Water immersion and the kidney: implications for volume regulation

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Epstein M. Water immersion and the kidney: implications for volume regulation. Undersea Biomed Res 1984; 11(2):113–121.—Studies from this laboratory have demonstrated that head-out immersion in isothermic water causes a cephalad redistribution of blood volume. The resultant central hypervolemia induces a marked natriuresis and diuresis and suppression of plasma renin activity, plasma aldosterone, and plasma arginine vasopressin. All of these changes are thought to be attributable to stimulation of cardiopulmonary receptors. Immersion also produces an augmentation of prostaglandin E (PGE) excretion, which reflects increased renal PGE synthesis. The ability of immersion to induce a prompt and profound central hypervolemia, without concomitant alterations in plasma composition, indicates that immersion might be a preferred investigative tool for assessing the effects of volume expansion on renal function and hormonal responsiveness in both normal individuals and patients with edematous disorders. In addition, this model constitutes an appropriate tool for simulating weightlessness.

water immersion
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Water immersion to the neck (NI) has long been known to produce a marked diuresis (1, 2). Several lines of evidence have suggested that this effect is mediated by a redistribution of blood volume with a relative increase in central blood volume (1–4). The past decade has witnessed the characterization of many of the hemodynamic alterations of immersion and also of the delineation of the myriad effects of immersion on renal function and renin-aldosterone responsiveness (1, 5). Studies of the efferent limb of the immersion model have demonstrated that NI produces a marked natriuresis, kaliuresis, and diuresis and a suppression of the renin-aldosterone system. In the following sections the salient renal and hormonal effects of NI are examined.

Renal sodium handling

We characterized the natriuretic response during various sodium intakes and various depths of immersion (6–9). Studies of mildly sodium depleted subjects (dietary intake of 10 meq/day)
disclosed that the absolute increase in sodium excretion was exceedingly small (< 7 meq/6 h), reflecting the constraints imposed by the sodium-depleted and volume-contrasted state of the subjects (6). In a subsequent study carried out with a sodium intake more nearly approximating that of the normal diet (150 meq/day) (8), sodium-replete normal subjects demonstrated an earlier (Hour 1 vs. Hour 4) and more profound (72 meq/6 h vs. 7 meq/6 h) natriuresis than during sodium depletion (Fig. 1). It was demonstrated that when the depth of immersion was varied (9), water immersion to the waist did not induce a natriuresis in either sodium-depleted or sodium-replete subjects, presumably because of a lessened pressure gradient and thus a lessened central hypervolemia.

**Correlation of degree of central volume expansion with magnitude of natriuresis**

In view of the postulate that the natriuresis of immersion is attributable to an increase in central blood volume with a resultant stimulation of mechanoreceptors (2, 10), a correlation

![Graph showing correlation](image)

**Fig. 1.** Comparison of effects of immersion on rate of sodium excretion ($U_{NaV}$) in subjects in balance on low-sodium (top) and high-sodium (bottom) diets. *Shaded areas* represent mean ± SE for control studies. A significant increase in $U_{NaV}$ occurs within the initial hour in sodium-replete subjects, but is delayed to the 4th h in subjects ingesting a sodium-restricted diet. Data for sodium-restricted subjects from Epstein and Sarruta (6) and for sodium-replete subjects from Epstein et al. (8). [Reproduced with permission from Epstein et al. (1).]
between the degree of engorgement of the central circulation and the magnitude of the natriuresis might be anticipated. This indeed appears to be the case. Previous studies have demonstrated that recumbency is associated with a translocation of approximately 400-500 ml of fluid into the central circulation. In contrast, head-out water immersion in the seated posture is associated with a greater degree of central engorgement (increase in central blood volume of 700 ml) (3). Similarly, the calculated increase in cardiac volume during immersion in the upright posture (180 ml) exceeds that associated with recumbency (100 ml) (11). It is not altogether surprising, therefore, that the magnitude of the natriuresis during seated immersion exceeds that during recumbency (8).

