Neurohormonal responses during positive pressure mechanical ventilation

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INSTRUCTIONS TO CE ENROLLEES

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EDUCATIONAL OBJECTIVES

Based on the content of the article, the enrollee should be able to:
1. Discuss the physiologic responses to partial pressure ventilation.
2. Identify the role of atrial natriuretic peptide and antidiuretic hormone in volume control.
3. Describe the action of the renin-angiotensin-aldosterone system.

Positive pressure mechanical ventilation is used daily in critical care units to support ventilation and improve oxygenation in critically ill patients. One adverse response to positive pressure mechanical ventilation is a reduction in urinary output and sodium and water retention. This consequence is attributed to complex neurohormonal responses intended to maintain hemodynamic homeostasis. This article reviews the physiologic nature of these responses and research findings related to these responses and provides clinicians with information about the importance of these responses, particularly in patients with underlying cardiac dysfunction. (Heart Lung® 1999;28:149-65)

Positive pressure mechanical ventilation (PPV) is frequently prescribed to support ventilation and improve oxygenation in critically ill individuals. In addition to these beneficial effects, PPV reduces urinary output and produces a state of water and sodium retention.[1,2] Initial research primarily focused on renal dysfunction as the causative factor for this hypervolemic state. However, a wide range of scientific investigations has provided evidence that this hypervolemic state is the result of a complex neurohormonal response that intends to maintain hemodynamic homeostasis. This article reviews the physiologic nature of these responses, research findings related to these responses and provides clinicians with information about the importance of these responses, particularly in patients with underlying cardiac dysfunction.

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0147-9563/99/$8.00 + 0 **2/1/98392**

Physiologic Alterations with PPV

Normally, during spontaneous inspiration, intrathoracic pressure becomes less than atmos-

pheric with descent of the diaphragm. Simultaneously, the pressure surrounding the intrathoracic vena cava is reduced. This pressure change augments the pressure gradient between the abdominal vena cava and the thoracic vena cava and subsequently increases venous return. As the diaphragm relaxes, the pressure within the thoracic cavity increases with chest wall recoil. This pressure change reduces the gradient between the abdominal and thoracic venae cavae and subsequently decreases venous return.

When PPV is prescribed, intrathoracic pressure is positive during inspiration. When positive end-expiratory pressure (PEEP) is applied, intrathoracic pressure remains positive during both inspiration and expiration. This alteration in the mechanics of ventilation dramatically reduces venous return, particularly with concomitant hypovolemia.[3,4] PPV with PEEP alters intrathoracic hemodynamics and influences intraabdominal hemodynamics and abdominal organ blood flow.[5] In particular, changes in renal blood flow have been documented with PEEP.[6,7] Scientists have described increases in renal venous pressure with concomitant reductions in renal blood flow that induced enhancement of sodium and water reabsorption.[6,7] Although elevation in renal venous pressure is thought to be one factor in the renal response to PPV, scientific evidence suggests that neurohormonal responses are the fundamental basis of this phenomenon. Global hemodynamic alterations with significant reduction in cardiac output and arterial blood pressure are often the immediate consequence of PPV. Homeostatic responses to these hemodynamic changes include short-term mechanisms that increase intravascular pressure and long-term mechanisms that increase intravascular volume.

Both high- and low-pressure baroreceptors detect the hemodynamic changes that accompany the initiation of PPV. These baroreceptors receive tonic stimulation from the vagus nerve that influences global vessel tone, heart rate, and strength of cardiac contraction. A reduction in mean arterial pressure "unloads" the high-pressure receptors in the carotid and aorta, whereas a decrease in venous return or preload "unloads" the low-pressure baroreceptors in the atria, ventricles, and pulmonary vessels. Tonic vagal activity is inhibited and sympathetic activity becomes dominant. Unloading of baroreceptors induces short-term homeostatic mechanisms that include vasoconstriction, elevated heart rate, and augmented cardiac contractility. Long-term homeostatic mechanisms stimulated by unloading of baroreceptors intend to increase intravascular volume and are the result of a complex interaction of neural and hormonal responses that are the focus of this review.

Hormonal Responses to PPV

Atrial natriuretic peptide. Atrial natriuretic peptide (ANP) is synthesized by mammalian atrial myocytes as a preprohormone.[8] This peptide is then converted and stored in the myocytes as 126–amino acid prohormone. The ANP prohormone is split by proteases on the surface of the myocyte at the time of secretion.[8] A number of structurally different but related ANP peptides have been identified; but the majority of the prohormone is converted to the active form, ANP, a 28–amino acid peptide hormone.[8,9]

ANP is released from atrial myocytes in response to an increase in atrial transmural pressure (transmural pressure is the pressure inside the atrium minus the pressure outside of the atrium) associated with atrial stretch.[10-12] Thus increased intrathoracic blood volume and augmented preload stimulate release of active ANP from cardiac myocytes. ANP elicits a number of responses that intend to reduce intrathoracic blood volume and subsequently, atrial stretch.

ANP is a potent diuretic and natriuretic agent. Diuresis and natriuresis are elicited by a number of complex renal effects. ANP alters renal hemodynamics by diverting a majority of renal blood flow to the inner renal medulla.[9] In addition, glomerular filtration rate is increased because glomerular capillary hydrostatic pressure is increased.[8,9,13] This augmentation in hydrostatic pressure is caused by an increase in efferent arteriolar resistance that is most likely combined with afferent arteriolar dilation. ANP also increases the fractional and absolute excretion of sodium by reducing renal tubule and medullary collecting duct sodium reabsorption.[14]

ANP is antagonistic to the renin-angiotensin-aldosterone system (RAAS). ANP inhibits renin secretion by the renal juxtaglomerular cells. This response is likely caused by an increased delivery of sodium to the macula densa in the distal tubule or to elevated hydrostatic pressure in the location of the stretch sensitive renal juxtaglomerular cells.[9,15] In addition, ANP reduces biosynthesis of aldosterone in the zona glomerulosa. Reduction of aldosterone level has been demonstrated to be independent of plasma renin activity, so this is considered a direct action of ANP.[15,16] ANP is also an important inhibitor of the actions of angiotensin II.

