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Changes in Muscle Sympathetic Nerve Activity, Venous Plasma Catecholamines, and Calf Vascular Resistance during Mechanical Ventilation with PEEP in Humans

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The sympathetic reflex response to mechanical ventilation with PEEP was studied in conscious human volunteers (n = 8). Muscle sympathetic nerve activity (MSNA) was measured from the peroneal nerve, calf blood flow, forearm venous plasma catecholamines, blood pressure, heart rate, airway pressure, and end-tidal CO_2 (%) during spontaneous breathing and during mechanical ventilation with 0–20 cmH_2O PEEP. MSNA increased ($P < 0.01$) during PEEP ventilation, from 22 bursts·min^{-1} at spontaneous breathing to 39 bursts·min^{-1} at 20 PEEP. This increase in MSNA was accompanied by an increase ($P < 0.01$) in calf vascular resistance (CVR) from 35 PRU_{100} at spontaneous breathing to 48 PRU_{100} at 15 PEEP with no further increase at 20 PEEP. Venous plasma norepinephrine concentrations increased ($P < 0.01$) during PEEP ventilation from 0.19 ng·ml^{-1} at spontaneous breathing to 0.31 ng·ml^{-1} at 20 PEEP, whereas plasma epinephrine and dopamine were less than 0.03 ng·ml^{-1} during the experiment. Blood pressure and heart rate were not affected by PEEP ventilation except at 20 PEEP, where blood pressure and heart rate increased ($P < 0.01$). The results show that PEEP ventilation induces a considerable reflex increase of MSNA, reflected also by an increase in CVR and venous plasma norepinephrine. It is proposed that the main mechanism responsible for these reflex adjustments is caused by a decreased activity of the cardiopulmonary low-pressure baroreceptors, in turn resulting from a decrease in cardiac transmural pressures due to PEEP ventilation. (Key words: Measurement techniques: microneurography. Sympathetic nervous system: plasma catacholamines; sympathetic nerve activity. Ventilation: positive end expiratory pressure.)

MECHANICAL VENTILATION with PEEP decreases cardiac output and stroke volume.[1–6] The mechanism by which cardiac output is reduced remains controversial. Cournand *et al.*[1] observed that mechanical ventilation lowered right ventricular end-diastolic transmural pressure, suggesting impaired venous return due to the increased intrathoracic pressure. It has also been suggested that the reduction of cardiac output may be caused by a humorally or reflexly mediated depression of cardiac function[7,8] or by a decreased distensibility of the left ventricle due to a leftward shift of the ventricular septum, impeding cardiac filling.[4,9,10] Reflex excitation of the sympathetic nervous system is probably important for the cardiovascular and humoral compensatory changes induced by mechanical ventilation, such as an increase in systemic vascular resistance,[4–7,11] an increase in the tone of the capacitance vessels,[12,13] and activation of the renin-angiotensin system.[14,15] It was recently shown that mechanical ventilation with increasing levels of PEEP induces reflex increases in renal and splanchnic sympathetic nerve activity in rats.[16,17] This reflex activation was explained by a decreased afferent activity from both arterial baroreceptors and cardiopulmonary low-pressure baroreceptors, due to a reduction of the transmural pressure in the carotid arteries and the aortic arch and a reduction in cardiac transmural filling pressure ("unloading" of the baroreceptors).

The present study was performed to analyze the effect of PEEP ventilation on the sympathetic outflow in conscious human volunteers. To this end, we have recorded muscle sympathetic nerve activity, calf blood flow, forearm venous plasma catecholamines, blood pressure, and heart rate during spontaneous breathing and during mechanical ventilation with increasing levels of PEEP.

Methods

Experiments were performed on eight healthy men (mean age, 34 yr; range, 29–42 yr); all were anesthesiologists and were well acquainted with the function of a modern ventilator and the laboratory procedures and without history of pulmonary disease. The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Göteborg, and all participants gave their informed consent.

