Dissociation of Blood Volume and Flow in Regulation of Salt and Water Balance in Burn Patients

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The relationship between effective blood volume and related hormones in burn patients following resuscitation is not well understood. Previous reports have suggested that hormone secretion is altered by a resetting of neural control mechanisms. Serum and urine sodium, plasma renin activity, serum ADH, cardiac index, effective renal plasma flow, and total blood volume were measured in seven burn patients (mean age, total burn size, and postburn day: 32 years, 56%, and 9 days, respectively). The same values (with the exception of cardiac index and blood volume) were measured in 10 control patients (mean age, 24 years). The blood volume of patients was measured by $^{51}$chromium red blood cell (RBC) labeling and compared to normal predicted values based on body surface area and sex. Mean serum sodium and osmolality were 138 mmol/L (millimolar) and 286 mosm/kg, respectively, in both patients and control subjects. Mean ± standard error of the mean total blood volume in the patients was low, 81% ± 4% of predicted values. Cardiac index and renal plasma flow were significantly elevated. Plasma renin activity and antidiuretic hormone (ADH) levels were elevated and altered in the direction expected from blood volume measurements despite the findings of increased blood flow. Dissociation of organ flow and hormonal response suggests that simultaneous direct blood volume measurements are necessary to elucidate factors other than altered neural control settings to explain hormonal changes in the flow phase of injury. Depressed total blood volume appears to promote elevated ADH levels in burn patients following resuscitation. Whether there is an additional role of altered neural control settings remains to be established.

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The views of the authors do not purport to reflect the positions of the Department of the Army and the Department of Defense.

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Factors responsible for sodium and blood volume regulation following injury are not clearly understood. Several authors have interpreted their data to imply that resetting of hormonal control mechanisms occurs following thermal injury and that this is a stress response that is not sodium or volume dependent. Although various studies have examined one or two factors responsible for sodium and volume regulation following thermal injury, no one has studied this system as a whole.

Antidiuretic hormone (ADH) response following thermal injury has been examined recently. Morgan et al. have concluded that ADH levels were elevated after burn and remained so for 7 to 10 days. In addition the increased ADH levels appeared to have little relation to serum osmolality and did not affect urine output. Shirani et al. observed elevated plasma ADH levels in association with hyponatremia in burn patients even beyond the first 10 days. Those results were interpreted as being consistent with the diagnosis of the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH). However in those studies blood or plasma volumes were not measured simultaneously with the measurement of ADH.

The renin-angiotensin-aldosterone axis has been examined following thermal injury. Shirani et al. suggested that the elevated plasma levels of renin activity, angiotensin I, angiotensin II, and aldosterone following thermal injury reflected a resetting of hormonal control and did not depend on an effective plasma volume deficit. No volume measurements were made in that study. In that group of patients, combinations of these hormones remained volume responsive, as verified by saline-loading tests.

Atrial natriuretic factor (ANF), a family of potent natriuretic and diuretic peptides, are present in mammalian cardiac atria. Central hypervolemia and increased blood
pressure have been postulated as factors that promote ANF secretion. An elevation of ANF has been shown to blunt aldosterone response to stimulation by angiotensin II. The effect of thermal injury on plasma ANF levels and how it, in turn, affects salt and water balance has not been described.

To define more precisely the mechanisms that regulate salt and water balance following thermal injury, we assessed plasma levels of ADH, ANF, and the renin-angiotensin-aldosterone axis simultaneously with measurement of blood volume and osmolality in burn patients 5 to 16 days after burn.

Materials and Methods

Ten healthy control subjects (seven men, three women) and seven burn patients (six men, one woman) whose characteristics are detailed in Table 1 were each studied during a 5-hour period, with blood and urine samples collected hourly for determination of electrolytes and creatinine. Controls were allowed to eat nothing by mouth beginning at 00:00 hours on the day of the study while the patients’ enteral feedings were continued but oral intake was held. The patients’ intravenous fluids were administered at a rate to maintain adequate urine output while allowing for an approximate 10% daily loss of the weight gain from initial resuscitation. The rate of fluid administration in the controls was matched to the mean patient hourly intake. Five patients weighed more than the preburn weight, while two weighed less than the preburn weight on the day of study (Table 1). The mean values during the study period were used as data for each patient. After a tracer bolus injection of 131I-hippuran (I-HIP) at the second hour of study; % PBW, % preburn weight.

