

Cardiovascular responses to dynamic exercise with acute anemia in humans

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Koskolou, Maria D., Robert C. Roach, José A. L. Calbet, Göran Rådegran, and Bengt Saltin. Cardiovascular responses to dynamic exercise with acute anemia in humans. *Am. J. Physiol.* 273 (*Heart Circ. Physiol.* 42): H1787–H1793, 1997.—We hypothesized that reducing arterial O₂ content (Ca_{O₂}) by lowering the hemoglobin concentration ([Hb]) would result in a higher blood flow, as observed with a low PO₂, and maintenance of O₂ delivery. Seven young healthy men were studied twice, at rest and during two-legged submaximal and peak dynamic knee extensor exercise in a control condition (mean control [Hb] 144 g/l) and after 1–1.5 liters of whole blood had been withdrawn and replaced with albumin [mean drop in [Hb] 29 g/l (range 19–38 g/l); low [Hb]]. Limb blood flow (LBF) was higher ($P < 0.01$) with low [Hb] during submaximal exercise (i.e., at 30 W, LBF was 2.5 ± 0.1 and 3.0 ± 0.1 l/min for control [Hb] and low [Hb], respectively; $P < 0.01$), resulting in a maintained O₂ delivery and O₂ uptake for a given workload. However, at peak exercise, LBF was unaltered (6.5 ± 0.4 and 6.6 ± 0.6 l/min for control [Hb] and low [Hb], respectively), which resulted in an 18% reduction in O₂ delivery ($P < 0.01$). This occurred despite peak cardiac output in neither condition reaching $>75\%$ of maximal cardiac output (~ 26 l/min). It is concluded that a low Ca_{O₂} induces an elevation in submaximal muscle blood flow and that O₂ delivery to contracting muscles is tightly regulated.

red blood cell; hemoglobin; skeletal muscle; vasodilatation; cardiac output

THE ACUTE AND CHRONIC cardiovascular and metabolic responses to low arterial PO₂ (Pa_{O₂}) during exercise are well documented. In contrast, the responses to low arterial O₂ content (Ca_{O₂}) due to an acute lowering of hemoglobin concentration ([Hb]) are much less studied, which is surprising in view of how common anemia is in the world today.

Maximal cardiac output (CO) during exercise in acute anemia is not elevated or not elevated to an extent to compensate for the impaired O₂ delivery (3, 16). At submaximal work, CO is elevated and partly compensates for the impaired O₂ delivery (3, 16). No studies are available on the regional responses to acute anemia during work. In a collection of cases with a range of [Hb] levels, summarized in the proceedings of a conference honoring Lars Hermansen (13), there were indications that the low Ca_{O₂} was countered at submaximal exercise by an increase in muscle blood flow, so that O₂ delivery was maintained. At peak exercise, a final conclusion could not be reached. In at least two cases, there was a suggestion of increased blood flow at peak exercise that, in part, maintained O₂ delivery. This notion is supported by the classic study of Sproule et al. (15) on cardiovascular function during

exercise in chronic anemic patients as they reached very high CO levels at low peak power outputs. Chronic anemia may have induced adaptations on the systemic as well as on the cellular level, obscuring effects of low [Hb] per se. Thus the question remains of how O₂ delivery is maintained on the regional level in response to an acute reduction in [Hb]. The hypothesis is that compensation occurs with an elevated muscle perfusion matched by an equal increase in CO or by reducing the blood flow to nonexercising tissues and organs. We further hypothesize that, in contrast to hypoxia, in acute anemia limb blood flow (LBF) is increased at peak exercise with small muscle mass exercise.

We used a two-legged knee extensor exercise model that allows for a fairly large muscle mass (~ 6 – 7 kg) to perform the exercise without taxing the capacity of the heart to match a possible elevation in LBF, even at the highest workloads. The effect of a lowered [Hb] was examined by repeating the studies twice, once with the subjects having a normal [Hb] (control [Hb]) and the second time after withdrawing whole blood and substituting it with an equal amount of albumin to reduce [Hb] by $\sim 20\%$ (low [Hb]).

