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Rabbit Cardiovascular Responses during PEEP before and after Vagotomy (40709)[1]

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Refractory hypoxemic patients with uniform pulmonary disease may improve arterial oxygenation by use of positive end expiratory pressure (PEEP). PEEP has been used to reexpand and stabilize atelectatic areas of the lung (1). However, PEEP may also produce undesired effects. Depending on the degree, PEEP may be followed by an increase or decrease in heart rate (2, 3), compromised cardiac output (4, 5), and reduced arterial blood pressure (2, 6). Recently, it was demonstrated that the mechanical factor of a reduced venous return was not the causative agent for the fall in cardiac output and arterial pressure (5, 7), and increased attention to neuroreflex mechanisms during PEEP-induced lung distension was suggested (7).

Mechanoreceptors in the cardiopulmonary regions, which are sensitive to change in lung volume or pressure, are considered to influence vasomotor and cardiac autonomic activity (2, 3, 6, 8). It has been suggested that these receptors are subserved primarily by vagally mediated afferents in the dog (4, 6, 9) and the rabbit (10–12). However, vagal cold block or vagotomy had little effect on the depression of cardiac output and only partially reversed the decreased arterial pressure resulting from positive pressure diffusion respiration in the sinoaortic denervated, paralyzed rabbit (10). Thus, it is not certain that only vagally mediated mechanoreceptors were involved.

Additionally, it is not clear how activation of cardiopulmonary mechanoreceptors results in modification of systemic baroreflexes. Glick *et al.* (4) recorded decreases in heart rate, cardiac contractility, and vascular resistance during lung inflation in total cardiopulmonary-bypass canine preparations. During their procedures they used rapid blood infusion in an attempt to control systemic blood pressure and baroreflexes. However, their records indicate that a constant pressure was not maintained by this method. Mancia *et al.* (13) suggested a dominant cardiovascular role for the carotid baroreflexes over the cardiopulmonary mechanoreflexes when the two systems interact. However, their mechanoreceptor stimulus was an increase in blood volume and not lung inflation. Volume expansion is not a selective stimulus to cardiopulmonary receptors, because it has been shown that attenuation of cardiovascular reflex responses during infusion, while not altered by vagotomy, are abolished by sinoaortic denervation (14). Thus, the direct cardiovascular effects as well as the modulation of systemic baroreflexes by cardiopulmonary mechanoreceptors need further study.

The object of this work was to investigate the hypothesis that increases in lung expansion or pressure during PEEP effect changes in heart rate and blood pressure before and during isolation of the arterial baroreflexes. A second objective was to determine what portion of the cardiovascular responses to PEEP might be reflexly mediated by vagal afferents. To accomplish these objectives, heart rate and blood pressure responses were measured during stepwise increases in PEEP in the intact (no nerves cut), in the aortic denervated, and then in the vagotomized rabbit. Changes in mean right atrial pressure and intrathoracic pressure were used as indices of pulmonary responses to PEEP. In the aortic denervated rabbit, to identify modulatory influences on the systemic baroreflexes, responses to PEEP were measured before and during vascular isolation of the carotid sinus and concomitant electrical stimulation of the cranial end of the left aortic nerve.

Methods. Fifteen rabbits of either sex (2.5 ± 0.3 kg (SE)) were anesthetized with sodium pentobarbital via an ear vein (Diabutal; Diamond Laboratories, Inc., 30 mg/kg, iv). A light level of surgical anesthesia was maintained by supplemental administration through a cannulated femoral vein. The de-

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scending aorta (via femoral artery) and right atrium (via jugular vein) were also cannulated and connected to Statham P23Ac and P23BB strain gauges for recording of mean arterial (MAP) and right atrial blood pressures (MRAP), respectively. Heart rate (HR) was recorded via sternal needle electrodes connected to a Grass EKG/Tachograph coupler. Permanent records were made on a Grass 7 recorder. The trachea was cannulated via a tracheostomy and the animal's respiration was controlled. Blood gases and pH were determined from frequent small blood samples analyzed in an IL 213 (Instrument Laboratories, Inc., Lexington, Mass.). Through a midventral incision, the left and right aortic and vagus nerves were located in the cervical region, carefully isolated from surrounding tissue for about 1 cm, and looped with a loose thread for identification prior to sectioning. In five animals the intrathoracic pressure (IP) was measured via insertion of an air-filled, blunt-tip catheter through the diaphragm into the cavity of the left or right lung. The respective tissues, diaphragm to skin, were sutured airtight around the catheter and the pneumothorax was minimized. The catheter was then opened via a three-way connector to a Grass (PT5A) volumetric pressure transducer. Values for MRAP and mean IP are expressed relative to atmospheric pressure.

