Vasoactive mediators and renal haemodynamics in exertional heat stroke complicated by acute renal failure

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Summary

Background: Although vasoactive substances may be important in the pathogenesis of some types of acute renal failure (ARF), their potential role in exertional heat stroke (ExHS) with ARF has not been explored.

Aim: To evaluate whether changes in concentration of individual vasoactive mediators correlated with alterations in renal function and haemodynamics in patients with ExHS and ARF.

Design: Prospective case-control study.

Methods: Systemic and renal haemodynamics, circulating vasoactive hormones and urinary vasodilator metabolites were determined in 12 military recruits who developed ExHS with ARF but without other organ failure during a three-year period. The control group consisted of 12 recruits who performed similar exercise under the same conditions without developing ExHS.

Results: There were significant elevations in circulating pressor hormones (catecholamines, renin, aldosterone and endothelin-1 (ET-1)) and significant decreases in the vasodilatory hormone prostaglandin E2 (PGE2) in the acute phase of ExHS with ARF when compared to ExC. There was also a significant rise in nitric oxide metabolites (NOx) in the acute phase of ExHS. All of these abnormalities in circulating hormones returned to normal range during the recovery phase of ExHS. The ERPF correlated positively with GFR and urinary PGE2 and negatively with plasma catecholamines, renin, ET-1 and NOx.

Discussion: The changes in the plasma levels of these hormones, together with enhanced NO production, may both contribute to the pathophysiology of ARF in ExHS.

Introduction

Exhaustive exercise during vigorous physical training in a hot and humid environment can result in exertional heat stroke (ExHS). This syndrome is characterized by marked hyperthermia (core body temperature above 40°C), severe neurological abnormalities, and different degrees of organ dysfunction. Evidence of acute renal dysfunction is common in patients with ExHS, and is associated with damage to both renal tubules and their blood supply system. In its milder form, the major damage is restricted to the kidney, whereas a more severe form leads to multiple organ failure.
Several factors appear to enhance the risk of developing ARF following strenuous exercise in a hot environment. These include hyperthermia, rhabdomyolysis, cytokine production, endothelial cell damage, hypokalemia, extracellular fluid volume depletion, endotoxins and disseminated intravascular coagulation. However, the precise mechanisms leading to ARF, and their time course in ExHS in a relatively homogenous and large population, have not been defined. Hence, our study focussed on patients with ExHS that almost exclusively led to kidney failure.

Vasoactive substances have been suggested to be important in the pathogenesis of some types of ARF such as ischaemic and septic models both in animals and in humans. Because the time course and potential role of vasoactive hormones in ExHS with ARF is limited, the goal of the present study was to correlate measurements of renal haemodynamics with the levels of endogenous vasoconstrictive and vasodilatory mediators in patients with ExHS and ARF during both the acute and recovery phases of their illness. To the best of our knowledge, this area has not been systemically explored previously.

Methods

Patients

All procedures and protocols involving human subjects were consistent with the principles of the Helsinki Declaration—they were reviewed and approved by the Human Ethics Committee of the National Defense Medical Center, ROC. Informed consent for participation was obtained from each patient with ExHS when they were fully conscious. Criteria for the diagnosis of ExHS included hyperpyrexia (body temperature measured by a rectal thermometer with values exceeding 40 °C in each patient), significant alterations of mental status, including delirium, stupor, coma, seizure and bizarre behaviour, and positive urinary orthotaulidine test without microscopic haematuria. ARF was defined as an acute decrease in GFR as evidenced by a rise in the plasma creatinine concentration to >1.5 mg/dl on admission, with a progressive elevation thereafter. Recovery was defined as the time when the plasma creatinine declined to <1.5 mg/dl. The clinical features, including the time of onset, vital signs, physical examination and all treatments given, were recorded.

From January 1999 to December 2001, there were a total of 20 recruits who developed ExHS after heavy physical training—their exercise included running 5000 m, and multiple push-ups and sit-ups in an environment whose Wet-Bulb Globe Temperature (WBGT) ranged from 25.2 °C to 29.5 °C. Of these, eight were excluded because they had shock and failure involving other organs. Thus the study group consisted of the remaining 12 patients in whom ExHS was milder in degree, in that ARF was the sole life-threatening abnormality.

