The Influence of Intrathoracic Pressure on Fluid and Electrolyte Balance

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As modern respiratory intensive care becomes increasingly well defined as a subspecialty, it is important to critically evaluate the effect of various types of ventilatory support on the patient as a whole. One aspect of the general care of the respiratory patient with which the physician must deal is fluid and electrolyte balance. The original report of Sladen et al., suggesting that sodium and fluid retention are associated with positive pressure ventilation, has been followed by other studies with similar findings. The magnitude of the clinical problems presented in these studies points out the potential importance of this association, but the existing clinical literature does little more than document the phenomenon in a retrospective fashion and does little to elucidate the mechanism in humans. On the other hand, the physiologic literature on the influence of intrathoracic pressure on fluid and electrolyte balance is replete with studies on the mechanism of this influence. Unfortunately, it is at the same time more confusing and often contradictory. The purpose of this article is to briefly review the literature in this field and point out how the thinking has shifted in recent years. It is the author's hope that such a review may crystallize the physiologic aspects of this topic and give some direction to future investigations into the clinical aspects.

Until recently the role of the left atrial stretch reflex, as first described by Henry, Gauer and Reeves in 1956, was the cornerstone of physiologic thinking regarding the influence of the chest on urine output. Recently, as will be discussed in detail below, the physiologic importance of left atrial stretch must be considered controversial because a significant number of investigators have reported findings which would minimize, or at least modify, the role of these receptors. Because the left atrial stretch reflex has occupied such a key position in the thinking of workers in the field, I will first discuss the documentation of this reflex per se, and then discuss its role as a mechanism for monitoring total blood volume. I will then summarize the evidence which would tend to minimize the physiologic importance of these receptors, and finally present an alternative mechanism by which pressures in the thorax might affect fluid and electrolyte balance.

The Left Atrial Stretch Reflex

In 1956, Henry, Gauer, and Reeves first documented the fact that distention of the left atrium resulted in an increase in urine flow which was composed mostly of an increase in free water excretion. Large numbers of investigations ensued to further characterize the response and elucidate its mechanism. A number of elegant reviews of the voluminous literature on this subject are available, and a detailed discussion would be redundant and beyond the scope of this article. Only the major findings and a few pertinent technical details will be discussed. It was documented on multiple occasions that if the left atrium were stretched, water diuresis would ensue. This response is generally considered secondary to an increase in firing rate of left atrial "type B" fibers as described by Paintal in 1953 and further characterized by Hakumaki in 1971. These receptors are clustered at the left atrial-pulmonary vein junction and send fibers up the vagus to the hypothalamus. When firing, these fibers tend to reduce levels of antidiuretic hormone (ADH) output from the posterior pituitary, and thus...
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cause a diuresis. The rate of firing is determined by the degree of stretch on the fiber.

The character of the diuresis observed in response to left atrial stretch deserves comment. When the atrium is stretched as described below, a reasonably brisk diuresis ensues after a lag period of 10-20 minutes. The diuresis peaks in about 60 minutes and then diminishes toward baseline urine output whether or not the stretch is continued. Thus, the response is mainly a diuresis (as opposed to saluresis), relatively brief, and self limited: all points of importance in reference to future discussion.

Most of the studies cited above produce left atrial stretch by the insertion of a left atrial balloon, utilizing the original procedure as described by Reeves.11 When the balloon is inflated, the atrium is stretched probably by mitral obstruction, as well as the effect of occupying space. Increase in atrial transmural pressure is used as the measure of stretch. The original studies all suddenly stretched the atrium until the atrial pressure increased 20 cm H2O. A recent attempt to utilize smaller, more physiologic degrees of atrial stretch on the range up to 7 cm H2O demonstrated a corresponding decrease in plasma ADH which was related to the degree of atrial stretch.12 However, opposite findings are reported by Goetz utilizing a different preparation.13 Thus, although the effects of large amounts of atrial stretch appear quite clear, the effects of small amounts of stretch remain to be worked out.

Although a single report appeared in 1959 suggesting that stretch of the right atrium alone decreased aldosterone levels,14 to my knowledge this has not been repeated or confirmed to date and no details of mechanism are known.