Carotid sinus isolation. A modified Moissejeff technique as developed by Schmidt *et al.* (15, 16), was used to permit reversible isolation of the carotid sinuses from the systemic circulation. Briefly, both internal carotids were tied beyond the sinus regions at approximately 0.5 cm from their points of origin. The external carotid artery was carefully isolated but remained patent. All other small vessels were ligated. Following heparinization (4 mg/kg iv, 150 units/mg, Hynson, Westcott, Dunning, Inc., Baltimore, Md.) the common carotid arteries were cannulated with an extracorporeal loop. This permitted perfusion of the sinus by the carotids (closed loop, CL), or pressure regulation of the sinuses, via an elevated pressure bottle, after occlusion of the external carotid arteries (open loop, OL). Under all conditions intrasinus pressure (ISP) was monitored by a pressure transducer (Statham P23Ac) in the extracorporeal system near the sinus. In every animal during the OL condition the ISP was held at equilibrium pressure (EP) for that animal. EP was that controlled ISP which reflexly resulted in an equal mean arterial pressure.

Control of respiration. Using a small animal respirator (Model 665, Harvard Apparatus), each rabbit's respiration was adjusted, to a low level of inspiratory positive pressure breathing (IPPB). Respiratory rate (40 to 60 cpm) and volume (15 ± 3 ml/kg) were adjusted to maintain arterial blood pH (>7.42) and blood gases ($pO_2 > 90$; $pCO_2 < 35$ mm Hg) and thereafter held constant. Exhalation was spontaneous through a tracheal T-tube connected to a low-resistance Silastic tube (0.6 cm i.d.). PEEP was regulated by submerging the opening of the exhalation tube in a calibrated column of water to 2.5, 5.0, or 7.5 cm H_2O.

Nerve stimulation. The rabbit was used for this study because it has easily identified aortic nerves which run separate from the vagi and subserve only baroreceptors (17). Additionally, reflex cardiovascular responses to electrical stimulation of the aortic nerve are well defined in this species (14, 17–20). Following data collection with all nerves intact, both right and left aortic nerves were cut and the left central end was placed on bipolar hook electrodes, platinum–irridium, for electrical stimulation (18, 19). Responses to left aortic nerve stimulation (LANS) were recorded with both carotid sinuses in the circulation (CL) and with both sinuses isolated (OL); pressures of the isolated sinuses were maintained constant at predetermined equilibrium pressure (EP). Responses to LANS were obtained under the above conditions both before and after vagotomy. Electrical stimulation was from a Grass S5 stimulator. Stimulus parameters were selected to maximize reflex cardiovascular responses as has been previously published (18–20). Briefly, stimulation bursts were composed of square wave impulses of 10 V and 0.3-msec duration. Stimulus frequency was 80 Hz with a burst duration of 25 to 30 sec.

Experimental procedures. All animals were instrumented as described above. A group of 10 animals were exposed to PEEP increases and LANS during CL and OL conditions. Eight of this group completed the experimen-

tal series through aortic denervation and vagotomy. One animal died following vagotomy and data from one animal were not included in the group analysis because its blood gas and pH analysis indicated a sustained metabolic acidosis. A second group of five animals had additional instrumentation for intrathoracic pressure measurements. Data from this latter group were analyzed separately from those of the first.

In the first group, prior to any denervation, a CL steady state was established with IPPB. Then PEEP was increased from 0.0 to 2.5, 5.0, or 7.5 in H_2O. The level of PEEP was randomized within and between procedures for each animal. Small arterial samples (0.3 to 0.5 ml) were drawn for gas and pH analysis at each PEEP steady state. Both aortic nerves were then cut and a second CL steady state was established with IPPB unchanged. An arterial blood sample was drawn for analysis. A PEEP increase was imposed and, following steady state, LANS started and continued through maximal heart and vascular response levels. LANS was terminated and cardiovascular parameters were allowed to return to prestimulus levels. Then OL responses were measured. The ISP was held at EP and a level of PEEP imposed followed by LANS. Between OL conditions, for each PEEP level, the animal was returned to the CL conditions. Following data collection in the aortic denervated animal, at each PEEP level in the CL and OL condition with LANS, the vagi were sectioned and the procedures repeated.

The second group of five animals went through essentially the same procedures but without LANS. This second group was used to determine the mean right atrial, intrathoracic, and transpulmonary pressure responses before and during IPPB with the various PEEP levels. Collection of data in this group was separate and followed that of the first.

Data analysis. All values were reported as means or mean differences ± the standard errors of the means (SEM). Statistical evaluation was made by use of the appropriate Student *t* test for paired or unpaired comparisons. Values of $P < 0.05$ were considered significant. Regression analysis employed programmed linear regression (Texas Instruments, Inc., Dallas, Tex.).