All patients received active cooling with cold, wet towels applied to the forehead, hand, neck, axillary, trunk and extremities immediately on arrival to the hospital. This management was continued until rectal temperature fell to 38 °C. The cooling time was defined as the time from the beginning of cooling in hospital until body temperature declined to <38 °C and remained at this level or lower for 2 h. A Foley’s catheter was inserted to monitor urine output on an hourly basis. Normal saline (1000 ml in 30 min) was administered in an attempt to raise the urine flow rate to at least 1 ml/min. For six patients who had oliguria, intravenous mannitol (25 g) was infused, followed by the administration of furosamide 120 mg. Two patients received haemodialysis therapy due to oliguric ARF (Table 1). The duration from the start of ARF to recovery ranged from 1 to 21 days.

The control group consisted of 12 recruits who went through the same physical training in the same hot environment without developing ExHS. Their blood samples were obtained at rest when they arrived at the hospital with the patients.

Arterial blood gases were obtained and throughout the study at one-day intervals. To measure vasoactive hormones, the first venous blood sample was collected through an indwelling catheter once the diagnosis of ARF was established, usually within one hour after admission. Additional venous sample were also obtained during the recovery phase of ARF. Urine samples were obtained for prostaglandin E2 (PGE2) and nitric oxide metabolites (NOx) including NO2− and NO3− measurements both in acute and recovery phase of ARF. An echocardiograph was performed during the first 1–2 h of cooling, followed by the nuclear medicine test for effective renal plasma flow (ERPF) and glomerular filtration rate (GFR). These examinations were repeated during the recovery of ARF.

Systemic haemodynamic evaluation

Blood pressure was recorded every 3 min with a semiautomated device (Dinamap 1846, Critikon). Pulse rate was recorded continuously on an electrocardiographic oscilloscope (Hewlett Packard). Mean arterial blood pressure (MAP) was calculated as
the diastolic pressure plus one third of the pulse pressure. Cardiac output (CO) was assessed by echocardiography (HP Sono 1000 with software). Total peripheral resistance (TPR) (dyne.sec.cm⁻²/CO⁻¹) was calculated as MAP⁻³×80/CO⁻¹.¹⁹

Renal haemodynamics and renal function evaluations

More comprehensive renal haemodynamics and renal function tests were performed including ERPF, GFR and renal vascular resistance (RVR)—these were determined by nuclear medicinal techniques using¹³¹I-orthoiodohippurate (¹³¹I-OIH) (Nuclear Science and Technology Development Center, Taiwan) and ⁹⁹ᵐTc diethylenetriamine-penta-acetic acid (⁹⁹ᵐTc DTPA) (Draximage), respectively. Renal blood flow (RBW) was calculated as ERPF/1-haematocrit. RVR (dyne.sec.cm⁻²/CO⁻¹) was calculated MAP⁻³×80/RBF.²⁰

Routine biochemical and hormone assays

Blood biochemical values were determined by automated methods (AU 5000 chemistry analyzer, Olympus). Plasma catecholamines, including nor-epinephrine (NE), epinephrine (EP) and dopamine (DA), were measured by high performance liquid chromatography with electrochemical detection as described previously.²¹ Plasma renin activity and aldosterone levels were measured by radioimmunoassay methods.¹⁰ Endothelin-1 (ET-1) was measured by enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems). PGE₂ was also analysed by ELISA (Amersham International). Plasma and urine NOx were measured using a colorimetric assay kit based on a simple two-step process.²²

Statistical analysis

Results are expressed as means±SD. The differences in clinical and metabolic characteristics between groups or between acute phase and recovery phase of ARF were analysed by unpaired or paired Student’s t test. The Mann-Whitney Rank-Sum test was used when the variables were not normally distributed between groups. Correlation analysis was by linear regression. p<0.05 was considered statistically significant.

