Lymphocyte subsets and adhesion molecules expression in heatstroke and heat stress

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Hammami, Muhammad M., Abderrezak Bouchama, Essam Shail, Hassan Y. Aboul-Enein, and Sultan Al-Sedairy. Lymphocyte subsets and adhesion molecules expression in heatstroke and heat stress. J. Appl. Physiol. 84(5): 1615–1621, 1998.—We examined the specificity of the recently reported alterations in circulating lymphocytes in heatstroke by determining lymphocyte subsets in 14 consecutive heatstroke patients before and after cooling and in 7 heat-stressed controls using single- or two-color immunofluorescence flow cytometry. The relationship with catecholamine levels was also studied. In heatstroke, percentages of T (CD3+/CD19−), T-helper (CD4+CD8−), T-inactive (CD3−/human leukocyte antigen-DR−), CD11a++, CD11c+, and CD44+ lymphocytes were significantly decreased, whereas percentages of T-suppressor-cytotoxic (CD8+/CD4−), natural killer (NK; CD3+/CD16+ or CD56−), CD3−/CD16+ or CD56−, CD3−/CD16+ or CD56+, and CD54+ lymphocytes were significantly increased, compared with 11 normal controls. The changes in the absolute numbers of lymphocyte subsets were in the same direction and were significant for T-helper, T-suppressor-cytotoxic, NK, CD3+/CD16+ or CD56−, and CD11c+ lymphocytes. Milder but significant changes in percentages of T-helper, T-suppressor-cytotoxic, CD11c+, and CD44+ lymphocytes were seen in heat stress. Cooling was associated with partial or complete normalization, further derangement (CD11a++, CD11c+), or overcorrection (NK, T-suppressor-cytotoxic, CD11b+) of abnormal percentages of lymphocyte subsets. Norepinephrine levels were significantly elevated in heatstroke (4.7-fold) and heat stress (3.2-fold), but did not significantly correlate with lymphocyte subsets. We conclude that heatstroke is associated with significant changes in percentages in absolute numbers of a wide range of circulating lymphocyte subsets that are not related to elevated catecholamine levels or totally normalized by cooling. Similar, albeit milder, changes are seen in heat stress, suggesting that the two syndromes represent a continuum.

catecholamines; cooling; pilgrimage

HEATSTROKE, an illness characterized by hyperthermia and neurological abnormalities on exposure to high ambient temperature (18), is a significant cause of morbidity and mortality in hot climates (18) and during heat waves in temperate climates (14). Increased susceptibility to infection (3), endotoxemia (7), and evidence of endothelial cells activation and/or injury (5, 6) have been reported in heatstroke, suggesting a possible alteration in the immune system and in leukocyte adhesion and activation. This was supported by our previous study (3), in which we used a small number of lymphocyte markers that showed significant changes in circulating lymphocyte subsets in patients who had heatstroke during the 1990 pilgrimage to Mecca, Saudi Arabia. However, several conditions that are common during the pilgrimage season, such as increased physical activity (11, 13, 16, 22), sleep deprivation (21), time-zone travel (23), heat exposure (15), mental stress (19), and sunlight exposure (12), have been associated with changes in lymphocyte distribution. This suggests that at least some of the observed changes in lymphocytes may not be due to heatstroke per se. The causes of these changes are not known. However, elevated catecholamine levels that may affect lymphocyte distribution (9) have been reported in heatstroke patients (1).

This study was conducted to 1) confirm and extend our previous observations by using additional lymphocyte markers, including adhesion molecules; 2) determine the differences in lymphocyte distribution between heatstroke patients and a control group that was exposed to the same living conditions [heat stress controls (HSC)]; 3) determine the effect of the conventional treatment of heatstroke (mainly cooling) on lymphocyte distribution; and 4) determine whether elevated catecholamine levels could explain the observed alteration in lymphocyte distribution.

MATERIALS AND METHODS

Heatstroke Patients, HSC, and Normal Controls (NC)

The study was conducted at the Heatstroke Center of King Faisal Specialist Hospital, Mecca, Saudi Arabia, during the 1993 pilgrimage season. Muslims from all over the world perform pilgrimage to Mecca, Saudi Arabia, at least once in their lives. The pilgrimage season takes place on the 12th mo of the Hejira (Lunar) calendar. In 1993, this corresponded to May–June. Pilgrimage activities entail a lot of sun exposure and walking. The weather in Mecca is hot and humid, and most pilgrims spend most of the pilgrimage season under crowded non-air-conditioned tents. The study was approved by the Institutional Review Board of King Faisal Specialist Hospital and Research Centre, Riyadh. The patients and controls of this study were also included in another study that has been recently reported (10).