Results. In eight neurally intact anesthetized rabbits (Table I) increasing PEEP by 2.5, 5.0, or 7.5 cm H_2O resulted in a proportional increase in heart rate (HR) and mean right atrial pressure (MRAP) and a decrease in mean arterial pressure (MAP). Left aortic nerve stimulation (LANS) was not attempted in the intact animal. Following bilateral sectioning of the aortic nerves the significant HR change at high PEEP level was not found. However, MRAP and MAP responses were essentially unchanged as compared to the responses of the intact animal.

Cardiovascular and reflex responses to left aortic nerve stimulation (LANS) during PEEP increases. Figure 1 represents an example of the cardiovascular responses of one aortic denervated animal during an increase in PEEP to 5.0 cm H_2O (arrows on time scale) both before (Panel A) and during (Panel B) carotid sinus isolation. Note in panel A, with the loop closed (CL), that at the start of the PEEP increase, the initial falls in MAP and ISP are maximal and then have a partial recovery phase. These results are indicative of the buffering capacity of carotid baroreceptors. No recovery in MAP is evident during repetition of the procedure with ISP held constant in open loop (OL) condition (panel B). Heart rate (HR) during either CL or OL conditions was essentially unaltered by an increase in PEEP. With establishment of

TABLE I. CARDIOVASCULAR RESPONSES TO POSITIVE END EXPIRATORY PRESSURE (PEEP) IN EIGHT ANESTHETIZED RABBITS.[a]

Parameter	Control	Change following PEEP increase (cm H_2O) of		
		2.5	5.0	7.5
HR (b/min)	290 ± 7.0	8.0 ± 0.7	12.6 ± 0.9*	18.1 ± 1.2*
MAP (mm Hg)	92.0 ± 3.0	−6.6 ± 1.0*	−17.0 ± 3.1*	−25.9 ± 4.2*
MRAP (mm Hg)	1.0 ± 0.4	1.2 ± 0.4	2.5 ± 0.7*	3.5 ± 0.9*

[a] HR = heart rate; MAP = mean arterial pressure; MRAP = mean right atrial pressure; values are mean ± 1 SEM.

* $P < 0.05$ (paired analysis) for values significantly different from control.

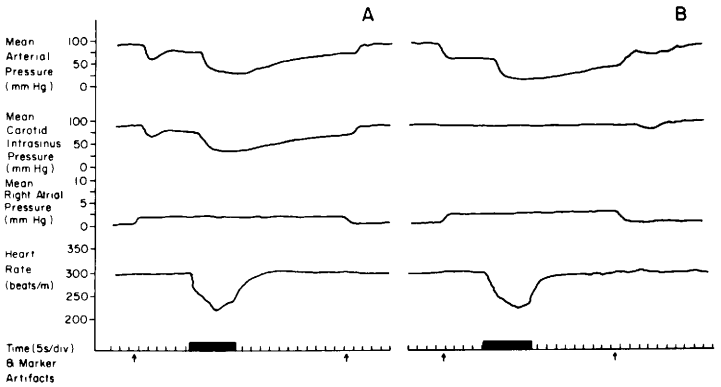

FIG. 1. Cardiovascular and reflex responses to left aortic nerve stimulation (LANS) during a 5-cm H_2O increase in positive end expiration pressure (PEEP) in one aortic denervated rabbit. Panel A, heart rate and vascular responses with the carotid sinuses able to detect systemic arterial pressure (closed loop (CL) condition). Panel B, heart rate and vascular responses during vascular isolation of the carotid sinuses (open loop (OL) conditions). Distance between arrows below the time line indicate the period of increased PEEP. Length of solid bars on time line indicates period of LANS.

steady state for HR and MAP during the PEEP increase, LANS was initiated (solid bars on time scale) and induced reflex falls in MAP and HR during both CL and OL conditions. The CL and OL maximal depressions in ΔMAP and ΔHR to LANS were recorded at each PEEP level, before and following vagotomy.

Heart rate responses to PEEP. The mean (± SEM) heart rates and ΔHR to LANS during CL and OL changes in PEEP for nine animals before (Panel A) and eight animals after (Panel B) vagotomy are presented in Fig. 2. Prior to aortic denervation HR responses (circled crosses) were progressively elevated during the CL state at each PEEP level (Fig. 2A, top; Table I). Following aortic denervation little change in HR responses (solid circles) occurred during CL increases in PEEP. However, HR responses (open circles) decreased slightly but significantly (10.0 ± 6.0 b/min) during the OL increase in PEEP of 7.5 cm H_2O when averages were compared to OL control (no PEEP) or the respective CL responses. No significant changes from control in CL or OL heart rates were observed after vagotomy at any PEEP level (Fig. 2B, top).