Left Atrial Stretch Receptors as Volume Receptors

Once the studies discussed above established that the left atrial stretch reflex existed, it was then credited with mediating a number of physiologic responses. It has been repeatedly pointed out that these receptors are ideally situated to monitor blood volume in that the fullness of the left atrium by and large reflects the total blood volume. Thus, the search for the receptors which sense "the fullness of the blood stream" popularized by J. P. Peters in 1935, appeared to be ended. Indeed, the reviews of the literature make a strong case that left atrial stretch receptors are, in fact, physiologically important volume receptors. Intuitively appealing as this hypothesis may be, final proof is hard to come by. Some studies, such as those of Goetz and co-workers,18 suggest that if atrial transmural pressure is held constant by certain special surgical techniques, the renal response to blood volume alterations is attenuated. This would suggest that atrial stretch receptors mediate at least part of the renal response to hemorrhage or transfusion. However, the work of Bargainer and Woods,16 showing that renal response to blood volume alterations is not modified by neurosurgical procedures which destroy the atrial type B pathways, would lead one to the opposite conclusion.

It should be emphasized at this point that what is in question is not whether or not a volume receptor exists, but where it is located. For example, the work of Johnson and coworkers17 clearly demonstrates an effect of small changes of blood volume on plasma ADH which can be separated from the concurrent osmotic effects. The effect of hypovolemia can cancel out the decrease in plasma ADH which would ordinarily occur in an animal which is hypoosmotic. The fact that the authors chose to measure left atrial pressure as the monitor of blood volume reflects their underlying belief that left atrial stretch fibers are in fact the "volume receptors" of the body, but cannot be used to prove that belief as most vessels or chambers in the low pressure system of the chest would have likewise reflected the induced blood volume changes, but do not necessarily contain "volume receptors" in their walls.

There is nevertheless a reasonably large amount of suggestive evidence that there are "volume receptors" in the thorax, if not specifically in the left atrium, which influence peripheral levels of ADH in response to maneuvers which shift portions of the total blood volume into or out of the chest. Thus, the observation that types of acceleration which would shift blood out of the thorax tend to raise levels of ADH and similar observations with respect to temperature and postural changes,19,20 as well as lower body negative pressure21 all suggest that intrathoracic volume receptors are controlling the level of ADH.

The opinion that the "volume receptors" of the body are intrathoracic is, however, not universal. For example, Share22 found that vagotomized dogs (left atrial type B fibers severed) showed only minimal ADH response to hemorrhage if the carotid sinuses were perfused at constant pressure. This led Share to suggest the "volume receptors" are actually in the carotid sinuses.

Finally, the observations of Bonjour and Malvin28 suggest that activation of the renin angiotensin system either endogenously or exogenously stimulates the release of ADH, raising the possibility that the physiologic maneuvers which shift
blood out of the chest lowering cardiac output, activating arterial baroreceptors, and lowering renal blood flow, may be increasing ADH levels by stimulating renin release, rather than by collapsing the left atrium.

It is not my intention to suggest that the above studies rule out the participation of left atrial stretch receptors in the renal response to changes in blood volume or its distribution. The overview would suggest that multiple mechanisms are involved in regulating ADH release. This discussion is intended only to point out that the matter is far from settled and needs to be re-evaluated in the light of alternative hypotheses which are becoming available.

**Negative Intrathoracic Pressure**

Having discussed the role of left atrial stretch in blood volume *per se*, we are now ready to turn our attention to how this might be related to intrathoracic pressure and its effect on fluid and electrolyte balance. If one believes that the left atrial stretch receptors are physiologically important, it would be a logical step to assume that any changes in intrathoracic pressures that would tend to distend or collapse the left atrium would have a corresponding effect on urine output mediated by changing levels of ADH. For example, it has long been known that continuous negative pressure breathing (CNPB) causes a diuresis in man and dog. It would seem likely that the decreased intrathoracic pressure associated with this maneuver would increase the gradient for return of blood to the chest and thus stretch the left atrium. Indeed, change in firing rate of left atrial stretch receptors is commonly invoked to explain this diuresis.

Arguments in favor of the diuresis of CNPB being caused by left atrial stretch include the following. CNPB causes a diuresis with many of the characteristics of the left atrial stretch diuresis previously discussed. These characteristics are that after a brief lag period, there is a diuresis lasting about one hour, and then the urine volume subsides spontaneously whether or not the negative pressure is continued. Many parameters, including blood pressure, cardiac output, glomerular filtration rate and effective renal plasma flow, have been measured, and it has been shown that the diuresis can occur even though these variables remain unchanged during the diuresis. The lack of change in these variables has added weight to the arguments in favor of left atrial stretch.

