Effects of Low-Dose Epinephrine Infusion on Cardiovascular and Renal Responses to Water Immersion in Humans

Hans-Joachim Kruse, Reinhold Kreutz, Martina Lennartz, Axel Overack, Klaus O. Stumpe, and Rainer E. Kolloch

Elevated plasma epinephrine concentrations may impair blood pressure homeostasis and renal sodium and volume excretion in response to central hypervolemia. We studied the effects of a low-dose epinephrine infusion (12 ng/kg/min) on cardiovascular and renal responses to a thermoneutral head-out water immersion in eleven healthy men.

Responses to water immersion without epinephrine were characterized by significant suppression of plasma renin activity (PRA), plasma aldosterone concentration, and renal norepinephrine excretion, and an augmentation of natriuresis and diuresis. Epinephrine infusion, which raised mean plasma epinephrine concentration 4.3-fold, slightly increased plasma norepinephrine and renal norepinephrine excretion, markedly stimulated PRA (+66.7%), but decreased plasma aldosterone (−11.7%), and augmented renal sodium and volume excretion. Despite the presence of the epinephrine infusion, water immersion continued both to suppress PRA and aldosterone, and to increase natriuresis and diuresis in a qualitatively similar pattern. During all conditions blood pressure and heart rate remained unchanged.

It is concluded that physiologic responses to central hypervolemia are not impaired at stress levels of circulating epinephrine. During epinephrine infusion, despite a concomitant increase in plasma norepinephrine and a stimulation of PRA, blood pressure remained constant in response to water immersion due to an augmentation of natriuresis and diuresis. Am J Hypertens 1996;9:902-908

KEY WORDS: Epinephrine infusion, head-out water immersion, blood pressure homeostasis, renal water excretion, renal sodium excretion.

Thermoneutral head-out water immersion by shifting circulating blood from peripheral veins to the central vasculature and the heart, produces an acute augmentation of thoracic blood volume. Immersion-induced central hypervolemia is associated with a suppression of the renin-angiotensin-aldosterone system and an augmentation of natriuresis and urine flow rate without changes in serum electrolyte concentrations and plasma osmolality. In addition, it has been suggested that the sympatho-adrenomedullary outflow is inhibited in response to water immersion. However, whether a sup-

Received September 5, 1995. Accepted February 27, 1996.
From the Medizinische Universitäts-Poliklinik, Bonn, Germany.
This work was presented in part at the 15th Scientific Meeting of the International Society of Hypertension, Melbourne, 1994.

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pression of the sympathetic nervous system and, in particular, a reduction of the adrenomedullary activity may contribute to the constancy of the systemic blood pressure observed during water immersion still remains unclear.2-5

Renal responses to water immersion are characterized by an increase of sodium and water excretion, both of which are differentially regulated by neurohumoral and hemodynamic variables.2,1 In a recent study, Miki et al. demonstrated that a reduction of renal sympathetic nerve activity plays a major role in the enhanced urinary sodium and volume excretion during water immersion in dogs. Moreover, in humans, Grossman et al. found reduced plasma levels of epinephrine and norepinephrine, and a concomitant decrease of renal epinephrine and norepinephrine excretion, during water immersion. On the other hand, in various pathophysiological states a restricted renal capacity to excrete sodium and water has been related to increased sympathetic activity.4,6

Thus, the role of the adrenomedullary system in blood pressure control and in renal responses to water immersion in humans remains unclear.2,3 Therefore, we tested the hypothesis that an increased adrenomedullary activity, simulated by a pharmacological elevation of circulating epinephrine, would impair blood pressure regulation and renal excretory responses to central hypovolemia. Epinephrine was infused intravenously at a rate high to raise plasma epinephrine concentrations to levels found in mild to moderate stress, and, as previously shown, to increase plasma norepinephrine concentration.7 A suppressor dosage of epinephrine was chosen in order to prevent pressure-dependent changes of circulatory control in this study.

MATERIALS AND METHODS

Subjects Eleven normotensive, non-obese men aged 19 to 29 years (mean 21 years) participated in the study. None of the subjects had a history of hypertension, cardiovascular and renal disease, or received any medication. The absence of any hormonal or renal dysfunction was confirmed by normal values for plasma epinephrine, plasma norepinephrine, plasma aldosterone, and plasma renin activity (PRA). The endogenous creatinine clearance and electrolyte excretion were also normal. All subjects were studied twice on two separate occasions with a 6 day interval. The participants served as their own controls under two conditions, to which they were randomly allocated in single-blind fashion: a control study with an intravenous placebo infusion and a study with an intravenous infusion of epinephrine. During both infusions they were subjected to a thermoneutral water immersion. The study protocol was approved by the ethics committee of the university and was in compliance with the principles set forth in the Declaration of Helsinki. The subjects gave their written informed consent. No complications occurred.

