Reductions in Systemic and Skeletal Muscle Blood Flow and Oxygen Delivery Limit Maximal Aerobic Capacity in Humans

José González-Alonso, PhD; José A.L. Calbet, MD, PhD

**Background**—A classic, unresolved physiological question is whether central cardiorespiratory and/or local skeletal muscle circulatory factors limit maximal aerobic capacity ($V_O^2_{max}$) in humans. Severe heat stress drastically reduces $V_O^2_{max}$, but the mechanisms have never been studied.

**Methods and Results**—To determine the main contributing factor that limits $V_O^2_{max}$ with and without heat stress, we measured hemodynamics in 8 healthy males performing intense upright cycling exercise until exhaustion starting with either high or normal skin and core temperatures (+10°C and +1°C). Heat stress reduced $V_O^2_{max}$, 2-legged $V_O^2$, and time to fatigue by 0.4±0.1 L/min (8%), 0.5±0.2 L/min (11%), and 2.2±0.4 minutes (28%), respectively (all $P<0.05$), despite heart rate and core temperature reaching similar peak values. However, before exhaustion in both heat stress and normal conditions, cardiac output, leg blood flow, mean arterial pressure, and systemic and leg $O_2$ delivery declined significantly (all 5% to 11%, $P<0.05$), yet arterial $O_2$ content and leg vascular conductance remained unchanged. Despite increasing leg $O_2$ extraction, leg $V_O^2$ declined 5% to 6% before exhaustion in both heat stress and normal conditions, accompanied by enhanced muscle lactate accumulation and ATP and creatine phosphate hydrolysis.

**Conclusions**—These results demonstrate that in trained humans, severe heat stress reduces $V_O^2_{max}$ by accelerating the declines in cardiac output and mean arterial pressure that lead to decrements in exercising muscle blood flow, $O_2$ delivery, and $O_2$ uptake. Furthermore, the impaired systemic and skeletal muscle aerobic capacity that precedes fatigue with or without heat stress is largely related to the failure of the heart to maintain cardiac output and $O_2$ delivery to locomotive muscle. *(Circulation. 2003;107:824-830.)*

**Key Words:** hemodynamics ■ blood flow, regional ■ cardiac output ■ hemodynamics ■ heat stress

During heavy exercise, large volumes of oxygen are transported through the links of the cardiorespiratory transport system to mitochondrial cytochromes for synthesis of ATP in the electron transport chain. The fastest rate at which the body can utilize $O_2$ during heavy exercise is defined as the maximum rate of oxygen uptake ($V_O^2_{max}$), which is an index of maximal cardiovascular function, provided pulmonary function and ambient $O_2$ concentration are normal.1 The working skeletal muscle cells, which account for more than 90% of the energy spent during severe exercise, largely determine $V_O^2_{max}$.1-4 Long-standing yet unresolved debates center on whether central cardiorespiratory and/or local skeletal muscle circulatory and metabolic factors limit $V_O^2_{max}$.1-7

Severe heat stress has been shown to markedly suppress $V_O^2_{max}$ and work capacity without altering the initial rate of rise in whole-body $V_O^2$.8 The mechanisms underlying the compensatory adjustments to heat stress early in exercise and the subsequent precipitated fatigue have never been investigated. During heavy exercise in normal environments, fatigue is often preceded by a plateau or even a decline in $V_O^2_{max}$.9 However, no study to date has determined whether central hemodynamics and skeletal muscle circulation are indeed impaired before fatigue during exercise that requires maximal aerobic capacity.

Therefore, the principal aim of this study was to identify the primary factor that limits $V_O^2_{max}$ in healthy trained humans. Another aim was to determine the mechanisms underlying the blunted $V_O^2_{max}$ and early fatigue associated with heat stress. To accomplish this, we used the novel approach of simultaneously measuring systemic hemodynamics and local skeletal muscle circulatory and metabolic factors during constant high-intensity exercise in conditions of markedly different $V_O^2_{max}$ due to the presence or absence of exogenous heat stress.

**Methods**

Eight healthy trained males gave written informed consent to participate in this study, which was approved by the ethics committee of Copenhagen and Fredericksberg. The subjects’ mean (±SD) age, body weight, leg muscle mass, height, maximal heart rate, and $V_O^2_{max}$ were 24±4 years, 78.1±7.4 kg, 9.8±0.9 kg, 181±5 cm, 191±6 bpm, and 4.7±0.5 L/min, respectively.