On the other hand, there are theoretical reasons to doubt whether CNPB actually would engorge the thoracic circulation. The major veins entering the thoracic cavity are collapsible structures and withstand very little transmural pressure. One might suppose that a small lowering of intraluminal pressure might be enough to collapse these veins and thus limit the increase of blood return to the chest. There is a considerable amount of evidence that this is the case. Direct studies of pressure at various points in the venous system have suggested that CNPB collapses veins as they enter the thorax. This creates a waterfall effect which maintains peripheral venous pressure only slightly below its normal value no matter how low the central pressure becomes. Several groups have used a dye dilution technique to measure the central blood volume and found no increase during CNPB, although this view is not universally held. Measurements of flow in the superior vena cava suggest that any increase in flow is only very transient, reflecting the emptying of veins on the central side of the collapse point, and then flow promptly decreases toward the baseline. Direct measurement of left atrial transmural pressure in postoperative patients shows no significant change if a negative pressure cycle is added during the expiratory phase. Finally, there is some evidence from study of renal function during the diuresis of CNPB that with certain fluid intakes, only a small portion of the increase in urine volume is secondary to an increase of free water clearance, suggesting a mechanism other than the changes in ADH associated with left atrial stretch. Therefore, it can be said that although no single alternative mechanism has much support, there is considerable evidence casting doubt on the theory that left atrial stretch is the initiating event in the diuresis of CNPB.

Before leaving discussion of negative intrathoracic pressure, one final point should be made with regard to clinical implications. Although respirators with negative pressure cycles during the expiratory phase are not currently in widespread use, there are a number of studies which suggest that the addition of such intermittent negative pressure (as opposed to continuous negative pressure) may in fact increase venous return and have a beneficial hemodynamic effect in patients where such influence would be desirable. Experimentally, it has been shown in healthy dogs that there is little difference in cardiac output or blood pressure between straight intermittent positive pressure breathing (IPPB) and a similar ventilator with a negative pressure expiratory phase (IPNPB). However, if peripheral pooling of blood is induced by high spinal anesthesia or barbiturate poisoning, cardiac output will fall during IPPB, but will be maintained with IPNPB. Further documentation of the
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possible salutory effects of IPNPB has been reported, but Grenvik, using a somewhat different type of ventilatory pattern, did not find a change in postoperative thoracic surgical patients. However, none of these studies has looked at the effect of this type of ventilation on urine output or ADH levels. One would suppose that intermittent negative pressure might increase venous return more than continuous negative pressure, since the veins entering the thorax would not be continually collapsed. Yet if left atrial stretch were the only mechanism of diuresis, the transient self-limiting nature of the response would make it unlikely that the effect would be clinically important. On the other hand, there are other possible mechanisms to be discussed below, where the difference in transmission of central venous pressure to the periphery might make a clinically significant difference in urine output. In view of the possible clinical benefits of IPNPB, further studies on the type of ventilation should certainly include information on fluid and electrolyte balance.

Positive Intrathoracic Pressure

The situation with respect to positive pressure is considerably more difficult. Unlike NPB, positive pressure breathing is associated with a number of changes in general hemodynamics which complicate the picture. These have been well documented and include decreases in venous return, cardiac output, and blood pressure. The resultant decrease in renal perfusion makes it difficult to separate the results which are secondary to changes in renal hemodynamics from those which might be induced by "volume receptors." Nonuniformity of type of ventilation, the pressures employed, and resultant effects on blood gases add to the confusion.

It is not surprising, therefore, that there is no uniform opinion on the effects of positive pressure ventilation on urine output. Most studies report a decrease in urine output associated with positive pressure breathing with or without positive end expiratory pressure. Those who find an antidiuresis are not in total agreement as to mechanism. Most feel that decreased venous return and resultant collapse of the left atrium with increasing peripheral levels of ADH is the primary mechanism. Other studies suggest that the effects of decreased cardiac output on renal hemodynamics are the primary mechanism of antidiuresis. Most authors, however, cautiously allow for participation of multiple mechanisms. Differing experimental animals, types of ventilation and experimental protocols are ready explanations for this apparent discrepancy.

