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Atrial Reflexes during High Frequency Oscillatory Ventilation (42209)

GEORGE REWA, PAUL MAN, AND C. TISSA KAPPAGODA

Department of Medicine, Surgical-Medical Research Institute, University of Alberta, Edmonton, Alberta T6G 2G3, Canada

Abstract. High frequency oscillatory ventilation (HFOV) is a new method of artificial ventilation which has been advocated for use in critically ill individuals. It alters the discharge in pulmonary stretch receptors (SAR) from a phasic to a continuous pattern. Since some cardiovascular neurones in the medulla are influenced by the discharge from SAR, experiments were undertaken to determine whether the reflexes from the left atrial (volume) receptors (LAR) were influenced by HFOV. The reflex increases in heart rate and urine flow which result from activation of the (LAR) were examined during both intermittent positive pressure ventilation (IPPV) and HFOV. In five dogs, the increase in heart rate was 23.9 ± 4.3 and 24.5 ± 5.4 beats/min during IPPV and HFOV, respectively. In six dogs the response of an increase in urine flow was examined and this response also was not altered by HFOV. It is concluded that the integrity of these reflexes was unaffected by HFOV in the anesthetized dog model.

It has been suggested that high frequency oscillatory ventilation (HFOV) could be used as a means of ventilating patients who are critically ill (1). Although it has been shown that adequate gas exchange could be achieved by HFOV (2) there is little evidence in the literature regarding the integrity of cardiovascular reflexes during this form of ventilation.

There is definitive evidence that HFOV alters the input from the slowly adapting pulmonary stretch receptors (SAR), from a phasic pattern to a continuous one (3). It is likely that this effect may be specific to the SAR (see under Discussion). It has been shown that the SAR project into nonrespiratory neurones in the medial subnucleus of the tractus nucleus solitarius (4) and it has been suggested that such projections could provide a pathway by which SAR could initiate reflex depressor effects upon the circulation (5). Other investigators have demonstrated neurones in this region which have a cardiac rhythm and to which both cardiovascular and pulmonary afferents converge (6, 7). Thus, in circumstances where the pattern of discharge from an important group of pulmonary receptors is altered dramatically (as in HFOV), it would be of interest to establish whether cardiovascular reflexes are modified.

One such group of reflexes which may be important in patients who are critically ill are those originating from the atrial receptors. These atrial receptors mediate reflexes which influence heart rate (8), urine flow (9), and renal blood flow (10) and are believed to play an important role in the regulation of intravascular volume in several species including primates (11–13). It has been shown that the afferent impulses which originate from these receptors are conveyed in myelinated branches of the cervical vagi to neurones in the medial region of the nucleus of the tractus solitarius also (14). There is some evidence to suggest that the activity of some of the central neurones which are influenced by the atrial receptors are modified by lung inflation (7).

Thus, the present investigation was undertaken to determine if the reflexes which originate from the left atrial receptors are preserved in animals maintained on HFOV. Specifically, the responses examined were the reflex increases in heart rate and urine flow. The experiments were undertaken in dogs anesthetized with α chloralose and the responses obtained from stimulation of the left atrial receptors during conventional intermittent positive pressure ventilation (IPPV) were compared with those obtained on HFOV.

Methods. Dogs weighing 15–22 kg were premedicated with morphine sulphate (dose, 7 mg subcutaneously) and 30 min later were anesthetized with an intravenous infusion of α chloralose (dose, 0.1 g/kg; Fisher Scientific, USA) administered via a polyethylene catheter introduced through the saphenous vein to the inferior vena cava. During the experiment a

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steady-state of light anesthesia was maintained by a continuous infusion of α chloralose (dose, 0.05 to 0.075 ml/kg/10 min).

The trachea was intubated with a cuffed endotracheal tube (i.d. 10 mm, length 28 cm, National Catheter Co., Argyle, N.Y.) and the animal was ventilated using a Harvard ventilator (Model 607, Harvard Instruments Co., Millis, Mass.) at a tidal volume of 15 ml/kg and a respiratory frequency of 18/min. A large-bore (i.d. 7 mm) three-way stopcock was interposed between the ventilator and the endotracheal tube so as to permit the animals to be connected to either the Harvard or the oscillatory ventilator.