Study Protocol The subjects were studied after an overnight fast that also excluded alcohol and caffeine intake. No eating restrictions, including sodium intake, were employed during the preceding days. Two hours prior to the study, they had a standardized breakfast and drank 0.3 L of tap water. Two indwelling canulas were placed into a vein of each forearm, one permitting sampling of blood, and the other for infusion of either physiologic saline solution as placebo or epinephrine dissolved in saline at a rate of 12 ng/kg/min via an infusion pump. Both infusions were started 15 min prior to a 1 h observation period before immersion, in order to achieve steady-state levels of epinephrine or placebo, respectively, at the beginning of the actual study. The subjects were seated upright during the pre- and postimmersion hours at a room temperature of 28°C and were covered with a blanket. Blood samples were drawn at hourly intervals for estimation of PRA, plasma epinephrine, norepinephrine and aldosterone concentrations, serum creatinine, sodium, potassium, and chloride concentrations, osmolality, and hematocrit. Urine samples were collected at hourly intervals for estimation of volume, norepinephrine, creatinine, sodium, and chloride concentrations, and osmolality. Blood pressure and heart rate were measured every 30 min during the whole study period. In order to maintain a sufficient urine flow, all subjects drank an initial water load of 0.5 L and a maintenance load of 0.2 L/h. A 1 h preimmersion period was followed by 2 h of head-out water immersion and a 1 h postimmersion period. The subjects were immersed up to their neck into water (34.5 ± 0.5°C) in a spa bath, where they remained in an identical body position as outside the tank. During immersion the arms were placed horizontally on the rim of the bath. The same height of the arms was achieved by using arm benches during pre- and postimmersion periods.

Measurements Blood pressure was measured using a standard sphygmomanometer using the fifth Korotkoff sound for the diastolic value. The mean of two repeated determinations within 5 min was used for further calculations. Mean arterial blood pressure was calculated by the equation: (systolic blood pressure + 2 × diastolic blood pressure)/3. Serum and urine electrolytes and hematocrit were determined by conventional laboratory methods. Serum and urine osmolality was measured with an electronic halomicroimeter (Knauer, Berlin, Germany). The alkaline picrate method (Jaffé reaction) was used for determination of serum and urine creatinine concentration (Gemsaec Fast Analyzer, Electro-Nucleonics, Fairfield, NY). Endogenous creatinine clearance (Ccr) was calculated with a standard...
Blood pressure (mean systolic and diastolic pressure values of 4 h during placebo 106 ± 3/65 ± 2 mm Hg vs epinephrine 108 ± 3/61 ± 2 mm Hg; P > .05 for hourly comparisons; Figure 1). Calculated mean arterial pressure tended to be lower by -1.5 mm Hg compared with placebo (not significant). Heart rate also remained constant during all study periods (placebo, 67 ± 3 beats/min vs epinephrine 69 ± 2 beats/min; P > .05 for hourly comparisons; Figure 1).

**Plasma Catecholamines** Epinephrine infusion increased plasma epinephrine concentration 4.3-fold (mean of 4 h placebo 53 ± 6 ng/l vs epinephrine 230 ± 26 ng/l; P < .001; Figure 2).

During epinephrine infusion, plasma norepinephrine concentration was slightly increased by 14.3% (mean of 4 h placebo 198 ± 19 ng/l vs epinephrine, 231 ± 12 ng/l; P < .05; Figure 2). There was no correlation between plasma epinephrine and norepinephrine concentration (r = -0.45, P > .05).

**Renal Norepinephrine Excretion** Infusion of epinephrine increased renal norepinephrine excretion rate by 16.2% (mean of 4 h placebo 25.9 ng/min vs epinephrine 30.1 ng/min; P < .05 for hourly comparisons). Two hours of water immersion induced a significant reduction of norepinephrine excretion of -19.1% and -25.9% (placebo) and of -16.6% and -16.9% (epinephrine; P < .05 compared with preimmersion for both studies; Figure 3).

