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 ($\dot{V}O_2$max) in humans. Severe heat stress drastically reduces $\dot{V}O_2$max, but the mechanisms have never been studied.

Methods and Results—To determine the main contributing factor that limits $\dot{V}O_2$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 $\dot{V}O_2$max, 2-legged $\dot{V}O_2$, 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 $\dot{V}O_2$ 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 $\dot{V}O_2$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 ($\dot{V}O_2$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 $\dot{V}O_2$max.[1–4] Long-standing yet unresolved debates center on whether central cardiorespiratory and/or local skeletal muscle circulatory and metabolic factors limit $\dot{V}O_2$max.[1–7]

Severe heat stress has been shown to markedly suppress $\dot{V}O_2$max and work capacity without altering the initial rate of rise in whole-body $\dot{V}O_2$.[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 $\dot{V}O_2$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 $\dot{V}O_2$max in healthy trained humans. Another aim was to determine the mechanisms underlying the blunted $\dot{V}O_2$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 $\dot{V}O_2$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 $\dot{V}O_2$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.

From The Copenhagen Muscle Research Centre (J.G.-A.), Rigshospitalet, University of Copenhagen, Denmark, and the Department of Physical Education (J.A.L.C.), University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain.

Correspondence to José González-Alonso, PhD, The Copenhagen Muscle Research Centre, Rigshospitalet, Section 7652, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark. E-mail jga@cmrc.dk

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

DOI: 10.1161/01.CIR.0000049746.29175.3F

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).[8] 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% $\dot{V}O_2$max) 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 $\dot{V}O_2$max in 3 to 5 minutes under normal environmental conditions (80% of 449±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.[8] 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 $\dot{V}O_2$, 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 $\dot{V}O_2$ was measured online with an Applied Electrochemistry OCM-2 metabolic cart. Cardiac output was measured by indocyanine (ICG, Akon Inc) dye dilution.[10] LBF was determined by the constant-infusion thermodilution technique.[11,12] 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). Two-legged blood flow was calculated by multiplying LBF by 2. Two-legged O_2 uptake was calculated by multiplying 2-legged blood flow by the difference in concentrations of O_2 between the femoral artery and vein. Hematocrit was measured in triplicate after microcentrifugation and corrected for trapped plasma (0.98). Hemoglobin concentration and blood O_2 saturation were determined spectrophotometrically (OSM-3 Hemoximeter, Radiometer). P_{O_2} was determined with the Astrup technique (ABL5, Radiometer) and corrected for measured blood temperature. Blood lactate was determined with an automated electrolyte-metabolite analyzer (EML 105/100, Radiometer). Plasma norepinephrine 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 assays[13] and muscle ATP by a luminometric method. Leg muscle mass was calculated from the whole-body dual-energy x-ray absorptiometry scanning (Lunar DPXIQ#5011) as the lean mass of the region.