Heatstroke patients. Fourteen consecutive patients with classic heatstroke diagnosed by a rectal temperature of >40.1°C and neurological abnormalities (delirium, convulsions, or coma) were recruited for the study. Vital signs were recorded immediately at the time of hospital admission. Neurological status on admission was assessed by the Glasgow coma score (24). The severity of heatstroke was calculated by using the simplified acute-physiology score (20). The patients were cooled based on the principle of dissipation of heat by evaporation (3). The mean cooling time (to a rectal temperature ≤39.4°C) was 88.6 min (range 25–255 min).

HSC. Seven pilgrims, friends, or relatives of heatstroke patients who were subjected to living conditions more or less similar to those of heatstroke patients and for the same duration were included in the study. All underwent a complete history and physical examination. Their vital signs,
including oral temperature, were normal. None was hyperventilating or had a recent cold drink when the temperature was recorded. Their mean age was 58 yr (range 40–76 yr).

NC. This group consisted of 11 healthy blood donors who were resting at room temperature.

Collection of Blood Samples

Blood samples were obtained from heatstroke patients immediately at the time of hospital admission before any treatment (n = 9), at 8 AM the next day after cooling was completed (n = 11, postcooling), and again 24 h later (n = 3, delayed postcooling). Six patients had both precooling and postcooling samples, and three had all three samples. Blood samples were obtained from HSC at arrival to the hospital.

Immunofluorescence Staining and Flow Cytometry Analysis

The Simultest IMK Plus Kit (Becton Dickinson, San Jose, CA) was used to enumerate the percentages of lymphocytes bearing CD3/CD19, CD4/CD8, CD3/human leukocyte antigen (HLA)-DR or CD3/CD16, or CD56. Lymphocytes bearing CD11a, CD11b, CD11c, CD18, CD44, or CD54 were identified by using anti-human leukocyte function antigen associated antigen (LFA)-1α, anti-Mac-1, anti-gp150,95, anti-human LFA-1β, anti-human leu-44, and anti-human leu-54 monoclonal antibodies, respectively (Becton Dickinson, San Jose, CA).

Blood samples were collected aseptically by venipuncture into sterile EDTA vacutainer tubes and stored for up to 6 h at room temperature until stained; 100 ml of whole blood were added to 10 ml of monoclonal antibodies and incubated for 15 min at room temperature. Red blood cells were lysed by adding 2 ml of fluorescence-activated cell sorter lysing solution and further incubating them for 10 min in the dark at room temperature. Cell pellets were collected by centrifugation at 300 g for 5 min, washed with 2 ml PBS, fixed in 0.5 ml 2.8% Formalin in PBS, and stored in the dark at 4°C for flow cytometry. All monoclonal antibodies (except for CD11b and CD11c) were obtained conjugated with fluorescein isothiocyanate (FITC) or phycoerythrin. For CD11b and CD11c, conjugation to FITC was carried out by an additional incubation with 10 ml goat anti-mouse Ig (GAM1g)-FITC for 15 min at room temperature before fixation. Flow cytometry was performed on Becton Dickinson FACSorty System by using Simultest software.

Catecholamine Levels

Norepinephrine and epinephrine were extracted from plasma by using activated alumina, as previously reported (2), and determined by high-performance liquid chromatography (model 501 Solvent Delivery System; Waters, Millford, MA) with electrochemical detector (Water's model 460).

Statistical Analysis

The data were analyzed by using JMP version 3.1 (SAS Institute, Cary, NC). All values are expressed as means ± SE. ANOVA was used to compare control, heat stress, and heatstroke groups. When a statistically significant difference was observed, Tukey-Kramer highest significant difference test was used. Paired r-test (two-tailed probability values) was used for comparing precooling with postcooling samples. Correlation was measured by Pearson's correlation coefficient. Differences were considered statistically significant when P < 0.05.