Angiotensin II, one end product of stimulation of the RAAS, is a potent vasoconstrictor and a powerful stimulus for aldosterone production and release of norepinephrine by the sympathetic nervous system.[8,9] In addition, angiotensin II stimulates thirst and the release of arginine vasopressin or antidiuretic hormone (ADH) by the posterior pituitary.[9] ANP inhibits renin release, the first step in the RAAS cascade, and reduces synthesis of aldosterone directly by inhibition of steroidogenesis and indirectly by inhibition of renin secretion.[9] ANP is antagonistic to the thirst response and the release of ADH provoked by angiotensin II.[8,9] ANP also inhibits release of norepinephrine and reduces sympathetic neural responses.[9] Release of ANP induces other systemic circulatory effects by altering vessel tone, fluid compartmentalization, and systemic hemodynamics.[8,9]

ANP produces vasorelaxation by a direct action on vascular smooth muscle similar to the action of endothelium-derived relaxing factor. This vasorelaxant response is especially pronounced with vasoconstriction produced by angiotensin II.[17] The degree of generalized vasorelaxation appears to depend on the basal state of vessel tone. ANP also shifts fluid from intravascular to extravascular spaces. The underlying mechanism for this response is most likely an increase in capillary hydraulic permeability.[18] Systemic blood pressure is also reduced in response to ANP secretion. This response is thought to be caused by antagonism of the actions of angiotensin II on baroreceptor function.[18] As a result, in many instances ANP enhances parasympathetic responses and attenuates the sympathetic responses to baroreceptor stimulation; however, equivocal research findings warrant further investigation.

The role of ANP level in the sodium and water retention induced by PPV has been a considerable focus of scientific inquiry in both human (Table I) and animal studies (Table II). The findings of a number of investigations support the hypothesis that a reduction in plasma ANP is associated with the fluid and sodium retention induced by PPV.[3,4,19-28] Studies have been performed in a variety of human populations, including healthy individuals,[3,4,19,29] patients ventilated for acute respiratory failure,[3,23,30] postoperative cardiac surgical patients,[31] postoperative esophageal surgery patients,[26] patients ventilated because of exacerbation of chronic obstructive pulmonary disease,[32] and patients with New York Heart Association class II to IV cardiac dysfunction.[27] In addition, a number of investigators have used animal models, primarily canine and swine, to clarify physiologic mechanisms underlying the role of ANP in this state of hypervolemia (Table II).

A majority of scientific investigations describe a negative association between ANP level and degree of positive intrathoracic pressure.[3,19-27,30,33] Thus ventilatory conditions that generate greater increases in intrathoracic pressure produce a greater reduction in ANP release. A number of investigators have suggested that a PEEP of <10 cmH_2O does not influence ANP concentration, whereas a PEEP of ≥ 10 cmH_2O reduces ANP release.[3,20-23,25,30,33] However, other scientists found no relation between PEEP ≥ 10 cmH_2O and ANP concentration.[2,28,29,34] These equivocal results are most likely caused by other important factors that may modulate the ANP response.

Volemic status has been found to be an important modifying factor in the ANP response to PPV in both human[4] and animal studies.[24] A preexisting hypervolemic state or aggressive administration of fluid maintains atrial transmural pressure and appears to reduce the effect of PPV on ANP concentration. Factors that influence atrial transmural pressure will alter ANP release. One group of investigators suggested that an open pericardium after cardiac surgery might significantly influence right atrial transmural pressure changes in response to PPV and preclude a reduction in ANP.[31]

Although a majority of scientists implicated a reduction in ANP concentration in the hypervolemic state induced by PPV, some did not find a correlation between PPV and plasma ANP concentration in patients in the intensive care unit,[28] in healthy canines,[28] or in patients after heart surgery.[31] These equivocal findings may be related to investigation of ANP and PPV during differential volemic states without full consideration of this confounding variable. Another potential confounding variable in critically ill patients is the degree of transmission of positive alveolar pressure produced by PPV to structures within the thoracic cavity. Some disease processes alter lung compliance and may significantly reduce transmission of alveolar pressure. Unfortunately, there are limited measures of intrathoracic pressure, particularly in human beings. Esophageal pressure is currently used as an indirect indicator of intrathoracic pressure.[35] However, transmission of alveolar pressure to intrathoracic structures varies within the thoracic cavity, so pressure changes measured in the midesophagus may be considerably different from the pressure changes transmitted to vascular structures within the thoracic cavity.[36]

Table I.
Summary of research findings in human studies of atrial natriuretic peptide and PPV

Authors	Purpose	Sample	Methods	Results and Conclusions
Leithner et al,[19] 1987	To measure the influence of PEEP on ANP levels in healthy patients and patients with ARF	7 Patients with ARF, 6 volume-expanded, healthy patients	Measurement of ANP at PEEP 0 and 15 cmH_2O in patients with ARF; PEEP 0 and 20 cmH_2O in healthy, volume-expanded patients	Patients with ARF decreased ANP level, cardiac output, urinary output, and urinary sodium excretion with PEEP 15 cmH_2O. Healthy volume-expanded patients also reduced ANP with application of PEEP 20 cmH_2O. Concluded (1) ANP decrease may be caused by decrease in venous return or atrial compression by increased lung volume; and (2) reduced ANP levels contribute to reduced urinary output, sodium excretion, and fluid retention seen with PEEP ventilation.
Frass et al,[3] 1988	To assess the effect of different PEEP levels on ANP concentration	11 Healthy patients	Measurement of ANP during PEEP of 0, 5, 10, and 15 20 cmH_2O	Release of ANP is reduced by PEEP ≥10 cmH_2O. Concluded reduction in ANP concentration may contribute to decreased urine volume and sodium excretion during PPV.
Andrivet et al,[30] 1988	To examine changes in ANP secretion and renal function in patients with ARF receiving PPV	7 Patients with acute respiratory failure	Measurement of ANP during PEEP of 0, 12, and 12 cmH_2O plus lower body pressure (MAST)	PEEP 12 cmH_2O reduced transmural right atrial pressure and ANP secretion. Subsequent use of MAST trousers increased right atrial transmural pressure and restored ANP levels. Concluded that acute variations in cardiac filling pressures modulated ANP release during PPV.
Teba, et al,[28] 1990	To determine the effect of PEEP on the release of ANP	22 Critically ill patients	Measurement of ANP after ≥6 h of prescribed PEEP setting (ranged from 0 to 15 cmH_2O)	Found no correlation between PEEP level and ANP concentration and no correlation between ANP and PAOP or CVP. Concluded in critically ill population a PEEP of ≤15 cmH_2O does not affect ANP release.
Andrivet, et al,[23] 1991	To investigate the influence of ANP on renal function during mechanical ventilation with and without PEEP	8 Patients with acute respiratory failure	Measurement of ANP after PEEP 0; PEEP 0 and ANP 5 ng/kg/min infusion; PEEP 10 cmH_2O; PEEP 10 cmH_2O and ANP 5 ng/kg/min infusion; PEEP 10 cmH_2O and ANP 10 ng/kg/min infusion	Baseline values of ANP (PEEP 0) were 3 times higher than normal. Addition of PEEP reduced urinary output and renal sodium excretion but only reduced ANP in 4 patients. Addition of ANP infusion to PEEP ventilation produced increase in sodium and water excretion. Concluded a decrease in ANP is not necessary for fluid and sodium retention with PEEP. ANP may serve as regulatory hormone in this situation.
Riddervold et al,[31] 1991	To determine endocrine responses to PEEP ventilation	9 Patients after cardiac surgery	Measurement of ANP with application of PEEP 0, 5 and 10 cmH_2O	No change in estimated right atrial transmural pressure or ANP level with application of PEEP 0, 5 and 10 cmH_2O. Concluded an open pericardium or recent cardiac arrest might have confounded ANP response in these patients.
Shirakami et al,[26] 1993	To investigate the role of ANP and BNP in the renal effects of PEEP ventilation	7 Patients after esophageal surgery	Measurement of ANP with application of PEEP 0, 5 and 10 cmH_2O Measurement of ANP and BNP before surgery (control), first day after surgery PEEP 0 and 15 cmH_2O	ANP and BNP increased first day after surgery on PEEP 0. Application of PEEP 15 cmH_2O for 1 h reduced both ANP and BNP, cardiac output/index, and urinary sodium excretion and increased right atrial, pulmonary artery, and occlusion pressures. Concluded natriuretic peptide system is active in antidiuresis observed with PEEP ventilation.

