THE USE OF water immersion as a therapeutic agent dates back to man's earliest days. The writings of all the ancient civilizations, Egyptian, Hebrew, Greek, Persian, Hindu, and Chinese, refer to the healing properties of water immersion. During the subsequent 3,000 years "hydrotherapy" has passed through various phases of fashion and popularity. During the past 15 years, water immersion has become more widely used as a means of simulating weightlessness. Despite its long history, the cardiovascular and renal physiology of immersion has remained undefined to a great extent, and its exploitation as an investigative tool in clinical medicine has been unrealized.

Over a century ago Hartshorne suggested that the heart possessed volume receptors capable of sensing the fullness of the blood stream induced by water immersion. The concept that water immersion constituted a means of acutely redistributing blood volume, with a resultant increase in central blood volume, was largely ignored during the subsequent 100 years. Largely through the influence of Gauer et al., the model of water immersion has been reintroduced to medicine. During the past decade studies by several groups of investigators have addressed themselves to various aspects of immersion. The delineation of the immersion model and its recent successful application to the study of volume homeostasis, as well as its utilization as an investigative tool for studying renal physiology in man, has prompted this review.

I. Elucidation of the "Afferent" Limb of the Immersion Model

Water immersion to the neck has been shown repeatedly to produce a profound diuresis. Several lines of evidence have suggested that these effects are mediated by a redistribution of blood volume with a relative increase in central blood volume. Although pressure measurements and determinations of central hemodynamics were reported, the fact that these early studies were carried out using whole body immersion with pressure-breathing equipment rendered them difficult to interpret. Depending on the pressure used, positive-pressure breathing can abolish the circulatory, renal, and hormonal effects of immersion. Recently, however, studies by Arborelius and co-workers have demonstrated that following the initiation of head-out immersion, there is an acute increase in central blood volume of 700 ml, with a concomitant increase in central venous pressure from 3 to 15 mm Hg. Mean cardiac output increases by 32% and mean stroke volume by 35%. Both right atrial and pulmonary arterial transmural pressure gradients increase, while systemic vascular resistance decreases. Plethysmographic determinations of peripheral venous tone revealed a prompt decline in the volume elasticity coefficient (E') from 16.6 to 13.5 mm Hg/ml per 100 g of tissue with a subsequent gradual decline to 11.8

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\*The volume elasticity coefficient (E') is a measure of venous tone determined at an intravenous pressure of 15 mm Hg. During venous occlusion plethysmography, forearm volume is measured with a mercury strain gauge and venous pressure is recorded simultaneously in a skin vein in the distal third of the forearm.

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... If the blood be thus driven (by the bath) from the external and internal parts, what becomes of the blood? The heart and great vessels, it would seem, must be burdened. Such is a degree the case; and it is perhaps the stimulus of this fullness and distention or its action on the elasticity of those great vessels and the heart that constitutes the reaction (which leads forth the urine in abundant effusion). Such overloading of the heart and great organs would be dangerous in every case if the volume of blood remained the same. —Henry Hartshorne, 1847