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Recordings of Muscle Sympathetic Nerve Activity (MSNA)

In the peroneal nerve at the fibular head, most fibers innervating skin and muscle travel in separate fascicles. A tungsten microelectrode, with a tip diameter of a few microns, was inserted in a muscle fascicle, which contains efferent sympathetic fibers, alpha and gamma motor neurons and various afferent fibers. Criteria that the electrode was positioned in a muscle fascicle, and not a skin fascicle of the nerve were: 1) weak electrical stimulation (1–3 V, 0.2 s, 1 Hz) through the electrode elicited involuntary muscle contractions but not cutaneous paresthesias; 2) tapping or stretching of the muscle innervated by the impaled fascicle elicited afferent mechanoreceptor discharge, whereas stroking the skin within the distribution area of the peroneal nerve did not evoke afferent impulses; 3) if a voluntary muscle contraction was made, an intense activity was recorded; and 4) arousal stimuli did not increase the recorded activity. When a correct position of the electrode in a muscle fascicle of the nerve was established, small electrode adjustments were made until multiunit, spontaneous, intermittent, and pulssynchronous bursts from efferent postganglionic sympathetic fibers could be recorded. Evidence that the impulses derived from efferent sympathetic fibers has been established previously and include: 1) injection of lidocaine around the nerve proximal and distal of the recording point, revealing the efferent nature of the impulses; 2) conduction velocities of approximately 1 $m \cdot s^{-1}$ are typical for sympathetic fibers; and 3) iv ganglion blockade reversibly blocks the impulse traffic.[18,19]

The original nerve signal was fed through a band pass filter with a band width of 700–2,000 Hz. Both filtered and mean voltage neurograms (obtained by passing the filtered neurogram through a RC integrating net work with a time constant of 0.1 s) were stored together with analogue signals of ECG (electrocardio-graphy) on an FM tape recorder (Sangamo Sabre VI). For analyses the mean voltage neurogram was displayed together with the ECG on an ink-jet recorder (Mingograph800, Siemens-Elema Ltd, Sweden) with a paper speed of 3 $mm \cdot s^{-1}$. Records were divided into 5-min periods, and for each period the nerve activity was determined from the chart by counting the number of pulse synchronous bursts in the mean voltage neurogram and the mean nerve activity over this period was expressed as bursts per minute. Total sympathetic activity (bursts $\cdot$ min^{-1} multiplied by mean burst amplitude) was not calculated because the mean burst amplitude is sensitive to even minor electrode displacements, which may have occurred during the course of the experiment (40–50 min). ECG was recorded by surface electrodes on the chest.

Catecholamine Assay

Blood samples were in all experiments taken from a left antecubital vein (the cephalic or basilic vein) without venous occlusion *via* a short indwelling teflon catheter, which was inserted into the vein 30 min before the experiment. Five milliliters was sampled in iced tubes containing 140 units of heparin and 100 μl of 0.4 M glutathione solution. The samples were placed in ice water for no more than 40 min before being centrifuged at 4,000 $r \cdot min^{-1}$ for 15 min at 4° C. The plasma was removed and frozen at −70° C until assay. The levels of epinephrine, norepinephrine, and dopamine were measured by electrochemical detection after high performance liquid chromatography.[20] A known amount of catechomamines was added to one sample in each series as an internal standard. The recovery of the added norepinephrine was 90 ± 1.4% (n = 8). No correction of this recovery was performed. The lower limit for the estimation was considered to be 0.03 $ng \cdot ml^{-1}$ of catecholamine in human plasma.

Recordings of Blood Pressure and Heart Rate

Blood pressure and heart rate were measured automatically every minute by sphygmomanometry (Nippon Colin, Sphygmomanometer BP-203, W. A. Baum Co. Inc.). In all experiments the cuff was placed around from the right arm at heart level. Mean arterial pressure was calculated as diastolic pressure plus one-third of the pulse pressure.

Measurement of Calf Blood Flow and Calculation of Calf Vascular Resistance (CVR)

Volume plethysmography with the strain gauge technique[21] was used for blood flow determinations with the subjects in the supine position. A silicone tube, completely filled with mercury, was mounted around the right calf and the change in calf circumference during proximal venous occlusion (50 mmHg) was recorded with a bridge amplifier and displayed on a Grass Polygraph (model 7D). The right leg was flexed in hip and knee, resulting in an elevation of the lower leg by 20 cm above the heart level. Therefore, perfusion pressure was defined as mean arterial pressure in the right arm minus 15 mmHg. During the experimental procedure, blood flow measurements were made every minute and during measurements, blood flow to the right foot was occluded using a pressure cuff around the ankle. CVR was calculated from perfusion pressure divided by the calf blood flow and was expressed as $mmHg \cdot min \cdot 100\ g \cdot ml^{-1}$ (PRU_{100}).