Table I. *(Cont'd)*
Summary of research findings in human studies of atrial natriuretic peptide and PPV

Authors	Purpose	Sample	Methods	Results and Conclusions
Frass et al,[22] 1993	To assess the effects of varied levels of PEEP on ANP secretion	27 Patients with ARF	Measurement of ANP at PEEP 0, 5, 10, 15, and 20 cmH_2O	No change in ANP concentration with PEEP 5 cmH_2O. Significant decrease in ANP with PEEP ≥10 cmH_2O. Significant inverse correlation between PEEP level and ANP concentration ($r = –0.47$, $P = .0001$). Change in ANP level occurred before change in CI. Concluded endocrine response may be more sensitive than pump function to changes related to PEEP ventilation.
Tanaka et al,[29] 1994	To assess the responses of sympathetic nerve outflow and neurohormones during PPV	10 Healthy patients	Measurement of ANP at CPAP 0 and 12 cmH_2O	No change in ANP concentration with CPAP 12 cmH_2O with significant reduction in cardiac output, stroke volume, and urinary output. Concluded ANP not active in sodium and water retention with PPV.
Chabot et al,[32] 1995	To examine hormonal response to acute hypercapnia with constant cardiac filling pressures and normal arterial oxygen tension	7 Patients with COPD	Measurement of ANP on mechanical ventilation with normocarbia and after increase in end-tidal CO_2 of 6-10 mm Hg	No change in ANP concentration with acute hypercapnia. Found no correlation between ANP and CO, right atrial pressure, pulmonary artery pressure, or wedge pressure. Concluded that $PaCO_2$ cannot be considered a stimulus for release of ANP.
Wilkins et al,[27] 1995	To determine the effects of posture change and continuous positive airway pressure on release of cardiac peptides in congestive heart failure	7 Patients with LVEF <40%, NYHA class II-IV, <70 years of age	Measurement of ANP and BNP with upright posture, recumbent posture, and recumbent posture plus nasal CPAP 10 cmH_2O	Baseline ANP levels elevated 5-6 times normal. ANP levels increased with change from upright to recumbent posture; this increase in ANP was prevented by application of nasal CPAP 10 cmH_2O. Concluded upright posture and use of nasal CPAP can redistribute blood volume to peripheral circulation and unload failing heart as demonstrated by decrease in ANP concentration.
Beuret et al,[4] 1996	To determine if volemic status influences the response of ANP to PEEP ventilation	21 Healthy patients	Measurement of ANP during PEEP with normovolemia, PEEP with hypervolemia, and spontaneous breathing with hypervolemia	ANP release decreased with application of PEEP in the hypervolemic state; however, with normovolemia and application of PEEP, ANP release was unchanged. No relation found between ANP and catecholamine levels. Concluded volemic state modulated response of ANP with application of PEEP. Activity of ANP in renal effects of PEEP might be limited to hypervolemic state.

ARF, Acute respiratory failure; *BNP,* brain natriuretic peptide; *CO,* cardiac output; *COPD,* chronic obstructive pulmonary disease; *CPAP,* continuous positive airway pressure; *LVEF,* left ventricular ejection fraction; *NYHA,* New York Heart Association; *PAOP,* pulmonary artery occlusion pressure; *MAST,* military antishock trousers.

Table II.
Summary of findings in animal studies of atrial natriuretic peptide and PPV

Authors	Purpose	Sample	Methods	Results and conclusions
Venus et al,[33] 1985	To determine if hormonal activation and renal changes with the application of PEEP can be prevented by maintaining perfusion pressure	23 Swine	Measurement of ANP in control group with normovolemia and PEEP 15 cmH_2O and a volume-expanded group with PEEP 15 cmH_2O	ANP concentration was reduced in normovolemia group with application of PEEP 15 cmH_2O. ANP level in volume-expanded group was unchanged with application of PEEP. Concluded ANP responses to PEEP ventilation can be eliminated by hydration.
Kharasch et al,[20] 1988	To examine the effect of a PEEP-induced decrease in right atrial transmural pressure on ANP release and renal changes with PEEP	7 Dogs	Measurement of ANP at PEEP 0 and 10 cmH_2O	ANP concentration reduced by 25% with application of PEEP 10 cmH_2O in conjunction with reduction in right atrial transmural pressure. Close temporal relation among PEEP, changes in transmural pressure, and ANP level. Concluded (1) PEEP 10 cmH_2O reduced atrial distention and decreased ANP release, and (2) ANP may mediate renal effects of PEEP.
Hevroy et al,[21] 1989	To assess the effects of PEEP on ANP level during acute left ventricular dysfunction	7 Dogs	Measurement of ANP with application of 0 and 10 cmH_2O, PEEP during normal left ventricular function and left ventricular dysfunction caused by coronary embolization	ANP concentrations increased with left ventricular dysfunction. ANP level decreased with PEEP application during both normal ventricular function and ventricular failure with a greater reduction in the failure condition. Concluded a reduction in atrial distention reduced release of ANP.
Teba et al,[28] 1990	To determine the effect of PEEP on the release of ANP	6 Dogs	Measurement of ANP at PEEP 0, 5, 10, and 15 cmH_2O	PEEP application reduced CO and urinary output and increased CVP. No correlation between ANP concentration and PEEP level. Concluded reduction in urinary output observed with PEEP is not related to ANP concentration.
Roissaint et al,[2] 1992	To determine if reduction in urine volume and urinary sodium excretion associated with PEEP is mediated by neurohormonal changes in the presence of volume expansion	6 Dogs	Measurement of ANP with application of CPAP 4 and PEEP 20 cmH_2O during volume expansion	PEEP 20 cmH_2O produced 43% reduction in urinary output and 44% reduction in sodium excretion without change in ANP level. Concluded in nonanesthetized, volume-expanded dogs, ANP does not participate in reduction of urinary volume and sodium excretion during short term (4 h) PEEP ventilation.
Christensen et al,[25] 1992	To examine the role of ANP in the renal response to PEEP during hypervolemia	7 Dogs	Measurement of ANP with application of PEEP 0 and 10 cmH_2O during volume expansion and during PEEP 10 cmH_2O with ANP infusion to same plasma concentration found with PEEP 0 cmH_2O	ANP level and renal sodium excretion decreased with PEEP application. These changes could be altered by infusion of synthetic ANP to same plasma concentration found with PEEP 0 cmH_2O. Concluded approximately 65% of change in sodium excretion with variation in end-expiratory pressure can be accounted for by plasma ANP.
Ramamoorthy et al,[24] 1992	To determine the relation between atrial transmural filling pressure and ANP level during PEEP ventilation	12 Dogs	Measurement of ANP during PEEP 0, 10, and PEEP 10 cmH_2O plus aggressive hydration	PEEP 10 cmH_2O reduced right atrial transmural pressure by 60%. ANP level decreased with PEEP application. Urine volume and sodium excretion decreased by 81% with PEEP. Aggressive hydration restored transmural pressure and ANP returned to baseline levels. Strong relation among ANP level, transmural pressure, and urine volume and urine sodium (r = 0.84 to 0.99). Concluded aggressive hydration during PEEP ventilation restores transmural pressure, ANP concentration, and diuresis/natriuresis.
Rossaint et al,[34]	To determine whether decreases in urine volume and urinary sodium excretion during PEEP plus hypervolemia is partially caused by elevated renal vein pressure	6 Dogs	Measurement of ANP during volume expansion with application of 4 h CPAP 4 cmH_2O, 2 h PEEP 20 cmH_2O, and 2 h elevation in inferior vena caval pressure by 5-8 mm Hg	ANP concentration increased 1 h after a 2-h application of PEEP 20 cmH_2O. ANP concentration did not change during CPAP 4 cmH_2O or elevation of inferior vena caval pressure. Concluded that most important factor in sodium and water retention during PEEP in hypervolemia is an increase in renal vein pressure and stimulation of RAAS.