— Henry Hartshorne, 1847
after 3 hours of immersion. Although E1, increased following cessation of immersion, it did not return to pre-study levels during the recovery hour. Lange et al. used a biplane roentgenometric technique and calculated that the initiation of immersion in upright normal subjects results acutely in a mean increase in heart volume of 180 ± 62 ml. Examination of the roentgenograms during immersion suggested that a major component of this increase in heart volume is localized in the atria. More recently, Begin et al. have studied central hemodynamics serially during a 4-hour immersion period using an acetylene rebreathing method. This study confirmed the 25–36% increment in cardiac index previously noted to occur acutely during immersion and demonstrated that this increment was sustained throughout the period of study. Pulmonary tissue plus capillary blood volume (VTPC) was unchanged throughout the immersion study. Because an increase in VTPC has been described as a sensitive indicator of mild to moderate expansion of lung water, these findings suggest that the central vascular engorgement induced by water immersion is directed primarily to the larger pulmonary vessels and intracardiac chambers, with only a small quantity of redistributed blood being directed into the pulmonary capillaries. Gauer et al. have proposed that this redistribution is mediated primarily by an immersion-induced hydrostatic pressure gradient acting on the vascular columns of the body. Since the pressure exerted on body surfaces increases by 22.4 mm Hg for each foot of water depth, the net effect of this gradient would be to force blood from the vessels of the lower extremities with the result that more blood returns to occupy the heart and intrathoracic vasculature. Additional support for this hypothesis recently has been provided by Epstein et al., who attempted to alter the gradient by varying the conditions of immersion. In one set of experiments these workers examined this postulate by studying renal sodium handling during immersion in supine subjects, a condition which would tend to minimize this gradient. Subjects were studied during a control period and during water immersion to the neck under identical conditions of diet and timing. Although assumption of the recumbent position was associated with a gradual increase in sodium excretion, the resultant increase did not differ from that following the assumption of recumbency in the absence of immersion (control). Since immersion in the supine posture tends to minimize this hydrostatic pressure gradient effect, these results are consistent with Gauer's postulate. In an attempt to examine this hypothesis further, normal subjects were studied serially during immersion at varying depths. It was anticipated that increasing the depth of immersion would increase the hydrostatic pressure gradient acting on the vascular beds of the lower extremities and body trunk, and thus enhance the rate of sodium excretion during immersion. Although immersion to the level of the midstchen resulted in a significant increase in sodium excretion, as compared to both control and waist immersion, immersion to the neck resulted in a further increase in sodium excretion. These data lend additional support to the hypothesis that an immersion-induced hydrostatic pressure gradient participates to a great extent in mediating the immersion-induced redistribution of circulating blood volume. In addition to these findings, it is probable that other mechanisms including a negative-pressure breathing effect and a redistribution of fluid between body fluid compartments may interact in an additive manner to induce the encountered redistribution.

NEGATIVE-PRESSURE BREATHING EFFECT

During immersion, a mean hydrostatic pressure force of approximately 20 cm of water is exerted on the thoracic wall and abdomen, in addition to atmospheric air pressure. However, the air pressure surrounding the subject's unimmersed head and neck is only 1 atm, and this pressure is transmitted throughout the airways into the alveolar spaces of the lung. The resultant imbalance between the pressure of the air in the alveolar spaces and the greater pressure exerted against the chest wall creates a condition of negative-pressure breathing. Since negative-pressure breathing per se can induce a natriuresis and diuresis (see Section VI), this effect may contribute to the natriuresis.

REDEMPTION OF BODY FLUID COMPARTMENTS

Davis and DuBois have speculated that during immersion there is a shift of fluid from the interstitial compartment to the plasma compartment of the extracellular fluid compartment. Crane and Harris reported a decrease in peripheral hematocrit during immersion, approximating 2.7–2.9 vol %, and suggested that these changes reflected an increase in plasma volume during immersion approximating 430 ml. These authors speculated further that immersion causes the transfer of interstitial (and possibly some intracellular) water into the intravascular space. The findings of Behn et al. and Kaiser et al. mitigate against such a possibility. These authors demonstrated a small but significant increase in hematocrit (3.1 vol % and 2.6 vol %, respectively) after 8 hours of water immersion in the supine posture. Behn calculated a 15 ± 3% (SD) decrease in plasma volume in slightly dehydrated normal subjects that exceeded the decrement anticipated if all fluid compartments were decreased proportionally during immersion. They concluded that the greater than anticipated decrease in plasma volume could be attributed to a concomitant shift of extracellular fluid from the plasma to the interstitial compartment. In contrast to these findings, Epstein et al. failed to observe a significant change in peripheral hematocrit sampled at 2-hour intervals in a large number of normal subjects undergoing immersion in the seated posture. It is possible that differences in the experimental design of the above studies, including body position and states of hydration, may account for the discrepant reports of changes in hematocrit during immersion. Thus, while fluid administration was not mentioned in the study by Crane and Harris, it should be noted that the authors reported urine flow rates of less than 1 ml/min in some of their subjects during immersion; this finding suggests a profound degree of dehydration. Similarly, the fluids administered during the actual period of control and immersion are not specified in the study of Behn et al. Moreover, the body position of the subjects varied markedly in the different studies; subjects were maintained in a "near vertical position" in the study by Crane and Harris, whereas they were recumbent in the study by Behn et al. Since it is well known that postural changes alter the plasma volume as well as
the concentration of certain blood constituents, including hematocrit, it is apparent that this variable probably contributed to the encountered changes. Finally, it should be noted that Behn et al. did not determine serial hematocrits during an 8-hour immersion study, but merely reported the changes after this 8-hour period. Similarly, Crane and Harris did not specify the frequency with which hematocrits were determined in their sodium-replete subjects; rather they reported the "average" hematocrit change associated with immersion. Future studies, in which body position and hydration are standardized and serial determinations of hematocrit obtained at more frequent intervals during immersion (i.e., 30-minute intervals), will probably resolve some of these apparent discrepant results.