Results

The clinical and laboratory features in patients with ExHS and ARF are shown in Tables 1 and 2. The plasma creatinine and blood urea nitrogen (BUN)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics in ExHS patients with ARF</th>
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<tbody>
<tr>
<td>Patient</td>
<td>Age (years)</td>
</tr>
<tr>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
</tr>
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<td>11</td>
<td>22</td>
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BT, body temperature; DOH, duration of hyperthermia; CT, cooling time; GSC, Glasgow coma score; HD, haemodialysis; T rec, time from ARF to recovery.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Laboratory features in controls and in patients with ExHS and ARF</th>
</tr>
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<tbody>
<tr>
<td>Parameters</td>
<td>Controls (n = 12)</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>42.2±2</td>
</tr>
<tr>
<td>Na⁺ (mEq/l)</td>
<td>140±2</td>
</tr>
<tr>
<td>K⁺ (mEq/l)</td>
<td>4.2±0.5</td>
</tr>
<tr>
<td>Cl⁻ (mEq/l)</td>
<td>106±2</td>
</tr>
<tr>
<td>HCO₃⁻ (mEq/l)</td>
<td>22.4±2.1</td>
</tr>
<tr>
<td>pH</td>
<td>7.41±0.03</td>
</tr>
<tr>
<td>pCO₂ (mmHg)</td>
<td>32±3</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>12±3</td>
</tr>
<tr>
<td>Ca²⁺ (mg/dl)</td>
<td>1.0±0.1</td>
</tr>
<tr>
<td>InP (mg/dl)</td>
<td>9.4±0.3</td>
</tr>
<tr>
<td>CPK (IU/l)</td>
<td>2725±3296</td>
</tr>
<tr>
<td>Alb (g/dl)</td>
<td>4.0±0.3</td>
</tr>
</tbody>
</table>

*p<0.01; **p<0.05.
concentration were significantly higher in the acute phase of ARF, compared to those of the controls. The patients in the experimental group had a mild degree of metabolic acidosis, hypocalcaemia, hyperphosphataemia, and hypoalbuminaemia. In contrast, there were no significant differences in plasma levels of sodium (Na\(^+\)), potassium (K\(^+\)) and chloride (Cl\(^-\)), compared to controls. Although patients with ARF and ExHS also had significantly higher plasma levels of creatine phosphokinase (CPK), there was no significant correlation between the plasma creatinine and CPK concentrations (\(r = 0.17\)).

Haemodynamic measurements are summarized in Table 3. Although there was no significant difference in cardiac output between the controls and ExHS groups, the mean MAP, HR and TPR were significantly higher in the acute phase of ARF. In the recovery phase, all of these parameters improved to values that were not significantly different from those in the controls. Impaired renal function, as indicated by a decline in both ERPF and GFR, was accompanied by an increase in RVR during the acute phase of ARF. In the recovery phase, the ERPF, GFR and RVR improved to values that were also not significantly different from those in controls.

There were significantly higher circulating vasoconstrictive hormones, including NE, EP, DA, ET-1, renin and aldosterone, in the acute phase of ARF with ExHS, compared to those of controls (Table 4). All elevated levels of vasoconstrictive hormones returned to values that were not significantly different from those of controls during the recovery phase of ARF.

There were significantly lower values of plasma PGE\(_2\) in the acute phase of ExHS, compared to controls. Noticeably, urinary PGE\(_2\): creatinine ratio was also significantly lower during the acute phase of ARF (2.7 ± 1.5 vs. 7.4 ± 2.0 pg/mg creatinine, \(p < 0.01\)) and returned to values seen in the control group during the recovery phase of ARF (Figure 2). The concentrations of NOx in plasma and urine, which were significantly higher in the acute phase of ARF, returned to near control values during the recovery phase of ARF (Figure 2).