**Dissociation of natriuresis from diuresis**

Although immersion is usually associated with both a diuresis and a natriuresis, the two events may be dissociated. Thus overnight fluid restriction abolished the diuresis of immersion without attenuating the natriuresis (12). Similarly the administration of aqueous vasopressin to hydrated normal subjects undergoing immersion abolished the diuresis, whereas the natriuresis remained intact (13). Finally, the differences in the temporal profile of the diuresis and natriuresis of immersion should be reemphasized. The diuresis of immersion is usually manifest by Hour 1 or 2. In contrast, the natriuresis is progressive and usually peaks by Hour 4 or 5. Together, these observations suggest the presence of separate mechanisms for the diuretic and natriuretic responses.

The demonstration of a highly significant increase in the fractional excretion of sodium during immersion indicates that the natriuresis is attributable primarily to an increased tubular rejection of sodium rather than to alterations in the filtered sodium load. The mechanism or mechanisms mediating the natriuresis are multifactorial and include aldosterone suppression, a humoral natriuretic factor, alterations in the release of renal prostaglandins, and possibly a decrease in sympathetic nervous activity (Fig. 2).

**Characterization of the renin-angiotensin-aldosterone system**

We have also characterized the changes of the renin-angiotensin-aldosterone axis during water immersion (6, 14). Blood was collected serially at 30-min intervals for plasma renin activity (PRA) and plasma aldosterone (PA) determinations (14). Immersion resulted in a progressive suppression of PRA beginning within 30 min of study. By 210 min PRA was suppressed maximally to 38% of the prestudy value. Cessation of immersion was associated with a prompt return of PRA toward prestudy values as early as 30 min of recovery.

The return of PRA to prestudy values rather than to levels greater than the prestudy values merits comment. On initial consideration, an overshoot to levels in excess of the prestudy levels would have been anticipated because of the progressive volume contraction of immersion. Nevertheless, careful examination of the conditions during immersion in the sodium-depleted state indicates that the absolute degree of volume contraction induced by immersion per se was minimal (7 meq/6 h vs. 72 meq/6 h for sodium-replete normal subjects). One may speculate that if the kinetics of PRA were assessed in the sodium-replete state, the degree of volume contraction induced during immersion would have resulted in an overshoot during the recovery hour.

We have also characterized the temporal profile of the suppression of aldosterone by direct measurement of PA (14). Studies in a group of normal subjects during dietary sodium restriction disclosed a significant suppression of PA beginning as early as 60 min of immersion, with
maximal suppression to 34% of the prestudy value by 210 min of immersion. Cessation of immersion was associated with a prompt return to prestudy values.

The suppression of PRA and PA induced by NI was similar in both magnitude and temporal profile to that observed during acute saline administration (2 liters/120 min) (15). This observation is consistent with the formulation that the suppression of PA is mediated primarily by a suppression of the renin-angiotensin system.

Additional studies were undertaken to assess the specificity of the immersion-induced suppression of aldosterone. Determinations of both aldosterone and 17-hydroxycorticosteroid (17-OHCS) release demonstrated that plasma 17-OHCS levels were not altered at a time when PRA and aldosterone were suppressed. These results suggest that the suppression of the renin-aldosterone system is selective and not a manifestation of a generalized decrease in adrenocortical activity.

Antidiuretic hormone

Although antidiuretic hormone (ADH) suppression during water immersion was documented only within the past decade, considerable evidence had suggested the possibility of such a change. Many investigators reported an increase in solute-free water clearance during head-
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out water immersion. In addition, the administration of vasopressin abolishes the diuresis of immersion (2, 13).

The development by Miller and Moses (16) of a sensitive and specific radioimmunoassay for urinary ADH permitted the assessment, by direct measurement, of the effect of immersion on ADH release. Urinary ADH excretion was determined in 10 normal subjects undergoing immersion after 14 h of overnight water restriction (12). Immersion resulted in a progressive decrease in ADH excretion from 80 ± 7 to 37 ± 6 μU/min. Furthermore, cessation of immersion was associated with a marked rebound, with ADH excretion increasing from 37 to 177 μU/min during the recovery hour (12).

Recent studies have suggested that the interpretation of studies of arginine vasopressin (AVP) that rely on urinary AVP excretion may be confounded by several factors, including changes in solute excretion. Thus, changes in AVP excretion may not necessarily reflect changes in AVP secretion or plasma AVP levels.