Reflex heart rate responses to LANS during PEEP. In aortic denervated animals the maximal fall (ΔHR) in OL heart rate responses (open circles) to LANS was significantly greater (average 17 b/min) as compared to

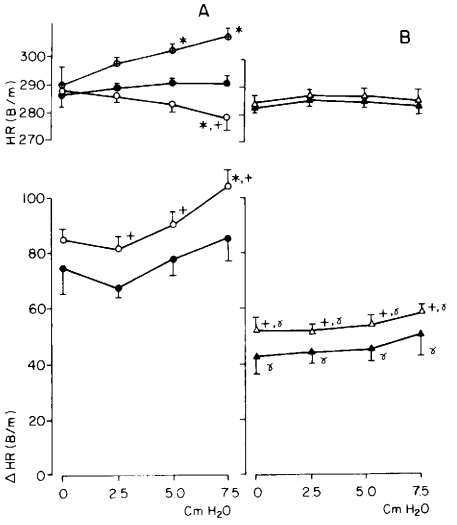

FIG. 2. Mean (± SEM) heart rate (HR) and peak reflex bradycardia (ΔHR) to left aortic nerve stimulation (LANS) during closed loop (CL) and open loop (OL) changes in PEEP for nine animals before (Panel A) and eight of the same after (Panel B) vagotomy. Circled crosses (⊕) indicate responses prior to aortic denervation; solid circles (●) indicate CL responses, and open circles (○) indicate OL responses of aortic denervated animals; solid triangles (▲) indicate CL responses, and open triangles (△) indicate OL responses following vagotomy; * indicates responses significantly ($P < 0.05$) different from control (no PEEP); + indicates OL responses significantly ($P < 0.05$) different from CL responses at the same PEEP level; and γ indicates responses significantly ($P < 0.05$) different when compared to respective pre-vagotomy responses.

that of the respective CL responses (solid circles) at all levels of increased PEEP (Fig. 2A, bottom). When PEEP was raised to 7.5 cm H_2O, open loop ΔHR to LANS was significantly increased (103 ± 10 b/min), as compared to responses at 0.0 cm H_2O PEEP (85 ± 5 b/min). Following vagotomy both open and closed loop ΔHR to LANS were significantly reduced as compared to the respective prevagotomy responses (Fig. 2B, bottom). A significant difference (average 11 b/min) persisted between OL (open triangles) and CL (solid triangles) responses when values were compared before and during each PEEP increase, respectively. However, no significant changes in OL ΔHR to LANS at any PEEP level were observed in the vagotomized animals.

Mean arterial blood pressure (MAP) responses to PEEP. MAP and reflex falls in MAP (ΔMAP) to LANS for nine animals before and eight after vagotomy are summarized in Fig. 3. The falls in CL steady state MAP during PEEP in aortic denervated animals (Fig. 3A, top, solid circles) were not significantly different when values were compared with respective values for intact animals (circled crosses). In the aortic denervated animals, prior to PEEP, the control MAP was 94.0 ± 5.0 mm Hg in the CL and 91.0 ± 4.0 mm Hg in the OL. To remove vascular influences from vagally mediated cardiopulmonary mechanoreceptors the vagi were sectioned. Vagotomy resulted in an increase in control MAP (Fig. 3B, top). Following vagotomy, CL MAP fell from 104.0 ± 4.0 mm Hg with each respective increase in PEEP and OL MAP fell from 97.0 ± 3.0 mm Hg, respectively. CL MAP responses to PEEP at levels of 5.0 and 7.5 cm H_2O following vagotomy were significantly different from prevagotomy values. All OL MAP responses to PEEP were likewise significantly different after vagotomy.

Reflex MAP responses to LANS during PEEP. Reflex blood pressure changes to LANS are extremely sensitive to baroreflex compensation from the carotid sinus baroreceptors (20). Thus, to determine if PEEP affects the reflex vascular responses during LANS, responses were measured before and during vascular isolation of the carotids. In the aortic denervated animals, there was a decreased fall in peak arterial blood pressure

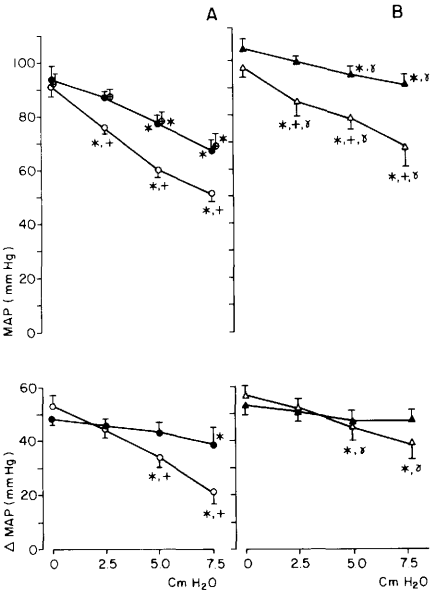

FIG. 3. Mean (± SEM) arterial pressure (MAP) and peak reflex fall in arterial pressure (ΔMAP) to LANS. Responses measured during CL and OL changes in PEEP in the same nine animals before (Panel A) and eight after (Panel B) vagotomy, as in Fig. 2. Symbols and abbreviations are the same as those in Fig. 2.