Received July 18, 2002; revision received October 24, 2002; accepted October 24, 2002.

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*Circulation* is available at http://www.circulationaha.org

DOI: 10.1161/01.CIR.0000049746.29175.3F

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On the day of the experiment, subjects reported to the laboratory ∼2 hours before the experiment after breakfast. On arrival, they rested in the supine position. Catheters were placed into the femoral artery, bilateral femoral veins, and antecubital forearm vein by the Seldinger technique under local anesthesia. The femoral artery and vein catheters were positioned 1 to 2 cm proximal or distal from the inguinal ligament. A thermistor to measure venous blood temperature was inserted through the femoral venous catheter orientated in the anterograde direction. The catheter for femoral venous blood sampling was inserted in the retrograde direction to avoid any contamination from blood coming from the great saphenous vein.

Thereafter, subjects completed 3 cycle ergometer exercise tests in the upright position (Excalibur), starting with either high (H; test 1) or normal (N; tests 2 and 3) skin and core temperatures (+10°C and +1°C, respectively, in H versus N). In tests 1 and 3, subjects cycled until volitional fatigue, whereas in test 2, they cycled for the same duration as in heat stress. In every test, power output was held constant at 356±14 W. Each exercise test was separated by 1 hour of rest and was preceded by 10 to 15 minutes of light-intensity cycling (<50% VO2max) and 5 minutes of rest. The exercise intensity was selected such that the subjects would become exhausted within 5 to 10 minutes, and it elicited VO2max in 3 to 5 minutes under normal environmental conditions (80% of 44±4 W peak power output obtained in pretests).

To restore bodily fluid compartments and bodily energy stores, subjects ingested ∼2 L of a carbohydrate-electrolyte solution (Gatorade) during resting periods. Internal body and skin temperatures were elevated before the maximal aerobic tests by perfusion of hot water (44°C) into a jacket in contact with the skin of trunk and arms while the subject was wearing rain trousers during the light cycling and rest periods. In N trials, subjects wore only shorts while cycling with 2 fans blowing at an ambient temperature of 14°C to 16°C. During the resting period before each intense exercise bout, a muscle biopsy from the vastus lateralis was obtained. During exercise, heart rate, pulmonary VO2, blood pressure, and venous blood temperature were recorded continuously. Cardiac output (Q) and leg blood flow (LBF) were measured periodically during exercise. Arterial and venous blood samples (10 mL) were drawn simultaneously at 0.5, 1.5, 3, 5.5±0.5, and 7.6±0.4 minutes of exercise. On completion of each exercise bout, a postexercise muscle biopsy was obtained within 20 to 40 seconds.

Pulmonary VO2 was measured online with an Applied Electrochemistry OCM-2 metabolic cart. Cardiac output was measured by indocyanine (ICG, Akon Inc) dye dilution. LBF was determined by the constant-infusion thermodilution technique. Heart rate was obtained from the continuously recorded ECG signal. Arterial blood pressure was continuously monitored from the femoral artery with the transducer positioned at the height of the inguinal ligament (Pressure Monitoring Kit, Baxter). Systemic and leg vascular conductances were calculated as the quotient between Q or LBF, respectively, and mean arterial blood pressure (MAP).

Results

VO2max and time to fatigue were significantly diminished in H compared with N (4.28±0.15 versus 4.72±0.18 L/min and 5.45±0.23 versus 7.63±0.42 minutes, respectively), despite attainment of similar peak values for femoral venous blood temperature, heart rate, and pulmonary ventilation (VE 167 to 177 ±6 L/min; Figure 1). Furthermore, whole-body VO2 during N declined by 0.27±0.09 L/min before exhaustion (P<0.05; Figure 1). In both H and N, Q, LBF, and MAP declined significantly before exhaustion compared with the corresponding peak exercise values (1.5 to 2.6 L/min and 13 to 14 mm Hg, respectively; Figure 2; P<0.05). The decline in

![Figure 1. Femoral venous blood temperature, heart rate, and pulmonary oxygen uptake during intense cycling exercise during heat stress and normal trials. Note that femoral venous blood temperature reflects esophageal temperature, being only 0.1°C higher. Data are mean±SEE for 8 subjects. *Significantly lower than peak VO2 value during exhausting normal trial, P<0.05. †Significantly different from normal trials, P<0.05.](image-url)
Muscle glycogen, lactate, ATP, and creatine phosphate (PCr) were similar before the 3 exercise bouts. However, when subjects exercised for the same duration in H compared with N (5.5 ± 0.2 minutes), muscle lactate accumulation, PCr hydrolysis, and ATP hydrolysis were greater, and the rate of leg lactate release tended to be higher (P = 0.15; Table 2).