RESULTS

Clinical and Laboratory Data in Heatstroke Patients

Table 1 shows the relevant data obtained from heatstroke patients at the time of hospital admission. The preponderance of men is likely a reflection of the gender distribution of the pilgrims. Three patients had a rectal temperature of >43°C. Two patients were in shock (systolic blood pressure <90 mmHg), and three required intubation and mechanical ventilation. White blood cell count (WBC) showed mild leukocytosis (normal range is 3.6–9.6 × 10⁹/l), whereas hematocrit values were normal (normal range is 38–52% in males and 36–46% in females). One patient died. After cooling, four patients had persistent neurological deficits (stupor, coma), and one suffered from bleeding.

| Major Lymphocyte Subsets in Heatstroke and Heat Stress

The precooling of T (CD3⁺/CD19⁻), B (CD3⁻/CD19⁻), and natural killer (NK) (CD3⁻/CD16⁺ or CD56⁺) lymphocytes in heatstroke and HSC are shown in Table 2. In heatstroke, there was a decrease in the mean percentage of T lymphocytes and an increase in the mean percentage of NK lymphocytes. There was no significant change in the percentage of total lymphocytes or B lymphocytes.

The changes of these lymphocytes in HSC were in the same direction; however, they were not significantly different from NC. Heatstroke patients’ results were compared by using ANOVA and Tukey-Kramer honestly significant difference (HSD) test.

| Table 1. Clinical and laboratory data of 14 heatstroke patients on admission |
| Age, yr | 58.1 ± 5.4 |
| Sex, male-to-female ratio | 7:1 |
| Rectal temperature, °C | 42.3 ± 0.2 |
| Systolic blood pressure, mmHg | 116 ± 8.4 |
| Glasgow coma score | 3.9 ± 0.54 |
| Simplified acute-physiology score | 14.8 ± 0.8 |
| Creatinine, μmol/l | 126.4 ± 11.2 |
| Creatine kinase, U/l | 373 ± 9.7 |
| Cooling time, min | 88.6 ± 17.9 |
| White blood count, ×10⁹/l | 10.8 ± 1.64 |
| Lymphocytes, % | 27 ± 3.7 |
| Hematocrit, % | 41.5 ± 1.4 |

Values are means ± SE.

Values are means ± SE. Nos. in parentheses indicate no. of subjects in each group. Total, total lymphocytes determined by LeucoGATE and light-scatter gates. T, B, and natural killer (NK) lymphocyte subsets were determined by immunofluorescence flow cytometry. T, CD3⁺/CD19⁻; B, CD3⁻/CD19⁻; NK, CD3⁻/CD16⁺ or CD56⁺. ANOVA was used to compare control, heat stress, and heatstroke groups. Brackets connect groups that are significantly different by Tukey-Kramer honestly significant difference (HSD) test.

| Table 2. Percentages of major lymphocyte subsets in heatstroke and heat stress |

<table>
<thead>
<tr>
<th></th>
<th>Control (11)</th>
<th>Heat Stress (7)</th>
<th>Heatstroke (8)</th>
<th>ANOVA</th>
<th>Postcooling (13)</th>
<th>Delayed Postcooling (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>33 ± 2.4</td>
<td>23 ± 2.6</td>
<td>27 ± 3.7</td>
<td>0.08</td>
<td>8.7 ± 1.4</td>
<td>4 ± 1</td>
</tr>
<tr>
<td>T</td>
<td>72 ± 1.6</td>
<td>69 ± 2.7</td>
<td>56 ± 5.1</td>
<td>0.007</td>
<td>64 ± 3.6</td>
<td>55 ± 8.5</td>
</tr>
<tr>
<td>B</td>
<td>14 ± 1.1</td>
<td>12 ± 1.9</td>
<td>12 ± 1.6</td>
<td>0.55</td>
<td>23 ± 2.9</td>
<td>27 ± 6.8</td>
</tr>
<tr>
<td>NK</td>
<td>12 ± 1.7</td>
<td>17 ± 3.6</td>
<td>30 ± 4.5</td>
<td>0.002</td>
<td>7.8 ± 0.9</td>
<td>6.7 ± 1.2</td>
</tr>
</tbody>
</table>

Values are means ± SE.
The percentages of T-helper (CD4+/CD8\(^-\)), T-suppressor-cytotoxic (CD4\(^-\)/CD8\(^+\)), T-active (CD3\(^+\)/HLA-DR\(^-\)), T-inactive (CD3\(^+\)/HLA-DR\(^+\)), T\(^\text{CD}3\)/CD16\(^-\) and CD56\(^-\), and T CD16\(^+\) or CD56\(^+\) lymphocytes in heatstroke and HSC are shown in Table 3. In heatstroke, there was a significant increase in the percentages of T-suppressor-cytotoxic and T CD16\(^+\) or CD56\(^+\) lymphocytes and a significant decrease in the percentages of T-helper and T-inactive lymphocytes.