In fact, the phenomenon of antidiuresis associated with positive pressure is not undisputed, some studies actually demonstrating a diuresis on IPPB. Baratz and co-workers, for instance, noted diuresis in dogs on IPPB associated with a fall in peripheral ADH levels which the authors attributed to mechanical stimulation of left atrial stretch receptors. In a later study from the same laboratory, a decrease in urine output was noted if positive end expiratory pressure was utilized in dogs. This antidiuresis was associated with an increase in plasma ADH but was not modified by bilateral cervical vagotomy, leading the authors to conclude that intrathoracic volume receptors were not involved in this response. Unfortunately, bilateral cervical vagotomy was not performed in their original series with IPPB, so it is possible that vagotomy may not have altered the diuresis of IPPB that they noted.

The picture is further complicated by the effect of CO₂ per se on urine output: increased Pco₂ leads to diuresis associated with ADH inhibition. This study suggested that if CO₂ was added to the inspired gas to prevent the usual fall in Pco₂ associated with IPPB, then the antidiuresis was prevented. Thus, in those studies reporting antidiuresis on respirator therapy, decreased Pco₂ must be ruled out as a possible mechanism.

Definitive studies with respect to the effects of positive pressure breathing on urine output, as well as the mechanism of the effects, are unavailable. However, it is apparent that such effects exist and may vary with the ventilatory pattern, the pressures and flows employed, and the state of fluid and electrolyte balance at the time of initiation of respiratory therapy. In view of the extensive clinical use of IPPB, as well as the increasing popularity of positive end expiratory pressure ventilation in patients with "respiratory distress syndrome," further evaluation of this problem seems indicated.

An Alternative Hypothesis

Dissatisfaction with present theories has led studies at this laboratory in a new direction, and reporting our preliminary results seems worthwhile in terms of directing future study.

The movement of protein-poor fluid from the vascular to extravascular space when venous pressure is elevated would be predicted because of the resultant unbalance of Starling forces affecting fluid filtration at the level of the peripheral capillary. This had been documented during venous congestion of extremities many years ago. More recently it has been quite accurately quantitated in
the work of Oberg and Mellander. In 1948, some movement of fluid out of the vascular tree was noted during pressure breathing, but accurate quantitation and time course have not been documented under these conditions. In 1958, Brown et al demonstrated that protein-poor fluid loss of from 3-10 percent of blood volume can be observed within 10-20 minutes in healthy humans who increased systemic venous pressure by 11-21 cm of H2O by repeated Valsalva maneuvers. This was documented by changes in venous hematocrit and plasma protein determinations. We are presently in the process of further quantitating and documenting the time course of this phenomenon using a different method.

Utilizing morphine and chloralose anesthetized dogs, indocyanine green (Cardiogreen) was infused into a peripheral vein at a rate equal to that of hepatic excretion. Therefore the concentration of the dye remained constant in the intravascular compartment to which it is largely confined. The concentration of the dye was monitored continually by a Waters X250 densitometer coupled to a Grass polygraph on blood drawn from the femoral artery by a Harvard constant withdrawal pump model 600-910/920 at a rate of 5.7 ml/min. At a time when no change in dye concentration was being noted, IPPB was applied to a cuffed endotracheal tube at the rate of 16 breaths per minute with a peak inspiratory pressure of 18 cm H2O and an end expiratory pressure of zero.

Figure 1 shows one of 20 such exposures which represents a typical response. Note that within 30 seconds a distinct rise in optical density is noted and maintained throughout the two minute exposure. Hematocrits drawn at the peak of the increase in optical density exceeded those drawn at the baseline by about 2.0 percent. This fact, coupled with the fact that a similar but somewhat smaller increase in optical density was noted without dye in the blood, indicates that at least part of the rise in optical density is secondary to increased hematocrit. Quantitative aspects, as well as further details of serum changes, such as osmolality, remain to be worked out but this at least suggests that rapid and significant fluid shifts may take place at the onset of IPPB therapy. The duration of the effect is still unknown, but the results of the study by Brown suggest a stable elevated plateau by about 15 minutes after onset.

