Respiratory Support and Renal Function

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Introduction

CONTROLLED MANDATORY VENTILATION (CMV) is commonly used to treat patients with respiratory failure. Oxygenation in some patients is improved when CMV is combined with positive end-expiratory pressure (PEEP).1-6 PEEP may also be used in patients breathing spontaneously (SV) to increase arterial oxygen content.7-9 The physiologic consequences of these respiratory modali-
INTRAVASCULAR VOLUME

The kidney responds to changes in systemic arterial pressure and cardiac output by altering glomerular filtration rate (GFR), renal blood flow (RBF), free water clearance (C\(_{\text{H}_2\text{O}}\)), osmolar clearance (C\(_{\text{osm}}\)), and urinary sodium excretion.\(^{29,31}\) During periods of increased intravascular volume which result in hypertension, a diuresis is established which is an appropriate response by the kidney to decrease intravascular volume and blood pressure to normal. In some studies of the renal effects of mechanical ventilation, the intravascular volume of the patients or experimental animals was not stated or controlled\(^{28,32-37}\) and in other studies, the experimental animals were acutely volume loaded to produce a diuresis.\(^{38-41}\) Interpretation of renal responses in the clinical situation must include consideration of the patient’s vascular volume at the time that mechanical ventilation is begun. Qvist et al. and others have demonstrated that increasing the blood volume increases cardiac filling pressures and reduces the hemodynamic changes produced by CMV with PEEP.\(^{14,42}\) If the cardiovascular effects of CMV with PEEP are prevented by increasing intravascular volume, it is likely that the renal effects will be altered by this procedure.

GENERAL ANESTHESIA

General anesthesia has significant effects on renal function. Inhalational and intravenous agents produce changes in GFR, RBF, free water and osmolar clearance, and urinary volume and sodium excretion.\(^{43,44}\) Changes in cardiovascular function and renal perfusion are probably responsible for the renal effects of general anesthesia, although this has not been studied specifically.\(^{43}\) Some studies of renal function during mechanical ventilation have been done with the experimental animals anesthetized and paralyzed\(^{34-36,38,39}\) while others have used awake patients.\(^{24-28}\) Cox has demonstrated that pentobarbital anesthesia (30 mg/kg) produced only transient effects on the cardiovascular function of trained dogs when no noxious stimuli were applied during the study period.\(^ {45}\) When dogs were anesthetized with pentobarbital and received stimulation such as during the insertion of monitoring catheters, there was severe hypertension associated with an increase in plasma renin concentration and autonomic neural activity.\(^ {46}\) In another study, pentobarbital anesthesia in dogs resulted in a decrease in renal blood flow and a shift of blood flow away from cortical nephrons.\(^ {47}\) Burger et al. suggested that this effect was mediated by the renin-angiotensin system and demonstrated that it could be prevented by a high salt intake prior to the study. Pentobarbital anesthesia and stimulation affect renal function through both hormonal and neural mechanisms.

Halothane anesthesia was used during some studies of the effect of mechanical ventilation on renal function.\(^ {39}\) There is a redistribution of cardiac output with a decrease in renal blood flow during halothane-induced anesthesia.\(^ {43,46,49}\) With deep halothane anesthesia, renal blood flow may be reduced to 31 per cent of control with similar changes in GFR. The effect of anesthesia on renal and cardiovascular function must be considered when comparing studies in anesthetized animals and awake patients.

LUNG AND CHEST WALL COMPLIANCE

When airway pressure is increased during positive pressure ventilation, the increase in intrapleural pressure depends on both lung and chest wall compliance.\(^ {17,50}\) In patients or animals with restrictive lung disease or respiratory failure, lung compliance is decreased. In these conditions, increased airway pressure is not transmitted to the intrapleural structures to the same degree as in animals with normal lungs. Renal studies during mechanical ventilation of normal lungs may differ from those in which disease exists.

Chest wall compliance is a secondary factor which affects intrapleural pressure during positive pressure ventilation. Muscle relaxants, thoracic disease, and narcotic analgesics are factors which may change chest wall compliance and are variables in studies of renal function.

VENTILATORY PATTERN AND LEVEL OF PEEP

The amount and duration of the increase in the intrapleural pressure during positive pressure ventilation is determined in part by tidal volume,\(^ {20}\) inspiratory and expiratory time,\(^ {19}\) and level of PEEP.\(^ {10}\) As intrapleural pressure is changed, cardiovascular hemodynamics are altered and this may contribute to variations in renal performance. In the studies of the effect of mechanical ventilation on renal function many patterns of ventilation have been used and from 5 to 20 cm H\(_2\)O PEEP has been applied.