In HSC, the changes were in the same direction but were significant only for T-helper and T-suppressor-cytotoxic lymphocytes. On the other hand, heatstroke was significantly different from HSC in regard to T-helper and T-inactive lymphocytes.

The percentage of lymphocytes negative for both CD4 and CD8 was significantly increased in heatstroke (37.3 ± 4.4) compared with NC (24.6 ± 1.5) and with HSC (25 ± 2.2).

Lymphocytes Expressing Adhesion Molecules in Heatstroke and Heat Stress

The percentages of lymphocytes expressing various adhesion molecules in heatstroke and HSC are shown in Table 4. In heatstroke, lymphocyte expression of CD11a, CD11c, and CD44 was significantly decreased, whereas lymphocyte expression of CD54 was significantly increased. No significant change was observed in lymphocyte expression of CD11b or CD18.

In HSC, the changes in the expression of these molecules were in the same direction but were significant only for CD11c and CD44. The differences between heatstroke and HSC were not significant for any of the adhesion molecules studied.

The percentage of lymphocytes expressing CD11b correlated significantly with the percentage of NK cells in heatstroke (r = 0.75, P = 0.02).

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**Table 3. Percentages of T-lymphocyte subsets in heatstroke and heat stress**

<table>
<thead>
<tr>
<th></th>
<th>Control (11)</th>
<th>Heat Stress (7)</th>
<th>Heatstroke (9)</th>
<th>ANOVA</th>
<th>Postcooling (11)</th>
<th>Delayed Postcooling (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-helper</td>
<td>43 ± 2.1</td>
<td>31 ± 3</td>
<td>15 ± 2.1</td>
<td>&lt;0.0001</td>
<td>44 ± 2.7</td>
<td>38 ± 5.1</td>
</tr>
<tr>
<td>T-suppressor-cytotoxic</td>
<td>28 ± 1.5</td>
<td>42 ± 4.2</td>
<td>46 ± 3.9</td>
<td>0.0006</td>
<td>21 ± 1.9</td>
<td>19 ± 1.9</td>
</tr>
<tr>
<td>T-active</td>
<td>12 ± 1.8</td>
<td>14 ± 1.9</td>
<td>19 ± 3.5</td>
<td>0.15</td>
<td>9.3 ± 0.9</td>
<td>11 ± 1.7</td>
</tr>
<tr>
<td>T-inactive</td>
<td>63 ± 2.5</td>
<td>56 ± 3.9</td>
<td>40 ± 3.8</td>
<td>&lt;0.0001</td>
<td>59 ± 3.0</td>
<td>47 ± 9.5</td>
</tr>
<tr>
<td>T CD16(^-) and CD56(^-)</td>
<td>59 ± 6</td>
<td>59 ± 3</td>
<td>42 ± 4.7</td>
<td>0.05</td>
<td>58 ± 3.4</td>
<td>45 ± 8.9</td>
</tr>
<tr>
<td>T CD16(^+) or CD56(^+)</td>
<td>6.7 ± 1.1</td>
<td>10 ± 1.8</td>
<td>17 ± 3.2</td>
<td>0.01</td>
<td>9.2 ± 2.2</td>
<td>12 ± 3.4</td>
</tr>
</tbody>
</table>