**II. Effects on Renal Function**

**RENAL WATER HANDLING**

Chronologically, the initial emphasis on delineating the renal effects of immersion was directed toward documentation of changes in renal water handling. Behn et al. studied renal water handling in normal subjects undergoing immersion after two different states of hydration for the 3 days preceding immersion: a "hydrated state" (water intake - 3.1% of body weight/day) and a "hydropenic state" (water intake = 1.7% of body weight/day). These workers reported a significant diuresis during immersion for the "hydrated group" that was attributed primarily to an increase in free water clearance. In contrast, the increase in urine flow in the "hydropenic" subjects was smaller and attributable solely to an increase in osmolar clearance. These findings were similar to those of Epstein et al., who noted that when a cumulative water load averaging 2,000 ml (2.9% of body weight, approximately the same load given the hydrated group of Behn et al.) was administered, the increase in urine flow induced by immersion was attributable to both an increase in free water clearance and osmolar clearance. However, when subjects were studied after overnight water deprivation, the small but significant increase in urine flow noted during immersion was due solely to an increase in osmolar clearance.

**Mechanism of the Diuresis**

Several lines of evidence have suggested the presence of an antidiuretic hormone (ADH) release participate in mediating the diuresis of immersion. Eckert demonstrated that the administration of vasopressin during immersion, either as a single bolus injection (0.5 mU/kg) or by continuous infusion (0.24 mU/kg initially, followed by an intravenous infusion of 0.25 mU/kg for 30 minutes), significantly reduced urine flow from 6 ml/min to 1 ml/min. Subsequently, Kaiser et al. reported that immersion did not significantly enhance the already elevated flow rates in subjects who had been given a large water load prior to undergoing immersion. The latter studies, however, were carried out under conditions of supine posture; an experimental condition which precludes direct inferences with respect to immersion in seated posture. Recently, Epstein et al. determined urinary ADH excretion in 10 normal subjects undergoing immersion after 14 hours of overnight water restriction. They reported that immersion resulted in a progressive decrease in ADH excretion from 80 ± 7 to 37 ± 6 μU/min. Cessation of immersion was associated with a marked rebound, with ADH excretion increasing from 37 to 177 μU/min during the recovery hour. These studies are consistent with the suggestion that in hydrated subjects undergoing immersion (for whom ADH radioimmunoassay may not be applicable due to the low baseline values), suppression of ADH release also may contribute to the enhanced free water clearance.

**RENAL SODIUM HANDLING**

In 1959 Gowenlock et al. reported that the natriuresis of recumbency persists when an erect posture is assumed during immersion in water, in contrast to the usual antinatriuresis caused by quiet standing in air. Subsequently, Graveline and Jackson and Hunt reported a natriuresis during water immersion. However, because these early studies were carried out using whole body immersion with pressure-breathing equipment, their interpretation is difficult. In 1969 Behn et al. reported a significant natriuresis (53-127% increase above control) in normal subjects undergoing head-out water immersion. Epstein and coworkers characterized the natriuretic response during varying sodium intakes and varying depths of immersion. Studies of sodium-depleted subjects immersed to the neck disclosed that immersion produced a marked natriuresis. Although the rate of sodium excretion (U_{Na}/V) during immersion by subjects in balance on a 10-mEq sodium diet was 20-fold greater than during the control period, the absolute increase in sodium excretion during water immersion was exceedingly small; this reflected the limitations imposed by the sodium-depleted and volume-contracted state of the subjects. This interpretation was supported by results of an additional study during which sodium intake were more nearly approximated that of the normal diet (150 mEq/day). Sodium-replete normal subjects demonstrated an earlier (hour 1 vs. hour 4) and more profound (72 mEq/6 hours vs. 7 mEq/6 hours) increase in sodium excretion than did comparable subjects studied during sodium depletion.