Results

As expected several hemodynamic variables differed significantly between the two groups in a manner consistent with the hyperdynamic response to injury (Table 2). The patients were tachycardic, with a widened pulse pressure. Flow variables (effective renal plasma flow and CI) were significantly increased in patients (Table 2).
SALT AND WATER BALANCE IN BURNED PATIENTS

TABLE 2. Hemodynamic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>62 ± 6*</td>
<td>119 ± 36</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>83 ± 3</td>
<td>77 ± 3</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>45 ± 3</td>
<td>58 ± 4†</td>
</tr>
<tr>
<td>ERPF (mL/min/1.73 m²)</td>
<td>525 ± 26</td>
<td>774 ± 96‡</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>[norm 2.3–4.1]</td>
<td>7.78 ± 0.52§</td>
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</tbody>
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HR, heart rate; MBP, mean blood pressure; PP, pulse pressure; ERPF, effective renal plasma flow measure by 131I Hippuran; CI, cardiac index.
* Mean ± SEM.
† p < 0.05; ‡ p < 0.01; § p < 0.001.

The patients' RBC volumes measured by 51Chromium-labeled red blood cells were significantly less than predicted. Plasma volumes were 100% of the predicted values based on body surface area, while total blood volumes were 81% of the mean predicted values (Fig. 1). Because the observed/predicted total blood volumes had a wide variance (95% confidence limits of this value range from 70% to 92% for this patient population), patient values were also compared to the laboratory reference normal range for blood volumes based on body weight. Three patients had total blood volume measurements that were within the reference normal range, while four patients (two measured twice) had total blood volumes that were less than the lower value of the normal range (Table 3).

Mean plasma sodium and osmolality were identical for the two groups (Table 4). Urine flow was significantly greater in control subjects, while urine osmolality was significantly greater in the patients, despite similar intravenous fluid administration rates. Free water clearance was 2.43 mL/min/1.73 m² in controls and -1.65 mL/min/1.73 m² in patients. Elevated urinary potassium concentrations and K+/Na+ ratios were noted in the patients in association with slightly lower serum potassium levels and nondepressed urinary sodium values (Table 4).

Hormone values for patients and controls are tabulated in Table 5. AM cortisol levels were significantly greater in patients, as expected, while patient ACTH levels were not elevated. Plasma renin activity, ADH, and atrial natriuretic peptide levels were significantly greater in patients. Plasma aldosterone levels tended to be greater in patients but not significantly so when compared to the control population. Antidiuretic hormone levels were normal for the three patients with normal blood volumes and elevated for the four patients with decreased blood volumes (p = 0.05) (Table 6).

**Discussion**

Altered neural set points controlling the release of ADH and the renin-angiotensin-aldosterone axis have been invoked as an explanation for the elevated levels of these hormones, which are characteristic of the postresuscitative phase of burn care. Previous reports by Soroff et al., Collentine et al., Dolocek, and Shirani et al. have all assumed that the findings of significant sodium excretion and urine flow, hyponatremia in some patients, low or normal plasma osmolality, and elevated blood flow as