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Mechanical Ventilation

A Servo 900C ventilator (Siemens-Elema Ltd, Solna, Sweden) was used. The subjects were connected to the ventilatory system by a anatomically shaped mouthpiece, which offered low ventilatory resistance. A clip was placed over the nostrils. A single-use humidifier (Humidvent, Giebeck, Sweden) was placed close to the mouthpiece. End-tidal CO_2 (%) was measured in the expired air with a Normocap (Datex, Finland). Samples from the expired air were taken from a connecting tube placed next to the mouthpiece. During mechanical ventilation recordings of tidal volume (ml · breath^{-1}), peak and mean airway pressure (cmH_2O), and end-tidal CO_2 (%) were made every minute. During spontaneous breathing (control and recovery periods) the subjects were breathing normally with a noncontrolled tidal volume and during PEEP ventilation, tidal volume was adjusted according to the end-tidal CO_2 (%) value. No extra oxygen was added.

Two series of experiments were performed in each of the eight subjects on two different occasions. In the first series MSNA was measured and in the second series calf blood flow and venous plasma catecholamines were measured during spontaneous breathing and mechanical ventilation with 0–20 cmH_2O PEEP. With the subjects in a comfortable supine position, and after adaptation to the ventilatory system, the nerve recording electrode was inserted or the strain gauge attached. After a resting period with spontaneous breathing (15–20 min), recordings were made during seven periods. *Period 1.* Spontaneous breathing (this was regarded as the control period). *Period 2.* Mechanical ventilation with zero end-expiratory pressure (ZEEP). *Periods 3–6.* Mechanical ventilation with 5, 10, 15, and 20 cmH_2O of PEEP, respectively. *Period 7.* Spontaneous breathing (recovery period). Each period included five measurements of all variables, and a given value from a period is the mean value from the five measurements. Blood samples for catecholamine assay were taken during the last 2 min of the control period, of periods 4 and 6 (10 and 20 PEEP), and of the recovery period.

Statistics

For each period the mean values of the different variables were calculated and expressed as mean ± SEM. Testing for significant changes of measured and calculated variables from control was performed by a one-way analysis of variance for repeated measurements followed by Dunnet's multiple range test. The correlation between muscle sympathetic activity (bursts per minute) and venous plasma norepinephrine levels was evaluated using a standard linear regression analysis. In both tests differences were considered statistically significant when $P < 0.05$.