When the depth of immersion was varied, it was demonstrated that water immersion to the waist did not induce a natriuresis in either sodium-depleted or sodium-replete subjects.

**Mechanism of the Natriuresis**

The demonstration of a highly significant increase in 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 filtered sodium load. The natriuresis observed during immersion is associated with a suppression of aldosterone release, the rapidity of onset of the natriuresis (initial hour of immersion) and the concomitant kaliuresis suggest that the natriuresis cannot be attributed solely to decreased aldosterone levels. In an attempt to delineate the quantitative contribution of aldosterone suppression to the natriuresis of water immersion, renal sodium handling was examined in subjects undergoing immersion, before and after administration of exogenous mineralocorticoid (deoxycorticosterone acetate). These studies demonstrated that pharmacological doses of a potent mineralocorticoid failed to abolish the natriuresis of water immersion (Fig. 1).

Several lines of evidence have suggested the presence of a circulating natriuretic factor that normally depresses renal
FIGURE 1. Effect of deoxycorticosterone (DOCA) pretreatment on renal sodium handling during water immersion to the neck (NI). The shaded area represents the mean ± SE for control studies (C) following pretreatment with deoxycorticosterone (control + DOCA). Although DOCA pretreatment blunted the natriuresis of immersion, the rate of sodium excretion (U NaV) was still 3- to 4-fold greater during immersion + DOCA than during the comparable periods for control + DOCA (P < 0.01).

tubular reabsorption in response to extracellular fluid (ECF) volume expansion.14 The possibility of such a natriuretic factor is relevant to considerations of the mechanism(s) of the natriuresis of immersion. Studies during a recovery hour following immersion revealed a continuing natriuresis that occurred despite the progressive volume contraction induced by the earlier period of immersion.18 This delay in the disappearance of the natriuresis suggests that a humoral factor rather than more rapidly acting hemodynamic and neural mechanisms may contribute to the natriuresis.14 The demonstration by Favre et al.18 that the humoral natriuretic factor which was previously reported during renal failure also is present in normal dogs during mineralocorticoid escape suggests that such a humoral natriuretic factor also may participate in the natriuresis of immersion.

Recent observations from our laboratory have disclosed the presence of a natriuretic factor, as assessed by rat assay, in the urine of normal subjects undergoing immersion.24 As assessed by rat assay, in the urine of normal subjects undergoing immersion.24 Furthermore, a sodium transport inhibitor also has been found in the serum of normal subjects undergoing immersion (Fig. 2). When blood obtained during immersion was fractionated and applied to toad hemibladder,25 there was significant inhibition of short circuit current (SCC) (U. Michael and M. Epstein, unpublished observations). Of interest, blood similarly obtained and prepared from a normal subject who did not manifest a natriuresis (subject 10 in the study by Epstein et al.25) did not alter SCC (Fig. 2, upper panel). These observations suggest that a humoral factor may contribute to the natriuresis of immersion.

Finally, it is possible that a decrease in sympathetic nervous system activity may be responsible in part for the natriuresis of immersion. Karim and co-workers12 reported that left atrial distention results in a decrease in renal sympathetic nerve activity. Because several recent studies have provided evidence for a direct effect of the renal sympathetic nerves on renal tubular sodium transport in the absence of alterations in renal hemodynamics,18 it is conceivable that a decrease in renal sympathetic activity may contribute to the encountered natriuresis.

The demonstration of a progressive kaliuresis during immersion13 suggests that the natriuresis of immersion is multifarious in nature and is mediated in part by an increased rejection of sodium proximal to the diluting site, in addition to that component of the natriuresis which is secondary to a decline in circulating aldosterone. This interpretation is supported by previous data from our laboratory which showed: (1) an augmented free water clearance at a time when sodium excretion was enhanced, suggesting an increase in sodium delivery to the diluting site;27 and (2) an immersion-induced increase in bicarbonate excretion with a concomitant increase in the urine to blood Pco2 gradient, suggesting an increased proximal tubular rejection of sodium bicarbonate.18