**TABLE 4. Serum and Urine Levels**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Patients</th>
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</thead>
<tbody>
<tr>
<td>Plasma Na⁺ (mmol/L)</td>
<td>137.5 ± 0.8*</td>
<td>137.7 ± 1.5</td>
</tr>
<tr>
<td>Urine Na⁺ (mmol/L)</td>
<td>39.1 ± 4.5</td>
<td>70.0 ± 22.4</td>
</tr>
<tr>
<td>Na⁺ excretion (meq/hr/1.73 m²)</td>
<td>11.5 ± 1.0</td>
<td>7.8 ± 3.5</td>
</tr>
<tr>
<td>Plasma K⁺ (mmol/L)</td>
<td>4.52 ± 0.9</td>
<td>3.96 ± 0.12‡</td>
</tr>
<tr>
<td>Urine K⁺ (mmol/L)</td>
<td>8.9 ± 0.9</td>
<td>52.3 ± 6.3§</td>
</tr>
<tr>
<td>Urine K⁺/Na⁺</td>
<td>0.24 ± 0.03</td>
<td>14.3 ± 9.2†</td>
</tr>
<tr>
<td>Plasma OSM (mosm/kg)</td>
<td>286 ± 1</td>
<td>286 ± 6</td>
</tr>
<tr>
<td>Urine OSM (mosm/kg)</td>
<td>150 ± 12</td>
<td>656 ± 45§</td>
</tr>
<tr>
<td>Urine output (mL/hr/1.73 m²)</td>
<td>303 ± 19</td>
<td>87 ± 15§</td>
</tr>
<tr>
<td>FWCL (mL/min/1.73 m²)</td>
<td>2.43 ± 0.3</td>
<td>-1.65 ± 0.15§</td>
</tr>
<tr>
<td>Intake (mL/hr)</td>
<td>250</td>
<td>284 ± 32</td>
</tr>
</tbody>
</table>

FWCL, free water clearance.
* Mean ± SEM.
† p < 0.05; ‡ p < 0.01; § p < 0.001.

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**Discussion**

Altered neural set points controlling the release of ADH and the renin-angiotensin-aldosterone axis have been invoked as an explanation for the elevated levels of these hormones, which are characteristic of the postresuscitative phase of burn care. Previous reports by Soroff et al., Collentine et al., Dolocek, and Shirani et al. have all assumed that the findings of significant sodium excretion and urine flow, hyponatremia in some patients, low or normal plasma osmolality, and elevated blood flow as

![Fig. 1. The percentage of predicted red cell volume (RCV), plasma volume (PV), and total blood volume (TBV) for all patients is depicted. The RCV and TBV differs significantly from predicted values (p < 0.01), while calculated plasma volume was normal.](image-url)
indexed by increased glomerular filtration rates and cardiac output are an indication of normal or increased blood volume. These findings, in combination with less than maximally dilute urine and elevated plasma levels of ADH, have led to the diagnosis of SIADH. The apparent dissociation of blood volume and flow indices documented in our patients indicates that the finding of increased flow may not support the assumption that a volume factor is absent in burn-induced SIADH, especially when plasma ADH and urine osmolality are high, even in the setting of a low plasma tonicity. Thus it is possible that if free water delivery is high enough, low blood volume-induced ADH secretion may promote hyponatremia, as seen in many burn patients. Although we did not test this hypothesis in our patients, the mean 20% decrement in total blood volume would suggest that the elevated levels of plasma ADH are an appropriate response in an attempt to restore blood volume.

Although hypotension and increased serum osmolality, by stimulation of stretch and osmo receptors, respectively, are the most potent stimulators of ADH release, modest decrements in blood volume also may cause appreciable pituitary release of this hormone. A 10% decrease in blood volume has been previously shown to result in a two- to threefold increase in plasma ADH levels. In addition blood volume deficits of 10% to 15% are known to decrease the osmotic threshold for the release of ADH, although the linear relationship between plasma osmolality and plasma ADH levels is maintained. In our patients a 19% blood volume deficit resulted in a 4.5-fold increase in plasma ADH levels. The significantly decreased free water clearance and increased urine osmolality seen in our patients, as compared to the control population, document the expected influence of elevated ADH levels on the kidney.