SPECIES VARIATION

Most of the studies of the effect of respiratory support on renal function have been performed using dogs or human subjects, although others have used monkeys or swine. Because of species variation, the renal response to mechanical ventilation may be different. Responses to drugs or to other stimuli are sometimes different between these species. For example, experiments in dogs demonstrated that narcotics cause an increase in antidiuretic hormone (ADH)\(^ {51}\) while large doses of morphine can be administered to humans without an increase in ADH.\(^ {52,53}\) The choice of animal model may be particu-
Table 1. Renal Effects of CMV with ZEEP*

<table>
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<tr>
<th>Author</th>
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<th>RBF</th>
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</tbody>
</table>

P = patients; D = dogs; NL = normal lungs; ARF = acute respiratory failure.

* Only statistically significant changes are noted. Increase (↑), decrease (↓), or no change (→) in measurement.

larly important when analyzing the causes of the renal responses to mechanical ventilation.

**Method of ADH Measurement**

ADH is involved in the control of body osmolarity, intravascular volume, and blood pressure.44,45 The decrease in urine volume and negative free water clearance during positive pressure ventilation was thought to be an effect of ADH, although hormone levels were not measured.44,45 Later investigators used a modification of a bioassay for measuring ADH concentration.56 More recently, a radioimmunoassay has been developed for ADH with much greater accuracy and precision.57 The advent of this improved method of measurement has helped clarify the role of ADH in the changes in renal function during ventilatory support.

**Renal Function Tests During Respiratory Support**

**CMV with Zero End Expiratory Pressure**

In 1968, Sladen et al. described a group of patients requiring prolonged CMV with zero end expiratory pressure (ZEEP) who retained water resulting in an increased alveolar–arterial oxygen tension gradient and a decreased serum sodium concentration and hematocrit.25 The patient’s fluid overload was treated with diuretic administration and fluid restriction. In another clinical study of patients requiring CMV for respiratory failure, Gett et al. demonstrated that a positive sodium and water balance occurred during ventilation and produced pulmonary edema.27 These two clinical studies demonstrated that some patients with respiratory failure requiring CMV with ZEEP had renal changes resulting in decreased elimination of sodium and water.

Using anesthetized, volume loaded dogs, Baratz et al. demonstrated no statistically significant changes in urine output, osmolar clearance, or free water clearance during CMV.38 When awake patients without pulmonary disease were ventilated with CMV with ZEEP, urine flow rate decreased, although there were no significant changes in osmolar or free water clearance.26 Other measurements of renal function were not made. Plasma ADH concentration measured by bioassay increased in these patients during CMV with ZEEP. Although there was no decrease in free water clearance, the usual effect of an increase in ADH concentration, the authors suggested that the stress of CMV in the awake patients released ADH which decreased urine output. In previous studies in dogs, this had been prevented by anesthesia (table 1).

Moore et al., using awake, restrained infant monkeys, demonstrated a decrease in cardiac output, total renal blood flow, and the proportion of RBF delivered to cortical nephrons during CMV with ZEEP.34 These changes in RBF were associated with an increase in renal vascular resistance (RVR). Urine flow rate and clearance measurements were not made in this study. The redistribution of RBF from the cortical nephrons observed by Moore may contribute to the changes in urine output and sodium that were observed by other investigators using this form of mechanical ventilation.

The data from these studies suggest that CMV with ZEEP can alter renal blood flow and renal function, although the extent of the changes differed throughout these studies. Plasma ADH concentration increased with CMV with ZEEP in some studies, but this was not a consistent observation.