Percentages out of total no. of lymphocytes presented as means ± SE. Nos. in parentheses indicate no. of subjects in each group. T-helper, CD4\(^+\)/CD8\(^-\); T-suppressor-cytotoxic, CD4\(^-\)/CD8\(^+\); T-active, CD3\(^+\)/HLA-DR\(^-\); T-inactive, CD3\(^+\)/HLA-DR\(^+\); T CD16\(^-\) and CD56\(^-\), CD3\(^-\)/CD16\(^-\) and CD56\(^-\); T CD16\(^+\) or CD56\(^+\), CD3\(^+\)/CD16\(^+\) or CD56\(^+\). ANOVA was used to compare control, heat stress, and heatstroke groups. Brackets connect groups that are significantly different by Tukey-Kramer HSD test.
Levels of Catecholamines and Correlation With Lymphocyte Distribution

In heatstroke, the levels of epinephrine and norepinephrine were elevated (315 ± 68 and 1,600 ± 174 pg/ml, respectively) compared with NC (152.6 ± 22.1 pg/ml, not significant; 344.6 ± 42 pg/ml, significant; respectively) and correlated with rectal temperature (r = 0.5, P = 0.02; r = 0.6, P = 0.003, respectively).

In HSC, epinephrine levels were decreased (98 ± 34 pg/ml, not significant) and norepinephrine levels were significantly elevated (1,101 ± 129 pg/ml) compared with NC. The differences between heatstroke and HSC were significant for epinephrine but not for norepinephrine levels.

Epinephrine levels correlated significantly with norepinephrine levels (r = 0.57, P = 0.007) in heatstroke. However, catecholamine levels did not correlate significantly with percentages or absolute numbers of any of the major lymphocyte subsets.

Effect of Cooling on Lymphocyte Distribution

Postcooling blood samples were analyzed from 11 heatstroke patients, and delayed postcooling samples were analyzed in three (Tables 2–4). Six patients had paired preclooling and postcooling samples, and three of the six had delayed postcooling samples.

Cooling was associated with significant changes in the percentage of several lymphocyte subsets, some of which are shown in Fig. 2. In addition, the percentages of T-inactive, T CD16<sup>+</sup> and CD56<sup>+</sup>, and T CD16<sup>+</sup> or CD56<sup>+</sup> lymphocytes, and of total lymphocytes showed significant changes (P = 0.03, P = 0.0009, P = 0.02, and P = 0.02, respectively).

It is of note that 1) the percentage of total lymphocytes, which was not significantly different from NC precooling, significantly decreased after cooling; 2) the percentage of B lymphocytes, which was not significantly different from NC precooling, significantly increased after cooling; and 3) the percentages of CD11a<sup>+</sup> and CD11c<sup>+</sup> lymphocytes continued to decrease after cooling (P = 0.1, P = 0.2, respectively). Other significant derangements observed in heatstroke were partially corrected (T-helper, T-inactive), or overcorrected (NK, T-suppressor-cytotoxic) after cooling.

Cooling was associated with a significant decrease in epinephrine (106 ± 32 pg/ml, P = 0.04) but not in norepinephrine levels (1,442 ± 286 pg/ml, P = 0.7).

Absolute Numbers of Lymphocytes

The absolute numbers of lymphocytes in heatstroke and heat stress are shown in Table 5. The changes of lymphocyte subsets in absolute numbers were in general, reflective of the changes in their percentages.

In heatstroke, compared with NC, there was an ~25% increase in the total number of lymphocytes. This was accompanied by a significant 2- to 3-fold increase in the numbers of NK, T-suppressor-cytotoxic, and CD3<sup>+</sup>/CD16<sup>+</sup> or CD56<sup>+</sup> lymphocytes. On the other hand, the numbers of T-helper and CD11c<sup>+</sup> lymphocytes significantly decreased by 60 and 76%, respectively, despite the increase in the total number of lymphocytes.

In heat stress, compared with NC, the number of T-suppressor-cytotoxic lymphocytes increased 1.5-fold, whereas the numbers of T-helper and CD11c<sup>+</sup> lymphocytes decreased by 27–78%. However, only the change in the number of CD11c<sup>+</sup> was significant.

Postcooling, there was a 57% decrease in the total number of lymphocytes (P = 0.02) accompanied by an...
89% decrease in the number of NK (P = 0.01), 80% decrease in the number of T-suppressor-cytotoxic (P = 0.02), 81% decrease in the number of CD11b+ (P = 0.01), 33% decrease in the number of T CD16- and CD56- (P = 0.09), 61% decrease in the number of CD11a+ (P = 0.02), and 76% decrease in the number of CD11c+ (P = 0.04) lymphocytes. In addition, the number of T-helper lymphocytes (P = 0.4) increased 1.4-fold despite the marked decrease in the total number of lymphocytes. All these changes in absolute numbers were in the same direction as the changes in percentages. However, the changes in the absolute number of B (P = 0.04), T-inactive (P = 0.07), and T CD16+ or CD56+ (P = 0.03) lymphocytes were opposite to the changes in their percentages.