CHANGES IN RENAL HEMODYNAMICS

Kaiser et al.24 determined inulin clearance (CIn) and p-aminohippuric acid clearance (CPAH) in normal subjects undergoing 8 hours of immersion in the supine posture. They reported small but significant increases in both CIn and in CPAH (10% and 13%, respectively, compared to the 2 hours preceding immersion). However, because a separate control...
study bracketing the same time period as immersion was not carried out, it is difficult to ascertain to what extent the conditions of the experiment may have contributed to the relatively minor changes reported. Similarly, Crane and Harris recently reported increments in creatinine clearance $C_{\text{cr}}$ (74 ± 61%) and urea clearance (230 ± 220%) during water immersion in "upright" subjects. Again, because of the lack of an appropriate control period, it is difficult to determine to what extent the reported changes can be attributed to immersion per se. In an attempt to circumvent these difficulties, Davis and DuBois and Epstein et al. have examined $C_{\text{cr}}$ in a large group of normal subjects undergoing both a control study and an immersion study using an identical seated position and conducted at the identical time of day. Although these investigators noted occasional small changes of $C_{\text{cr}}$, averaging 18-20%, these small increments invariably were restricted to the initial hour of immersion, and a sustained increase in $C_{\text{cr}}$ during immersion never was detected in over 150 normal subjects undergoing immersion. More recently, this group examined the effects of immersion on renal hemodynamics by assessing $C_{\text{in}}$ and $C_{\text{PAH}}$ during a control study and during water immersion under identical conditions of posture and time of day. Immersion did not alter $C_{\text{in}}$ or $C_{\text{PAH}}$ from control despite the occurrence of a marked and progressive natriuresis. These data are consistent with the interpretation that the natriuresis of water immersion is mediated independently of alterations in renal hemodynamics.

III. Comparison of Water Immersion and Saline Infusion as Volume Determinants of Renal Sodium and Water Handling

While there are several potential advantages to the capability of water immersion to provide a volume stimulus without the necessity of increasing absolute total blood volume, it was unclear whether the magnitude of the stimulus was comparable to that induced by standard saline-induced extracellular volume expansion. Thus, studies were carried out on a group of normal subjects in an attempt to compare the relative central hemodynamic and renal responses to water immersion and to standard saline infusion. A noninvasive rebreathing method was used and the increment in cardiac output induced by head-out water immersion was shown to be similar to that observed during extracellular fluid volume expansion (ECVE) by acute administration of saline (2 liters/120 min) (M. Epstein and M.A. Sackner, unpublished observations). In a subsequent study, the increment in U$_{\text{Na}}$V during immersion was indistinguishable from that noted after saline infusion in seated subjects. In addition, the kaliuretic response during immersion was similar to that induced by saline infusion in seated subjects. These data suggest that the "volume stimulus" of immersion is similar to that of standard saline-induced ECVE in normal, seated subjects. Furthermore, the ability of immersion to induce a natriuresis without a concomitant increase in total blood volume and with a decrease in body weight rather than the increase which attends saline infusion suggests that immersion may be a preferred investigative tool to assess the effects of volume expansion on renal electrolyte homeostasis and renin-aldosterone responsiveness in edematous patients and patients with hypertension.

IV. Alterations in Renin-Aldosterone

CHANGES IN PLASMA RENIN ACTIVITY

Although the changes in renin-aldosterone responsiveness during water immersion have been delineated only recently, several studies have suggested the possibility of such changes. Two decades ago, Barter and Gann demonstrated that constriction of the supradiaphragmatic inferior vena cava consistently increases aldosterone secretion, presumably by producing a relative depletion of blood above the constriction. Subsequent studies have demonstrated a similar increase in plasma renin activity (PRA) in the dog with inferior vena cava constriction. Since immersion to the neck produces an opposite hemodynamic redistribution, characterized by an increase in intrathoracic volume, one would anticipate a decrease in both PRA and aldosterone. Korz et al. were the first to report a suppression of PRA during immersion. These authors reported a 28% decrease in PRA after water immersion for 6 hours, compared to preimmersion levels. Unfortunately, the absence of a control study carried out at an identical time of day complicates the interpretation of these findings, since the decrease may have been attributable in part to the normal diurnal variation. Subsequently, Epstein and Saruta studied the effect of water immersion for 6 hours on PRA in normal male subjects in balance on a diet containing 10 mEq of Na and 100 mEq of K. All subjects were studied on three occasions: control, immersion to the level of the umbilicus (waist immersion), and immersion to the neck. Waist immersion produced a decrease of one-third in PRA at 2 hours without any further depression at 4 or 6 hours. Neck immersion produced a similar suppression of PRA at 2 hours with a further suppression at 4 hours and 6 hours. Crane and Harris studied the effect of head-out water immersion on PRA in normal subjects maintained in a "near vertical position." Immersion caused a 51% decrease in PRA after 2 hours of immersion, without a further suppression at the end of 4 hours of immersion. However, the interpretation of their findings is confounded by the absence of dietary control of sodium and potassium intake, and the marked difference in posture and activity during immersion ("near vertical position") and control (2 hours of ambulation).