Elevated plasma renin activity and aldosterone levels have been noted in burn patients during the postresuscitative phase. As in the previously referenced ADH studies, blood volumes were not measured and the findings of elevated creatinine clearance and normal plasma tonicity were used as evidence for at least normal blood volume at the time of study. These findings, in concert with a normal plasma aldosterone decrease after a mild volume stimulus, were interpreted to mean that the renin-angiotensin-aldosterone system remained volume responsive in burn patients but that the elevated level of function occurred because of resetting of control mechanisms. The excess renin release was attributed, at least in part, to excess sympathetic activity, which occurs following burn injury and is also known to increase renin release. In our patients plasma renin activity was significantly elevated compared to the control population. Plasma aldosterone levels, although elevated, were not statistically different from normal. The elevation in PRA in our patients is consistent with the anticipated increase in sympathetic activity in burn patients. It is possible that the one time measurement of fluctuating plasma aldosterone may not have been sufficient to reveal an elevated integral aldosterone level that may have been present in light of the elevated urinary K+/Na+ ratio. Nevertheless the relatively small aldosterone response to plasma renin activity has been described commonly in critically ill patients. Our concurrent finding of increased atrial natriuretic factor levels has been described commonly in critically ill patients. The finding of elevated atrial natriuretic factor levels does not fit entirely with our understanding of the normal stimuli for this cardiac hormone's release. Typically elevations in blood pressure and atrial distension secondary to blood volume excess are the stimuli that result in an increase in ANF release. Neither of these mechanisms were operative in our patients. Recently it has been reported that, in vitro, elevated levels of ADH and angiotensin added to the media with freshly excised rat atria resulted in a significant increase in ANF release. Thus the elevated ADH levels documented in our patients may result in an increased release of ANF. Elevated levels of ANF have been reported following thermal injury and resuscitation. Other investigators have reported a correlation between heart rate and ANF release that is independent of volume. The tachycardia documented in our patients thus may be partially responsible for the elevated levels of plasma renin activity.

Of the threefold increase in plasma ADH documented in our patients indicates that the finding of increased GFR and car- in our patients is consistent with the anticipated increase with a normal plasma aldosterone decrease after a mild

<table>
<thead>
<tr>
<th>Value</th>
<th>Controls</th>
<th>Patients</th>
</tr>
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<tbody>
<tr>
<td>ACTH (pg/mL)</td>
<td>27.6 ± 5.7</td>
<td>13.0 ± 2.2</td>
</tr>
<tr>
<td>Cortisol (g/dL)</td>
<td>10.8 ± 1.1</td>
<td>22.6 ± 2.8*</td>
</tr>
<tr>
<td>PRA (ng/mL/hr)</td>
<td>1.3 ± 0.3</td>
<td>28 ± 8†</td>
</tr>
<tr>
<td>Aldosterone (ng/dL)</td>
<td>4.2 ± 1.4</td>
<td>11.7 ± 5.6</td>
</tr>
<tr>
<td>ADH (pg/mL)</td>
<td>1.2 ± 0.1</td>
<td>5.6 ± 2.5*</td>
</tr>
<tr>
<td>ANF (pg/mL)</td>
<td>76 ± 6</td>
<td>167 ± 34†</td>
</tr>
</tbody>
</table>

* p < 0.05; † p < 0.01; ‡ p < 0.001.

Table 6. Comparison of ADH Levels for Patients with Low and Normal Blood Volumes

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Predicted TBV</td>
<td>75.8 ± 2.8</td>
<td>91.8 ± 2.7†</td>
</tr>
<tr>
<td>ADH level (pg/mL)</td>
<td>7.72 ± 2.5</td>
<td>1.97 ± 0.26*</td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

TBV, total blood volume.

* p = 0.05; † p < 0.01.
evated levels of ANF, although this mechanism has recently been disputed. This, in turn, may have a negative effect on aldosterone secretion. Atrial natriuretic factor appears to decrease aldosterone levels by inhibiting synthesis of this hormone in the adrenal glomerulosa.

Except for the absence of hyponatremia, our patients are remarkably similar to those previously reported. Shirani et al. studied nine burn patients in whom elevated ADH levels were documented. Those patients had hypertonic urine with a urine output of 2.7 L/day, a mean urine osmolality of 500 mosm/kg, and a mean urine sodium of 80 mmol/L (millimolar). Those values are quite comparable to those of the present study patients, who had a mean urine flow of 2.3 L/day, a urine osmolality of 656 mosm/kg, and a mean urine sodium of 70 mmol/L. The mean plasma ADH level of 6.8 pg/mL reported previously was very close to the levels documented in our patients (5.6 pg/mL). The only differences between the two patient populations were the serum sodium and osmolality: the former was 138 mmol/L in our patients compared to 130 mmol/L in the earlier study. The mean plasma osmolality of the patients in the earlier study was lower than in the patients in the present study (276 versus 286 mosm/kg). The serum sodium of 130 mmol/L was interpreted as being consistent with a free water excess indicative of increased blood volume. However those laboratory findings are also consistent with an intravascular volume deficit in association with a large intravascular sodium deficit, which may occur with excessive third space fluid losses and an osmotic diuresis prompted by urea; both circumstances occur following thermal injury.