(ΔMAP) responses to LANS, during CL conditions, as each level of PEEP was increased (Fig. 3A, bottom, solid circles). CL control (0.0 cm H_2O PEEP) ΔMAP was 48.0 ± 2.0 mm Hg. In the OL condition, the reduction in MAP to LANS was even more evident as PEEP levels were raised (Fig. 3A, bottom, open circles). OL control ΔMAP was 53.0 ± 4.0 mm Hg.

Following vagotomy the CL and OL ΔMAP responses to LANS were greater with each increase in PEEP (Fig. 3B, bottom) as compared to the respective prevagotomy responses. CL control ΔMAP to LANS in the vagotomized animals was 52.0 ± 5.0 mm Hg, and OL control ΔMAP was 56.0 ± 3.0 mm Hg. However, again both CL and OL responses decreased with each increase in PEEP, respectively.

Mean right atrial pressure (MRAP) and intrathoracic pressure (IP) responses. Prior to vagotomy MRAP changes at each level of increased PEEP were not significantly different when respective responses of the intact (Table I) and aortic denervated animals were compared. In the aortic denervated animals with the carotids able to detect systemic blood

pressure (CL), MRAP increased from the control (no PEEP) value of 1.0 ± 0.6 mm Hg with each increase in PEEP. With the carotids isolated (OL) MRAP was 1.0 ± 0.6 mm Hg and also increased with each respective increase in PEEP. Following vagotomy MRAP again increased with added PEEP; however, responses were significantly ($P < 0.05$) reduced as compared to responses in the aortic denervated animal. Following vagotomy, with the carotids in the CL condition, control MRAP was 0.2 ± 0.9 mm Hg and 0.4 ± 0.9 mm Hg in the OL condition.

The significantly different MRAP responses following vagotomy suggest that transpulmonary pressures developed at each fixed PEEP level were altered when compared to respective prevagotomy values. To determine if this might be true in five rabbits the MRAP and mean intrathoracic pressure (IP) responses to PEEP were simultaneously determined during CL conditions for intact (no nerves cut), aortic denervated, and vagotomized animals (Figs. 4A–C). In the intact animals, prior to controlled ventilation, MRAP and IP were 0.7 ± 0.2 and −1.3 ± 0.1 mm Hg, respectively. With positive ventilation (O-IPPB) both MRAP (solid circles) and IP (crosses) increased. Then, as PEEP was increased both MRAP and mean IP responses increased in roughly parallel fashion. This relationship was not altered by aortic denervation (Fig. 4B) or vagotomy (Fig. 4C). However, while absolute MRAP and IP responses to PEEP were not significantly altered by aortic denervation, they were significantly ($P < 0.05$) reduced following vagotomy. For example, at 7.5 cm H_2O PEEP, MRAP and IP were 3.7 and 2.2 mm Hg in aortic denervated animals and 2.8 and 1.6 mm Hg after vagotomy, respectively. Transpulmonary pressure changes averaged 1.9 mm Hg, as calculated from the differences in IP responses to 0.0 and 7.5 cm H_2O PEEP both before and after vagotomy. However, the ranges of the transpulmonary pressure changes, calculated from either IP or MRAP changes, while still proportional to PEEP changes were shifted down following vagotomy.

Comparison of MAP and ΔMAP with MRAP responses during control and PEEP increases of 2.5, 5.0, and 7.5 cm H_2O. Following vagotomy with both CL and OL preparations, MAP, ΔMAP, and MRAP responses at each PEEP level were reduced when their respective values were compared to the prevagotomy response values, as noted earlier. It was considered that if vagal mediated pulmonary mechanoreceptors reflexly influenced vasomotor activity, then regression analysis of pre- and postvagotomy MAP (and