**PRA and Aldosterone** Infusion of epinephrine resulted in an overall increment of PRA of 66.7% (mean

![FIGURE 1. Effects of a 4 h low-dose epinephrine (12 ng/kg/min) versus placebo infusion on blood pressure and heart rate responses to 2 h of head-out water immersion in 11 healthy men (epinephrine: ■, placebo: □: values are mean ± SD, bpm beats per min). Both infusions were started 15 min before time zero in order to achieve steady state levels of epinephrine or placebo, respectively.](image)

![FIGURE 2. Effects of a 4 h low-dose epinephrine (12 ng/kg/min) versus placebo infusion on plasma epinephrine and norepinephrine concentrations in 11 healthy men (placebo: solid bar, epinephrine: open bar; values represent the mean of 4 h ± SEM: *P < .001 for plasma epinephrine concentration; **P < .05 for plasma norepinephrine concentration; epinephrine versus placebo).](image)
Renal excretory responses  During epinephrine infusion mean sodium excretion rate increased by 16.8% (mean of 4 h placebo 190 ± 23 nmol/min vs 220 ±
24 nmol/min; P < .05 for hourly comparisons, except postimmersion). In both studies, 2 h of water immersion augmented natriuresis in a comparable fashion. During placebo, natriuresis increased by 20.0% and 60.0%, during epinephrine it increased by 29.4% and 58.8% (P < .01 compared with preimmersion for both studies; Figure 4).

Urinary chloride excretion rates were related to the degree of natriuresis during all conditions (Table 1).

Intusion of epinephrine resulted in a significant greater diuresis of 28.6% (mean of 4 h placebo 5.6 ml/min vs epinephrine 7.2 ml/min; P < .01 for hourly comparisons, except postimmersion). During both infusions, diuresis significantly increased in response to 2 h of water immersion. The relative increment during epinephrine was smaller due to an almost doubled di-

*FIGURE 3. Effects of a 4 h low-dose epinephrine (12 ng kg$^{-1}$ min$^{-1}$) versus placebo infusion on renal norepinephrine excretion, PRA and plasma aldosterone concentration 2 h of head-out water immersion in 11 healthy male (epinephrine; □ placebo □; values are mean ± SEM; *P < .05 for renal norepinephrine excretion and plasma aldosterone concentration; **P < .01 for PRA, epinephrine versus placebo). Both infusions were started 15 min before time zero in order to achieve steady-state levels of epinephrine or placebo, respectively.

*FIGURE 4. Effects of a 4 h low-dose epinephrine (12 ng kg$^{-1}$ min$^{-1}$) versus placebo infusion on renal sodium and volume excretion during 2 h of head-out water immersion in 11 healthy male (epinephrine; ■ placebo; □; values are mean ± SEM; *P < .05 for sodium excretion; **P < .01 for volume excretion; epinephrine versus placebo). Both infusions were started 15 min before time zero in order to achieve steady state levels of epinephrine or placebo, respectively.

of 4 h placebo 1.2 ± 0.2 ng/mL/3 h vs epinephrine 2.0 
+ 0.3 ng/mL/3 h; P < .001 for hourly comparisons).

In both studies, during 2 h of water immersion PRA 
was suppressed in a qualitatively similar manner. In 
the placebo study PRA fell by -46% and -59%; in the 
epinephrine study PRA fell by -44% and -59%; (P < .01, compared with preimmersion for both studies; Figure 3).

Epinephrine infusion induced an overall reduction 
of plasma aldosterone concentration of -11.7% (mean 
of 4 h placebo 35 ± 4 pg/mL vs epinephrine 31 ± 3 pg /
mL; P < .05 for hourly comparisons, except preimme

sion). Again, 2 h of water immersion caused a similar 
suppression pattern of aldosterone in both studies. Dur-
ing placebo infusion, aldosterone was reduced by 
-8.1% and -16.2%, whereas during epinephrine infu-
sion aldosterone was reduced by -14.7% and 17.6% 
(P < .01 compared with preimmersion; Figure 3).
TABLE 1. EFFECTS OF A 4 h EPINEPHRINE INFUSION ON RENAL VARIABLES DURING 2 h HEAD-OUT WATER IMMERSION

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preimmersion 1 h</th>
<th>Immersion 2 h</th>
<th>Immersion 3 h</th>
<th>Immersion 4 h</th>
<th>Postimmersion 4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>U&lt;sub&gt;e&lt;/sub&gt;V (µmol/min)</td>
<td>P 160 ± 22</td>
<td>210 ± 26</td>
<td>250 ± 29</td>
<td>220 ± 20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E 200 ± 26*</td>
<td>230 ± 29*</td>
<td>290 ± 29*</td>
<td>240 ± 22*</td>
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<tr>
<td>Osmolality (mOsm/L)</td>
<td>P 306 ± 64</td>
<td>208 ± 57</td>
<td>153 ± 11</td>
<td>257 ± 28</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E 205 ± 58*</td>
<td>113 ± 26#</td>
<td>147 ± 21</td>
<td>274 ± 26</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;n&lt;/sub&gt; (mL/min)</td>
<td>P 142 ± 17°</td>
<td>132 ± 20</td>
<td>138 ± 15</td>
<td>133 ± 17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E 135 ± 22</td>
<td>143 ± 25</td>
<td>132 ± 21</td>
<td>128 ± 14</td>
<td></td>
</tr>
</tbody>
</table>

P, placebo; E, epinephrine. *P < .05, #P < .01, epinephrine vs placebo, n = 11.