One mechanism by which this type of fluid shift might affect urine output revolves around the fact that the capillary wall is a semipermeable membrane with a non-diffusible anion (plasma protein) on one side. Thus, a Gibbs-Donnan equilibrium exists which results in an unequal distribution of ions, an electrical charge, and an unequal osmolality (interstitium hypotonic) which is balanced by a hydrostatic pressure within the lumen. Thus, if sufficient interstitial fluid were moved into the vascular tree, total serum osmolality would be reduced acutely, as well as the plasma protein and hematocrit. Movement of fluid outward would result in shifts in the opposite direction.

Let us, for example, consider what might happen in the peripheral capillary when peripheral venous pressure is acutely raised as a reflection of increased intrathoracic pressure associated with positive pressure breathing. Prior to the onset of increased venous pressure, the net filtration across the capillary is zero. The classic Starling forces are balanced - i.e., the mean capillary hydrostatic pressure and tissue osmotic pressure, both of which tend to filter fluid outward, are just balanced by the plasma osmotic pressure and tissue hydrostatic pressure, which tend to move fluid into the capillary. Of
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course, it is unlikely that this is true for any single capillary, but is probably true for the tissue as a whole.

Now, if the venous pressure is raised, other things being equal, the pressure drop across the capillary is diminished and the mean capillary hydrostatic pressure is increased. If the other Starling forces remain unchanged, there will be a net tendency to filter fluid out of the vessels into the interstitium. This is commonly seen clinically as the development of peripheral edema associated with increased venous pressure of congestive heart failure or with local venous obstruction. This outward movement of fluid would result in concentration of hemoglobin and protein in the plasma remaining behind in the vessels. In addition, in as much as the osmotic gradient of the Gibbs-Donnan equilibrium were maintained across the capillary wall, the fluid leaving the vessels would be slightly hypotonic and the vascular fluid remaining behind would correspondingly become hypertonic. The interested reader is referred to the detailed discussions of Von Diringshofen.\textsuperscript{60}

Therefore, the antidiuresis of positive pressure breathing could be mediated, at least partially, by known osmoreceptors in the hypothalamus. The degree of antidiuresis would depend on the amount of elevation of peripheral venous pressure which would depend on the pattern of respiration, length of inspiratory vs expiratory phase, and the pressures involved. The diuresis of negative pressure breathing could be explained on the basis of decreased venous pressure causing dilution of blood with hypotonic interstitial fluid. The mild, self-limited characteristics of the diuresis might be explained by collapse of the veins entering the thorax, allowing only a small decrease in peripheral venous pressure despite a large decrease in central venous pressure.

Other possible mechanisms by which fluid shifts on respirator therapy might be linked to urine output are related to changing the filtered load of ions and water presented to the renal tubule. Alternatively, "volume receptors," not necessarily in the left atrium, might be responding to the change in intravascular volume. Clinical as well as laboratory studies are certainly necessary to evaluate these phenomena. One further consideration is necessary with respect to the pulmonary circulation. To this point we have mentioned the effect of positive pressure respiration raising peripheral venous pressure and increasing fluid filtration at the level of the peripheral capillary. However, the positive pressure is also applied to the parenchyma of the lung through the tracheobronchial tree. Here the effect on fluid transfer would be the opposite of the peripheral effect in that the increased interstitial tissue pressure would tend to push any interstitial fluid present into the vessels. The precise hydrostatics involved were pointed out by Von Diringshofen in 1948,\textsuperscript{60} However, there is very little free interstitial fluid in the normal lung because the normal osmotic forces tending to pull fluid in are balanced only by the hydrostatic pressure in the pulmonary circuit which is quite low relative to systemic pressure. Therefore, the predominant fluid shifts would take place in the periphery. However, in pulmonary edema from various causes, where significant amounts of fluid are available to be moved into the pulmonary capillaries, this effect may be one by which pulmonary edema is reduced by positive pressure in addition to the effect of keeping blood out of the thoracic cavity and reducing the load on the heart.

Finally, these rapid fluid shifts need to be evaluated in light of recent reports of adverse effects of IPPB treatment on patients with chronic lung disease,\textsuperscript{61} many of whom have elevated hematocrits and in whom acute hemoconcentration could be hazardous.

ACKNOWLEDGMENT: I would like to express deep gratitude to Dr. Arthur DuBois who has collaborated on all of this work, and who has been an invaluable source of inspiration.

REFERENCES


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