In heatstroke patients, the number of NK lymphocytes correlated with the number of CD3- /CD19- lymphocytes (r = 1, P < 0.0001) and the number of CD11b+ lymphocytes (r = 0.95, P = 0.0001), confirming that they may represent the same population.

**DISCUSSION**

We have previously shown that heatstroke is associated with leukocytosis and profound alteration in the percentages and absolute numbers of circulating lymphocyte subsets, namely, a marked increase in T-suppressor-cytotoxic and NK lymphocytes accompanied by a marked decrease in T-helper lymphocytes and T-helper-to-T-suppressor-cytotoxic ratio (3). In this study, we have examined whether, on one hand, cooling could affect this alteration and, on the other, whether similar changes could be seen in heat-stressed subjects, i.e., before the development of the syndrome of heatstroke.

We made the following observations. 1) Heat-stressed subjects displayed a significant increase in the percentage of T-suppressor-cytotoxic lymphocytes and a significant decrease in the percentage of T-helper lymphocytes, a pattern of distribution that resembled that of heatstroke, albeit milder. 2) When heatstroke developed, the changes in lymphocyte subsets became more pronounced. 3) Finally, after cooling, there was a partial or complete correction of only some of lymphocyte subsets, whereas other subsets were either overcorrected (NK, T-suppressor-cytotoxic lymphocytes) or further deranged (total lymphocytes, CD11a+, CD11c+).

These changes, together with our recent findings of hypercytokinemia (7, 10), coagulation and fibrinolysis activation (4), and endothelial cell activation (5, 6), which start in heat stress, become profound when heatstroke develops and are not normalized by cooling. They add further evidence that early systemic inflammation may be implicated in the pathogenesis of hyperthermia and clinical manifestations of heatstroke. Furthermore, they strongly suggest that factors other than hyperthermia may be responsible for the persistence of the disturbance in homeostasis in heatstroke, and they may lead to new prophylactic and therapeutic strategies.

The present study extends our previous findings (3) and indicates that heatstroke is associated with changes in a wider spectrum of lymphocyte subsets, including T CD16+ or CD56+, T-inactive, CD44+, CD54+, CD11a+, and CD11c- lymphocytes. Interestingly, the heat stress...
was also associated with significant changes in CD11c and CD44+ lymphocytes. Lymphocytes express cell surface adhesion molecules that mediate several lymphocyte functions such as T-cell-mediated killing, T-helper functions, T-cell proliferative response, and B-cell activation (17). The observed decrease in CD11c and CD44+, and to a lesser extent in CD11a+ lymphocyte, may contribute to the increased susceptibility to infection reported in heatstroke (3). On the other hand, the increase in CD54+ lymphocytes suggests a state of lymphocyte activation (8) and may play a role in endothelial cell activation and/or injury in heatstroke (5, 6).

The underlying causes of the observed changes in lymphocyte subsets are not clear. However, several environmental factors (11–13, 15, 16, 19, 21–23) that are present during pilgrimage as well as hemodynamic changes (3) and elevated levels of cytokines (7, 10), are present during pilgrimage as well as hemodynamic changes (3) and elevated levels of cytokines (7, 10), may be responsible for some of the alteration in lymphocyte subsets in heatstroke. We found that the levels of norepinephrine were significantly elevated in heatstroke compared with normal controls. However, elevated catecholamine levels did not account for the changes observed in the expression of adhesion molecules or in the percentages or absolute numbers of major lymphocyte subsets, namely, NK, B, T-helper, and T-suppressor/cytotoxic lymphocytes.

In summary, heatstroke is associated with significant changes in a wide range of lymphocyte subsets that are not related to elevated catecholamine levels and that are not totally normalized by cooling. Similar, albeit milder, changes are seen in heat stress, suggesting that the two syndromes represent a continuum rather than separate entities. The role of these changes in the pathogenesis of heatstroke and its complications deserves further studies.

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