Discussion
There were 3 major findings in this study. First, heat stress drastically reduced $V_{\text{O2max}}$ compared with the normal condition by accelerating the declines in $Q$ and MAP that led to decrements in locomotive skeletal muscle blood flow, $O_2$ delivery, and $O_2$ uptake. Second, the declining skeletal muscle $V_{\text{O2}}$ before fatigue with or without heat stress was solely attributed to a similar lowering in systemic and skeletal muscle $O_2$ delivery, because arterial $O_2$ content, exercising leg $O_2$ extraction, and leg vascular conductance were unaltered. Third, the reduced leg $V_{\text{O2}}$ with heat stress was accompanied by an enhanced muscle lactate accumulation and ATP and PCr hydrolysis, yet muscle energy stores were not depleted on fatigue. Together, the present findings suggest that impaired skeletal muscle aerobic energy provision and work capacity during maximal aerobic exercise in healthy trained humans are directly related to the inability of the heart to maintain $Q$ and $O_2$ delivery to locomotive skeletal muscle.

This is the first study to demonstrate that $Q$, locomotive muscle blood flow, MAP, and systemic and locomotive muscle $O_2$ delivery decline significantly during exhaustive maximal aerobic exercise in humans. Although heat stress clearly exacerbated cardiovascular instability and drastically reduced $V_{\text{O2max}}$, systemic and exercising LBF and $O_2$ delivery declined similarly before exhaustion when subjects were exposed to both severe heat stress and cold environmental conditions. Therefore, our present findings provide crucial insight into the long-standing debate about the factors that limit maximal aerobic capacity in humans and how blood flow is distributed in hot and cold environments.

During the early stages of exercise, we observed that when heat stress was added and the skin vasodilated, $Q$ was higher ($\approx 1.5 \text{ L/min}$) and blood flow to the legs was lower (0.7 to 2.7 L/min), but systemic and locomotive muscle $V_{\text{O2}}$ were strikingly similar among conditions. Importantly, the lower LBF with heat stress was met by elevations in $C_{\text{a,o2}}$, arteriovenous $O_2$ difference, and $O_2$ extraction, which permitted $V_{\text{O2}}$ by the legs to be maintained. These precise circulatory adjustments are consistent with evidence that acute alterations in $C_{\text{a,o2}}$ with anemia, hypoxia, anemia plus hypoxia, hyperoxia, CO plus normoxia, and CO plus hyperoxia evoke reciprocal changes in LBF and arteriovenous $O_2$ difference compared with normoxia, such that muscle $V_{\text{O2}}$ is kept constant. They are also in accord with the progressive augmentation in arteriovenous $O_2$ difference but equal leg $V_{\text{O2}}$ observed during prolonged exercise in the heat, when LBF declines in parallel to the dehydration-induced hemococoncentration. Hence, the distinct LBF response seen here during the initial part of exercise does not appear to be related to the presence of heat stress but rather to concomitant hemococoncentration. Nevertheless, the enhanced $Q$, the lower
LBF, and the plausibly diminished splanchnic and renal blood flow\(^2,17\) appear to fully account for the expected 3- to 5-fold elevation in skin blood flow with H compared with N.\(^{18}\)

Although the higher Q, hemoconcentration, and enhanced O\(_2\) extraction afforded a similar initial rate of rise in V\(_{\text{O}_2}\), heat stress severely suppressed V\(_{\text{O}_\text{max}}\) and 2-legged V\(_{\text{O}_2}\) (0.4 to 0.5 L/min). There are several reports documenting a blunting of V\(_{\text{O}_\text{max}}\) with marked heat stress.\(^8\) The present novel finding was that the impairment in V\(_{\text{O}_\text{max}}\) was initiated by the more rapid decline in Q and MAP, which led to the fastened fall in exercising muscle blood flow, O\(_2\) delivery, and O\(_2\) uptake compared with normal conditions. This interpretation is supported by the observation that leg vascular conductance did not change in either exhaustive trial, which in turn suggests that the lowering in LBF and O\(_2\) transport was due to the reduction in Q and perfusion pressure rather than an augmented muscle vasoconstriction. Moreover, fatigue in the control condition was preceded by similar cardiovascular instability that produced a small but significant fall in V\(_{\text{O}_\text{max}}\) and leg V\(_{\text{O}_2}\). Therefore, it appears that heat stress more quickly pushes the cardiovascular system to its absolute regulatory limit, where Q and O\(_2\) transport to the locomotive muscles can no longer be maintained despite the skeletal muscle remaining below its maximal capacity to consume O\(_2\).