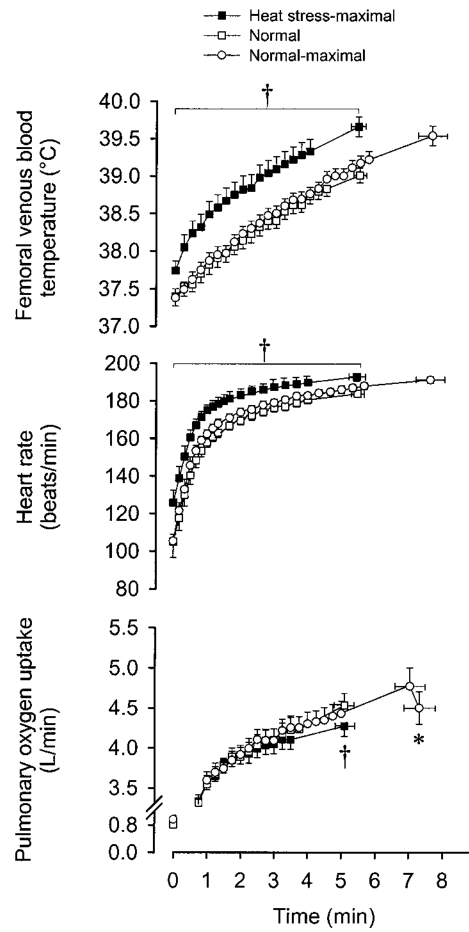

Figure 1. Femoral venous blood temperature, heart rate, and pulmonary oxygen uptake during intense cycling exercise during heat stress and normal trials. Note that femoral venous blood temperature reflects esophageal temperature, being only 0.1°C higher.[14] Data are mean±SEE for 8 subjects. *Significantly lower than peak $\dot{V}O_2$ value during exhausting normal trial, $P<0.05$. †Significantly different from normal trials, $P<0.05$.

Statistical Analysis

A 2-way (trial-by-time) repeated-measures ANOVA was performed to test significance between and within treatments. After a significant F test, pairwise differences were identified by Tukey's honestly significant difference post hoc procedure. To determine whether exhaustion was preceded by rapid changes in cardiovascular hemodynamics, final values were compared with peak values during exercise by 1-way repeated-measures ANOVA with Tukey's honestly significant difference post hoc procedure. The significance level was set at $P<0.05$. Data are mean±SEM.

Results

$\dot{V}O_2$max 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 $\dot{V}O_2$ 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

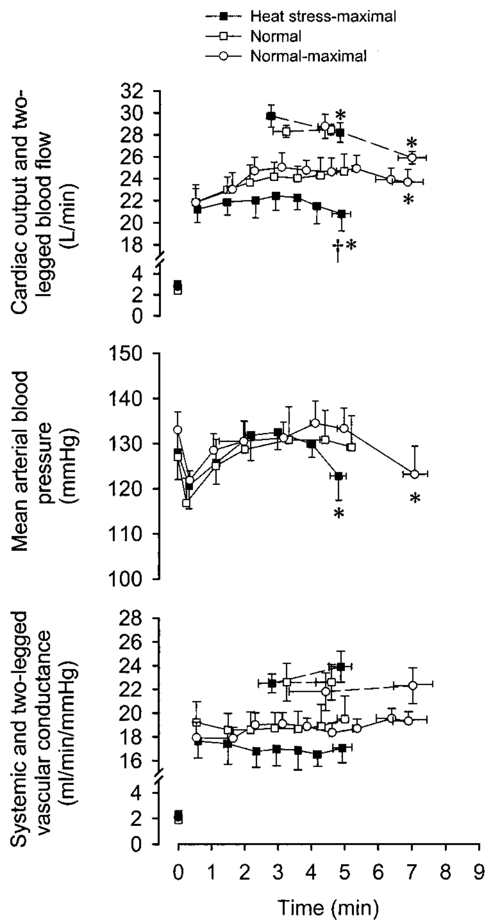

Figure 2. Cardiac output and 2-legged blood flow, MAP, and systemic and 2-legged vascular conductance during intense cycling exercise during heat stress and normal trials. Data are mean±SEE for 6 to 7 subjects. *Significantly lower than corresponding peak exercise values, $P<0.05$. †Significantly lower than normal trials, $P<0.05$.

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 O_2 saturation and PO_2 were accompanied by a proportional increase in hemoglobin concentration (Table 1), which allowed the maintenance of arterial O_2 content during exercise (Figure 3). Before exhaustion in both H and N, systemic O_2 delivery and O_2 delivery to the legs decreased by 0.3 to 0.5 L/min compared with their corresponding peak values during exercise (Figures 3 and 4). In sharp contrast, leg O_2 extraction increased progressively by up to 91% in both exhausting trials, yet 2-legged $\dot{V}O_2$ decreased by 0.2 L/min in both trials (Figure 4). The suppression in $\dot{V}O_2$max and 2-legged $\dot{V}O_2$ in H compared with N was similar, amounting to 0.4 to 0.5 L/min.