It appears that the central problem in our cohort of patients involves mobilization of the edema fluid to the intravascular space. Five of the seven patients' weights were markedly more than their preburn weights on the day of study. In addition, because the total 24-hour intake surrounding the study period exceeded the estimated wound evaporative loss by at least maintenance fluid requirements in each patient, they were all considered to have received adequate replacement of ongoing fluid losses. Fluid administration rates were dictated by the patients' urinary output and serum sodium. In their management, decreasing urine outputs and increasing serum sodium levels were interpreted to be consistent with a contracting blood volume and resulted in an increase in the rate of relatively hypotonic intravenous fluid administration. Failure to adjust the rate was normally followed by an increase in serum BUN and creatinine levels and other signs of prerenal azotemia. After resuscitation shifts of water from the interstitial to the intravascular space normally occur secondary to differences in oncotic pressure, which normally favors water movement from the interstitial to intravascular space. Following burn injury and resuscitation, the intravascular colloid osmotic pressure is low, thus decreasing the net force that determines water movement. Whether artificially increasing plasma colloid osmotic pressure during this time period would improve edema mobilization cannot be answered from these data.

Findings of increased blood flow associated with a hyperdynamic circulation (elevated cardiac output) and increased organ flow (increased effective renal plasma flow, increased wound blood flow) have previously been interpreted to indicate a normal or supranormal blood volume. Our findings of increased flow in conjunction with modest decrements in total blood volume appear to be paradoxical. The reasons for the dissociation of flow and volume may lie in the neural peripheral vascular response to injury. The effects of the markedly elevated beta adrenergic activity, which occurs following injury in association with what amounts to an effective arterial-venous shunt in the wound, may be enough to counterbalance the measured decrements in blood volume. Thus the decrease in peripheral vascular resistance typical of the flow phase of injury may serve to decrease afterload and raise the effective arterial capacity, which is underfilled at sites of hormone control.

The interpretation of blood volume measurements is complicated by various factors. First there is a difficulty in obtaining simultaneous measurements of RBC volume and plasma volume. The use of chromium-labeled RBCs represents a well-standardized and accepted method for the measurement of RBC volume. To obtain plasma volume estimates, one may either measure the space directly by the use of radiolabeled albumin or estimate it by the use of RBC volume and hematocrit levels. Use of labeled albumin in critically ill patients significantly overestimates plasma volumes due to the expanded volume of distribution for this molecule. Because of this plasma and total blood volumes in burned patients are usually estimated from the RBC volume and hematocrit measurements. Normal total blood volume has been reported to range from 60 to 80 mL/kg for men and 55 to 75 mL/kg for women. However, for comparison, we first expressed our measured patient values each as a percentage of the expected normal volume for that patient estimated from BSA according to previously reported regressions. As a group our patients had a total blood volume that was 81% of the predicted value. We then compared each individual patient to the reference range. Three patients had blood volumes within the normal reference range, while the remaining four (two measured twice) had blood volumes that were less than the expected range. The three patients with normal blood volumes had ADH levels that were not different from the normal controls. The patients with low blood volumes had elevated levels of ADH, the expected response based on blood volume.

It appears from our data that cardiac output and renal
DISCUSSION

Dr. D. Wilmore (Editor, Massachusetts): The group at the US Army Institute of Surgical Research have had a long-term interest in fluid regulation and water and sodium balance in burn patients. This is another interesting and provocative paper that is a continuation of work in this area that has originated from this Institute.

There are a number of things that could be added to the paper that would help us understand accounts of both studies performed with burn patients: Na+/volume-responsive but not Na+/volume-responsive. For example, it would be quite helpful if it could be included in the manuscript.

The US Army Institute of Surgical Research reported in an earlier paper that patients do not have full colonization of burn wounds, and that over time colonization occurs. Could it be that the bacteria on the wound's surface elicits factors that are vasoactive and over time could change blood volume regulation? We need to know more about the microbiology of these particular patients.