Limitations to the diffusion of O\(_2\) from the muscle capillary to the mitochondrial cytochrome have been postulated to restrict V\(_{\text{O}_\text{max}}\).\(^{1,19}\) The question then arises whether diffusive O\(_2\) transport across the leg muscles was impaired in the present study. The observations that leg arteriovenous O\(_2\) difference and O\(_2\) extraction increased progressively until the end of exercise preclude any sudden drop in O\(_2\) diffusion at the time O\(_2\) delivery to the legs was falling. Thus, the greater decline in convective O\(_2\) transport to the leg muscles was clearly the cause of the reductions in leg V\(_{\text{O}_2}\) before exhaustion in either environmental condition (Figure 4). In the present study, however, leg O\(_2\) extraction and femoral venous blood oxygen reached strikingly equal values of 91% (range 87% to 95%) and 20 mL/L (P\(_{\text{O}_2}\) 10 to 15 mm Hg) when exposed to either heat stress or normal conditions. The fact that there was some O\(_2\) left in the femoral venous blood could be interpreted to mean that muscle O\(_2\) extraction was not maximal. However, femoral venous blood reflects mixed blood from all leg tissues (skin, bone, connective tissue, and fat account for 20% of the 12.1 kg of leg in these subjects), including muscles with presumably different levels of activation, metabolism, and O\(_2\) extraction during exercise.\(^{20}\) It could then be envisioned that most active muscle fibers were extracting nearly all circulating O\(_2\), particularly in those 4 subjects with 94% to 95% average leg O\(_2\) extraction, and that the remaining O\(_2\) in the femoral vein could be accounted for, at least in part, by the lower O\(_2\) extraction of skin, connective tissue, fat, and bone. In this context, the contribution of muscle O\(_2\) conductance in limiting locomotive muscle V\(_{\text{O}_2}\) during whole-body exercise in trained humans is very small.

The observation that Q, LBF, and MAP declined significantly before maximal heart rate was reached indicates that
maximal cardiovascular function was attained below maximal heart rate. The decline in stroke volume clearly caused the drop in Q (1.5 to 2.9 L/min), although the underlying mechanisms remain obscure. The classic study of Rowell et al using untrained men showed that heat stress during moderate exercise caused significantly lower stroke volume, central blood volume, and Q, yielding the hypothesis that the reduction in central blood volume and cardiac filling secondary to the increased skin blood flow and volume was the cause of the impaired stroke volume with heat stress. The present results that stroke volume was similar early in exercise and that, before exhaustion, it tended to decline even more in the cold than in the heat stress condition (20°C versus 10°C) strongly argue against a role of skin circulation. Instead, the fall in stroke volume during the last 2 minutes of exercise in both fatiguing trials coincided with a declining MAP, an internal body temperature of 39°C, and almost-maximal heart rate (185 to 187 bpm). The reduced MAP rules out an augmented afterload as a contributing factor. An alternative possibility is that different factors interact to alter preload and/or left ventricular systolic and diastolic function and impair stroke volume. In support of a role of hyperthermia and concomitant tachycardia, we have recently shown that blunting hyperthermia and thereby slowing the rate of rise in heart rate in dehydrated individuals restores 65% of the fall in Vo2max evoked by hyperthermia alone or combined dehydration and hyperthermia. Therefore, the decline in stroke volume during heavy exercise could be related in part to the simple restriction in left ventricular filling time and left ventricular end-diastolic volume that accompanies severe tachycardia.