**CMV with PEEP**

Renal function has been evaluated in both laboratory animals and patients during CMV with PEEP (table 2). In anesthetized dogs without pulmonary disease, Hall et al. measured a 40 per cent decrease in urine flow rate, a 23 per cent decrease in creatinine clearance level, and a 63 per cent decrease in urinary sodium excretion during CMV with 10 cm H2O PEEP.35 They reported no change in total renal blood flow, but found a redistribution of flow from the cortical to juxtamedullary nephrons, as measured by the 85Kr washout technique. Other investigators have also demonstrated a decrease in urine flow rate, urinary sodium excretion, and GFR after initiation of CMV with PEEP in laboratory ani-
mals. In contrast to the work of Hall et al., renal blood flow was decreased by CMV with PEEP in several studies. Both Fewell and Bone and Marquez et al. observed no change in C\textsubscript {H\textsubscript{2}O} during this form of ventilation, although only one group measured a decrease in C\textsubscript{osm}. Similar studies have been performed in patients with respiratory failure. Addition of PEEP to CMV produced a decrease urinary flow rate, creatinine clearance level, and urinary sodium excretion. Jarnberg et al. measured a 12 per cent decrease in effective renal plasma flow while patients received CMV with 10 cm H\textsubscript{2}O PEEP. They demonstrated no change in C\textsubscript{H\textsubscript{2}O}, in contrast to Kaukinen and Eerola who found C\textsubscript{H\textsubscript{2}O} to be less negative during the same ventilatory pattern.

**SV with PEEP**

Drury et al. used awake volunteers to show that continuous pressure breathing decreased urine output and urea clearance and that the renal changes were greater as higher levels of pressure were applied. Continuous positive pressure breathing of 24–26 torr in another group of patients with normal lungs produced a decrease in urine flow, GFR, RBF, C\textsubscript{H\textsubscript{2}O}, C\textsubscript{osm}, and renal sodium excretion.

When 7 torr PEEP was applied to swine breathing spontaneously, there was a decrease in urinary flow, GFR, and urinary sodium excretion, but no change in free water clearance or osmolar clearance. These same renal changes were produced when the mode of ventilation was changed from spontaneous with ZEEP to CMV with 7 torr PEEP. Although the mechanism may differ, in this study, PEEP with both SV and CMV had similar renal effects.

**Respiratory Support and ADH**

Early investigators postulated that antidiuretic hormone was responsible for the decrease in urine volume and free water clearance during both CMV with ZEEP and SV with PEEP. An increased ADH concentration would change renal function in a manner that was consistent with the clinical findings of water retention and hyponatremia, observed in the patients described by Sladen et al. In early studies, CMV with ZEEP in anesthetized, volume expanded dogs produced either no change or a decrease in plasma ADH when measured by bioassay. In a later study, Khammatta and Baratz reported an increase in plasma ADH and a decreased urine volume, but no change in C\textsubscript{H\textsubscript{2}O} during CMV with ZEEP in normovolemic patients. With the increase in plasma ADH during CMV with ZEEP, free water clearance should become more negative, although this was not observed.

Studies both in dogs and patients demonstrated an increase in plasma ADH during CMV with PEEP. In only one of these studies was free water clearance or urine osmolality measured. In this study, although ADH increased, there were no consistent changes in C\textsubscript{H\textsubscript{2}O} or urine osmolality. Kumar et al. suggested that the decreased urine flow in these patients was a result of cardiovascular changes rather than ADH.

In a more recent study using a radioimmunoassay, Marquez et al. found an increase in the plasma ADH level during CMV with 7 torr PEEP in swine but no increase in the hormone concentration during SV with 7 torr PEEP. Although both modes of ventilation were associated with a similar decrease in urinary flow, neither produced a change in C\textsubscript{H\textsubscript{2}O}. This is another study in which ADH concentration did not correlate with renal function changes during CMV with PEEP.

Baratz and Ingram using SV with 11.4 or 18.6 torr PEEP in dogs measured a large increase in ADH associated with oliguria and decreased GFR. Free water clearance was not measured. In this report, similar changes in renal function and ADH were noticed after hemorrhage of 25 per cent of the animals' blood volume. The authors concluded that circulatory depression due to decreased central blood volume produced the renal changes either through direct or reflex mechanisms. They also reasoned that ADH was not increased as a result.

### Table 2. Renal Effects of CMV with PEEP

<table>
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<tr>
<th>Author</th>
<th>PEEP (cmH\textsubscript{2}O)</th>
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* Only statistically significant changes are noted. Increase (†), decrease (‡), or no change (→) in measurement.
Fig. 1. The effect of antidiuretic hormone on the nephron. (Left) When ADH is present, the epithelium of the collecting duct is permeable to water which diffuses into the medullary interstitium. Under these conditions, hyperosmolar urine results. (Right) In the absence of ADH, the epithelium of the collecting ducts is impermeable to water and dilute urine results. The numbers indicate osmolality and the arrows show movement of Na and Cl or H₂O.

of osmoreceptor activation since serum sodium concentrations remained constant.