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 $\dot{V}O_2$max 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 $\dot{V}O_2$ 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 $\dot{V}O_2$ 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 $\dot{V}O_2$max, 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 (≈1.5 L/min) and blood flow to the legs was lower (0.7 to 2.7 L/min), but systemic and locomotive muscle $\dot{V}O_2$ were strikingly similar among conditions. Importantly, the lower LBF with heat stress was met by elevations in C_aO_2, arteriovenous O_2 difference, and O_2 extraction, which permitted $\dot{V}O_2$ by the legs to be maintained. These precise circulatory adjustments are consistent with evidence that acute alterations in C_aO_2 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 $\dot{V}O_2$ is kept constant.[15,16] They are also in accord with the progressive augmentation in arteriovenous O_2 difference but equal leg $\dot{V}O_2$ 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 be related to the presence of heat stress but rather to concomitant hemoconcentration. Nevertheless, the enhanced Q, the lower

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

	Time, min										
	Heat Stress-Maximal					Normal-Maximal					
	Rest	0.5	1.5	3.0	5.5±0.2	Rest	0.5	1.5	3.0	5.5±0.2	7.6±0.4
Hemoglobin, g/dL											
a	15.2±0.5	15.6±0.5	15.7±0.5	15.7±0.5	15.8±0.3	14.2±0.4	14.7±0.4	14.9±0.4	15.0±0.4*	15.1±0.4*	15.1±0.4*
v	15.3±0.5	15.6±0.5	15.7±0.5	15.7±0.5	15.9±0.4	14.1±0.4	14.7±0.4	14.8±0.4	15.0±0.3*	15.1±0.3*	15.0±0.4*
Po_2, mm Hg											
a	104±3	94±3†	91±2	86±3*	87±3*	108±3	100±3	94±3	87±3*	85±2*	86±3*
v	36±2	17±1	15±1	14±1*	13±1*	33±1	16±1	16±1	16±1	15±1*	14±1*
O_2 saturation, %											
a	98.2±0.3	97.1±0.2	96.8±0.4	96.0±0.4*	95.2±0.4*	98.5±0.2	97.6±0.2	96.4±0.3	95.5±0.4*	94.6±0.5*	93.9±0.6*
v	68.0±1.9	17.9±2.2	13.6±1.7*	12.0±1.6*	9.1±1.1*	60.9±2.4	20.1±1.6	14.9±1.7*	13.2±1.8*	10.7±1.2*	9.0±1.0*
O_2 content, mL/L											
a	210±7	213±6	214±7	212±6	211±6	197±6	203±6	203±5	202±6	201±5	200±5
v	146±8	40±6	31±5*	27±4*	21±3*	120±5	42±4	32±4*	28±4*	23±3*	20±2*
Norepinephrine, nmol/L											
a	4.1±0.7†	...	...	...	34.1±4.9	2.0±0.3	...	...	...	29.9±3.6	48.9±8.9‡
v	5.4±1.0†	...	...	...	35.4±4.6	2.4±0.3	...	...	...	29.0±3.4	49.3±8.3‡
Epinephrine, nmol/L											
a	1.0±0.2	...	...	...	6.4±2.7	1.0±0.2	...	...	...	6.3±1.4	10.2±2.1‡
v	0.7±0.1	...	...	...	5.5±2.3	0.6±0.1	...	...	...	5.3±1.1	9.6±1.5‡

a indicates arterial; v, femoral venous. Values are mean±SE for 8 subjects.
*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, $P<0.05$.

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 $\dot{V}O_2$, heat stress severely suppressed $\dot{V}O_2$max and 2-legged $\dot{V}O_2$ (0.4 to 0.5 L/min). There are several reports documenting a blunting in $\dot{V}O_2$max with marked heat stress.[8] The present novel finding was that the impairment in $\dot{V}O_2$max was initiated by the more rapid decline in Q and MAP, which led to the hastened 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 $\dot{V}O_2$max and leg $\dot{V}O_2$. 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 $\dot{V}O_2$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 $\dot{V}O_2$ before exhaustion in either environmental condition (Figure 4). In the present study, however, leg O_2 extraction and femoral venous blood reached strikingly equal values of 91% (range 87% to 95%) and 20 mL/L (PO_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 $\dot{V}O_2$ 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