### Correlations

There was no significant correlation between body temperature, circulating mediators and renal haemodynamics (\(p > 0.05\)). There was a positive correlation between the ERPF and the GFR in the acute as well as the recovery phases of ARF (Figure 1). Circulating vasoconstrictive hormones and NOx during the acute and recovery phases of ARF correlated negatively with the effective renal plasma flow rate in ExHS patients (Figure 3). However, the urinary vasodilator PGE\(_2\), which is mainly derived from the kidney, correlated positively with the effective renal plasma flow rate in ExHS patients (Figure 3).
Discussion

Although a rise in body temperature and exertion are two components of ExHS with ARF, the factors responsible for the development of ARF remain to be evaluated in a sufficiently large and homogeneous population. Hypokalaemia and rhabdomyolysis may contribute to the development of ARF in patients with heat illness. In this study, patients with ExHS and ARF did not have significant differences in their plasma $K^+$ concentration, compared to the control group. Peak plasma CPK levels have been reported to be directly related to the plasma creatinine concentration. When peak CPK values exceed 10,000 IU/l, ARF is much more likely to occur in ExHS. Although our patients with ExHS and ARF had significantly higher plasma CPK concentration, their initial average plasma CPK concentrations were only about 6000 IU/l. In addition, their CPK concentrations were not significantly related to their plasma creatinine concentration. In agreement with our findings, many patients with ExHS and ARF did not have higher levels of CPK, suggesting that factors other than rhabdomyolysis might have been centrally involved in the pathogenesis of ARF in heat illness.

The roles of circulating vasoconstrictive and vasodilatory hormones in the acute and recovery phases of ARF in ExHS were explored. The major findings were that renal haemodynamics were compromised, in conjunction with a significant elevation in BP, HR, and TPR. In contrast, there was not a significant change in CO in the acute phase of ARF, as compared to both the controls and the recovery phase of ExHS patients with ARF. There were significant elevations in circulating vasopressor hormones and a decrease in PGE$_2$. Nevertheless, there was also an increase in NOx in this

![Figure 1](https://academic.oup.com/qjmed/article-abstract/96/3/193/1563320)

**Figure 1.** Correlation between ERPF and GFR in patients with ExHS and ARF.

![Figure 2](https://academic.oup.com/qjmed/article-abstract/96/3/193/1563320)

**Figure 2.** Plasma and urinary PGE$_2$ and NOx in acute and recovery phase of ExHS patients with ARF and controls (ExC). $^*p<0.01$, acute vs. controls and $^+p<0.01$, acute vs. recovery.
acute phase. A significant fall in plasma levels of vasoconstrictive hormones was seen in the transition from the acute to the recovery phase of ARF. Moreover, there was a positive correlation between ERPF and the vasodilator PGE2. Our data suggest that both vasoconstrictive and vasodilatory hormones play important roles in the pathogenesis of the ARF in ExHS.

The lack of significant correlation between body temperature and circulating mediators or renal haemodynamics suggests that the measured body temperature was not the most important factor causing the higher levels of circulating mediators and altered renal haemodynamics. Other factors such as stress, hypovolaemia, renal vascular constriction, toxin, direct heat injury and cytokines may have contributed to the higher levels of circulating mediators and thus the change of renal and systemic haemodynamics.

In terms of ExHS, most of the studies reported in the literature focus on the role of cytokines and endothelial dysfunction. Multiple organ failure was often present. Furthermore, hypotension, ECF volume depletion and rhabdomyolysis were three factors involved in the pathogenesis of ARF. Our study is unique because the study group consisted...
of patients in whom ExHS was milder in degree, in that ARF was the sole life-threatening abnormality and was not accompanied by multiple organ failure. Compared to the previous studies of ExHS, our study also provides the association between the comprehensive systemic and renal haemodynamics and circulatory vasoactive mediators. To the best of our knowledge, detailed exploration in this area is lacking.