The current availability of a precise and highly reproducible radioimmunoassay for plasma AVP prompted us to undertake a subsequent study in order to characterize the effects of immersion-induced acute osmotic volume expansion on plasma AVP in normal man (17). Normal subjects were studied after 14 h of dehydration on two occasions: control, and during 4 h of NI. Blood was obtained every 30 min for AVP; AVP was unaltered during the control period. In contrast, there was a prompt and sustained suppression of AVP throughout NI (P < 0.05 vs. control). There were no concomitant changes in plasma osmolality. Since the changes in AVP occurred consequent to central volume expansion but in the absence of concomitant changes in plasma composition, these data support the concept that acute osmotic central volume expansion in humans results in a suppression of plasma AVP (17).

Renal prostaglandins

Additional studies demonstrated a profound effect of NI on endogenous prostaglandin synthesis. Studies in sodium-replete subjects disclosed that immersion is associated with a progressive increment in renal prostaglandin E (PGE) excretion, reaching a peak by Hour 2 of immersion (18). Cessation of immersion led to a prompt decrement in PGE excretion during the recovery hour to prestudy levels. Subsequent studies after indomethacin administration (50 mg every 6 h × 5) resulted in an attenuation of but did not prevent the immersion-induced increment in PGE (18). Thus although indomethacin pretreatment led to a decrease in basal PGE excretion of greater than 50%, there was still a significant, albeit smaller, rise in PGE excretion during the subsequent immersion study. When five of these subjects were restudied after dietary sodium restriction, a similar pattern was noted and the attenuation of the immersion-induced increment in PGE was more pronounced after indomethacin administration (18).

In contrast to previous reports suggesting a parallelism between renal prostaglandin levels and renin-aldosterone, immersion resulted in a dissociation of these two hormonal systems, with a suppression of plasma renin activity at a time when PGE excretion was enhanced (19).

Role of a humoral natriuretic factor

Finally, evidence has been adduced suggesting that water immersion to the neck (NI) stimulates the release of a circulating natriuretic factor that may contribute to the encountered natriuresis. Within the past several years increasing evidence has accumulated suggesting the presence of a circulating natriuretic hormone that normally depresses renal tubular sodium reabsorption in response to volume expansion of extracellular fluid (20). We undertook,
therefore, to determine whether the natriuresis of NI is associated with increased activity of a natriuretic factor (21). Urine collected during both seated control and NI studies was fractionated, and the fractions were tested in the rat assay preparation using animals with a single remnant kidney (22). With the control fractions there was no significant change in sodium excretion. In contrast, the fractions from the NI study resulted in significant increments in both rate of sodium excretion \((U_{Na^+}\text{V})\) and fractional excretion of sodium \((\text{FE}_{Na^+})\). Thus, there is good evidence that the natriuresis of NI is associated with increased activity of natriuretic hormone (22).

**Kallikrein-kinin system**

The interdependence of prostaglandins and other vasoactive hormonal systems dictates that consideration should be given to the effects of immersion on the kallikrein-kinin system. Before reviewing the results of our studies, a brief consideration of the experimental difficulties in assessing the kallikrein-kinin system is appropriate.

Previous studies have attempted to examine the response of urinary kallikrein to volume expansion using a number of manipulations, including intravenous saline administration and intravenous water loading (23, 24). Such attempts at extracellular fluid volume expansion (ECVE) with exogenous volume expanders are accompanied by concomitant alterations in plasma composition that might confound the interpretation of the resultant alterations in urinary kallikrein activity. Furthermore, ECVE with exogenous volume expanders produces an increase in urine flow rate in addition to a natriuresis. Since increases in urine flow rate per se have been reported to be associated with increased urinary kallikrein activity (23, 24), it is difficult to ascertain if the observed changes in urinary kallikrein activity are indeed attributable to alterations in ECVE. The successful characterization of the water immersion model (NI), and the demonstration that it induces central volume expansion without the effects on plasma composition seen with exogenous loading (1, 5), commended its utilization in a recent investigation. We studied normal subjects after 11 h of dehydration on two occasions: control and during 4 h of NI. Urinary sodium, potassium, and kallikrein excretion were measured hourly. Water immersion was associated with a marked increase in urinary sodium excretion [from 70 ± 15 to 206 ± 18 (SE) µeq/min; \(P < 0.005\)]. Concomitantly, urinary kallikrein excretion was unchanged.