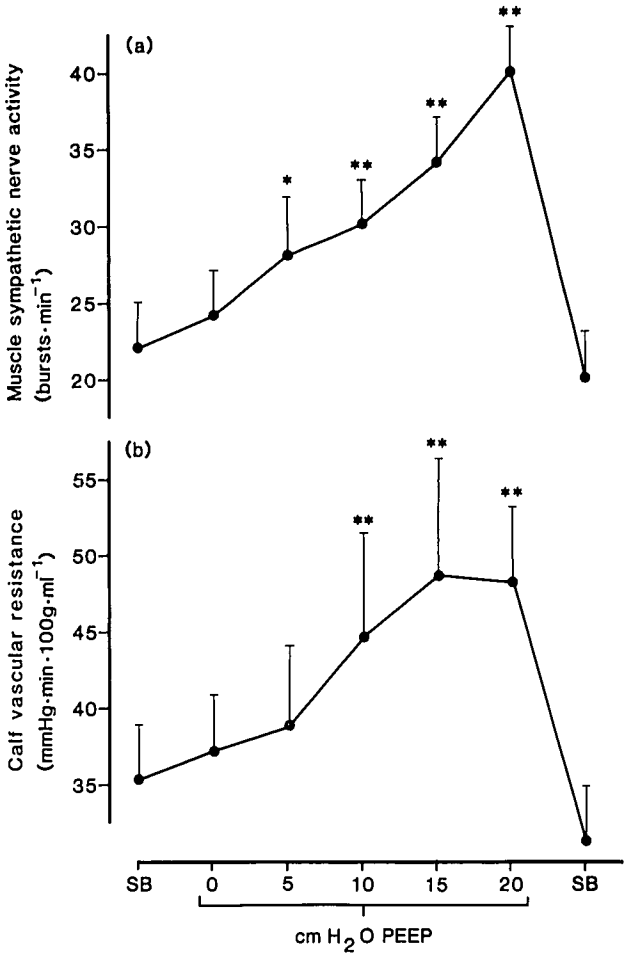

FIG. 1. Muscle sympathetic nerve activity (MSNA) and calf vascular resistance (CVR) during the control period (spontaneous breathing), during mechanical ventilation with 0–20 cmH_2O PEEP and during the recovery (spontaneous breathing). All values are compared with values recorded at the control perod. *$P < 0.05$; **$P < 0.01$.

Results

Mean values of MSNA and CVR are given in figure 1. Data from the catecholamine measurements in the second series are given in table 1. Mean values of systolic, diastolic, and mean arterial pressure and heart rate from both series are presented in table 2. Mean values of end-tidal CO_2 (%), tidal volumes, and peak and mean airway pressures from both series are presented in table 3.

Mechanical ventilation with increasing levels of PEEP induced progressive and significant increases in MSNA (fig. 1). Figure 2 shows recordings of muscle sympathetic nerve activity and ECG from one of the subjects during spontaneous breathing, during ventilation with 10 and 20 cm H_2O. PEEP and finally during the recovery period. Note the increase in MSNA, both in number of bursts

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TABLE 1. Forearm Venous Plasma Catecholamine Concentrations during the Control Period (spontaneous breathing), during Mechanical Ventilation with 10 and 20 cmH_2O PEEP, and during the Recovery Period (spontaneous breathing)

	Control (n = 8)	10 PEEP (n = 8)	20 PEEP (n = 8)	Recovery (n = 5)
Norepinephrine (ng/ml)	0.19 ± 0.02	0.23 ± 0.02	0.31 ± 0.03*	0.18 ± 0.03
Epinephrine (ng/ml)	<0.03	<0.03	<0.03	<0.03
Dopamine (ng/ml)	<0.03	<0.03	<0.03	<0.03

Values are mean ± SEM.
* $P < 0.01$ compared with control.

per minute and mean voltage amplitudes of the bursts, when PEEP ventilation was applied. This figure also demonstrates the rapid decrease in MSNA when mechanical ventilation with 20 cm H_2O PEEP was changed to spontaneous breathing.

The increase in MSNA was accompanied by a significant increase in CVR at 10–20 cm H_2O PEEP. Maximal CVR was reached during 15 cm H_2O PEEP and there was no further increase during 20 cm H_2O PEEP. During the recovery period (spontaneous breathing after 20 cm H_2O PEEP), both MSNA and CVR returned rapidly to values slightly less than control. There were no significant differences when comparing the values of MSNA and CVR during control period with values in the recovery period.

Forearm venous plasma norepinephrine concentration increased following the application of PEEP, and the increase reached statistical significance at 20 cm H_2O PEEP. During recovery plasma norepinephrine was not significant different from the control value. Plasma levels of epinephrine and dopamine were below 0.03 $ng \cdot ml^{-1}$ throughout the experiment. The plasma concentration of norepinephrine correlated significantly with the level of muscle sympathetic nerve activity ($P < 0.01$, $r = 0.523$; fig. 3).

Mechanical ventilation with increasing levels of PEEP induced no significant changes in systolic, diastolic, or mean arterial blood pressure at PEEP levels below 15 cm H_2O. At 15 cm H_2O PEEP, in the second series the systolic blood pressure increased significantly, and at 20 cm H_2O PEEP there were significant increases in blood pressures in both series. There were no significant changes in heart rate at PEEP levels below 20 cm H_2O. At 20 cm H_2O PEEP in the first series, heart rate increased significantly. During the recovery period blood pressures and heart rate did not differ significantly from control values.

During mechanical ventilation with PEEP, end-tidal CO_2 (%) decreased in the first series (from 4.7% to 4.3%, $P < 0.05$) but not in the second series. Tidal volumes did not change significantly throughout the experiments. Peak and mean airway pressure increased to the same extent in both series of experiments.