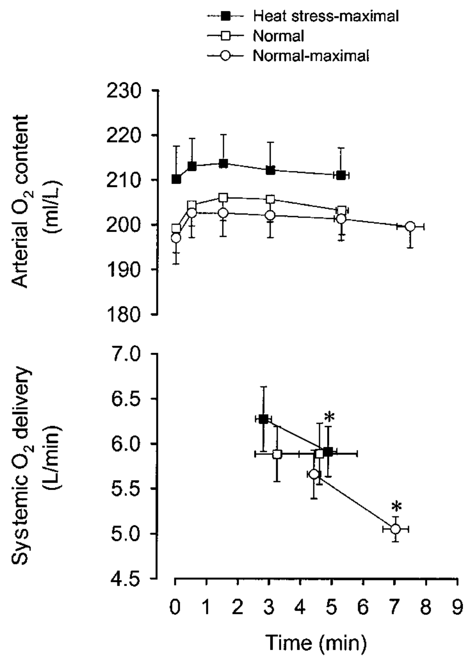

Figure 3. Arterial oxygen content and systemic oxygen delivery during intense cycling exercise during heat stress and normal trials. Data are mean±SEE for 7 to 8 subjects. *Significantly lower than previous value in heat stress and normal exhausting trials, $P<0.05$.

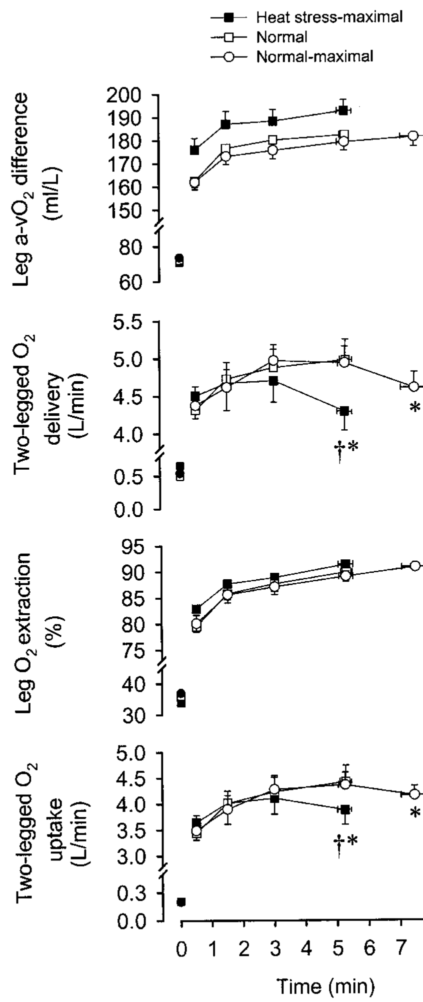

Figure 4. Leg arteriovenous O_2 difference, 2-legged O_2 delivery, leg O_2 extraction, and 2-legged O_2 uptake during intense cycling exercise during heat stress and normal trials. Data are mean±SEE for 6 subjects. *Significantly lower than peak value in heat stress and normal exhausting trials, $P<0.05$. †Significantly lower than normal trials, $P<0.05$.

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±4 versus 10±4 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°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 $\dot{V}O_2$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 $\dot{V}O_2$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 $\dot{V}O_2$. Consistent with our circulatory data, we observed that the reduced leg $\dot{V}O_2$ 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,

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

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

Values are mean±SE for 7 subjects.
*Significantly different from normal, $P<0.05$.
†Significantly lower than resting value, $P<0.05$.

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.[14] Thus, it could be postulated that the abrupt accumulation in muscle cells of P_i, 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 $\dot{V}O_2max$ 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 $\dot{V}O_2$ 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.

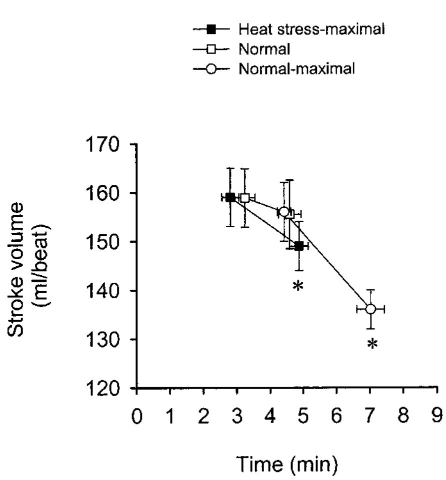

Figure 5. Stroke volume during intense cycling exercise in heat stress and normal trials. Data are mean±SEE for 7 subjects. *Significantly lower than previous value in heat stress and normal exhausting trials, $P<0.05$.