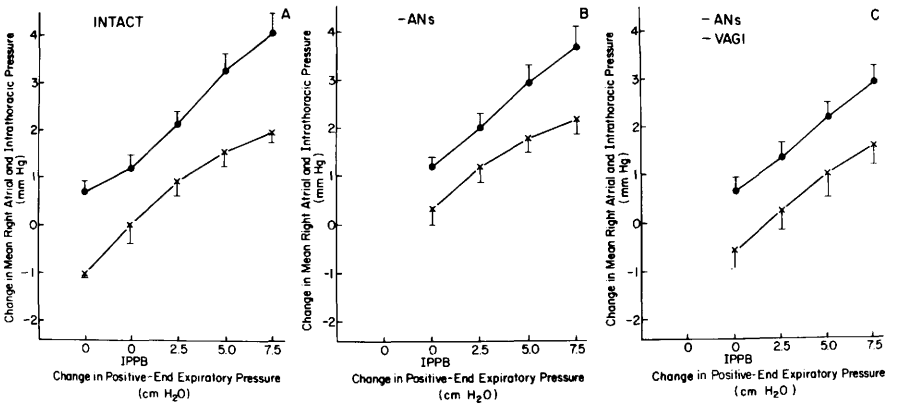

FIG. 4. Mean (± SEM) right atrial pressure (●) and intrathoracic pressure (X) responses before and during inspiratory positive pressure breathing (IPPB) and increasing positive end expiratory pressure (PEEP) of 0.0, 2.5, 5.0, and 7.5 cm H_2O in five rabbits. Panel A: Responses in the intact rabbits (no nerves cut). Values to the left of the IPPB zero were measured prior to cannulation of the trachea, and control of respiration. Panel B: Responses of the same animals following aortic denervation (−ANs). Panel C: Responses of the same animals following aortic denervation and vagotomy. Values were not significantly changed following aortic denervation (Panels A and B). All values following vagotomy were significantly ($P < 0.05$) reduced as compared (Student t test, paired observations) to prevagotomy values at the same level of IPPB and PEEP (Panels B and C). For further description, see text.

ΔMAP) with MRAP responses would indicate this by variation in regression slopes. A plot of these responses and the regression parameters involved are presented in Fig. 5 and Table II, respectively. There was a significant negative correlation between all CL (Fig. 5A) and OL (Fig. 5B) MAP and MRAP responses to the PEEP changes. There was a significant difference, however, between the closed and open loop relationships. Similarly, all ΔMAP to LANS responses were negatively correlated to the MRAP responses during PEEP (Figs. 5C and D), while CL and OL relationships were significantly different when compared. However, comparisons of pre- to postvagotomy regression relationships were not found significantly different within either the CL or the OL condition.

Discussion. Results of this study demonstrate that both heart rate (HR) and mean arterial pressure (MAP) are altered by an increase in positive end expiratory pressure (PEEP) in the anesthetized rabbit. In the intact animal HR increased with each increase in PEEP (Fig. 2A, top). These results were similar to those observed by Hainsworth in the dog (2). Following bilateral aortic denervation these HR increases were not observed. Since transpulmonary pressure has been observed to increase during PEEP both here and in other studies (1, 5), it is possible that cardioreflex activity from bronchopulmonary stretch receptors could be involved (8). However, under the present experimental conditions the observed tachycardia can be explained only if afferent fibers from these stretch receptors traveled in the aortic nerve. Little evidence for this possibility exists; in fact stimulation of the central end of the whole aortic nerve (17, 19, 20) or a few fibers (18, 21) resulted in a proportional reflex bradycardia. It is also possible that cardiac output alterations during PEEP (5, 8) may have produced the HR increase. However, following aortic denervation the pronounced tachycardia even at the higher PEEP levels was abolished. This would indicate that intrinsic

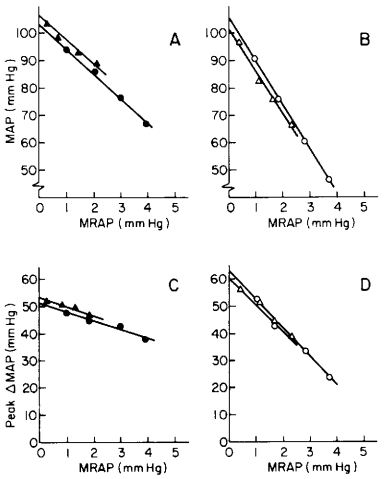

FIG. 5. Linear regression plots of MAP vs MRAP responses, and ΔMAP to LANS vs MRAP responses, during (left to right) 0.0, 2.5, 5.0, and 7.5 cm H_2O PEEP in nine rabbits before and eight after vagotomy. Panel A: MAP vs MRAP with carotid sinus in closed loop condition; (●) before and (▲) after vagotomy. Panel B: MAP vs MRAP with carotid sinus in open loop condition; (○) before and (△) after vagotomy. Panel C: ΔMAP to LANS vs MRAP with carotids in closed loop condition; (●) before and (▲) after vagotomy. Panel D: ΔMAP to LANS vs MRAP with carotids in open loop condition; (○) before and (△) after vagotomy. For further description, see text.