Discussion

The main findings of this study were that mechanical ventilation with increasing levels of PEEP induced a significant increase of MSNA together with significant increases in CVR and forearm venous plasma norepinephrine. Only minor blood pressure changes occurred during PEEP ventilation, with a small increase at the highest PEEP levels. A systematic relationship between MSNA and forearm venous plasma concentrations of norepinephrine has been found previously[22] and also in the present study, there was a positive correlation between venous plasma norepinephrine and MSNA (fig. 3). Therefore, it is likely that the increase in forearm venous

TABLE 2. Blood Pressure and Heart Rate during Spontaneous Breathing and Mechanical Ventilation with Increasing Levels of PEEP

	First Series							Second Series						
			PEEP (cmH_2O)							PEEP (cmH_2O)				
	SB (Co)	ZEEP	5	10	15	20	SB (Rec)	SB (Co)	ZEEP	5	10	15	20	SB (Rec)
Systolic pressure (mmHg)	121 ± 4	118 ± 3	119 ± 4	119 ± 4	121 ± 3	125 ± 4	123 ± 4	117 ± 2	119 ± 2	118 ± 2	119 ± 3	122 ± 3†	127 ± 4*	116 ± 3
Diastolic pressure (mmHg)	73 ± 3	72 ± 2	73 ± 3	73 ± 3	76 ± 3	77 ± 3	72 ± 3	71 ± 2	72 ± 2	73 ± 4	71 ± 2	73 ± 2	76 ± 3†	72 ± 3
Mean arterial pressure (mmHg)	91 ± 3	91 ± 2	92 ± 3	92 ± 2	93 ± 2	97 ± 3*	89 ± 3	92 ± 2	89 ± 2	87 ± 2	89 ± 3	92 ± 3	96 ± 3*	89 ± 2
Heart rate (beats/min)	64 ± 3	65 ± 3	63 ± 3	63 ± 3	66 ± 3	69 ± 3*	65 ± 3	68 ± 3	66 ± 3	64 ± 3	64 ± 3	64 ± 3	67 ± 4	70 ± 3

Values are mean ± SEM. SB = spontaneous breathing; Co = control; Rec = recovery.
* $P < 0.01$ compared with control.
† $P < 0.05$ compared with control.

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TABLE 3. End-tidal CO_2(%), Tidal Volume, and Airway Pressure during Mechanical Ventilation with Increasing Levels of PEEP

	First Series					Second Series				
		PEEP (cm H_2O)					PEEP (cm H_2O)			
	ZEEP	5	10	15	20	ZEEP	5	10	15	20
CO_2 (%)	4.7 ± 0.2	4.4 ± 0.2*	4.3 ± 0.2*	4.3 ± 0.2†	4.3 ± 0.2†	4.8 ± 0.1	4.8 ± 0.1	4.8 ± 0.1	4.8 ± 0.1	4.9 ± 0.1
Tidal volume (ml)	655 ± 21	648 ± 23	655 ± 17	648 ± 18	645 ± 18	580 ± 27	591 ± 22	581 ± 21	584 ± 20	598 ± 18
Peak pressure (cmH_2O)	12.4 ± 2.0	16.4 ± 1.1	19.5 ± 0.8	24.9 ± 1.2	30.5 ± 1.4	11.0 ± 0.8	14.0 ± 0.8	19.3 ± 0.9	24.5 ± 1.6	32.1 ± 1.7
Mean airway pressure (cmH_2O)	2.5 ± 0.2	6.7 ± 0.3	11.1 ± 0.2	15.8 ± 0.3	20.7 ± 0.5	3.2 ± 0.2	8.3 ± 0.3	12.2 ± 0.3	17.0 ± 0.3	21.6 ± 0.3

Values are mean ± SEM.
* $P < 0.01$ compared with ZEEP.
† $P < 0.05$ compared with ZEEP.

plasma norepinephrine primarily reflected a spillover of norepinephrine from sympathetic nerve endings in muscles to the veins draining the muscle vascular bed. Our data on the effects of PEEP ventilation on plasma catecholamines agree with those of Payen *et al.*,[6] who found that increasing PEEP levels (0–15 cm H_2O PEEP) resulted in a significant rise in venous plasma norepinephrine, while epinephrine was unchanged. There are several mechanisms to be considered when explaining the increases in MSNA, CVR, and venous plasma norepinephrine during PEEP ventilation.