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 Møller, 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

1. Mitchell JH, Blomqvist G. Maximal oxygen uptake. *N Engl J Med*. 1971;284:1018–1022.
2. Rowell LB. Human cardiovascular adjustments to exercise and thermal stress. *Physiol Rev*. 1974;54:75–159.
3. Saltin B. Hemodynamic adaptations to exercise. *Am J Cardiol*. 1985;55: 42D–47D.
4. Wagner PD. Determinants of maximal oxygen transport and utilization. *Annu Rev Physiol*. 1996;58:21–50.
5. Holloszy JO. Biochemical adaptations in muscle: effects of exercise on mitochondrial oxygen uptake and respiratory enzyme activity in skeletal muscle. *J Biol Chem*. 1967;242:2279–2282.
6. Rowell LB, Marx HJ, Bruce RA, et al. Reductions in cardiac output, central blood volume, and stroke volume with thermal stress in normal men during exercise. *J Clin Invest*. 1966;45:1801–1816.
7. Hill AV, Lupton H. Muscle exercise, lactic acid and the supply and utilization of O_2. *Quart J Med*. 1923;16:135–171.

8. Nybo L, Jensen T, Nielsen B, et al. Effects of marked hyperthermia with and without dehydration on $\dot{V}O_2$ kinetics during intense exercise. *J Appl Physiol*. 2001;90:1057–1064.
9. Åstrand PO, Saltin B. Oxygen uptake during the first minutes of heavy exercise. *J Appl Physiol*. 1961;16:971–976.
10. Boushel R, Calbet JAL, Rådegran G, et al. Parasympathetic neural activity accounts for the lowering of exercise heart rate at high altitude. *Circulation*. 2001;104:1785–1791.
11. Anderson P, Saltin B. Maximal perfusion of skeletal muscle in man. *J Physiol*. 1985;366:233–249.
12. González-Alonso J, Calbet JAL, Nielsen B. Muscle blood flow is reduced with dehydration during prolonged exercise in humans. *J Physiol*. 1998; 513:895–905.
13. Lowry OH, Passonneau JV. *A Flexible System of Enzymatic Analysis*. New York, NY: Academic; 1972.
14. González-Alonso J, Calbet JAL, Nielsen B. Metabolic and thermodynamic responses to dehydration-induced reductions in muscle blood flow in exercising humans. *J Physiol*. 1999;520:577–589.
15. Koskolou MD, Roach RC, Calbet JAL, et al. Cardiovascular responses to dynamic exercise with acute anemia in humans. *Am J Physiol*. 1997;273: H1787–H1793.
16. González-Alonso J, Olsen DB, Saltin B. Erythrocyte and the regulation of human skeletal muscle blood flow and oxygen delivery: role of circulating ATP. *Circ Res*. 2002;91:1046–1055.
17. Rowell LB, Blackmon JR, Martin RH, et al. Hepatic clearance of indocyanine green in man under thermal and exercise stresses. *J Appl Physiol*. 1965;20:384–394.
18. González-Alonso J, Mora-Rodríguez R, Coyle EF. Stroke volume during exercise: interaction of environment and hydration. *Am J Physiol*. 2000; 278:H321–H330.
19. Roca J, Hogan MC, Story D, et al. Evidence for tissue diffusion limitation of VO_2max in normal humans. *J Appl Physiol*. 1989;67:291–299.
20. Marconi C, Heisler N, Meyer M, et al. Blood flow distribution and its temporal variability in stimulated dog gastrocnemius muscle. *Respir Physiol*. 1988;74:1–14.
21. Allen DG, Westerblad H. Role of phosphate and calcium stores in muscle fatigue. *J Physiol*. 2001;536:657–665.