The high frequency ventilator used (Model VSMV, Metrex Instruments Ltd., Mississauga, Ontario) had an eccentric cam mechanism which drove a rubber diaphragm. The oscillatory volume, the oscillatory frequency, and the bias flow were set at 5 ml/kg, 16 Hz, and 10 liter/min, respectively. The circuit for ventilation is shown in Fig. 1. The ventilator was connected to a four-way connector using a thick-walled silastic tubing (i.d. 15 mm, Dow Corning Corp. Midland, Mich.). Two opposing ports of this four-way connector were used to provide a cross (bias) flow. The gas mixture (air: 6 liter/min and oxygen: 4 liter/min) entered the connector having passed through a flow gauge (J. Nageldinger and Sons, Inc., New York) which permitted this flow to be maintained constant. The gas leaving the connector passed through a flexible tube (i.d. 10 mm, length 210 cm, the tip of which was placed under water to maintain constant the mean airway pressure (2–3 mm Hg).

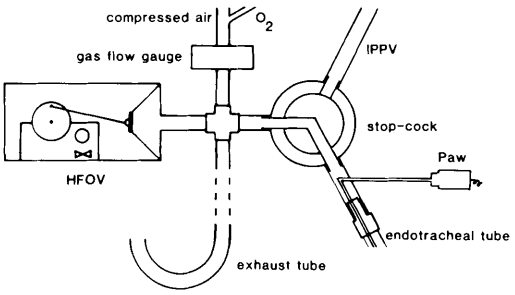

FIG. 1. High frequency oscillatory ventilation circuit. High frequency oscillatory ventilator has an eccentric cam which drives the rubber diaphragm (left). It is connected to a bias flow arrangement and a three-way stop-cock to permit connection of the animal to either the intermittent positive pressure ventilator or the high frequency oscillatory ventilator.

The mean pressure in the trachea was measured at the level of the carina with a polyethylene cannula (i.d. 1.67 mm) with multiple side holes at the terminal portion and a transducer (Model P23 db; Gould Statham Instruments, Hato Rey, Puerto Rico). After the chest was opened, this pressure represented the transpulmonary pressure. The systemic pressure was measured through a cannula (i.d. 1.67 mm) inserted into the right femoral artery and connected to a transducer (Model P23 db, Gould Statham). The frequency response of the system for measuring blood pressure was flat to 30 Hz (±2%). The output of both transducers was amplified and recorded along with the electrocardiogram (lead II) on light-sensitive paper (Model VR 12, Electronics for Medicine/Honeywell, Pleasantville, N.Y.).

A polyethylene cannula with multiple side holes (i.d. 1.77 mm) was inserted into the inferior vena cava via the right femoral vein for the purpose of administering drugs, and maintaining a fluid infusion. In Section II (below) it was used for measuring the venous pressure below the level of the diaphragm. An infusion of dextrose (5% w/v)/saline (0.9% w/v) (2/1) was maintained at a rate such that the total rate of infusion (including α chloralose) was 0.1 ml/kg/min. The temperature of the animal was maintained at 37 ± 1°C by means of heating blankets. The pH and arterial pCO_2 were maintained within physiological limits by the administration of sodium bicarbonate intravenously and by adjusting the ventilation. Sodium bicarbonate (8.4% w/v) was added to the intravenous infusion at a rate of 0.01 mmole/kg/min.

Surgical preparation. The chest was opened in the fourth intercostal space on the left, and an expiratory resistance provided by placing the expiratory line under 3 cm of water (during IPPV). The following specific methods were then adopted in each of the two sections of the experiment.

Series I: Heart rate response due to stimulation of left atrial receptors. After opening the chest, small latex balloons mounted on polyethylene cannulae (i.d. 1.59 mm) were inserted into the left upper and left middle pulmonary veins and positioned at the vein–atrial junc-

tion (8). A larger balloon mounted on the similar cannula was inserted into the left atrial appendage (15). A polyethylene cannula (i.d. 1.67 mm) was inserted into the atrium through the appendage to record pressure. Following this cannulation the upper and middle lobes of the left lung were tied off. In order to elicit the response of an increase in heart rate, the left atrial receptors were stimulated by stretching the left atrial appendage and the pulmonary vein–atrial junctions by distending the balloons with saline; the appendage with approximately 3–4 ml and each vein–atrial junction with approximately 1.0–1.5 ml.