TABLE II. LINEAR REGRESSION ANALYSIS PARAMETERS OF MAP VS MRAP AND ΔMAP TO LANS VS MRAP, FOR NINE RABBITS BEFORE AND EIGHT AFTER VAGOTOMY, DURING 0.0–7.5 cm H_2O PEEP.[a]

Response vs MRAP	Condition	Regression slope	Parameter intercept	Correlation (r)
MAP	CL prevagotomy (●)	−9.3	103.5	0.999
	CL postvagotomy (▲)	−7.9	105.5	0.973
	+OL prevagotomy (○)	−16.6	106.8	0.998
	+OL postvagotomy (△)	−15.7	101.6	0.966
MAP to LANS	CL prevagotomy (●)	−3.2	51.3	0.950
	CL postvagotomy (▲)	−3.0	53.1	0.886
	+OL prevagotomy (○)	−10.7	64.0	0.998
	+OL postvagotomy (△)	−8.9	60.2	0.985

[a] Responses and regression curves are plotted in Fig. 5. Symbols and abbreviations are the same as those in Figs. 3–5. + indicates OL response relationship significantly ($P < 0.05$) different from respective CL response relationship. For further description see text.

mechanisms of the heart were not a major factor in the response. The most likely possibility is that the transpulmonary pressure increase (Fig. 4) and systemic pressure decrease (Fig. 3) during PEEP cause a decrease in aortic transmural pressure. For example, prior to increased PEEP average aortic transmural pressure in the CL intact animals was calculated to be 92.4 mm Hg. With 7.5 cm H_2O PEEP this value fell to 64.5 mm Hg. This fall in aortic distension pressure would then be detected by the aortic sinus baroreceptors (22), with a resultant reflex increase in HR that is lost following aortic denervation.

In aortic denervated animals in which PEEP was increased 7.5 cm H_2O, and during control of the carotid sinus pressure (OL), HR was significantly reduced from control (0.0 PEEP) levels (Fig. 2A, top). This did not occur when the carotid baroreceptors were able to sense systemic blood pressure (CL) or following vagotomy. Also, during 7.5 cm H_2O PEEP and controlled carotid pressure, the ΔHR to LANS was significantly increased prior to vagotomy (Fig. 2, bottom). Previously, it has been indicated that tonic vagal restraint of the heart is minimal in the rabbit (14) and LANS effects a fall in HR by reflex suppression of cardiac sympathetics and stimulation of vagal efferents (14, 18). Thus, contrasting the results of pre- and postvagotomy HR and ΔHR to LANS responses during increased PEEP suggests two conclusions. First, the cardiac efferent vagal and/or sympathetic tone is altered during increased PEEP via vagally mediated cardiopulmonary mechanoreceptors, and second, the mechanical components of the PEEP levels used in this study has minimal effects on heart rate.

Following each PEEP increase MAP was depressed (Fig. 3A). Responses in the intact (circled crosses) and CL aortic denervated (solid circles) animals were essentially similar. These results demonstrate that aortic baroreflexes did not complement carotid baroreflexes in buffering the fall in systemic blood pressure during PEEP. These findings support the suggestion by Allison *et al.* (22) that aortic baroreflexes may have a "hypertensive role," as contrasted to the normotensive buffer functions of the carotid baroreflexes. With increased PEEP the MAP decreased during OL conditions (open circles) more than responses during CL conditions (solid circles). These data indicate the extent of buffering by carotid baroreflexes and suggest a modulatory rather than "dominant" role (13) for these arterial pressure receptors when they complement the cardiopulmonary mechanoreflexes during PEEP in the rabbit.

The peak reflex fall in MAP to LANS was reduced in the OL condition (open circles) as compared to responses in the CL conditions (solid circles) at PEEP above 2.5 cm H_2O (Fig. 3A, bottom). Earlier studies have indicated that electrical stimulation of the aortic nerve induced a reflex-mediated decrease in vasomotor tone (17, 19, 21). Thus, present results indicated that vasomotor tone was more reduced during PEEP when the carotid sinuses were vascularly isolated. Assuming a commonality of the vasomotor paths, as suggested by the work of Daly *et al.* (6), this decrease in vasomotor tone could, in part, be mediated by cardiopulmonary mechanoreflexes since carotid baroreflex influence was held constant during OL conditions.

Control (0.0 PEEP) CL MAP was increased following vagotomy (Table I, Fig. 3). These results are similar to those observed in the dog (2, 6, 9, 23) and the rabbit (10–12). With imposition of each PEEP increase the CL and OL fall in MAP (Fig. 3B, top) was less as compared to respective prevagotomy responses. In addition, the CL and OL ΔMAP responses to LANS (Fig. 3B, bottom) were significantly increased as compared to prevagotomy responses. These results indicate that vasomotor tone in both the CL and the OL condition is increased following vagotomy at all PEEP levels. However, since the OL fall in MAP and the decrease in OL ΔMAP to LANS, at increased PEEP levels, were still observed in the vagotomized animals, it is clear that the involvement of nonvagal factors is indicated. Daly *et al.* (6) suggested that the principal afferent fibers from the pulmonary receptors which interacted with baroreflex mechanisms during lung inflation ran in the vagosympathetic trunk with a lesser role attributed to fibers ascending through the stellate ganglia. Unfortunately, their open chest canine preparations did not allow quantification of transpulmonary pressure changes that could occur

during PEEP or following vagotomy (24, 25).