TABLE 2. EFFECTS OF A 4 h EPINEPHRINE INFUSION ON BLOOD VARIABLES DURING 2 h HEAD-OUT WATER IMMERSION

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preimmersion 1 h</th>
<th>Immersion 2 h</th>
<th>Immersion 3 h</th>
<th>Immersion 4 h</th>
<th>Postimmersion 4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mmol/L)</td>
<td>P 138 ± 2</td>
<td>139 ± 2</td>
<td>139 ± 2</td>
<td>138 ± 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E 139 ± 2</td>
<td>140 ± 2</td>
<td>140 ± 2</td>
<td>139 ± 2</td>
<td></td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>P 102 ± 2</td>
<td>102 ± 2</td>
<td>102 ± 2</td>
<td>102 ± 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E 102 ± 2</td>
<td>102 ± 2</td>
<td>102 ± 2</td>
<td>102 ± 2</td>
<td></td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>P 4.0 ± 0.1</td>
<td>4.0 ± 0.2</td>
<td>4.0 ± 0.2</td>
<td>3.9 ± 0.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E 3.7 ± 0.2*</td>
<td>3.7 ± 0.2*</td>
<td>3.8 ± 0.1*</td>
<td>3.7 ± 0.1*</td>
<td></td>
</tr>
<tr>
<td>Osmolality (mOsm/L)</td>
<td>P 279 ± 3</td>
<td>279 ± 4</td>
<td>279 ± 4</td>
<td>278 ± 4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E 278 ± 4</td>
<td>281 ± 4*</td>
<td>281 ± 3*</td>
<td>281 ± 4*</td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>P 41.6 ± 2</td>
<td>42.3 ± 1</td>
<td>42.0 ± 2</td>
<td>42.9 ± 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E 41.1 ± 2</td>
<td>42.2 ± 2</td>
<td>42.2 ± 2</td>
<td>42.5 ± 3</td>
<td></td>
</tr>
</tbody>
</table>

P, placebo; E, epinephrine. *P < .05, epinephrine vs placebo, n = 11.

DISCUSSION

The present study was designed to test the hypothesis that elevated plasma epinephrine concentrations may impair blood pressure homeostasis and renal excretory responses to central hypervolemia induced by water immersion. To achieve high physiological plasma epinephrine levels, as can be seen in mild mental stress,11 healthy men were subjected to a 4 h intravenous epinephrine infusion at a subpressor dosage of 12 ng/kg/min,11 during which they were immersed in water to their neck for 2 h at thermoneutral conditions.1

The main finding of the study is that during water immersion, with and without epinephrine, arterial blood pressure and heart rate remained unchanged. Despite the pharmacological simulation of an ins-

urexisis in the preimmersion hour (placebo 222% and 97% epinephrine 61% and 24.6%, P < .001 compared with preimmersion for both studies; Figure 4).

Blood Variables Epinephrine infusion did not alter serum sodium and chloride concentration and hematocrit (Table 2). In contrast, serum potassium was significantly suppressed by -7.5% during epinephrine infusion (mean of 4 h placebo 4.0 ± 0.1 mmol/L vs epinephrine 3.7 ± 0.2 mmol/L, P < .01 for hourly comparison; Table 2).

Whereas serum osmolality was unchanged during placebo (mean of 4 h, 279 ± 4 mOsm/L), it slightly increased in the second hour of immersion and peaked in the postimmersion period (mean increment compared with placebo: 1.8 mOsm/L, P < .05 for hourly comparisons, except preimmersion, Table 2).

Body Weight Immersion during placebo infusion was associated with a decrease of mean body weight of 0.70 ± 0.1 kg compared with 0.95 ± 0.2 kg during epinephrine (P < .01).
increased sympathoadrenomedullary activity and the concomitant increase of plasma renin activity by the epinephrine infusion, sodium and volume excretion during water immersion were even enhanced.