Because the determination of PRA at 2-hour intervals in all the above studies precluded assessment of the rapidity of changes resulting from initiation or discontinuation of immersion, a study was undertaken recently to characterize the temporal profile of the suppression of PRA during immersion. Blood was collected serially at 30-minute intervals for PRA determination. Immersion resulted in a progressive suppression of PRA beginning within 30 minutes of initiating immersion (Fig. 3). By 210 minutes, PRA was suppressed maximally to 38% of the prestudy value. Cessation of immersion was associated with a prompt (in as early as 30 minutes) return of PRA toward prestudy values.

MECHANISM OF PRA SUPPRESSION

Although the mechanism for the suppression of PRA remains to be established, recent studies by Mancia et al. are of interest. These investigators demonstrated that block-
The possibility that water immersion suppresses aldosterone was suggested by several findings. Several investigators had reported an increase in urinary Na/K concentration ratio during immersion.** Several investigators had reported an increase in aldosterone excretion produced by a change in position from recumbency to the standing position in normal subjects undergoing immersion. Additional studies undertaken to assess the effect of water immersion on aldosterone demonstrated a decrease in aldosterone excretion in sodium-restricted normal subjects undergoing immersion. These results suggest that the suppression of the renin-aldosterone system is selective and not a manifestation of a generalized decrease in adrenocortical activity. More recently, Crane and Harris reported a significant suppression of plasma aldosterone (PA) after 1 hour of immersion in a group of normal subjects, with a subsequent decline of 71% and 74% at 2 and 4 hours of immersion. Qualitatively similar changes were noted in the two normal subjects studied during dietary sodium restriction. Epstein et al. recently assessed the temporal profile of the suppression of PA during immersion in a group of normal subjects studied during dietary sodium restriction. They demonstrated a progressive suppression of PA beginning as early as 60 minutes, with maximal suppression by 210 minutes of immersion (Fig. 3). Cessation of immersion was associated with a prompt return to prestudy values.

V. Methodological Considerations

During immersion, there is a marked reduction in sweating that minimizes fluid losses by this route. Furthermore, the subjects breathe approximately 5 cm above the surface of water at 34.5°C. Therefore the difference in water vapor saturation between the inhaled and exhaled air is very small, hence respiratory water losses are minimal. The temperature of the bath should be maintained constant within an extremely narrow range (±0.5°C) because an increase in temperature from 34.5°C to 36.5°C after 2 hours of immersion promptly reverses an established natriuresis (M. Epstein, unpublished data). It is possible that an increase in temperature results in peripheral vasodilation, which is associated with a resultant abolition of the natriuresis. On the other hand, lowering the temperature of the bath significantly discomforts the subject so that immersion cannot be extended beyond several hours.

VI. Other Experimental Maneuvers that Induce Central Hypervolemia

**POSITIVE- AND NEGATIVE-PRESSURE BREATHING**

Positive-pressure breathing decreases intrathoracic blood volume while negative-pressure breathing may increase intrathoracic blood volume. As one would anticipate, the increase in intrathoracic blood volume induced by negative pressure breathing significantly alters renal function and renin-aldosterone responsiveness as manifested by a natriuresis, diuresis, and a suppression of PRA. However, the spontaneous subsidence of the diuresis and the subjective discomfort experienced by subjects during this maneuver have precluded its use in investigation.