Series II: Renal response due to stimulation of left atrial receptors. The chest was opened and a single large latex balloon mounted on a cannula was placed in the left atrium (9) along with a second polyethylene cannula (i.d. 1.67 mm) to record pressure. Both these cannulae were placed through the appendage. The ureters were cannulated (i.d. 1.2 mm) through a suprapubic incision in the midline and the urine was collected and measured at 10 min intervals. In order to elicit the response of an increase in urine flow, the atrial receptors were stimulated by distending the balloon so as to obstruct partially the mitral orifice and increase the pressure in the left atrium by approximately 12 cm H_2O.

In all experiments a period of at least 30 min was allowed after surgery for stabilization.

Experimental protocols. Series 1: The heart rate response due to stimulation of left atrial receptors. The left atrial receptors were stimulated by distending the balloons positioned at the pulmonary vein–atrial junctions, and the atrial appendage first during IPPV, then during HFOV (frequency 16 Hz; volume 5 ml/kg) and again during IPPV. Each sequence was repeated twice. Then the right and left ansae subclaviae were crushed and a third sequence of distension completed. During each sequence of stimulation experimental records were taken for at least 2 min as an initial control period. The recording was continued as the stimulus was applied for 2 min. Then the stimulus was removed and a further recording obtained for 5 min, or until the heart rate stabilized. The heart rate returned to controlled values usually within 3 to 5 min (8). For the purpose of analyzing the data, the heart rate was counted over the final minute of each period. The control value was taken to be the average of the two control periods, and this value was compared with the value obtained during the period of stimulation for the heart rate and for the other physiological parameters.

Series II: Renal response to stimulation of left atrial receptors. Following a period of stabilization after surgery, 10-min urine collections were obtained until three consecutive ones had stabilized to ±1.0 ml. These were taken as the initial control value. The mitral valve was then obstructed partially by inflating the balloon in the left atrium for 30 min. During the period of stimulation and for 40 min after deflation of the balloons, urine was collected every 10 min and the volume was measured. Samples of urine were analyzed for sodium (Flame Photometer, Model 430, Corning EEl, Evans Electroselenium Ltd., Waltham, Mass.) and osmolarity (Osmette S. Model 4402 Precision Systems, Waltham, Mass.). In all stimulations the data for the initial three 10-min periods, and the final three 10-min periods were averaged to provide the initial and final "control" values, respectively. The data from the last two 10-min periods during stimulation and the first 10-min period after stimulation, were averaged to yield a "test" value. In half the animals, selected randomly, the procedure was done on IPPV, HFOV, and IPPV while in the remaining animals the order was reversed. During HFOV the oscillatory volume was 5 ml/kg and frequency was 16 Hz.

Statistical analysis. All data are given as the arithmetic mean ± the standard error of the mean. Statistical significance was taken at $P < 0.05$. Where two or more treatments were compared by an analysis of variance, the least significant difference test (LSD) at $P < 0.05$ was used to establish statistical significance.

Series I: Heart rate response to left atrial receptor stimulation. In Series I a paired Student's t test was used to determine if the heart rate response during stimulation under a given set of experimental conditions was significant. In addition, the same test was used to determine if the other physiological parameters changed during the period of stimulation.

Series II: Renal response with left atrial receptors stimulation. The data for urine flow, urinary sodium concentration, total sodium

excretion, and osmolarity were analyzed by the paired Student *t* test.

Results. The experiments were undertaken in 11 dogs. The heart rate, arterial pressure, left atrial pressure, and mean airway pressure at the commencement of the experimental runs on IPPV were 92.2 ± 7.4 beats/min; 113.3 ± 4.6 mm Hg, 8.3 ± 0.8 cm H_2O, and 3.8 ± 0.3 cm H_2O, respectively. The pH, pCO_2, and PO_2 of the arterial blood was 7.38 ± 0.01, 34.8 ± 1.7 mm Hg, and 195.6 ± 17.8 mm Hg, respectively.

Series I: Heart rate responses to stimulation of left atrial receptors. This part of the study was completed on five dogs. In these animals, the control heart rate was 89.9 ± 6.7 beats/min during IPPV and 112.7 ± 11.3 beats/min during HFOV. This difference was significant statistically. The control values for arterial, left atrial, and mean airway pressure during IPPV and HFOV, respectively, were not different significantly. (The profile of the wave form for airway pressure was different under the two circumstances; see Fig. 2).