The results of our study demonstrated clearly that acute central volume expansion in normal man failed to alter kallikrein excretion despite the concomitant induction of a profound natriuresis. The possibility must be considered that effects related to the experimental design, other than redistribution of blood volume, might have explained the absence of a change in urinary kallikrein. Since it has been suggested that hypertension can influence kallikrein excretion (25), we studied only normotensive subjects. Furthermore, since acute volume expansive manipulations, such as saline administration, are associated with an increase in urine flow as well as a natriuresis, and since it has been previously noted that kallikrein excretion may be related primarily to urinary volume (24, 26), we modified our experimental protocol to control for this variable. Previous studies from our laboratory have demonstrated that it is possible to dissociate the natriuretic and diuretic response of immersion by modifying the state of hydration of the subject before immersion. Thus we have previously reported that the immersion-induced volume stimulus in hydropenic subjects results in a profound natriuresis that is indistinguishable from that noted in hydrated subjects despite a marked attenuation or abolition of the diuretic response (1, 12). Thus, in the present study, the subjects underwent both control and immersion studies after 11 h of fluid restriction in order to assess the relation between sodium and kallikrein
excretion without the confounding effect of concomitant changes in urinary volume. Our observations, therefore, must truly represent the absence of augmented kallikrein excretion in response to water immersion.

**Plasma catecholamines**

Because stimulation of left atrial and/or cardiopulmonary receptors in experimental animals results in a diminution of autonomic nervous system activity, it might be anticipated that maneuvers that augment central blood volume such as water immersion might decrease plasma catecholamine levels and that such alterations may participate in the encountered changes in renal function. Although there have been two previous attempts to examine the response of catecholamines during water immersion (27, 28), methodological considerations and divergent observations have precluded firm conclusions regarding the effect of immersion on catecholamines. We therefore recently designed a study utilizing more updated methodology to determine whether NI alters plasma catecholamines in normal humans (29). Eight normal subjects were studied on two occasions: during a seated control study; and during 4 h of NI. Norepinephrine and epinephrine levels, determined by radioenzymatic assay, were measured hourly. Despite the induction of a marked natriuresis and diuresis indicating hemodynamically significant central hypervolemia, NI failed to alter plasma norepinephrine or epinephrine levels compared with those of either control or the corresponding prestudy 1.5 h. Furthermore, the diuresis and natriuresis varied independently of norepinephrine. Our findings suggest that the response of the sympathetic nervous system to acute volume alteration may differ from the reported response to chronic volume expansion (29).

**CONCLUSIONS**

The studies reported here indicate renewed interest in the physiology of immersion. In the last several years several laboratories have succeeded in delineating the circulatory, renal, and endocrine changes induced by water immersion in man. These studies have demonstrated that immersion in the seated posture results in a redistribution of blood volume with a relative central hypervolemia. Consequently, profound alterations in fluid and electrolyte homeostasis ensue, including a marked natriuresis, kaliuresis, and diuresis as well as a suppression of the renin-aldosterone system and ADH release. Concomitantly, renal prostaglandin release is stimulated.

Although the delineation of the immersion model is of great physiological interest, it must be underscored that the implications of this characterization transcend such considerations. Thus the characterization of the effects of immersion has facilitated its application to studies of disease states characterized by deranged volume homeostasis, such as advanced liver disease (30, 31). Furthermore, the numerous similarities between water immersion and the renal and cardiovascular effects that attend manned spaceflight commended the use of water immersion as an experimental analogue of weightlessness (32).

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arginine plasmaticque. Il est d'avis que tous ces changements sont attribuables à la stimulation des récepteurs cardiopulmonaires. L’immersion produit également une augmentation de l'excrétion de prostaglandines E (PGE), laquelle réflète une synthèse rénale accrue de PGE. L’abilité de l’immersion à induire une synthèse rénale accrue de PGE. L’abilité de l’immersion à induire une hypervolémie centrale prompte et prononcée, sans modification concomitante dans la composition plasmaticque, indique que l’immersion peut être un moyen d’investigation préféré pour évaluer les effets d’une expansion de la volémie sur la fonction rénale et la sensibilité hormonale et chez les individus normaux et les patients avec des troubles oedémateux. De plus, ce modèle constitue un moyen approprié pour simuler l’apesanteur.

immersion dans l’eau
hypervolémie centrale
prostaglandines rénales

natriurèse
diurèse

REFERENCES