Table III.
Summary of findings in human studies of RAAS and ADH responses and PPV

Authors	Purpose	Sample	Methods	Results and conclusions
Hemmer et al,[41] 1980	To investigate the effect of long-term mechanical ventilation on ADH secretion, water, and electrolyte balance and renal response to ADH	8 Patients with flail chest	Measurement of ADH excretion during PEEP 0 and 7 cmH_2O, CPAP 0 and 7 cm/water	ADH excretion was significantly greater during PEEP 7 cmH_2O than other 3 conditions. Concluded that increased ADH excretion during PEEP ventilation could represent one mechanism for water retention.
Annat et al,[42] 1983	To explore the factors involved in fluid retention induced by positive pressure ventilation	7 Patients with primarily multiple trauma	Measurement of urinary ADH, PRA, aldosterone during PEEP 0 and 10 cmH_2O	PEEP decreased cardiac output, glomerular filtration, renal blood flow and urine output, whereas PRA, aldosterone, and urinary ADH increased. Changes with PEEP were reversed with removal of PEEP. Concluded that reduction in urine output with PEEP ventilation is a function of hemodynamic impairment. Hormones that produce sodium and water retention may also participate in this phenomenon.
Payen et al,[43] 1987	To assess the role of hemodynamic changes and neurohormone release on renal function during PEEP ventilation	7 Patients with neurologic injury	Measurement of ADH and PRA with PEEP 0 and 15 cmH_2O	PEEP produced a 21% decrease in cardiac index, 55% decrease in urine output, and 39% decrease in renal sodium excretion. ADH level was unchanged with PEEP. PRA increased significantly with PEEP. Concluded ADH is not involved in fluid and sodium retention during PEEP. Acute antidiuresis with PEEP results from activation of the RAAS with a parallel increase in sympathetic nerve activity.
Shirakami et al,[26] 1993	To investigate the role of natriuretic peptides in renal effects of PEEP ventilation	7 Patients after esophageal surgery	Measurement of ADH, PRA, and aldosterone level before surgery (control), first day after with PEEP 0 and 15 cmH_2O	Application of PEEP for 1 h decreased cardiac output/index and urinary sodium and increased right atrial, pulmonary artery, and wedge pressures. ADH increased by 127%, PRA increased by 109%, and aldosterone increased by 91% with the application of PEEP. Concluded secretion of ADH, PRA, and aldosterone during PEEP ventilation may contribute to the renal effects of PEEP.
Tanaka et al,[29] 1994	To assess responses of sympathetic nerve outflow and neurohormones during continuous positive pressure ventilation	10 Healthy patients	Measurement of ADH, PRA, and aldosterone with CPAP 0 and 12 cmH_2O	Cardiac output and stroke volume decreased with CPAP 12 cmH_2O. ADH and PRA increased with CPAP, whereas aldosterone level was unchanged. Concluded that CPAP unloaded low-volume baroreceptors and stimulated sympathetic nervous system and RAAS. ADH and RAAS activity contributed to renal effects of PPV.
Chabot et al,[32] 1995	To examine hormonal responses to acute hypercapnia with constant cardiac filling pressures and normal PaO_2	7 Patients with COPD	Measurement of ADH, PRA, and aldosterone on mechanical ventilation with normocarbia and after increase in end-tidal CO_2 by 6-10 mm Hg	No change in ADH, PRA, or aldosterone during hypercapnia. Concluded that isolated hypercapnia is not a stimulus for ADH release or activation of RAAS.
Farge et al,[44] 1995	To evaluate the effect of lower body positive pressure on renal hemodynamics and function during PEEP and analyze subsequent changes in hormone levels	6 Patients ventilated because of neurologic disorder	Measurement of ADH and PRA with PEEP 0, 15, and 15 cmH_2O with application of lower body positive pressure	PEEP induced antidiuresis and antinatriuresis continued after application of lower body positive pressure. PEEP increased PRA and this increase continued with lower body positive pressure. No change in ADH seen. Concluded that elevation in renal pressure with lower body positive pressure did not obliterate the renal effects of PEEP ventilation, which indicated renal effects of PEEP are primarily mediated by RAAS.

Abbreviations as in Table I.