The mean increase in heart rate during IPPV was 23.9 ± 3.4 beats/min (n = 20). During HFOV the mean increase in heart rate was 24.5 ± 5.4 beats/min (n = 10). An example of each type of response (from two animals) is shown in Fig. 2. These responses are not different statistically. Even when the data from each dog was averaged and compared, the results were qualitatively the same (increase of 24.6 ± 4.3 and 24.5 ± 5.4 beats/min during IPPV and HFOV, respectively). The mean increase in heart rate after sectioning the ansae subclaviae was 2.1 ± 1.0 beats/min, (n = 10) on IPPV and 2.0 ± 2.0 beats/min (n = 5) on HFOV. These increases were not statistically significant nor were they different from each other.

There were no significant changes in mean blood pressure or mean airway pressure during these stimulations. However, during both IPPV and HFOV there was a small statistically significant increase in left atrial pressure during stimulation (mean increase + 1.0 ± 0.3 cm H_2O). The changes in left atrial pressure were not correlated with the increases in heart rate observed during IPPV and HFOV (r = −0.13 and r = +0.16, respectively).

Series II: Renal response with left atrial receptors stimulation. The sequence of stimulation described under Methods was completed in six dogs resulting in a total of nine stimulations each during IPPV and nine during HFOV, respectively. Figure 3 shows examples of responses obtained with each form of ventilation. During IPPV the urine flow increased from a value of 6.7 ± 2.0 ml/10 min during the initial control period to 14.7 ± 3.6 ml/10 min during stimulation and returned to 8.1 ± 2.2 ml/10 min during the final control period. The corresponding values during HFOV were 7.8 ± 2.0, 14.4 ± 2.4, and 8.0 ± 1.4 ml/10 min, respectively. These results are summarized in Fig. 4. Taken individually both of these responses were significant but no significant difference existed between them. The values for the concentration (meq/liter) and excretion rate (meq/10 min) of sodium in urine, arterial blood pressure, and left atrial pressure are summarized in Table 1. These findings are similar to those reported by several other investigators (16, 9). [Since there were two responses on IPPV in three animals and two on HFOV in the remaining three (see under Methods) a second analysis was undertaken after averaging the duplicates. These averaged results were not significantly different from those quoted above.] The inferior vena caval pressure was recorded also and found to be not significantly altered by HFOV.

Discussion. The reflexes which originate from the left atrial receptors are believed to play a significant role in the regulation of intravascular fluid volume (11), because of their influence upon salt and water excretion (17, 12) and renal blood flow (10). Thus, the integrity of such reflexes could be of importance in individuals who are critically ill and require life support systems. It has been suggested that HFOV could be of particular value in such situations (1).

The left atrial receptors of the dog are complex unencapsulated nerve endings located on the endocardial surface, mainly at the pulmonary vein–atrial junctions and in the atrial appendage. These receptors discharge into myelinated branches of the cervical vagi (18). In anesthetised dogs maintained on IPPV, localized stretch of the regions in which the receptors are located results in reflex increases in heart rate (8, 18) and urine flow (19). It has been shown previously that the reflex increase in urine flow obtained by stretching the pul-