Hemmer et al. measured 24-hour urinary ADH excretion in patients with respiratory failure, due to fluid chest, who were initially treated with CMV with PEEP and subsequently weaned to SV with ZEEP.⁶⁴ The use of radioimmunoassay to quantitate urinary ADH concentration and its correlation with urinary free water clearance has been previously validated.⁶⁴ Total urinary ADH excretion was greatest and fluid balance was positive while the patients were being treated with CMV with PEEP. ADH excretion was less while CINV increased during SV with PEEP and SV with ZEEP. During CMV with PEEP, ADH excretion was increased without a corresponding increase in free water retention in contrast to spontaneously breathing patients.

The above data suggests that during CMV with ZEEP or PEEP, ADH may not be directly responsible for the decreases urine volume. Antidiuretic hormone is formed in the paraventricular and supraoptic nuclei of the hypothalamus and is secreted by the posterior pituitary in response to several stimuli. Receptors in the hypothalamus detecting small increases in plasma osmolality cause ADH to be released.⁵⁴,⁵⁵ At low plasma concentrations, ADH permits water to be reabsorbed by the convoluted tubules and collecting ducts of the nephron and results in a decrease in free water clearance (fig. 1). When water is retained in excess of sodium, the serum sodium concentration decreases. ADH release in response to activation of osmoreceptors decreases urine flow rate, increases urine osmolality, and decreases plasma osmolality.

CARDIOVASCULAR RECEPTORS AND ADH RELEASE

Low pressure volume receptors in the left atrium of experimental animals have been found to stimulate ADH release through vagal afferent nerves.⁶⁶–⁷² Small decreases in blood volume that do not change arterial pressure result in increased ADH concentration, presumably through atrial receptors.⁷² When the left atrium is stretched, ADH release is inhibited by increasing afferent impulses along the vagus nerve from the receptors. In the dog, left atrial distension produced a diuresis associated with a decrease in ADH concentration.⁷⁰

When intravascular volume decreases so that pulse pressure or mean arterial pressure is decreased, baroreceptors in the aorta and carotid arteries act on the hypothalamic nuclei to produce a very high plasma ADH concentration.⁷²,⁷³ Share and Levy investigated the effect of changes in arterial pulse pressure on ADH concentration in vagotomized dogs.⁷⁴ When mean arterial pressure was held constant, a change from pulsatile to nonpulsatile perfusion of the carotid sinus resulted in an increase in plasma ADH concentration. In other studies in rabbits, bilateral section of the afferent nerves of the aortic baroreceptors produced an increase in plasma ADH.⁷⁵ These studies indicate that aortic and carotid baroreceptors have a tonic inhibitory effect on the release of ADH.

ADH or arginine vasopressin (AVP) is a potent vasoconstrictor and may maintain blood pressure during hypovolemia. Using dogs which had been prepared so that peripheral sympathetic neural function and the renin-angiotensin system were inactive, Cowley et al.
demonstrated that endogenously released vasopressin can quickly restore arterial pressure during hemorrhage. In awake dogs, infusions of ADH which produced serum concentrations within a physiologic range resulted in increased total peripheral vascular resistance.

Murdaugh et al. suggested that the changes in renal function observed during positive pressure breathing were produced by ADH release, as mediated by the atrial stretch receptors in response to decreased central blood volume. When studies were performed by others, the role of ADH and atrial receptors was questioned. Baratz et al. demonstrated that bilateral cervical vagotomy in dogs ventilated with PEEP did not prevent the increase in plasma ADH concentration or decrease in urine flow. Since the neural pathway between the atrial volume receptors and the hypothalamus had been interrupted, the change in ADH was not a result of changes in left atrial distention. However, the systemic arterial baroreceptors had intact afferent nerves in this study and could have been responsible for the increased ADH release in response to cardiovascular alterations.

Several studies suggest that mechanisms other than ADH exist to produce hyponatremia and a hypertonic urine. During conditions in which there is a decrease in glomerular filtration rate, there is an increased reabsorption of sodium and chloride in the proximal tubule of the nephron. There is then a decreased delivery of sodium and chloride to the diluting sites in the distal tubule. Without sodium and chloride for reabsorption, the distal nephron cannot generate dilute urine for excretion of free water. Under these circumstances, water intake, either orally or as hypotonic intravenous fluids, results in hyponatremia and a relatively concentrated urine. Changes in cardiovascular function which decrease RBF or GFR may, thus, be responsible for the changes in free water excretion and urine volume observed in some patients during prolonged respiratory care. The inconsistent correlation between ADH concentration and free water clearance in previous studies could be explained if ADH release was the result of the activation of baroreceptors rather than by osmoreceptors. During respiratory support, ADH appears to function as a vasopressor secreted in response to the changes which are produced in cardiovascular hemodynamics.