Table IV.
Summary of findings in animal studies of RAAS and ADH responses and PPV

Authors	Purpose	Sample	Methods	Results and conclusions
Bark et al,[40] 1980	To define mechanisms involved in ADH release during PEEP ventilation	62 Dogs	Measurement of ADH and PRA during PEEP of 0, 10 and 15 cmH_2O in 7 groups of subjects: PEEP alone; PEEP with hypervolemia; PEEP and controlled pneumothorax; PEEP and denervation (vagus and carotid sinus); correlation of ADH and PRA; PEEP and altered intracranial pressure; PEEP with normal intracranial pressure and denervation (vagus and carotid sinus)	PEEP 10 and 15 cmH_2O produced significant increases in ADH secretion. This increase was prevented by hypervolemia. Changes in ADH secretion were not related to lung volume, left atrial transmural pressure, or serum osmolality. Denervation attenuated the rise in ADH. ADH secretion was significantly reduced with decreased intracranial pressure. Concluded that ADH levels during PEEP are influenced by multiple factors that include baroreceptors in aortic arch and carotid sinus as well as sensors of intracranial pressure.
Bond et al,[47] 1983	To examine role of renal nerves in mediating changes in renin secretion during PEEP ventilation	12 Dogs	Measurement of PRA with controlled renal perfusion pressure during PEEP 10 cmH_2O in 2 groups: with intact renal nerves and with bilateral renal denervation	PEEP reduced mean arterial pressure and pulse pressure, whereas heart rate was increased. Renal perfusion pressure was maintained at a constant value. PRA significantly increased with PEEP ventilation in dogs with intact renal veins. Renal vein denervation and PEEP produced no change in renin secretion. Concluded that PEEP ventilation increases renin secretion via renal nerve stimulation.
Venus et al,[33] 1985	To determine if hormonal activation and renal changes with PEEP application can be prevented by maintaining perfusion pressure	23 Swine	Measurement of ADH and PRA in controls with normovolemia and PEEP 15 cmH_2O and a volume-expanded group with PEEP 15 cmH_2O	In normovolemic controls, cardiac output decreased by 35% and mean arterial pressure by 20% with application of PEEP. Also observed significant decrease in urine output with concomitant increase in ADH and PRA. None of these changes occurred in the volume expanded group with application of PEEP. Concluded aggressive hydration prevents PEEP induced change in hormonal levels and renal function.
Rossaint et al,[2] 1992	To determine if renal changes associated with PEEP are mediated by neurohormonal changes in the presence of volume expansion	6 Dogs	Measurement of ADH, PRA, and aldosterone with application of PEEP 4 and 20 cmH_2O with volume expansion	Application of PEEP 20 cmH_2O decreased urine output by 43% and renal sodium excretion by 44%. Aldosterone decreased with PEEP cmH_2O. No significant change seen in ADH with PEEP, but PRA increased. Concluded that in nonstressed, awake dogs ADH does not participate in renal changes induced by PEEP. Activation of RAAS may contribute to these renal changes.

Table IV. *(Cont'd.)*
Summary of findings in animal studies of RAAS and ADH responses and PPV

Authors	Purpose	Sample	Methods	Results and conclusions
Kaczmarczyk et al,[1] 1992	To determine if administration of ACE inhibitors decreases change in renal function with PEEP ventilation	5 Dogs	Measurement of ADH, PRA, and aldosterone during CPAP 4 cmH_2O, PEEP 20 cmH_2O, and PEEP 20 cmH_2O with ACE inhibition in the presence of volume expansion	PEEP 20 cmH_2O decreased urine output, urinary sodium, and glomerular filtration rate. ADH level increased with PEEP application, whereas PRA was unchanged. With PEEP and ACE inhibition observed greater excretion of sodium and water than with PEEP alone. Concluded a significant portion of salt and water retention during PEEP is from activation of the RAAS.
Rossaint et al,[34] 1993	To determine whether renal changes during PEEP and hypervolemia are partially caused by increased renal vein pressure	6 Dogs	Measurement of ADH, PRA, and aldosterone with volume expansion and the application of CPAP 4 cmH_2O; PEEP 20 cmH_2O; and elevation of inferior venous pressure by 5-8 mm Hg	Urine output and renal sodium excretion decreased with both PEEP and inferior vena caval pressure increase. ADH levels did not change. Aldosterone decreased with all 3 conditions. PRA increased during PEEP but not with elevation of vena caval pressure. Concluded that in volume-expanded dogs, activation of RAAS and increase in inferior vena caval pressure are most important mechanisms altering renal function.
Kaczmarczyk et al,[46] 1993	To examine effect of volume expansion on vasoactive hormones, hemodynamics, and renal function during PEEP ventilation	5 Dogs	Measurement of ADH, PRA, and aldosterone in normovolemic state and CPAP 4 cmH_2O, normovolemia and PEEP 20 cmH_2O, hypervolemia and CPAP 4 cmH_2O, and hypervolemia and PEEP 20 cmH_2O	In normovolemic state, PRA, aldosterone, and ADH increased with PEEP 20 cmH_2O. No change in ADH or aldosterone with volume expansion plus PEEP. PRA decreased with PEEP 20 cmH_2O in volume-expanded state. Concluded that increase in ADH, PRA, and aldosterone during PEEP in normovolemia may be a mechanism to maintain mean arterial pressure during PEEP. Volume status mediates hormonal response and renal function with PEEP ventilation.
Kaczmarczyk et al,[51] 1996	To determine if increase in ADH or stimulation of RAAS during PEEP ventilation prevents hemodynamic change in normovolemia	6 Dogs	Measurement of ADH, PRA, aldosterone in normovolemic state with PEEP 20 cmH_2O, PEEP 20 cmH_2O after administration of ADH receptor antagonist, PEEP 20 cmH_2O after administration of ACE inhibitor, and PEEP 20 cmH_2O after administration of ADH receptor antagonist and ACE inhibition	ADH levels increased with application of PEEP and with PEEP plus ACE inhibition. PRA and aldosterone increased with PEEP 20 cmH_2O and PEEP 20 cmH_2O plus ADH receptor antagonist. Mean arterial pressure and glomerular filtration rate maintained in all states except PEEP 20 cmH_2O plus ADH receptor antagonist and ACE inhibition. Concluded ADH and RAAS contribute to the maintenance of arterial pressure and glomerular filtration rate during PEEP ventilation.

Abbreviations as in Table I.