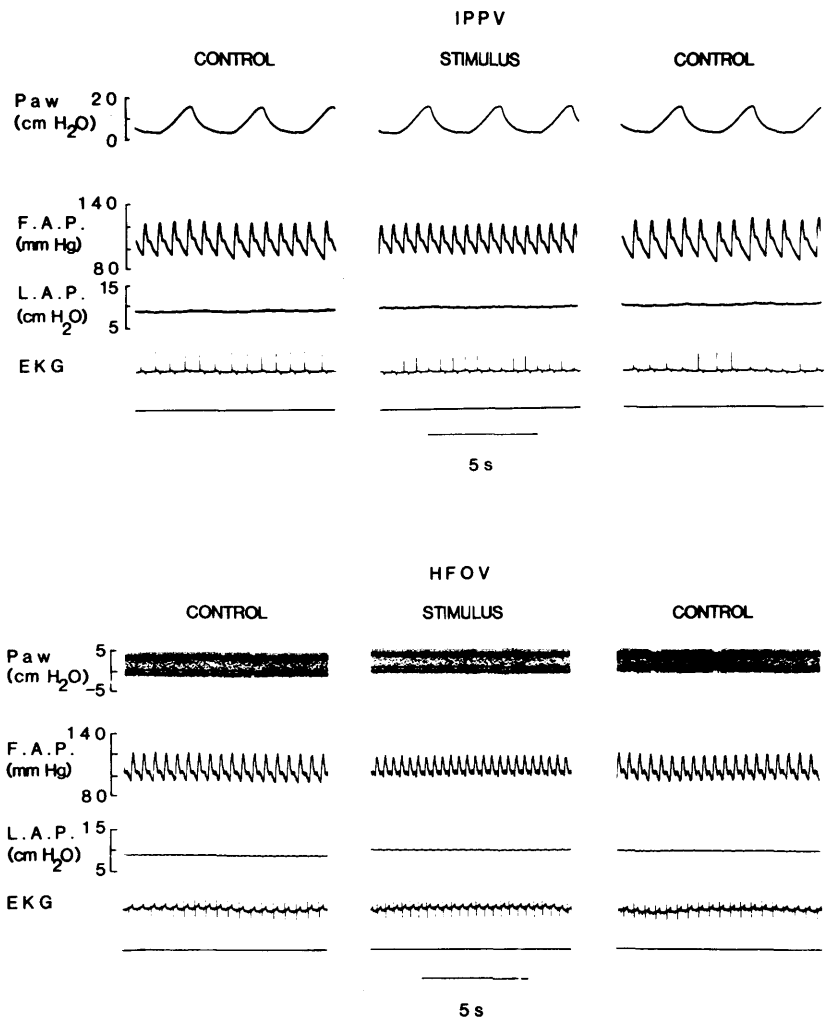

FIG. 2. Examples of increases in heart rate elicited by stimulating the left atrial receptors. (The left atrial receptors were stimulated as shown in Fig. 2, Left). Top: A response elicited during IPPV. Bottom: A response elicited during HFOV. In each section, P_{aw} = airway pressure (cm H_2O); F.A.P. = femoral arterial pressure (mm Hg); L.A.P. = mean left atrial pressure (cm H_2O); and EKG = electrocardiogram. The left hand panels, show records taken during the control period before application of stimulus, middle panel show records taken during stimulation, and the right hand panels show records taken 3 min after removal of the stimulus.

monary vein–atrial junctions was similar qualitatively to that obtained by Henry *et al.* (17), from partial obstruction of the mitral valve. In the investigations reported here, the pulmonary vein–atrial junctions and the left atrial appendage were stretched discretely to elicit the reflex increase in heart rate from stimulation of the left atrial receptors (8, 15). The mitral valve was obstructed partially in the manner of Henry *et al.* (17) to demonstrate the reflex increase in urine flow. The efferent path of the reflex increase in heart rate is predominantly in the sympathetic nerves to the heart (8) and that of the reflex increase in urine flow is believed to be, in part, humoral in nature (20).

Under the conditions of the present study, HFOV has been shown to increase the activity

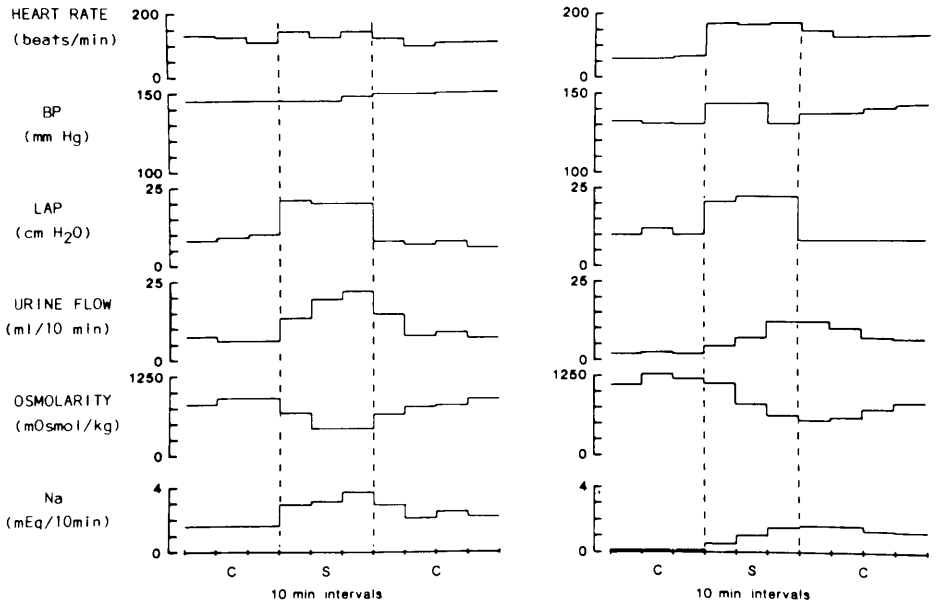

FIG. 3. Examples of the responses of urine flow to stimulation of left atrial receptors. (Left atrial receptors were stimulated as shown in Fig. 2, Right). Left: a response obtained during IPPV. Right: a response obtained during HFOV. Each mark on the horizontal axis represents 10 min. In each response "S" refers to the period of distension of the balloons and "C" refers to the control periods before and after the distension, respectively. BP: arterial pressure (mm Hg); LAP: left atrial (cm H_2O); Na: Sodium excretion/10 min period (meq/10 min). See text for details of protocol.