Respiratory Support and Cardiovascular Function

As investigators noticed that the renal effects of CMV with ZEEP or PEEP could not be adequately explained by changes in ADH concentration, they suggested that changes in cardiovascular function were responsible. Many investigators have demonstrated that CMV with PEEP affects venous return and cardiac preload, pulmonary vascular volume and resistance, left ventricular geometry, and cardiac afterload, with a resulting decrease in cardiac output. The effect of respiratory support on cardiopulmonary hemodynamics will be reviewed briefly as a basis for understanding their effect on renal function.

CMV with PEEP

Within a few respiratory cycles after PEEP is added to CMV, there is a decrease in cardiac output. As the amount of PEEP is increased, cardiac index, stroke index, and mean arterial pressure decrease. Currently, there are two mechanisms proposed by which this mode of mechanical ventilation decreases cardiac output.

CMV with PEEP increases intrapleural pressure and may decrease venous return and cardiac filling. In anesthetized dogs with normal lungs, Qvist et al. measured a decrease in transmural right atrial pressure, transmural right ventricular end diastolic pressure, and transmural pulmonary capillary wedge pressure associated with a decrease in cardiac index after instituting CMV with 12 cm H2O PEEP. There was a significant increase in heart rate during CMV with PEEP, but the decrease in stroke index was so great that the tachycardia was not sufficient to maintain the cardiac index. When transmural cardiac filling pressures were restored to pre-PEEP values with transfusion of 25 ml/kg body weight of whole blood, the cardiac index and stroke index increased to control levels. When CMV with PEEP increases intrapleural pressure, inferior vena cava pressure is also increased, as was demonstrated by Hall et al. and Marquez et al. Other investigators have used intravenous contrast to demonstrate compression of the inferior vena cava in dogs mechanically ventilated with PEEP.

Additional studies have suggested a second mechanism which may produce a reduction in cardiac output. Right and left ventricular end-diastolic volumes are decreased in dogs and humans with normal lungs during CMV with PEEP. Although this may be due to a decrease in preload, Jardin et al. have used two-dimensional echocardiography to demonstrate a shift of the interventricular septum toward the left ventricle. As PEEP was increased above 10 cm H2O in patients with acute respiratory failure, cardiac output decreased and right and left transmural ventricular filling pressures equalized, but at pressures less than the values prior to PEEP. Since pulmonary vascular resistance increases as alveoli are distended, right ventricular afterload is increased, and the interventricular septum shifts to the left. When this occurred, blood volume expansion did not increase cardiac index to pre-PEEP values. Since right and left ventricular transmural pressures became similar during PEEP, it suggests that the pericardium or other extrinsic...
forces limited ventricular expansion. Volume loading at high levels of PEEP therefore had limited effect on increasing left ventricular dimensions, since it also increased the degree of septal flattening.10

**SV with PEEP**

SV with PEEP has been shown to change cardiovascular hemodynamics. In swine with normal lungs, 7 torr PEEP during spontaneous ventilation produced a decrease in stroke volume and an increase in pulse rate and inferior vena caval pressure. Cardiac output decreased although the change was not statistically significant. Zarins et al. using normal baboons demonstrated that 20 cm H₂O PEEP during SV with two mechanical breaths per minute resulted in a 30 per cent decrease in cardiac output.23 Mean arterial pressure was unchanged during SV with PEEP although there was an increased pulse rate. Kirby et al. have provided contrasting data from normal monkeys during SV with 20 torr PEEP and positive pressure ventilation at a rate sufficient to maintain normocarbia.22 PEEP produced no change in cardiac output but intravenous fluids were given continuously to maintain a minimum transmural pulmonary capillary wedge pressure of 5–15 torr. Cardiovacular changes were possibly prevented by the intravascular volume loading.

**Comparison of Cyclical Cardiac Pressure Changes**

In most studies evaluating cardiovascular function, pressure measurements are reported for only one part of the respiratory cycle, i.e., end-expiration. During respiration, the cyclical changes in intrathoracic pressure affect cardiac filling and output so that they vary from beat to beat. To understand the effect of PEEP during CMV and SV, it is necessary to examine cardiac function during both inspiration and expiration.