Table V.
Summary of findings in human studies of sympathetic activation and PPV

Authors	Purpose	Sample	Methods	Results and conclusions
Payen et al,[43] 1987	To assess role of hemodynamic changes and neurohormone release on renal function during PEEP ventilation	7 Patients with neurologic injury	Measurement of epinephrine and norepinephrine with PEEP 0 and 15 cmH_2O	With PEEP, cardiac index and renal blood flow decreased. Norepinephrine increased in parallel with renin ($r = 0.80$, $P < .01$). No significant change seen in epinephrine with PEEP. Concluded that PEEP reduced cardiac index and renal blood flow, which stimulated the RAAS and the sympathetic nervous system. RAAS and SNS were main factors causing reduced urine output and sodium retention during PEEP.
Sellden et al,[48] 1989	To measure sympathetic response to PEEP ventilation	8 Healthy patients	Measurement of muscle sympathetic nerve activity, vascular resistance, and plasma catecholamines during PEEP 0, 5, 10, 15 and 20 cmH_2O	Muscle sympathetic nerve activity increased as PEEP increased. Vascular resistance also increased as PEEP increased, but reached a plateau at 15 cmH_2O PEEP. Plasma norepinephrine increased with PEEP application and this increase was significant with PEEP 20 cmH_2O. Plasma epinephrine and dopamine were unchanged by PEEP. Concluded that PEEP ventilation produces a reflex increase in sympathetic nerve stimulation most likely caused by a decrease in the tonic activity of the cardiopulmonary, low-pressure baroreceptors.
Tanaka et al,[29] 1994	To assess responses of sympathetic nerve outflow and neurohormones during continuous PPV	10 Healthy patients	Measurement of muscle sympathetic nerve activity of right peroneal nerve, epinephrine, and norepinephrine with CPAP 0 and 12 cmH_2O	Cardiac output, stroke volume and urine output decreased with CPAP 12 cmH_2O. CPAP produced a significant increase in muscle sympathetic nerve outflow and norepinephrine concentration. Concluded that sympathetic stimulation by CPAP may alter renal function directly by altering renal tubule function or indirectly alter renal function by stimulation of RAAS.
Farge et al,[44] 1995	To evaluate effect of lower body positive pressure on renal hemodynamics and function during PEEP and to analyze subsequent changes in hormone levels	6 Patients ventilated because of neurologic disorder	Measurement of epinephrine and norepinephrine with PEEP 0, 15, and 15 cmH_2O with application of lower body positive pressure	PEEP induced antidiuresis and antinatriuresis continued after application of lower body positive pressure. PEEP increased norepinephrine level but did not alter epinephrine level. Increased norepinephrine was not decreased with the application of lower body positive pressure. Concluded that sustained sympathetic outflow and high plasma renin activity were the main factors contributing to sodium and water retention with PEEP.

Abbreviations as in Table I.

Table VI.
Summary of findings in animal studies of sympathetic activation and PPV

Authors	Purpose	Sample	Methods	Results and conclusions
Venus et al,[33] 1985	To determine if hormonal activation and renal changes with PEEP application can be prevented by maintaining perfusion pressure	23 Swine	Measurement of epinephrine and norepinephrine in controls with normovolemia and PEEP 15 cmH_2O and a volume-expanded group with PEEP 15 cmH_2O	In normovolemic controls, PEEP decreased cardiac output, mean arterial pressure and urine output with concomitant increase in both epinephrine and norepinephrine. None of these changes occurred in volume-expanded group with application of PEEP. Concluded that renal effects of short-term PEEP ventilation are mediated by hormones in response to reduction in blood pressure. Volume expansion prevents these effects.
Sellden et al,[50] 1986	To examine effects of PEEP on sympathetic nerve activity and hemodynamics before and after vagotomy	23 Wistar rats	Before and after bilateral vagotomy, measurement of splanchnic and renal nerve sympathetic activity in 8; measurement of cardiac output and central blood volume in 10; and measurement of right and left transmural pressure in 5 during PEEP of 0, 5, and 10 cmH_2O	Before and after vagotomy, cardiac output, central blood volume, and stroke volume were all reduced with increasing PEEP, whereas heart rate and total peripheral resistance were increased as PEEP increased. Sympathetic nerve activity increased by up to 90% of baseline as PEEP increased. Increase in sympathetic nerve activity was significantly less after vagotomy. Concluded that increase in sympathetic nerve activity is likely from activation of multiple cardiovascular reflexes that include arterial baroreceptors and cardiopulmonary mechanoreceptors.
Sellden et al,[49] 1987	To evaluate role of cardiopulmonary receptors with vagal afferents in reflex control of sympathetic nerve activity during PEEP	35 Wistar rats	Measurement of renal sympathetic nerve activity at PEEP 0, 5, and 10 cmH_2O in 8 intact animals, after sinoaortic denervation (n = 17), and after sinoaortic denervation and bilateral vagotomy (n = 10)	PEEP 10 cmH_2O increased renal sympathetic activity by 66% in intact rats and by 22% in sinoaortic denervation group. Renal sympathetic activity was unchanged by PEEP in sinoaortic denervation plus vagotomy animals. Concluded that cardiopulmonary receptors that contain vagal afferents contribute to reflex stimulation of sympathetic nerves during PEEP ventilation.

Table VI. *(Cont'd.)*
Summary of findings in animal studies of sympathetic activation and PPV

Authors	Purpose	Sample	Methods	Results and conclusions
Aibiki et al,[52] 1988	To investigate interaction between carotid sinus baroreceptors and cardiopulmonary receptors in reflex control of renal nerve activity during PEEP	36 Dogs	Measurement of renal nerve activity during PEEP 10 and 20 cmH_2O in 4 groups: intact animals (n = 12), vagal and aortic nerve denervation (n = 6), carotid sinus denervation (n = 6), and carotid sinus, vagal, and aortic nerve denervation (n = 12)	Renal nerve activity was unchanged in intact group with application of PEEP at both levels. Carotid sinus denervation produced initial decrease in renal nerve activity in response to PEEP, followed by recovery to nearly control level. Renal nerve activity significantly increased in vagal/aortic denervation group in response to PEEP and animals with carotid, aortic, and vagal denervation had no renal nerve response to PEEP. Concluded that PEEP alters renal nerve activity by interaction between carotid sinus baroreceptors and cardiopulmonary receptors. The excitatory stimulation is carried by carotid sinus nerves, whereas inhibitory effects are carried over vagal afferents.
Kaczmarczyk et al,[51] 1996	To determine if increase in ADH or stimulation of RAAS during PEEP ventilation prevents hemodynamic change in normovolemia	6 Dogs	Measurement of epinephrine and norepinephrine in normovolemic state with PEEP 20 cmH_2O; PEEP 20 cmH_2O after administration of ADH receptor antagonist; PEEP 20 cmH_2O after administration of ACE inhibitor; and PEEP 20 cmH_2O after administration of ADH receptor antagonist and ACE inhibition	Mean arterial pressure and glomerular filtration rate were reduced with PEEP plus administration of ADH receptor antagonist and ACE inhibition. There were no changes in norepinephrine with any condition. Epinephrine significantly increased with PEEP plus ADH receptor antagonist and ACE inhibitor. Concluded that acute stimulation of sympathetic nervous system by application of PEEP was insufficient to stabilize mean arterial and glomerular filtration rate in absence of ADH and angiotensin II.

Abbreviations as in Table I.

In summary, a majority of studies support the hypothesis that PPV-generated decreases in venous return and atrial transmural pressure reduce plasma ANP level and contribute to the sodium and fluid retention observed with PPV. The greater the intrathoracic pressure increase with PPV, the greater the reduction in ANP release in a normovolemic or hypovolemic state. Aggressive hydration with restoration of atrial transmural pressure can avert this response.