**ANTI-G SUIT INFLATION**

The anti-G suit is known to be an effective means of increasing tolerance to positive radial acceleration (+G). Theoretical considerations have suggested that the anti-G suit would induce a redistribution of blood volume with an increase in central blood volume analogous to that caused by...
water immersion. Indeed, it has been proposed that this device might provide a means to normalize blood volume distribution in patients with disease states associated with decreased effective blood volume. Studies by Shubrooks et al. have demonstrated that the standard Air Force anti-G suit (CSU-12/P) does not reverse the marked natriuresis shown to occur with +Gα, and that the initial increase in central venous pressure that occurs after suit inflation in the seated position is not sustained.

Sackner and Dougherty assessed the effects of anti-G suit inflation on pulmonary capillary blood flow using a noninvasive, nitrous oxide body plethysmographic method and reported that inflation of the suit did not significantly increase stroke volume or cardiac output in either the seated or supine position. The authors suggested these results may be attributable to the tendency of the abdominal bladder to pressurize slightly before the leg bladders, resulting in a tourniquet effect on the lower extremities which cancels the increase of venous return produced by compression of the splanchic and pelvic venous beds. It is apparent therefore that the standard anti-G suit is ineffective in redistributing blood volume. Perhaps a modified suit designed for sequential inflation upward from the calf to abdominal bladders will succeed in inducing such a redistribution.

LOWER BODY POSITIVE PRESSURE

Lower body positive pressure has been used to redistribute blood volume. Essentially, the method consists of placing a subject in a box with the lower body enclosed to the level of the xiphoid and increasing the pressure around the lower body to levels exceeding 30 mm Hg. This results in a shift of blood from the periphery into the upper parts of the body. This maneuver has not been used widely and data describing its effect on renal function are not available.

HEAD-DOWN POSITION

Although orthostasis may be functionally comparable to hemorrhage in its ability to pool blood in the periphery and thereby reduce intrathoracic blood volume, the opposite maneuver of head-down tilt does not result in significant expansion in central blood volume. As a function of the relative distensibility of the capacitance vessels of the upper and lower halves of the body, the filling pressure of the right and left atria may actually decrease. Hence diuresis has been reported only sporadically in association with head-down tilt.

VII. Physiological Studies in Normal Man

THE USE OF WATER IMMERSION AS AN ANALOG OF WEIGHTLESSNESS

Theoretical considerations have suggested that the exposure of astronauts to prolonged periods of a gravity-free environment would result in the development of abnormalities of sodium and volume homeostasis. Recent reports on subjects of manned orbital space flights have indeed borne out this concept and demonstrated a significant natriuresis and weight loss. Because of the inherent difficulties in performing in-flight physiological investiga-

VIII. Studies in Disease States

STATES OF ABNORMAL VOLUME REGULATION

Several lines of evidence have suggested that the renin-aldosterone system plays an important role in the pathogenesis of a number of clinical syndromes characterized by secondary hyperaldosteronism, including congestive heart failure, the nephrotic syndrome, and cirrhosis of the liver. Although the abnormal retention of sodium and water in one of these disease entities, Laennec’s cirrhosis, has been the subject of intense study, its precise pathogenesis remains obscure. Although a diminished "effective" blood volume has been postulated to mediate in large measure the sodium and water retention, this remains controversial. Despite the demonstration of an improvement in renal sodium and water handling after rapid volume expansion, the lack of specificity of these maneuvers, which may increase the volume of all fluid compartments, and the presumed concomitant alterations in plasma composition have precluded definitive statements regarding the etiological role of a diminished effective plasma volume. While reinfusion of ascites approximates immersion more nearly, it also induces additional changes which may confound the interpretation of the results encountered. Thus, during reinfusion, fluid sequestered in a third space (peritoneal cavity) is added to the circulating blood volume with a resultant expansion of total blood volume. In contrast, immersion redistributes circulating blood volume without significantly altering the total blood volume. The delineation of the immersion model and the demonstration that it constitutes a potent "central volume stimulus" have permitted its application recently to an assessment of the role of "effective" volume in mediating the impairment of renal sodium and water handling in cirrhosis. These studies have demonstrated that immersion results in a marked natriuresis and kaliuresis in the majority of patients with Laennec’s cirrhosis and avid renal sodium retention. Furthermore, immersion induced a striking improvement in free water clearance in a majority of these patients. Additional studies during chronic administration of spironolactone demonstrated a marked increase in sodium excretion during immersion plus spironolactone administration, compared to a modest increase in sodium excretion after only spironolactone administration. The observed sodium retention was due to elevated aldosterone levels per se, one would have anticipated a significant natriuresis with spironolactone administration alone. Taken together, these data demonstrate that the renal sodium
retention of cirrhosis is attributable only in part to hyperaldosteronism and support the suggestion that a diminished "effective" blood volume is a major determinant of the abnormal renal sodium handling by cirrhotics.

