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 (VO\(_2\)\textsubscript{max}) in humans. Severe heat stress drastically reduces VO\(_2\)\textsubscript{max}, but the mechanisms have never been studied.

**Methods and Results**—To determine the main contributing factor that limits VO\(_2\)\textsubscript{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 VO\(_2\)\textsubscript{max}, 2-legged VO\(_2\), 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 VO\(_2\) 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 VO\(_2\)\textsubscript{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 (VO\(_2\)\textsubscript{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 VO\(_2\)\textsubscript{max}.\(^1\)-\(^4\) Long-standing yet unresolved debates center on whether central cardiorespiratory and/or local skeletal muscle circulatory and metabolic factors limit VO\(_2\)\textsubscript{max}.\(^1\)-\(^7\)

Severe heat stress has been shown to markedly suppress VO\(_2\)\textsubscript{max} and work capacity without altering the initial rate of rise in whole-body VO\(_2\).\(^8\) 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 VO\(_2\)\textsubscript{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 VO\(_2\)\textsubscript{max} in healthy trained humans. Another aim was to determine the mechanisms underlying the blunted VO\(_2\)\textsubscript{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 VO\(_2\)\textsubscript{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 VO\(_2\)\textsubscript{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.
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 thermodilution 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 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).10 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°±48 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.6 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.11 LBF was determined by the constant-infusion thermodilution technique.12,13 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. Hematocrit was measured in triplicate after microcentrifugation and corrected for trapped plasma (0.98). Hemoglobin concentration and blood O2 saturation were determined spectrophotometrically (OSM-3 Hemoximeter, Radiometer). PO2 was determined with the Astrup technique (ABL5, Radiometer) and corrected for measured blood temperature. Blood lactate was determined with an automated electrolyte-metabolite analyzer (EMI 105/100, Radiometer). Plasma normetanephrine and epinephrine concentrations were determined with high-performance liquid chromatography with electrochemical detection. Biopsy samples were frozen in liquid nitrogen within 5 to 10 seconds and stored at −80°C until analysis. Muscle biopsies were homogenized and analyzed for lactate, creatine phosphate, and glycogen by fluorometric assays14 and muscle ATP by a luminometric method. Leg muscle mass was calculated from the whole-body dual-energy x-ray absorptiometry scanning (Lunar DIXIQ®5011) as the lean mass of the region.

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.](http://circ.ahajournals.org/doi/figure/10.1161/01.CIR.0000110068.11002.H1)
Q during the last ~2 minutes of the exhausting exercise bouts was associated with a greater reduction in stroke volume (10 to 20 mL/beat), because heart rate still increased from 185 to 187 bpm to maximal levels of 191 to 193 bpm (Figure 1). In all trials, the magnitude of changes in LBF paralleled those of MAP, and thus, leg vascular conductance was unchanged throughout exercise (Figure 2). Systemic vascular conductance was also maintained during the last ~2 minutes of exercise in all the trials (Figure 2), despite the fact that arterial norepinephrine concentration increased over time (Table 1).

During both exhausting exercise bouts, the progressive declines in arterial O2 saturation and P02 were accompanied by a proportional increase in hemoglobin concentration (Table 1), which allowed the maintenance of arterial O2 content during exercise (Figure 3). Before exhaustion in both H and N, systemic O2 delivery and O2 delivery to the legs decreased by 0.3 to 0.5 L/min compared with their corresponding peak exercise values, P<0.05. **Significantly lower than normal trials, P<0.05.†Significantly lower than normal trials, P<0.05.**

The 2 major findings in this study. First, heat stress drastically reduced VO2max compared with the normal condition by accelerating the declines in Q and MAP that led to decrements in locomotive skeletal muscle blood flow, O2 delivery, and O2 uptake. Second, the declining skeletal muscle VO2 before fatigue with or without heat stress was solely attributed to a similar lowering in systemic and skeletal muscle O2 delivery, because arterial O2 content, exercising leg O2 extraction, and leg vascular conductance were unaltered. Third, the reduced leg VO2 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 O2 delivery to locomotive skeletal muscle.

This is the first study to demonstrate that Q, locomotive muscle blood flow, MAP, and systemic and locomotive muscle O2 delivery decline significantly during exhaustive maximal aerobic exercise in humans. Although heat stress clearly exacerbated cardiovascular instability and drastically reduced VO2max, systemic and exercising LBF and O2 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 (~1.5 L/min) and blood flow to the legs was lower (0.7 to 2.7 L/min), but systemic and locomotive muscle VO2 were strikingly similar among conditions. Importantly, the lower LBF with heat stress was met by elevations in C02, arteriovenous O2 difference, and O2 extraction, which permitted VO2 by the legs to be maintained. These precise circulatory adjustments are consistent with evidence that acute alterations in C02 with anemia, hypoxia, anemia plus hypoxia, hyperoxia, CO plus normoxia, and CO plus hyperoxia evoke reciprocal changes in LBF and arteriovenous O2 difference compared with normoxia, such that muscle VO2 is kept constant.15,16 They are also in accord with the progressive augmentation in arteriovenous O2 difference but equal leg VO2 observed during prolonged exercise in the heat, when LBF declines in parallel to the dehydration-induced hemoconcentration.12 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 hemoconcentration. Nevertheless, the enhanced Q, the lower

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 VO2max compared with the normal condition by accelerating the declines in Q and MAP that led to decrements in locomotive skeletal muscle blood flow, O2 delivery, and O2 uptake. Second, the declining skeletal muscle VO2 before fatigue with or without heat stress was solely attributed to a similar lowering in systemic and skeletal muscle O2 delivery, because arterial O2 content, exercising leg O2 extraction, and leg vascular conductance were unaltered. Third, the reduced leg VO2 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 O2 delivery to locomotive skeletal muscle.