ADH. ADH is a 9–amino acid, peptide hormone synthesized primarily in the supraoptic nuclei of the hypothalamus. ADH is transported to the posterior pituitary and stored in secretory granules. Release of ADH into the vascular system is stimulated by changes in osmolarity, angiotensin II, a decrease in atrial stretch, and a reduction in stimulation of the high- and low-pressure baroreceptors. Thus a reduction in venous return and atrial stretch with a decrease in central blood volume and pressure may directly (by a decrease in atrial stretch and reduction in stimulation of baroreceptors) and indirectly (by RAAS) induce ADH release.[23,31,32]

Circulating ADH promotes water reabsorption in the distal tubules and renal collecting ducts by increasing water permeability. ADH is currently hypothesized to promote the formation of pores that permit the free diffusion of water from the renal tubular fluid into the peritubular fluid.[37] This action promotes water reabsorption and formation of concentrated urine. In addition, ADH is a potent vasoconstrictor and generates increases in mean arterial pressure by this mechanism.

Early scientific investigations in search of the underlying mechanisms for PPV induced sodium and water retention concluded ADH secretion was a fundamental component of this phenomenon.[38-40] Later studies in both human (Table III) and animal subjects (Table IV) have been equivocal in their findings regarding ADH secretion during PPV. A number of studies in critically ill populations (flail chest, multiple trauma, esophageal surgery) have found increased secretion of ADH in response to PPV, particularly with PEEP.[26,41,42] However, other investigations in human beings have not demonstrated a relation between PPV and ADH secretion.[43,44] This is likely because of the variable volemic status of the patients at the time of study. Other potential factors that may confound the ADH response to PPV include serum osmolarity, degree of intracranial pressure and, in particular, baroreceptor responses.

Resetting of low-pressure baroreceptors may be implicated in the equivocal responses of ADH to PPV described in prior investigations. Iwasaki et al[45] described resetting of the low-pressure baroreceptors that stimulate ADH secretion in response to hemodynamic and blood volume changes. Sustained hypovolemia in a rat model produced a resetting of these baroreceptors within 32 hours of the initiation of this hypovolemic status. ADH secretion in response to a constant or increased level of hypovolemia was then significantly reduced once the low-pressure baroreceptors were adaptively reset. In effect, resetting of low-pressure baroreceptors establishes a new, lower normal intrathoracic blood volume for an individual. In this instance, ADH would not be secreted in response to this lower volume, particularly without a change in serum osmolarity. A much greater reduction in intrathoracic blood volume would be required to stimulate secretion of ADH in this instance.

Currently the majority of data support the hypothesis that ADH secretion may significantly contribute to the water retention induced by PPV. However, the role of ADH appears to depend highly on individual volume status at the time of PPV institution.[46] In addition, the low-pressure baroreceptors may adapt to reduced intrathoracic blood volume and establish a new normal volume. Thus hypothetically a reduction in ADH secretion and ADH effects should occur after a modest period of PPV. Therefore equivocal findings related to ADH secretion may also be significantly related to the variable time of ventilation in experimental subjects.

RAAS. Renin, an amino acid peptide, is synthesized in juxtaglomerular renal cells in an inactive form (prorenin). These juxtaglomerular cells are located proximal to the glomerulus in the walls of the afferent arteriole. A reduction in vascular pressure in this area activates biochemical processes that split the prorenin molecule. Once active renin, an enzyme, is released into systemic circulation; it acts on angiotensinogen, a globulin formed by the liver. Renin cleaves the angiotensinogen molecule and angiotensin I, a 10–amino acid peptide, is the weakly active molecule formed by this reaction. In capillaries, angiotensin-converting enzyme (ACE), synthesized by endothelial cells, splits angiotensin I further. The primary active product of this biochemical reaction is angiotensin II, an 8–amino acid peptide hormone. The activation of the RAAS with subsequent production of angiotensin II induces a number of responses to increase sodium and water reabsorption and augment vascular volume.

Angiotensin II increases vascular pressure by inducing potent vasoconstriction at the arteriole level. Constriction of venous vessels also occurs,

but to a lesser degree, and subsequently increases venous return. Angiotensin II also exhibits direct renal effects that generate sodium and water reabsorption. Primarily, renal blood flow and subsequent glomerular filtration is reduced because of vasoconstriction of renal vessels. Angiotensin II further alters renal function through a direct effect on renal tubules that enhances sodium and water reabsorption. As previously discussed, angiotensin II stimulates a thirst response, the release of ADH by the posterior pituitary and the sympathetic nervous system. In addition, angiotensin II is a potent stimulus for release of aldosterone by the adrenal gland.

Aldosterone, a steroid hormone, is synthesized and secreted by the zona glomerulosa or outer cell layer of the adrenal gland in response to elevated serum potassium levels or angiotensin II. In the renal tubules, aldosterone enhances sodium reabsorption and simultaneous excretion of potassium. Concurrently, water moves by osmosis from the tubular fluid into the peritubular fluid and intravascular volume is expanded. The potent ability of the RAAS to significantly expand extracellular volume has led scientists to hypothesize that this response was fundamental to the hypervolemic status of ventilated patients.[1,2,23,26,31,33,43,47]

A preponderance of both human (Table III) and animal (Table IV) studies have implicated the activity of the RAAS in sodium and water retention with PPV. The importance of the RAAS to the hypervolemic state induced by PPV was demonstrated by Kaczmarczyk et al.[1] In this experiment, dogs were exposed to PPV with PEEP before and after ACE receptor antagonist therapy. Renal function, serum and urinary electrolytes, and hemodynamics were measured. Administration of an ACE receptor antagonist significantly facilitated sodium and water excretion in these canine subjects exposed to PEEP ventilation. Although some scientists report modulation of the RAAS response by volume status,[1,33,34,46] a majority of investigators agree that the RAAS is a significant contributor to the hypervolemic state induced by PPV.

Neural Responses to PPV

Sympathetic nervous stimulation with the subsequent release of catecholamines has been described with the application of PPV in both human beings[29,43,44,48] (Table V) and animals[33,49-51] (Table VI). Increased sympathetic neural activity is most likely the result of activation of the high- and low-pressure baroreceptors in response to intrathoracic hemodynamic alterations. In addition, angiotensin II stimulates the activity of the sympathetic nervous system. Sympathetic activity is often evaluated by serum concentrations of norepinephrine and epinephrine. However, a number of studies have directly measured sympathetic nerve activity in human muscle[29,48] and animal splanchnic and renal sympathetic nerves.[49,50,52]

Activation of the RAAS is closely associated with increased sympathetic outflow. Angiotensin II stimulates the sympathetic nervous system, and sympathetic nervous stimulation indirectly activates the RAAS by producing intense vasoconstriction of renal vessels and altering renal hemodynamics. In addition, sympathetic stimulation is also thought to directly produce activation of the RAAS by stimulating release of renin. Although a majority of investigations have confirmed a positive association between sympathetic activity and plasma renin activity, it is difficult to determine whether the initial response to PPV is sympathetic activity or activation of RAAS because the two are so closely associated.