Of course the crux of the contention is that we can measure blood volume using this chromium label technique, and it is a very well-established technique, but it would be good to know what the variation in blood volume measurement was if the technique were used in normal individuals and what the reproducibility of the measurement was with successive determinations from week to week measurements. Such data would give us a good deal of confidence concerning these measurements.

Moreover it may well be that in expressing blood volume, we should express it in terms other than kilogram body weight or body surface area. As you recall these patients were edematous, and we really do not know their "true" or actual body weight. Would it be better to measure total body water and express blood volume as a unit of lean body mass or to...
use bioclectrical impedance to express blood volume as a unit of lean body mass, correcting or adjusting for edema? Have the authors given blood to these patients and seen alterations in their vasoactive or salt-retaining hormones as blood is infused? It seems to me that that would be a much more dynamic type of functional measurement if it could be performed.

Finally in this modern age of biotechnology, could this whole presumed deficit be resolved by giving recombinant erythropoietin to stimulate blood volume mass, which is low in these patients? This is an interesting and indeed a provocative paper, and as we learn more about the regulation of blood and fluid volume, I am sure that this new information will help us take better care of our critically ill patients.

DR. DONALD GANN (Baltimore, Maryland): I think this is a very important study that was very carefully executed. Part of what I have to say will echo some of Dr. Wilmore's comments, but I have a somewhat different perspective.

I also am grateful to the authors for sending me the manuscript, because it demands very careful examination. It is very meaty indeed. I also am particularly grateful for this study, because when Dr. Shirani first suggested that inappropriate antidiuretic hormone (ADH) secretion was a feature of the burn patient, I discussed the paper and suggested that in this setting it actually could be attributable to the volume. Thus this study demonstrates a remarkable, if not astounding, paradox. It really flies in the face of traditional wisdom previously published by these authors. They showed that given a clear choice between maintaining volume and main-

demonstrates a remarkable, if not astounding, paradox. It really flies Leaf and Bartter then, in a brilliant series of experiments in humans, as in the patients? The control subjects excreted in excess of 7 L of water could stand.

It seems to me that that would be a much more dynamic type of functional measurement if it could be performed.

Those observations that I have mentioned suggest to me several questions, perhaps the most important one of which is that mentioned by Dr. Wilmore: namely, what was the intake in the normal subjects as well as in the patients? The normal and injured subjects-in that case, Harvard medical students who were presumed normal—could drink themselves into water intoxication, implying persistent elevation of vasopressin.

In the early 1960s, Hastings, Wright, and I showed that in postoperative patients, the administration of saline could suppress vasopressin sufficiently to produce free water. That, in a less severely injured population, is the answer to Dr. Wilmore's question: namely, you can indeed turn off those hormones. Cross and others from my own laboratory, in a paper published about a year ago in the *Annals* showed, in a group of postoperative cardiac surgical patients the counter-regulatory hormones could be suppressed by volume loading. Dr. Vaughan from Dr. Pruitt's group and others reported consistent elevation in cortisol in burn patients. Have you changed your clinical practice since the prior publication of your group and others reported consistent elevation in cortisol in burn patients? Have you changed your clinical practice since the prior publication of your group and others reported consistent elevation in cortisol in burn patients?
taining osmolality by ADH increases, the body would always prefer to retain sodium. Even Volney's idea had to be a little bit changed.

Also there are neural and other sensory pathways involved. David Hume, before he became a pioneer transplanter, was working in this field. We did a lot of work together on this subject. Either anesthesia is a strong stimulus to ADH, as is morphine analgesia. A bleed with prompt retransfusion immediately stimulates ADH. Finally we discovered that the first few milliliters that were lost (even the venipuncture itself) would stimulate ADH secretion. High altitude and low PO₂ will increase ADH secretion. In fact some of the headache that is seen in people at high altitude is due to excess loading of water and salt in the body and a disproportionate representation in the cerebral spinal fluid.

So we have to be very, very careful before we call ADH "inappropriate." We have got to be careful before we assign it to some one cause such as tonicity or volume, when so many things can stimulate this water-saving survival response.

In young men going to bed at night, there is a strong antidiuresis. Sadly this is not seen in older men. Just why old men lose this God-given ability to concentrate their urine and lower their voiding volume at night, I have never been able to figure out. But it has only bothered me for a few years, so there is still hope—or is there?