When measured at end expiration, there is a similar increase in intrapleural pressure (Ppl) during SV or CMV with the application of PEEP (fig. 2). Although the inferior vena cava pressure (Pivc), right atrial pressure (Ptra), and left ventricular end diastolic pressure (Plved) are increased under these conditions, the transmural right atrial pressure (Ptra) and left ventricular end diastolic pressure (Plved) are decreased. Therefore, the increased Ppl during both CMV and SV with PEEP results in decreased right and left sided cardiac filling at end-expiration. At the same time, transmural aortic pressure (Ptao), which is part of left ventricular afterload, is decreased.32–34 Decreased cardiac output and stroke volume are observed presumably because of the greater effect of decreased cardiac filling. With inspiration during CMV with PEEP, Ppl is further increased while Ptra, Plved, and cardiac preload are decreased as compared to end-expiration (fig. 3). With CMV with PEEP, transmural filling pressures are decreased for the entire respiratory cycle.

Inspiration during SV with PEEP causes Ppl to become more negative and although venous return and Ptra and Plved are increased, Ptao is increased (fig. 3). This increase in left ventricular afterload appears to be the factor which produces the decrease in stroke volume.33,34
The decrease in stroke volume during SV with PEEP can, therefore, be explained by decreased preload at end-expiration and increased afterload during inspiration.

When cardiovascular hemodynamics are altered by changes in intrapleural pressure, baroreceptors initiate neural and humoral mechanisms to preserve adequate perfusion. Using flow probes and intravascular catheters, Fewell et al. measured a transient decrease in aortic pressure and the lowest blood flow three heart beats after adding PEEP to CMV. Arterial pressure returned to control level after 3 to 5 min. The sympathetic nervous system and the renin-angiotensin system are reflexly activated to maintain arterial pressure during periods of decreased cardiac output and both may affect renal function.

**CMV with PEEP, Baroreceptors and Renal Sympathetics**

Although there is constant tonic stimulation of the renal sympathetic nerves, an increased stimulation results in a decrease in renal blood flow, a redistribution of blood flow from the cortical to the juxtamedullary nephrons, and a decrease in renal sodium excretion. A decrease in mean systemic arterial pressure or a decrease in pulse pressure decreases the firing of the carotid sinus baroreceptors, which normally inhibit the sympathetic efferent nerves to the kidney. Katz and Shear demonstrated a decrease in RBF, GFR, and urinary sodium excretion in dogs after bilateral carotid occlusion. Conversely, chronic renal denervation resulted in an increase in renal plasma flow, GFR, and sodium excretion due to loss of the tonic renal sympathetic stimulation.

Renal sympathetic stimulation during hypotension results in decreased urinary sodium excretion and renal blood flow, which tend to restore central blood volume and arterial pressure. The aortic and carotid baroreceptors continuously respond to changes in arterial pressure and can rapidly modify systemic pressure by their effect on sympathetic stimulation and more slowly by their effect on intracardiac volume by changing renal function.

Bond demonstrated in dogs that the renal sympathetic nerves are in part responsible for the changes in renal function during CMV with 10 cm H₂O PEEP. Dogs were prepared by completely denervating one kidney prior to study. There was a decrease in urine flow, sodium excretion, effective renal plasma flow, GFR, and C téc in the innervated kidney during CMV with PEEP while these measurements did not change from control values in the denervated kidney.

In another study, Fewell and Bond assessed the role of cardiopulmonary receptors with vagal afferents and sinoaortic baroreceptors in producing the changes in renal function observed during CMV with PEEP. Dogs with either bilateral cervical vagotomy or with intact nervous systems had the usual decrease in urine flow.
rate, sodium excretion, GFR, and C RET during CMV with 10 cm H2O PEEP. In contrast, dogs in which the sinoaortic baroreceptors were denervated had no changes in renal function while the lungs were mechanically ventilated with PEEP. The low pressure atrial receptors which were denervated by cervical vagotomy were not necessary to alter renal function during this mode of ventilatory support. This study demonstrates that the high pressure baroreceptors in the aorta and carotid sinus sense changes in cardiovascular hemodynamics induced by CMV with PEEP and initiate responses which affect urinary flow, sodium excretion, and GFR.

Low pressure, atrial stretch receptors may alter renal vascular tone and renal salt and water excretion.91-94 Decreasing atrial pressure increases renal vascular constriction as a result of increased renal sympathetic activity. Although these receptors may modulate renal function under some conditions in the dog,91 recent evidence suggests that in nonhuman primates this relationship does not exist.95 Further research is necessary to determine the effect of the atrial receptors acting through the renal sympathetic nerves on renal function in humans.