The declining systemic O2 delivery and Vo2max during heavy exercise indicate that the mechanisms of fatigue were undoubtedly complex, possibly involving inhibitory signals that originated in different bodily tissues and organs. Clearly, the locomotive skeletal muscle was the main bodily tissue accounting for the reductions in peripheral blood flow and Vo2. Consistent with our circulatory data, we observed that the reduced leg Vo2 with heat stress was accompanied by enhanced net PCr hydrolysis, net ATP hydrolysis, muscle lactate accumulation, and somewhat higher net leg lactate release, which added together apparently sustained total leg energy turnover. Depletion of muscle ATP, PCr, and glycogen does not appear to be the cause of fatigue with or without heat stress, because the levels of these substrates were still high on exhaustion. Regardless of this, the dramatic metabolic changes in contracting muscle cells that preceded exhaustion were quite likely mirrored by increases in intramuscular P, ADP, and H⁺, which have been shown to depress contractile function in skinned and intact fibers. Moreover,
exhaustion in both trials coincided with a similar femoral venous blood temperature of 39.5°C to 39.7°C, which indicates that leg muscle temperature was 40°C to 41°C. Thus, it could be postulated that the abrupt accumulation in muscle cells of Pi, ADP, and H+/H1 together with the high muscle temperature might have inhibited muscle contractile processes and thus contributed to fatigue during heavy exercise.

In summary, we showed that heat stress reduces \( \dot{V}O_2 \text{max} \) by accelerating the declines in Q and MAP that lead to decrements in locomotive skeletal muscle blood flow, \( O_2 \) delivery, and \( O_2 \) uptake. Furthermore, we showed that the fall in locomotive muscle \( \dot{V}O_2 \) before fatigue in either condition was associated with the reduction in systemic and muscle \( O_2 \) delivery. Finally, fatigue with or without exogenous heat stress was not related to depletion of muscle glycogen, PCr, or ATP. Taken collectively, our findings suggest that the suppressed systemic and locomotive skeletal muscle aerobic capacity that precedes fatigue with and without heat stress in trained subjects is closely related to the inability of the heart to maintain Q and \( O_2 \) delivery to locomotive muscle. Future experiments should address whether the same phenomenon occurs in untrained individuals of different ages and sexes.

**Acknowledgments**

This study was supported by grants from the Danish National Research Foundation (504-14), the Gatorade Sports Science Institute, and Team Denmark. The excellent technical assistance of Birgitte Jessen, Karin Hansen, Carsten Nielsen, Kristina Möller, and Ingelise Kring is acknowledged. Special thanks are given to Dr Lene Rørdam from the Department of Clinical Physiology, Bispebjerg Hospital, Copenhagen, for performing the body composition analysis by DEXA scanning.

**References**


**TABLE 2. Muscle Metabolites During Intense Exercise in Heat Stress and Normal Trials**

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Heat Stress-Maximal</th>
<th>Normal</th>
<th>Normal-Maximal</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP, mmol/kg wet weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>5.6±0.6</td>
<td>5.4±0.3</td>
<td>5.5±0.3</td>
</tr>
<tr>
<td>After</td>
<td>4.1±0.2†</td>
<td>4.6±0.3†</td>
<td>4.1±0.4†</td>
</tr>
<tr>
<td>PCr, mmol/kg wet weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>18.8±1.4</td>
<td>17.8±1.7</td>
<td>18.7±1.1</td>
</tr>
<tr>
<td>After</td>
<td>10.0±1.1*</td>
<td>13.7±1.6</td>
<td>12.5±0.8</td>
</tr>
<tr>
<td>Lactate accumulation, mmol/kg wet weight</td>
<td>2.2±0.5</td>
<td>2.4±0.4</td>
<td>2.3±0.6</td>
</tr>
<tr>
<td>After</td>
<td>16.3±2.1*</td>
<td>11.5±2.4</td>
<td>15.6±2.3</td>
</tr>
<tr>
<td>Lactate release, mmol/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>0.1±0.1</td>
<td>-0.3±0.1</td>
<td>-0.3±0.1</td>
</tr>
<tr>
<td>End exercise</td>
<td>17.4±4.1</td>
<td>13.0±2.9</td>
<td>16.6±1.8</td>
</tr>
<tr>
<td>Glycogen, mmol/kg wet weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>104±6</td>
<td>96±8</td>
<td>100±10</td>
</tr>
<tr>
<td>After</td>
<td>66±5</td>
<td>57±11</td>
<td>46±6</td>
</tr>
</tbody>
</table>

Values are mean±SE for 7 subjects.

*Significantly different from normal, \( P<0.05 \).
†Significantly lower than resting value, \( P<0.05 \).

**Figure 5.** Stroke volume during intense cycling exercise in heat stress and normal trials. Data are mean±SEE for 7 subjects.

*Significantly lower than previous value in heat stress and normal exhausting trials, \( P<0.05 \).


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Circulation. 2003;107:824-830; originally published online January 27, 2003; doi: 10.1161/01.CIR.0000049746.29175.3F
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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