore, the overall ventilation-perfusion ratio ($\dot{V}_A/\dot{Q}$) during exercise is thought to be smaller under elastic loading than without loads. Hypoxemia and hypercapnia observed during elastic loading with exercise appears to be partly due to this overall low $\dot{V}_A/\dot{Q}$ and increased cardiac output. To assess whether $A\text{-}aDO_2$ is widened by the combination of low $\dot{V}_A/\dot{Q}$ and increased cardiac output, in additional experiments we measured $A\text{-}aDO_2$ in three moderately anesthetized dogs which were mechanically ventilated at similar tidal volumes and frequencies to those observed during exercise with elastic loads. In six trials, twice in each dog, there were no significant change in $A\text{-}aDO_2$ (from 14.3 ± 3.0 torr, mean $\pm$ S.E. at rest to 15.1 ± 4.8 torr during exercise). This may suggest that the simple combination of low $\dot{V}_A/\dot{Q}$ and increased cardiac output was not a crucial factor in the widening of $A\text{-}aDO_2$ during exercise with elastic loads. However, the behavior of pleural pressure is quite different between spontaneous breathing and artificial ventilation, still leaving the possibility that shunt component associated with low $\dot{V}_A/\dot{Q}$ played some role in increasing $A\text{-}aDO_2$ in the present experiment.

Although transpulmonary pressure is unlikely to have changed, large intrapleural negative pressure was generated with inspiratory elastic loading (Table 1). The large intrathoracic negative pressure may have profound influences on the cardiovascular system, including increase in venous return and hindrance of outflow of blood from the left ventricle etc. (Scharf et al. 1979; Scharf 1984). The effect of impeding ventricular emptying is to increase left atrial pressure, measured relative to pleural pressure. This effect would tend to increase the driving pressure for fluid to move from the pulmonary capillary to the pulmonary interstitial space (Scharf 1984). We observed that the main pulmonary arterial

pressure decreased during inspiration under elastic loading, however the degree of decrease was about 80% of the change observed in the intrapleural pressure. If we assume that the interstitial fluid pressure is highly dependent on pleural pressure, there is a possibility that the transmural pressure of the pulmonary capillaries increases during inspiratory elastic loading. Actually, Scharf et al. (1979) have reported an increase in pulmonary artery transmural pressure during inspiratory loading.

Loyd et al. (1986) have reported that inspiratory resistive loading, which produced a fall in central airway pressure by 12 cmH_2O, increased lung lymph flow and decreased the lymph-to-plasma protein concentration ratio in awake sheep. They concluded that inspiratory loading is associated with an increase in the pulmonary transvascular hydrostatic gradient, possibly by causing a greater fall in interstitial perivascular pressure than in microvascular pressure. Although ventilation became almost stable during elastic loading alone, the low $\dot{V}_A/\dot{Q}$ observed may suggest that the steady states were not achieved in those conditions. If the respiratory quotient (R.Q.) had been greater, A-aDO_2 might have been widened even during loading alone. This tends to be consistent with the findings by Loyd et al. Hypoxic vasoconstriction may also act to increase the transvascular hydrostatic gradient at pulmonary capillaries during loading.

Pulmonary edema, if it occurs, may increase the shunt component, when accompanied by an increase in cardiac output, such as in exercise (Lynch et al. 1979). However, the resting values of ventilation, PaO_2 or $PaCO_2$ did not change significantly before or after elastic loading with exercise. Therefore, we think that manifest pulmonary edema did not occur in this experiment. Indeed in three dogs we examined after the experiment, the excised lungs showed no evidence of alveolar edema either macroscopically or histologically. However, it is certainly possible that transient interstitial edema occurs during exercise with inspiratory elastic loading, where large negative intrapleural pressure is combined with increased cardiac output.

An association between pulmonary edema and certain upper airway diseases such as laryngospasm (Jackson et al. 1980), croup, epiglottitis (Travis et al. 1977), tumor (Oswald et al. 1977; Stradling and Bolton 1982), tonsils and adenoid hypertrophy (Luke et al. 1966) has been reported. The results of the present experiment may imply that mild exercise can cause deterioration of pulmonary gas exchange in patients with upper airway obstruction. It is known that A-aDO_2 increases from rest to mild exercise in patients with pulmonary fibrosis, and this has been attributed to the ventilation-perfusion inequality or diffusion impairment due to organic disorder of the lung (Crystal et al. 1976; Wagner et al. 1976; Risk et al. 1984). However, the present experiment suggests that large swings in intrathoracic pressure combined with the increase in cardiac output may be partly responsible for this phenomenon.

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