Comparison of MRAP and mean intrathoracic pressure (IP) responses, before and after vagotomy, indicated that proportional increases in transpulmonary pressure occurred with each increase in PEEP (Figs. 4A–C). Following vagotomy both MRAP and mean IP were reduced for a given level of PEEP when responses (Fig. 4C) were compared to prevagotomy responses (Fig. 4B). These results suggested that following vagotomy a change in the mechanical properties of the lung occurs. With each increase in PEEP the separation of MRAP and IP responses was maintained or slightly increased. Right atrial transmural pressure in aortic denervated animals increased slightly from 0.8 mm Hg (0.0 PEEP) to 1.5 mm Hg (7.5 PEEP) and from 0.9 to 1.2 mm Hg in the vagotomized animals, respectively. These results indicated that while transpulmonary pressure increased, net or right atrial transmural pressure was maintained even at 7.5 cm H_2O PEEP. These results were similar to those found in the dog (5, 7).

In order to estimate the influence of vagally mediated cardiopulmonary mechanoreceptors on systemic blood pressure and the carotid and aortic baroreflexes during PEEP, both closed and open loop MAP vs MRAP and ΔMAP (to LANS) vs MRAP were plotted for nine animals before and eight after vagotomy, and linear regression analysis was applied (Fig. 5, Table II). Prior studies, in the rabbit (10–12) and dog (2–4, 6, 9, 13, 23), have suggested a vagally mediated cardiopulmonary mechanoreflex depression of arterial blood pressure. However, these earlier studies did not compare transpulmonary and systemic pressure responses to PEEP pre- and postvagotomy. Results of the present study demonstrate that as PEEP was increased, indices (MRAP and IP) of transpulmonary pressure increased while systemic arterial pressure decreased. Following vagotomy these responses during PEEP were still proportional but reduced (Figs. 4B and C). It was considered that the effect of vagally mediated mechanoreflex activity on systemic blood pressure during PEEP should most likely be observed in the aortic denervated animal when the carotid intrasinus pressure was held constant and the responses were compared before and after vagotomy. Figure 5B represents a plot of MRAP vs MAP responses to 0.0–7.5 cm H_2O PEEP before (open circles) and after (open triangles) vagotomy, with carotid intrasinus pressure held constant. Linear regression analysis did not indicate a significant difference between the relationships of these response curves. If vagally mediated cardiopulmonary mechanoreflexes had effected a depressor influence during PEEP, then the response curve following vagotomy (open triangles) should have had a more gradual slope than the prevagotomy response curve (open circles). Following a similar rationale, Fig. 5A indicates that carotid baroreflex activity was not modulated by vagally mediated mechanoreflexes during PEEP; Fig. 5D indicates that maximal aortic baroreflex depressor activity was not modified by vagally mediated mechanoreflexes during PEEP; and Fig. 5C suggests that vagotomy did not effect the carotid–aortic facilitory baroreflex potential. Thus, in the rabbit, vagally mediated cardiopulmonary mechanoreceptors have a minimal influence on systemic blood pressure or baroreflexes during PEEP. Vagotomy alters the mechanical properties of the rabbit's lung, and it is the mechanical and/or the nonvagally mediated cardiopulmonary receptor influences which affect systemic blood pressure or baroreflexes during PEEP.

Summary. Heart rate (HR), mean arterial pressure (MAP), and mean right atrial pressure (MRAP) were measured in 15 pentobarbital-anesthetized rabbits, with vascularly isolated carotid sinuses, during increases in positive end expiratory pressures (PEEP) of 2.5, 5.0, and 7.5 cm H_2O. Also, peak reflex bradycardia (ΔHR) and depression of arterial blood pressure (ΔMAP) to left aortic nerve stimulation (LANS) were recorded during the PEEP changes in aortic and subsequently vagal denervated animals. Responses were measured with the carotid sinus receptors detecting systemic pressure (closed loop (CL) condition) and with sinus region pressures held constant (open loop (OL) condition). Results demonstrated that both HR and MAP were altered by an increase in PEEP. Analysis of HR, and ΔHR to LANS responses during OL conditions, suggested the reflex involvement of cardiopulmonary afferent to cardiac efferent vagal fibers during PEEP changes. Vascular responses to increased

PEEP occurred in the presence or absence of arterial baroreceptors and, while reduced, were not abolished following vagotomy.

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