Turning to the role of vasoconstrictor and vasodilator hormones in ExHS with ARF, augmented catecholamine release occurs with both exercise and a rise in temperature. Another stimulus for catecholamines release is extracellular fluid (ECF) volume depletion. Consistent with the previous report, increased catecholamine secretion was also observed in patients with classic heat-stroke. Increased secretion of catecholamines is associated with renin and angiotensin II secretion. The α-receptor-mediated effects of catecholamines and the vasoconstrictor effect of the renin/aldosterone system could be expected to lead to both ExHS and ARF, because they could impair heat dissipation as well as cause renal arterial constriction. Infusion of dopamine might increase ERPF and GFR as well as decrease RVR in this situation. ET-1, another potent vasoconstrictor, may be an important mediator of ARF because of its intense vasoconstrictive properties. In addition, administration of the ET-1 receptor antagonist resulted in an improvement of renal blood flow and a significant decrease in proximal tubular necrosis. ET-1 levels were significantly elevated in the acute phase of ExHS in this study, and this rise was similar to that in patients with classical heatstroke. Endothelial injury/activation and endotoxin/cytokine production might augment ET-1 secretion in ExHS. Taken together, sympatho-adrenal activation, increased renin/aldosterone secretion, and increased ET-1 production may act in concert to contribute to the development of ARF in ExHS.

Regarding the vasodilatory mediators, urine PGE2 excretion was lower and NOx production was higher in the acute phase of ARF in ExHS. The higher temperature of blood may result in vascular endothelial disruption, leading to a decreased systemic as well as renal PGE2 production, and failure to counterbalance the higher levels of vasoconstricter hormones. In an animal model of sepsis without severe ARF, urinary PGE2 levels were significantly increased—they then decreased when severe ARF supervened. In the kidney, PGE1 is not only produced in endothelial cells, but it is also abundant in renal tubular and medullary interstitial cells. Decreased urinary excretion of PGE2 might also be attributed to extensive tubulointerstitial damage in ExHS with ARF. In contrast to PGE2, NOx production was augmented and this may be associated with the increased release of pro-inflammatory cytokines such as TNF-α and IFN-γ which has been reported recently in patients with heat stroke. These pro-inflammatory cytokines may up-regulate the inducible nitric oxide synthase and result in an enhanced production of NO in patients with ExHS. The deleterious effect of NO is principally ascribed to its irreversible reaction with superoxide anion to produce the potent oxidant peroxynitrite.

We hypothesize that the following mechanisms play a major role in the pathogenesis of ARF in ExHS (Figure 4). Initially, the very large sweat loss and diversion of the cardiac output to skeletal muscles could result in severe central blood volume depletion that overwhelms sympathetic compensation and leads to ischaemic organ damage. Heat and ischaemic injury could then trigger endothelial injury/activation; sympathetic activity; and enhanced release of renin and aldosterone. These changes in mediator levels together with augmented endothelin/NOx and attenuated PGE2 production could contribute to the observed decrease in GFR and ARF.

What are the clinical implications from this study? Unlike classic HS, ExHS usually occurs typically in younger, physically active patients with no predisposing diseases, not only in military service, but also in settings such as jogging, football sports and marathon running. Limited sun exposure, adequate and electrolyte replacement and acclimatization are the key factors for prevention. Rapid evaporative cooling and support of vital organs are the essential factors in the management of ExHS. From this study, attempts to increase circulating PGEs, reduce NOx production and inhibit catecholamine, renin-aldosterone and ET-1 might ameliorate the severity of ARF in patients with ExHS.

There were some limitations to this study. First, there were no perfect controls for heat stroke without ARF. Second, the onset of ARF was not uniform. The time from onset of heat stroke to arrival at the hospital was a variable. Third, the control group obviously did not receive the same treatment as the ARF group.

In conclusion, the combination of elevated vasoconstrictive hormones and the lower plasma and urinary counterbalancing hormone PGE2 in the acute phase suggests that extensive vascular endothelial and renal tubulointerstitial damage might occur in patients with ExHS and ARF. It is also possible that enhanced NOx production in heat injury might also participate in renal damage. Whether vasodilators such as PGE2, iNOS inhibitors, and...
vasoconstrictor inhibitors such as angiotensin-converting-enzyme inhibitors (ACEI) and ET-1 antagonists might have therapeutic benefit in patients with ExHS and ARF merits further investigation.

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References