Scientific investigations have described increases in sympathetic neural activity as great as 90% of baseline values with the application of PEEP.[49] In addition, norepinephrine concentration has been shown to increase to as much as 60% of baseline values in response to PPV.[29] Norepinephrine is the neurotransmitter released when neural impulses reach a majority of postganglionic sympathetic neurons. Thus norepinephrine concentration would increase with increased sympathetic outflow. A majority of investigators concluded that increased sympathetic outflow, reflected by higher norepinephrine concentrations, induced adrenergic responses that augmented heart rate and cardiac contractility and produced vasoconstriction. Continued sympathetic stimulation maintained systemic pressure until volume was sufficiently increased to maintain a normal vascular pressure or until baroreceptors adapted to the lower intrathoracic pressure and volume.

Implications

Changes in renal function induced by PPV are intended to increase intravascular volume and produce hemodynamic homeostasis. These responses are most likely the result of a complex interaction of neural and hormonal responses that may be modulated by basal volume status. Significant sodium and water retention can produce hypervolemia in vulnerable patient populations that require ventilatory support. This hypervolemic state may be of particular importance in

patients with underlying cardiac dysfunction because this population may not be able to compensate adequately for additional intrathoracic blood volume.

A number of investigators have reported failure to wean from PPV because of hemodynamic or cardiac instability.[53-56] Demling et al[55] evaluated patients in general surgical/trauma intensive care who could not be weaned from PPV. This group of investigators found that 30% of the patients who could not be weaned from PPV had acute heart failure and pulmonary edema. Lemaire et al[56] described an average blood volume of 123% ± 22% of predicted in a group of patients (n = 15) who could not be weaned from PPV because of the development of acute heart failure. After aggressive diuresis with furosemide and a reduction of mean blood volume to 102% ± 19%, 60% of this group was weaned without difficulty. Epstein[57] evaluated weaning outcome and the cause of weaning failure in 249 patients in medical intensive care. Nearly one fourth of those patients who could not be weaned from PPV (n = 18) had congestive heart failure develop and required reinstitution of PPV. Clochesy et al[53] performed a descriptive, retrospective analysis of chronically ill patients (n = 174) who required PPV and subsequent weaning. A majority of this group (69%) was ultimately weaned from PPV. However, there were significant differences in fluid balance between those who were weaned and those who could not be weaned. Subjects who could not be weaned exhibited a significantly greater 24-hour fluid balance than those who were weaned (+1091 ± 1128 mL versus +201 ± 1106 mL, $P < .05$). Clochesy et al[54] later suggested that appropriate timing of administration of drugs, including diuretics, nitrates, calcium channel receptor antagonists, ACE receptor antagonists, and vasodilators, could improve physiologic functioning and increase the likelihood of weaning success in patients with underlying cardiac dysfunction.

In addition to increased intravascular volume, extravascular volume is also increased and may produce generalized edema. Even more significantly, gas exchange deteriorates as pulmonary extravascular fluid is increased, particularly in patients with acute respiratory failure. Demling et al[55] cited impaired gas exchange as the primary reason for weaning failure in their group of patients in general surgery/trauma (59% of patients could not be weaned because of impaired gas exchange). In addition to reduced gas exchange, increased respiratory muscle work is required when pulmonary extravascular fluid is increased. Jubran and Tobin[58] studied patients with chronic obstructive pulmonary disease who were ventilator dependent (n = 17) to determine the underlying mechanisms for their inability to ventilate independently. All subjects exhibited significant changes in ventilatory mechanics, including increased intrinsic PEEP, dynamic elastance and resistance, that produced acute respiratory failure. Increased pulmonary extravascular fluid reduces lung compliance and produces significant demand on the ventilatory muscles.

Clinicians must understand and anticipate these potential neurohormonal, homeostatic responses to PPV. Careful attention and consideration of ongoing fluid status is a vital component of care in all patients who require PPV. Although measurement of intake and output and daily weight appear to be crude measures of fluid balance, they are the primary noninvasive means of determining global fluid balance. Clinicians also evaluate skin turgor and temperature as indirect indicators of fluid volume status. Direct measurement of blood volume requires sophisticated and expensive nuclear techniques.

Although invasive hemodynamic monitoring provides important information about cardiac function and volume state, this type of monitoring is not available for many patients at the time of weaning from PPV. Meticulous observation of fluid volume balance and hemodynamic and cardiac function is vital in the care of ventilated patients. Vigilant attention to the potential consequences of these homeostatic responses provides the clinician with the opportunity to optimize intravascular volume and cardiac, renal and pulmonary function. Future nursing research should focus on elucidation of the physiologic importance of these neurohormonal responses in ventilated and weaning patients as well as the identification of valid and reliable indicators of fluid volume balance in critically ill patients.

Conclusion

PPV, particularly in conjunction with PEEP, reduces urinary output and produces a state of sodium and water retention. This consequence of PPV is attributed to a complex neurohumoral response intended to maintain a homeostatic state. Increased sympathetic outflow, activation of the RAAS, secretion of ADH and a reduction in plasma ANP have all been implicated in this consequence of PPV. Clinicians must be aware of these physiologic responses, so they may attempt

to optimize cardiac, pulmonary, and renal function in this vulnerable patient population.

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Single Topics. To receive CE credit for this test, mark your answers on the answer form that follows the test, complete the enrollment information, and submit it with the $9.00 processing fee (in U.S. dollars) to Buchanan & Associates. Answer forms must be postmarked by May 18, 2001. Within 3 weeks of receiving your test form, Buchanan & Associates will send a CE certificate.

1. The adverse response to PPV includes the following EXCEPT:
a. Decreased urine output
b. Sodium retention
c. Water retention
d. Increased venous return

2. Intrathoracic pressure is positive in all the following EXCEPT:
a. PPV
b. PEEP
c. Normal inspiration

3. ANP inhibits the release of all the following EXCEPT:
a. Renin
b. Aldosterone
c. Angiotensin II
d. Vasorelaxation

4. Angiotensin II causes all the following EXCEPT:
a. Vasodilation
b. Increased aldosterone production
c. Increased release of norepinephrine
d. Increased release of arginine vasopressin

5. NP secretion causes:
a. Vasoconstriction
b. A shift of fluid into the intravascular space
c. Increased systemic blood pressure
d. Decreased release of ADH

6. What is the relation between ANP and intrathoracic pressure?
a. As intrathoracic pressure increases, ANP increases.
b. As intrathoracic pressure decreases, ANP increases.
c. As intrathoracic pressure increases, ANP decreases.
d. As intrathoracic pressure decreases, ANP decreases.

7. ADH release is stimulated by the following EXCEPT:
a. Changes in osmolarity
b. Changes in angiotensin II
c. Increased atrial stretch
d. Decreased stimulation of baroreceptors

8. Angiotensin II:
a. Stimulates thirst
b. Decreases ADH release
c. Decreases aldosterone release
d. Causes vasodilation

9. PPV weaning failures in patients were caused by:
a. Heart failure
b. Hypovolemia
c. High urine outputs
d. Limited mental capacities

ANSWER ENROLLMENT FORM

Article Title: Article Title: Neurohormonal responses during positive pressure mechanical ventilation
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