It may be suggested that the experimental situation with PEEP ventilation could cause mental stress and thereby activate the sympathoadrenal system. For several reasons this is an unlikely explanation for the present findings: 1) heart rate, which usually is a sensitive indicator of mental stress,[23–25] did not increase during the 40–50 min experimental procedure—the one exception was the minor increase at 20 cm H_2O PEEP in the first series; 2) it has been shown that during mental stress, peripheral venous plasma epinephrine often increases[23,25,26]; during the experiment levels of peripheral venous epinephrine were less than 0.03 ng · ml^{-1}; however, in arterial blood, not measured in this study, the levels of epinephrine may have been higher at some situations but inactivated after perfusing the tissue; and 3) in previous studies mental stress caused no or only minor increases of MSNA[19,27,28] or venous plasma norepinephrine,[23,25,26] *i.e.*, even if mental stress did occur, it would not have the observed effects.

Another and more likely explanation for the progressive increases of MSNA, CVR, and plasma norepinephrine concentrations during PEEP ventilation, and the prompt return to control levels after PEEP, is a cardiovascular reflex activation of sympathetic outflow. Several receptor populations should be considered as initiators of such effects.

Arterial baroreceptors in the carotid sinus can probably be ruled out. Even if they may affect MSNA in humans,[29] arterial blood pressure did not fall during PEEP, *i.e.*, no decrease in the transmural pressure of the arterial wall ("unloading" of the carotid receptors) occurred, which could have triggered a reflex increase in MSNA. There are no data in humans on the relative role of the aortic baroreceptors in cardiovascular reflex control. The increased intrathoracic pressure during PEEP would theoretically have caused a decrease in aortic transmural pressure, thus causing an unloading of the aortic receptors. However, in terms of aortic transmural pressure, the progressive increase of intrathoracic pressure would have been counteracted by the elevated arterial blood pressure at higher PEEP levels. Thus, the aortic receptors may have contributed, but probably not any large extent, for the PEEP-induced reflex increase in MSNA.

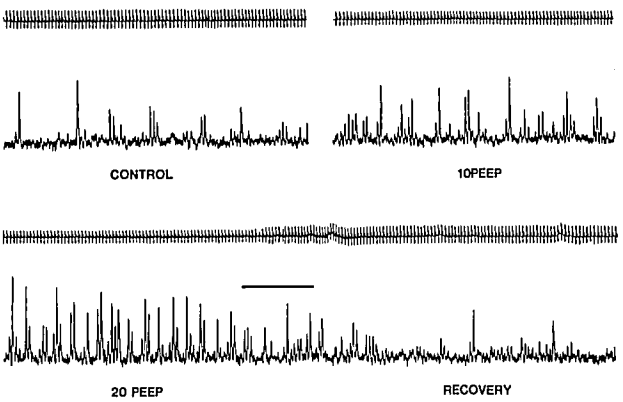

FIG. 2. Peroneal mean voltage neurogram and ECG from one subject during the control period (spontaneous breathing), mechanical ventilation with 10 and 20 cm H_2O PEEP, and finally during recovery (spontaneous breathing). At 10 and 20 cm H_2O PEEP the nerve activity was progressively enhanced compared with control, both in number of bursts per minute and in the mean voltage amplitude of each burst. There was a rapid decrease in sympathetic nerve activity when ventilation with 20 cm H_2O PEEP was changed to spontaneous breathing (recovery). The bar indicates 25 s.

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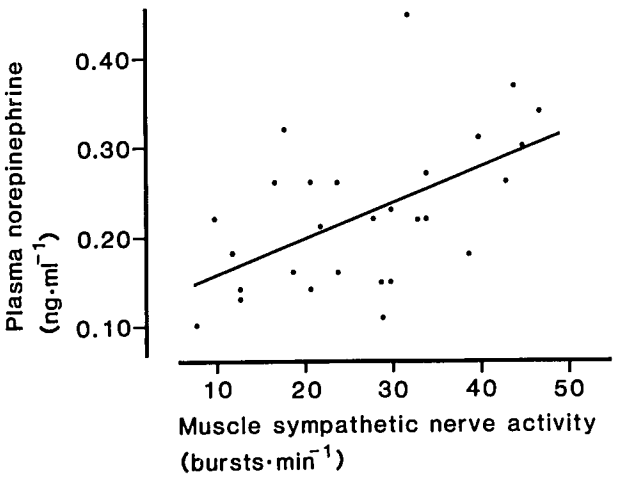

FIG. 3. Correlation between peroneal muscle sympathetic nerve activity and plasma norepinephrine during spontaneous breathing and mechanical ventilation with 0–20 cmH_2O PEEP. $r = 0.523$, $P < 0.01$ (linear regression analysis).