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**Figure 2.** Cardiac output and 2-legged blood flow, MAP, and systemic and 2-legged vascular conductance during intense cycling exercise during heat stress and normal trials. Data are mean±SEE for 6 to 7 subjects. *Significantly lower than corresponding peak exercise values, P<0.05. †Significantly lower than normal trials, P<0.05.
Although the higher Q, hemoconcentration, and enhanced O₂ extraction afforded a similar initial rate of rise in VO₂ max and leg V̇O₂, heat stress severely suppressed VO₂ max and 2-legged VO₂ (0.4 to 0.5 L/min). There are several reports documenting a blunting in VO₂ max with marked heat stress.⁸ The present novel finding was that the impairment in VO₂ max was initiated by the more rapid decline in Q and MAP, which led to the fastened fall in exercising muscle blood flow, O₂ delivery, and O₂ 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 O₂ 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 VO₂ max and leg VO₂. Therefore, it appears that heat stress more quickly pushes the cardiovascular system to its absolute regulatory limit, where Q and O₂ transport to the locomotive muscles can no longer be maintained despite the skeletal muscle remaining below its maximal capacity to consume O₂.

Limitations to the diffusion of O₂ from the muscle capillary to the mitochondrial cytochrome have been postulated to restrict VO₂ max.⁵,¹³ The question then arises whether diffusive O₂ transport across the leg muscles was impaired in the present study. The observations that leg arteriovenous O₂ difference and O₂ extraction increased progressively until the end of exercise preclude any sudden drop in O₂ diffusion at the time O₂ delivery to the legs was falling. Thus, the greater decline in convective O₂ transport to the leg muscles was clearly the cause of the reductions in leg VO₂ before exhaustion in either environmental condition (Figure 4). In the present study, however, leg O₂ extraction and femoral venous blood reached strikingly equal values of 91% (range 87% to 95%) and 20 mL/L (PO₂ 10 to 15 mm Hg) when exposed to either heat stress or normal conditions. The fact that there was some O₂ left in the femoral venous blood could be interpreted to mean that muscle O₂ 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 O₂ extraction during exercise.³⁰ It could then be envisioned that most active muscle fibers were extracting nearly all circulating O₂, particularly in those 4 subjects with 94% to 95% average leg O₂ extraction, and that the remaining O₂ in the femoral vein could be accounted for, at least in part, by the lower O₂ extraction of skin, connective tissue, fat, and bone. In this context, the contribution of muscle O₂ conductance in limiting locomotive muscle VO₂ 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

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**TABLE 1.** Femoral Blood Variables at Rest and During Intense Exhaustive Exercise in Heat Stress and Normal Trials

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Heat Stress-Maximal</th>
<th>Normal-Maximal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>0.5</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>a</td>
<td>15.2±0.5</td>
</tr>
<tr>
<td></td>
<td>v</td>
<td>15.3±0.5</td>
</tr>
<tr>
<td>PO₂, mm Hg</td>
<td>a</td>
<td>104±3</td>
</tr>
<tr>
<td></td>
<td>v</td>
<td>36±2</td>
</tr>
<tr>
<td>O₂ saturation, %</td>
<td>a</td>
<td>98.2±0.3</td>
</tr>
<tr>
<td></td>
<td>v</td>
<td>68.0±1.9</td>
</tr>
<tr>
<td>O₂ content, mL/L</td>
<td>a</td>
<td>210±7</td>
</tr>
<tr>
<td></td>
<td>v</td>
<td>146±8</td>
</tr>
<tr>
<td>Norepinephrine, nmol/L</td>
<td>a</td>
<td>4.1±0.7†</td>
</tr>
<tr>
<td></td>
<td>v</td>
<td>5.4±1.0†</td>
</tr>
<tr>
<td>Epinephrine, nmol/L</td>
<td>a</td>
<td>1.0±0.2</td>
</tr>
<tr>
<td></td>
<td>v</td>
<td>0.7±0.1</td>
</tr>
</tbody>
</table>

*Significantly different from 0.5-minute value, P<0.05.
†Significantly different from normal, P<0.05.
‡Significantly higher than values at 5.2±0.2 minutes of exercise, P<0.05.
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.\(^6\) 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.\(^2,6\) 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/L110064 mL/beat; \(P=0.15;\) Figure 5) 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 \(39^\circ\text{C}\), 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.\(^18\) 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 \(V_{\dot{O}_2}\text{max}\) evoked by hyperthermia alone or combined dehydration and hyperthermia.\(^8\) 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 \(O_2\) delivery and \(V_{\dot{O}_2}\text{max}\) 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 \(V_{\dot{O}_2}\). Consistent with our circulatory data, we observed that the reduced leg \(V_{\dot{O}_2}\) 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\(_i\), ADP, and H\(^+\), which have been shown to depress contractile function in skinned and intact fibers.\(^21\) 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+ 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 VO_{2max} 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 VO_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

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References


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