Plasma norepinephrine concentration and urinary norepinephrine excretion, the former possibly reflecting local release of norepinephrine, and the latter representing discharge of the transmitter from renal sympathetic nerves, were significantly increased during epinephrine infusion by an average of 16.7% and 16.9%, respectively. These findings may be due to a prejunctional \( \beta \)-adrenoceptor mediated mechanism, where circulating epinephrine directly facilitates norepinephrine release.\(^{16-21} \) We did not find a direct relationship between plasma epinephrine concentrations and the respective plasma norepinephrine values during epinephrine infusion. Plasma norepinephrine responses of the subjects showed a high interindividual variability, with some responding in a more pronounced manner than others. This may be related to individually varying reactivity to epinephrine.\(^{12} \) Whether a reflex increase in sympathetic outflow due to postsynaptic \( \beta \)-adrenoceptor mediated vasodilator properties of epinephrine\(^{21} \) contributed to the elevation of plasma norepinephrine cannot be excluded in this study. Although the epinephrine infusion raised plasma epinephrine levels 4.5-fold and lead to a significant increase of plasma norepinephrine, the possible noradrenergic pressor effect of epinephrine may be fully compensated by direct \( \beta \)-mediated vasodilatation (a trend to reduce diastolic blood pressure could be seen), which as a net effect resulted in an unchanged mean arterial pressure. Therefore, direct studies, eg, norepinephrine spillover after intraarterial and intrarenal epinephrine infusions, would be required to permit a more definite interpretation of the observed increase in plasma norepinephrine levels.

Increased PRA has been regarded as a marker of increased sympathetic activity in high renin hypertensive patients without renal dysfunction.\(^{24} \) A variety of mechanisms have been shown to promote renin release: direct \( \beta \)-sympathomimetic stimulation of juxtaglomerular cells, or activation of intrarenal \( \beta \)-adrenoceptors by circulating catecholamines.\(^{16} \)

In addition, a \( \beta \)-adrenoceptor mediated acute fall in serum potassium observed during infusion of epinephrine\(^{22} \) may further stimulate renin release.\(^{22} \) On the other hand, even modest reductions of serum potassium, as can be seen in our subjects, result in a prompt suppression of aldosterone secretion.\(^{27} \) This may explain the dissociation of PRA and plasma aldosterone during epinephrine infusion.\(^{26} \)

Interestingly, the suppression pattern of PRA and aldosterone in response to water immersion was not influenced by the marked elevation of plasma epinephrine. Obviously, the regulatory mechanisms of the components of the renin-angiotensin aldosterone system during central hypervolemia appear not to be impaired by high plasma epinephrine levels.

Numerous studies have clearly demonstrated the natriuretic and diuretic effects of head-out water immersion.\(^{2} \) Apart from other mechanisms, a suppression of the renal sympathetic activity during immersion may considerably contribute to these excretory responses.\(^{7} \) On the other hand, in certain pathophysiological states a restricted natriuresis and diuresis has been related to an increased renal sympathetic tone.\(^{29} \) In contrast, in our subjects natriuresis and diuresis were enhanced during water immersion despite markedly elevated plasma epinephrine levels. A pressure-natriuresis-diuresis mechanism, which can be observed during increased renal perfusion pressure,\(^{31} \) cannot explain the observed magnitude of the enhancement of both parameters, since mean blood pressure remained constant during all phases of the study even during water immersion. A modulation of intrarenal hemodynamics by epinephrine is more likely to explain the elevated excretion of sodium and volume. Circulating epinephrine may lead to a vasodilatation of medullary vessels by direct stimulation of \( \beta \)-adrenoceptors. This is followed by a redistribution of intrarenal blood flow with a preference for medullary vessels. It is known that an elevated renal blood flow causes a washout of medullary tonicity.\(^{32} \) This washout may reduce the osmotic gradient for water movement, which impairs tubular water reabsorption and thereby increases natriuresis and diuresis.

Our data demonstrate that elevated plasma levels of circulating epinephrine do not impair blood pressure homeostasis during head-out water immersion. During the pharmacological simulation of an increased adrenomedullary discharge of epinephrine by means of a low-dose epinephrine infusion, plasma norepinephrine and PRA were significantly increased. These pressor mechanisms were fully compensated most likely by \( \beta \)-adrenoceptor-mediated vasodilatation, suppression of plasma aldosterone, and enhanced renal sodium and volume excretion. We therefore conclude that, despite stress levels of circulating epinephrine, blood pressure in response to water immersion remains constant due to an augmented natriuresis and diuresis.

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