**Direct Effects of Decreased Cardiac Output and Blood Pressure on Renal Function**

Beside acting through the sympathetic nervous system, a decrease in cardiac output or mean arterial pressure directly decreases renal blood flow, glomerular filtration rate, urine output and urinary sodium excretion.92,93 When Hemmer and Suter used dopamine infusions to increase cardiac output, stroke volume, and mean arterial pressure in patients with respiratory failure whose ventilation was supported by CMV with PEEP, urine output, sodium excretion, and GFR returned to pre-PEEP values.62 Whether the improvement in renal function was the direct result of the increase in renal perfusion pressure or was from changes in renal sympathetic tone as mediated through baroreceptors or renal dopaminergic receptors cannot be determined.

Gattinoni et al. were able to reduce the cardiovascular changes produced by CMV with 5 cm H2O PEEP by decreasing the respiratory rate to 2 breaths/min and using an extracorporeal membrane oxygenator for carbon dioxide removal.96 Under these conditions cardiac index increased by 26 per cent, and systemic vascular resistance decreased by 22 per cent, compared with animals receiving standard mechanical ventilation with 5 cm H2O PEEP while the venovenous bypass flow continued without gas exchange across the membrane lung. The cardiovascular changes during low frequency ventilation were associated with an increase in urinary flow rate and serum creatinine and osmolar clearances. This suggests that the frequent cyclical increase in intrapleural pressure with inspiration during CMV with PEEP is in part responsible for cardiovascular and in turn renal changes.

**CMV with PEEP and Renin-Angiotensin-Aldosterone**

The renin-angiotensin-aldosterone system is important in the maintenance of systemic arterial pressure and renal perfusion.97 Renin is released from the juxtaglomerular cells of the kidney in response to changes in renal perfusion, renal sympathetic stimulation, and the composition of the fluid in the distal tubule of the nephron. Renin is an enzyme which produces angiotensin I from the precursor, angiotensinogen while converting enzyme changes angiotensin I to angiotensin II, a potent vasoconstrictor. Angiotensin II stimulates the adrenal cortex to release aldosterone, which causes increased sodium reabsorption in the distal tubule of the nephron.

Cox et al. measured increased urinary aldosterone concentration in volunteers during CMV with PEEP.33 They suggested that aldosterone may be responsible for the decreased renal excretion of sodium, and in support of this, there was a decrease in the urinary sodium to potassium ratio.

CMV with 8 cm H2O PEEP in dogs produced an increase in peripheral renin concentration and a decrease in urine volume.98 In a second part of this study, renin concentration was measured in dogs with a single denervated kidney. Mechanical ventilation with PEEP in this preparation resulted in an increase in peripheral renin concentration. This suggests that renal innervation is not necessary to release renin under these experimental circumstances.

When Kaukinen and Eerola ventilated patients with 10 cm H2O PEEP, there was a 21 per cent decrease in urine output but no significant increase in plasma renin activity.61 Since the control renin activity was increased in these patients, the significance of the lack of change during CMV with PEEP is unclear.

**PEEP and Increased IVC Pressure**

When intrapleural pressure is increased with the application of PEEP, inferior vena cava and renal venous pressures increase. There is evidence to suggest that this changes renal peritubular capillary pressure which increases renal sodium reabsorption.83,99 This would provide an explanation for the renal function changes which occur during both CMV and SV with PEEP.

The decrease in venous return and increase in PIVC can be simulated experimentally by partial occlusion of
are more important than the increased P_{IVC} in producing the renal effects.

Partial occlusion of the IVC with a balloon above the renal veins decreased cardiac output, stroke volume, central venous pressure, renal blood flow, GFR, free water clearance, urine output, and urinary sodium excretion.\textsuperscript{102} If P_{IVC} was then held constant while transfusion restored cardiac output to normal, renal function returned to control values.