There is indirect evidence that important cardiovascular reflexes may be elicited by cardiopulmonary sensory receptors also in humans. From animal studies it is known that these receptors are located mainly in the left atrium and left ventricle, but also distributed in the right atrium and right ventricle, in the right and left vein–atrial junctions and in the pulmonary veins.[30–33] Application of lower body negative pressure (LBNP) to −20 mmHg decreases central venous pressure without changing mean arterial pressure, pulse pressure or heart rate, implying a selective unloading of the cardiopulmonary receptors.[34–37] LBNP also increases forearm vascular resistance[34,38,39] and MSNA.[36]

What is the evidence that also mechanical ventilation with PEEP decreases cardiac transmural pressures with a consequent decrease in the activity of the cardiopulmonary low-pressure baroreceptors?

In both animals and humans, PEEP ventilation decreases central blood volume,[2,5,16,40,41] right and left ventricular end-diastolic transmural pressures,[1,3,10,42] right and left atrial transmural pressures,[3,16,43] and left ventricular diameter.[4,9,10,42,44] Furthermore, it has recently been found in humans that mechanical ventilation with 15–20 cmH_2O PEEP decreases the ventricular, as well as the atrial volumes.[45,46] It is therefore likely that the PEEP-induced increase in MSNA, CVR, and plasma norepinephrine, as found in this study, to a large extent was caused by an unloading of cardiopulmonary low-pressure baroreceptors.

Pulmonary stretch receptors with vagal afferents respond to lung inflation. From animal experiments it is known that low levels of static lung inflation in dogs induces an excitatory reflex with tachycardia and vasoconstriction,[47–49] probably mediated by pulmonary A-fibers with a threshold airway pressure for activation around 5 cmH_2O.[50] At higher levels of static lung inflation, a depressor reflex with bradycardia and decrease in blood pressure is seen,[48,49,51–53] probably mediated by pulmonary C-fibers with a threshold around 15 cmH_2O. If these findings in animals can be applied in humans, and if activation of both types of pulmonary stretch receptors were significant for the MSNA reflex response to PEEP ventilation in humans, a biphasic response would have been expected. In other words, the sympathetic excitation during lower levels of PEEP would have been followed by an inhibition at higher PEEP levels. The present findings with progressive increases in MSNA, CVR, and plasma norepinephrine do not suggest an important role for pulmonary stretch receptors for the sympathetic reflex response to PEEP in humans.

Abdominal low-pressure baroreceptors with sympathetic afferents may also elicit excitatory sympathetic reflexes.[54] Because PEEP ventilation causes venous congestion, this may result in an activation of such venous baroreceptors and cause reflex sympathetic activation. In anesthetized animals PEEP ventilation induces a reflex increase in splanchnic and renal sympathetic nerve activity and in heart rate.[16,17] This sympathetic excitation was clearly attenuated when either arterial baroreceptors or cardiopulmonary receptors were selectively denervated. After deafferentation of both receptor populations, PEEP ventilation caused no change in sympathetic nerve activity. These findings do not support the hypothesis that abdominal venous baroreceptors are of importance for cardiovascular reflex adaptation during PEEP ventilation.

In the first series during MSNA recordings, end-tidal CO_2 (%) decreased significantly (from 4.7% to 4.3%) from ZEEP to 20 PEEP (table 3). Providing that the decrease in end-tidal CO_2 (%) was reflected by a similar decrease in arterial p_{CO_2}, this would slightly have attenuated the reflex excitation of MSNA, as it is known from animal work that hypocapnia decreases peripheral sympathetic discharge.[55,56]

In conclusion, the results of the present study demonstrated that mechanical ventilation with increasing levels of PEEP in conscious humans induces a reflex excitation of MSNA, concomitant with an increase of CVR, and an increase in venous plasma norepinephrine. This PEEP-induced reflex excitation of the sympathetic nervous system was probably elicited by unloading of cardiopulmonary low-pressure baroreceptors.

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