in PSR (3) and produce little change in the activity of the rapidly adapting receptors (21). Activation of the nonmyelinated afferents from the lung produce a profound bradycardia and hypotension (20). Since these latter features are not observed during HFOV, it is unlikely that pulmonary C fibers are influenced to any significant extent by this form of ventilation. Thus, HFOV, under the conditions of the present study is likely to provide a discrete stimulus to the PSR.

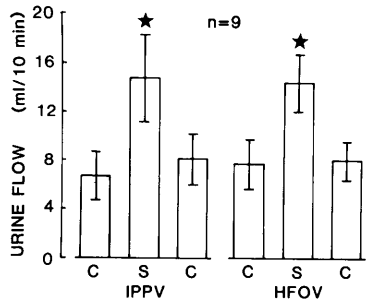

FIG. 4. Summary of the effects on urine flow (ml/10 min) of stimulating the left atrial receptors during IPPV and HFOV. (Left atrial receptors were stimulated as shown in Fig. 2, Right). C: Control. S: Stimulation.

During HFOV, it was found that the reflex increases in heart rate and urine flow which resulted from stimulation of the left atrial receptors were comparable during both forms of ventilation. With respect to the increase in heart rate, the response was present even though the control heart rate was increased significantly during HFOV. Similarly, the increase in urine flow which follows partial obstruction of the mitral valve was not altered either qualitatively or quantitatively by HFOV. These findings suggest that an alteration in the discharge from the PSR is unlikely to "interfere" with the neurones which mediate the reflex responses originating from the left atrial receptors.

However, the present study has indicated that HFOV is likely to cause significant changes in the "baseline" values of certain hemodynamic variables. The most significant change in this study was an increase in heart rate. Since HFOV increases mean airway pressure, it is possible that venous return was

TABLE I. CHANGES IN URINE COMPOSITION, MEAN ARTERIAL PRESSURE, AND MEAN LEFT ATRIAL PRESSURE PRODUCED BY MITRAL OBSTRUCTION

	IPPV			HFOV		
	C	S	C	C	S	C
Urine osmolarity (mOsm/kg)	940 ± 74	621 ± 72 $P < 0.05$	804 ± 71	853 ± 86	567 ± 56 $P < 0.05$	799 ± 82
Urinary Na Exc. rate (meq/10 min)	1.59 ± .48	2.57 ± .62 $P < 0.05$	1.84 ± .46	1.69 ± .43	2.72 ± .53 $P < 0.05$	1.81 ± .37
Urinary Na concn (meq/liter)	212 ± 37	201 ± 23 NS	228 ± 30	196 ± 35	168 ± 23 NS	206 ± 32
Mean arterial pressure (mm Hg)	112.9 ± 7.1	107.8 ± 8.3 NS	114.2 ± 8.0	109.7 ± 7.6	102.0 ± 6.7 NS	111.8 ± 7.9
Mean left atrial pressure (cm H_2O)	8.3 ± 0.6	20.4 ± 0.6 $P < 0.05$	8.0 ± 0.5	8.2 ± 0.4	19.7 ± 0.7 $P < 0.05$	7.8 ± 0.4

Note. *P* refers to comparisons between values obtained during stimulation (S) and the values obtained during control periods (C).

compromised resulting in an increase in heart rate through a baroceptor-mediated mechanism. However, in the present study, the chest was open throughout. Thus in spite of a modest increase in mean airway pressure, there was no significant increase in the pressure in the inferior vena cava. Therefore, the explanation for the increase in heart rate observed in the first protocol is likely to be elsewhere, e.g., activation of the receptors within the mediastinum (23) or as a manifestation of the lung inflation reflex (24). However, speculation upon these aspects is beyond the scope of the present discussion. In spite of the potential for such changes to modify the status of the cardiovascular system, it appeared that the integrity of the two major reflexes originating from the left atrial receptors were preserved during HFOV. However, it must be emphasized that this study was undertaken in open-chested animals and hence any extrapolation to a clinical situation should be done with caution.

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