HYPERTENSION

Many studies have indicated that hypertension is an extremely complex hemodynamic abnormality with derangements in a variety of cardiovascular and volume control mechanisms. Included among these abnormalities is a redistribution of blood volume in borderline hypertension. Ulrych et al. and Safar et al. have reported that cardiac output is elevated in borderline hypertension despite the fact that blood volume per se is normal or low, and have demonstrated a relative increase in central blood volume relative to the total blood volume. Because the immersion model reproducibly induces a similar redistribution, it may lend itself to the further delineation of the role of this volume-regulatory abnormality in hypertension. As an example, it might be anticipated that patients with borderline hypertension who already have an increased cardiopulmonary blood volume will manifest a much smaller blood volume redistribution during immersion and will therefore manifest a blunted natriuretic and diuretic response and a lessened suppression of plasma renin activity (PRA) and plasma aldosterone (PA) in comparison to patients with established hypertension. Indeed, a preliminary observation by Lange et al. lends support to this possibility. These workers reported that one of 10 subjects undergoing head-out immersion failed to redistribute his blood volume significantly and manifested only a very small change in cardiac blood volume in response to immersion; of interest, the subject had marked hypertension.

In addition, immersion may be used to delineate further the responsiveness of the renin-aldosterone system in hypertension. Several investigators have assessed the relationship between PRA and aldosterone in essential hypertension by inducing volume and/or postural manipulation, and have demonstrated a striking dissociation characterized by depressed aldosterone excretory response with an appropriate PRA response to dietary sodium restriction. Similarly, a dissociation in renin-aldosterone responsiveness to suppressive maneuvers such as oral salt loading also has been reported. In view of the demonstrated ability of immersion to comitantly suppress PRA and PA in a parallel manner, it may lend itself to the further elucidation of the relative autonomy of PRA and PA in hypertension. Finally, preliminary studies have suggested that immersion carried out under standardized conditions of posture and diet may constitute a more discriminating investigative tool than saline infusion for delineating the wide spectrum of alterations in sodium homeostasis characterizing essential hypertension.

Conclusion

Studies from several laboratories recently have succeeded in delineating the circulatory, renal, and endocrine changes induced in man by water immersion. These studies have demonstrated that immersion in the seated posture results in a redistribution of blood volume with a relative central hypervolemia. As a consequence, 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 of ADH release. Characterization of the immersion model and the demonstration that it constitutes a potent "central volume stimulus" that does not necessitate infusing exogenous volume expanders have permitted its successful application in the investigation of abnormal sodium and water homeostasis in patients with decompensated cirrhosis and, more recently, hypertension. Examples have been described of the successful application of the immersion model, commending its future use as an investigative tool to assess dynamically the control mechanisms for the renin-aldosterone system in normal man and in a wide array of disease states characterized by a deranged volume homeostasis. In an edematous or hypertensive subject, water immersion constitutes a less hazardous means to evaluate the effects of volume expansion than administration of a saline load. In contrast to saline administration, (1) water immersion is associated with a decrease in body weight rather than with the increase which attends saline infusion, (2) water immersion is associated with a significant, albeit slight, decrease in mean arterial blood pressure in contrast to the increase in blood pressure induced by saline administration, and (3) the "volume stimulus" of immersion is promptly reversible after cessation of immersion in contrast to the relatively sustained hypervolemia which follows saline administration.

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References

CARDIOVASCULAR AND RENAL EFFECTS OF IMMERSION/Epstein

627


Cardiovascular and renal effects of head-out water immersion in man: application of the model in the assessment of volume homeostasis.

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