Finally I would like to congratulate Basil and Dr. Mason and the team at Brooke. For some years I was a member of the Surgeon General's committee that inspected that unit, and our inspections were really quite long, because I wanted to learn everything that I could while I was there! You have been leaders in burn therapy for all these years, and so far as I know, care for the biggest load of severely burned patients in the United States. That has never dimmed your interest in discovering new things that would be helpful to everybody.

So I would like to congratulate you. But take it easy on that "inappropriate" business.

**DR. W. G. CIOFFI (Closing discussion):** Dr. Wilmore, your first question was about the standardization of the normal volunteers. They were admitted 1 day before study and were allowed food until 6 hours before their study. They were started on IV fluids (D5 in 1/4 NS) at rates that we hoped would match the IV intake in the patients, and this resulted in some of the discrepancies noted by Dr. Herndon in terms of urine output and sodium excretion.

The patients were receiving maintenance fluids, as well as hypotonic solutions to replace their estimated evaporative losses. This allowed approximately a 10% weight loss per day of their initial weight gain.

The patients were not infected. All patients were receiving enteral feedings at the time of the study, and their fluid management was as outlined. I do not have data on the bacterial density on their wounds; no patient, however, had a wound infection before or during the study.

We did not do the chromium label study on the normal volunteers. We do have data on normals, however, which are from our Nuclear Medicine Department, which performed this part of the study, and they have consistently shown patients who should be expected to be in the normal range to be so.

Your recommendation for expressing blood volume as an index of lean body mass is a good one, but we do not have the data available to do that.

The value of erythropoietin in these patients is not clear. Several papers presented last week at the American Burn Association demonstrated already high endogenous circulating levels of erythropoietin after injury. Whether or not the addition of exogenous erythropoietin will help to restore the red cell volume to normal is not clear.

Dr. Cannon, I think I have answered your question as far as the intakes in the normal controls as compared with the patients. I agree that the deficit we saw in total blood volume may well be responsible for the prolonged elevation to cortisol levels.

You asked about what we could do to assess the adequacy of fluid replacement after resuscitation in patients. If indeed cardiac output or urine output are not going to be reliable indicators. I think we do have several things that we could follow in our second study, which we plan to undertake soon, in which we will attempt to volume load these patients, either with red cells or with saline to a normal blood volume, and we will look at cardiac output to see if it will decrease, as well as looking at 

Dr. Cannon, you noted the paradox of our increased atrial natriuretic factor levels. Typically atrial distension has always been thought to be a stimulus for this hormone's release, but there are also significant data in the literature suggesting that elevated sympathetic tone, tachycardia, elevated vasopressin, and aldosterone levels also lead to hormone secretion. It also should be noted that atrial natriuretic factor (ANF) also serves to down-regulate plasma renin activity, angiotensin, and aldosterone, and it may be the elevated ANF levels that were responsible for a lack of a consistent finding of elevated aldosterone.

We did not measure plasma volume. It has been done before. We chose not to do that, because we believe there is no reliable marker to use in these patients at a time when albumin flux is continuing across into the wound, and thus radiolabeled albumin or similar markers would not give us an accurate assessment of plasma volume.

It is true that anemic patients with decreased red cell volumes increase their plasma volume to bring their blood volume back to normal. But that happens over a prolonged time and most notably in chronic renal failure patients. That is a chronic effect, and I wouldn't expect it to occur over postburn days 6, 7, or 8.

Our albumin levels were 2.2 or less in the patients. We did not measure COP levels.

There was not a good correlation between wedge pressure readings and blood volume. The mean pulmonary artery wedge pressure (PAWP) was 9. Our clinical practice has not changed since Dr. Shirani's study of several years ago.

As far as the liberal use of red cells for volume replacement, I would recommend that over the use of plasma volume expanders. We must take into consideration a report that we published several years ago, however, which did show a relationship between red cell transfusion and subsequent risk of infection, and thus we have to consider that before charging ahead and infusing many units of red cells into these patients.

Dr. Moore, I would like to thank you for your comments and couldn't agree more that the term "inappropriate" is probably inappropriate in this meeting.