Watkins \textit{et al.} implanted inflatable tourniquets around the thoracic IVC in dogs so that the vessel could be constricted over several days.\textsuperscript{103} Right atrial pressure and urinary sodium excretion decreased with obstruction to IVC flow. Plasma renin activity and aldosterone concentration simultaneously increased. Over several days as the animals were allowed to eat and drink, sodium and water were retained and body weight and measured plasma volume increased. As vascular volume increased, right atrial pressure increased to preocclusion values and urinary sodium excretion, plasma renin activity, and aldosterone concentration returned to the control values. When converting enzyme inhibitor was chronically administered while the IVC was partially occluded, the animals remained hypotensive and did not increase their intravascular volume. The renin-angiotensin system was necessary for maintenance of arterial pressure and for maximum sodium retention by the kidney. With chronic obstruction to cardiac venous return, a reduction of urine volume and sodium excretion provide a mechanism for increasing plasma volume until cardiac filling pressures and cardiac output return to normal. These renal mechanisms aided in restoring cardiac filling pressures but at the cost of an increase in total body water and salt to a degree that produced edema.

A study reported in abstract form demonstrated that with the initiation of CMV with PEEP in dogs, urine output and urinary sodium and free water excretion decreased.\textsuperscript{104} After 16 h of this mode of ventilation, these measurements of renal function increased from the initial values as the animals retained salt and water. Previous studies have examined the effect of CMV with PEEP on renal function for only short periods of time so that the concept of renal changes being a compensatory mechanism has not been stressed. Just as changes in renal function associated with chronic IVC obstruction have been shown to allow intravascular volume to increase and, thus restore cardiac filling, this study demonstrates that the same responses occur during prolonged CMV with PEEP.

**Summary**

**CMV with PEEP**

Renal function alterations are often produced by CMV with PEEP. The majority of evidence suggests that this
form of ventilatory support most commonly decreases urine volume and sodium excretion as a result of changes in cardiovascular function (fig. 4). Increased intrapleural pressure during both inspiration and expiration produces decreased venous return, cardiac output, and sometimes mean arterial pressure. Through direct effects on renal perfusion or through baroreceptors and the ADH, renin, or sympathetic systems, renal function is altered. These hormonal and neural mechanisms acutely serve to maintain arterial pressure during CMV with PEEP but in doing so affect the kidney.

The decrease in free water clearance observed during some studies of CMV with PEEP was originally attributed to the effect of ADH. Although ADH may be increased during mechanical ventilation in response to baroreceptors, it does not directly cause a decrease in urine volume or free water clearance. The role of ADH during CMV with PEEP seems to be that of maintaining circulatory homeostasis while the changes in free water clearance can be explained by intrarenal mechanisms. Free water administration at a time when the patient is unable to excrete a dilute urine results in hypotremia.

As in animal models of chronic partial obstruction of the thoracic IVC, CMV with PEEP produces hemodynamic alterations resulting in renal function changes which in time will increase intravascular volume. As water and sodium are retained, intravascular volume is increased which may improve cardiac output (fig. 4). This is a slow and inefficient mechanism for increasing intravascular volume as extracellular fluid including pulmonary interstitial fluid is also increased. This situation is familiar to clinicians caring for patients with respiratory failure who become edematous during treatment with CMV and PEEP. An increase in lung water may worsen pulmonary function during respiratory failure. Diuretics are commonly used in these cases to block the reuptake of sodium by the kidney. By decreasing intravascular volume, this treatment can result in a decrease in arterial pressure, renal perfusion pressure, or cardiac output which produced the renal function changes initially. The clinician is faced with the dilemma of choosing between a therapy that is favorable for the lungs or the kidney. Maintenance of optimal intravascular volume is necessary for normal renal, cardiac, and pulmonary function.

**CMV with ZEEP**

Similar changes in renal function may occur with CMV with ZEEP if intrathoracic pressure is altered so that cardiac output, stroke volume, or arterial pressure is significantly decreased. CMV with ZEEP increases intrapleural pressure during inspiration, and the factors discussed above will determine whether cardiovascular and renal function changes will occur. The mechanisms altering renal function during this mode of ventilation have not been as thoroughly investigated but, presumably, are the same as with CMV with PEEP.

**SV with PEEP**

SV with PEEP results in an increase in intrapleural pressure at end-expiration and during this time its cardiovascular effect is like CMV with PEEP. During inspiration, SV with PEEP produces an increase in left ventricular afterload. When these changes affect cardiac output or stroke volume during SV with PEEP, there is a decrease in urine flow and sodium excretion similar to that observed during CMV with PEEP.

Further investigation is necessary to determine the best method to assess and maintain intravascular volume during respiratory support so that renal, cardiovascular and pulmonary function are optimized. As the interactions between the cardiovascular and renal systems are further clarified, other techniques for preserving renal function during respiratory failure can be developed.

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