METHODS

Subjects. Seven young (age 24 yr, range 21–30 yr) healthy men participated in the study. Their physical characteristics averaged (range) 183 cm (167–187 cm) in height, 85.1 kg (67.3–102.3 kg) in weight, 3.3-kg (2.8–4.1 kg) knee extensor mass of one leg, and a mean capillary count of 404 capillaries/mm² (266–491 capillaries/mm²). Their maximal O₂ uptake ($\dot{V}_{O_{2max}}$) was 54.6 ml·kg⁻¹·min⁻¹ (41–70 ml·kg⁻¹·min⁻¹) and maximal CO during ordinary maximal bicycle exercise was 26.0 l/min (22.7–28.4 l/min). Six of the subjects had a [Hb] within the normal range for young men (mean 148 g/l, range 139–155 g/l), and one had a [Hb] of 126 g/l. All subjects had a normal iron status (ferritin > 33 mg/l and transferrin > 2.0 g/l). They were informed regarding possible risks and discomfort associated with the experiments and volunteered to participate, giving their signed consent. The study had the approval of the Copenhagen and Frederiksberg Ethical Committee.

Methodology. Blood volume (BV) was determined after the subjects had been supine for a minimum of 45 min, at 10, 20, and 30 min after injection of the tracer (¹³¹I-radioisotope serum albumin, ~ 250 kBq). The [Hb] and blood O₂ saturation (So₂) were measured with a CO-oximeter (AVL 912 CO-Oxylite). PO₂, PCO₂, and pH were determined by standard techniques (AVL Compact 2) and corrected for measured blood temperature. The coefficients of variation calculated for the measurements of [Hb], So₂, PO₂, PCO₂, and pH were 4.3, 1.3, 3.8, 2.4, and 1.4%, respectively. Hematocrit (Hct) determinations were made in triplicate with microcentrifugation and corrected for trapped plasma (1.5%). Plasma K⁺ was measured with ion-sensitive electrodes (AVL 983-S). Lactate

concentration ([Lac]) was measured in whole blood with Triton X as a red blood cell lysing agent (YSI 2300 Stat Plus; coefficient of variation 2%).

Pulmonary $\dot{V}O_2$ uptake ($\dot{V}O_2$), CO_2 production ($\dot{V}CO_2$), and ventilation ($\dot{V}E$) were measured with an on-line system (Medical Graphics CPX). Gases with known O_2 and CO_2 concentrations (micro-Scholander) were used for gas analyzer calibration. CO was measured by the dye-dilution technique with indocyanine green dye as the tracer. Arterial blood was withdrawn (Harvard pump), and the dye concentration was determined (Waters densitometer CO-10). The withdrawn blood was reinfused after each determination. Blood pressure was monitored by a transducer at the femoral level (mean distance from the heart 58 cm). Mean arterial pressure was estimated as two-thirds diastolic plus one-third systolic pressure. Heart rate (HR) was obtained either from the pulsatile pressure curve or from the continuously recorded electrocardiogram signal. LBF was measured in the femoral vein at the level of the inguinal ligament by the constant-infusion thermodilution technique during exercise (1). Briefly, ice-cold isotonic saline was infused in the femoral vein at a rate of 50–145 ml/min to obtain a drop of $\sim 1.0^\circ C$ in blood temperature as determined with a thermistor inserted through the venous catheter (TD probe 94-030-2.5F, Edwards Edslab, Baxter). The temperature was continuously recorded (Gould recorder). Values for LBF were obtained with the heat balance equation of Andersen and Saltin (1). At rest, a bolus injection (3 ml) was used because constant infusion cannot be applied. This is due to a too long mean transit time (MTT), which would require a duration for the infusion of ice-cold saline that is so long that it would cause cooling of not only the femoral venous blood but also the surrounding tissue. The obtained resting values are in the same range as observed with the ultrasound Doppler blood flow technique in the femoral artery at rest (11). The $\dot{V}O_2$ of the knee extensors (leg $\dot{V}O_2$) was calculated according to the Fick principle as the product of the femoral venous blood flow and the time-matched value of femoral arteriovenous (a-v) O_2 difference. Quadriceps muscle volume and mass were estimated (6), and muscle fiber types and capillaries were determined from a muscle biopsy sample taken from the lateral portion of the knee extensors (10).

Procedures. The subjects were studied in the morning after a light breakfast with control [Hb] and at least 1 wk later with low [Hb]. The afternoon before the low [Hb] experiment, 1–1.5 liters (average 1.3 ± 0.05 liters, corresponding to $\sim 20\%$ of the subject's BV) of whole blood were withdrawn and

replaced by an equal volume of human albumin (5% albumin). After the low [Hb] experiment was finished, the previously removed whole blood was reinfused into the subject.

A few days before the control [Hb] experiment, a resting electrocardiogram, thigh volume, [Hb], Hct, and iron status were determined in the subjects. They practiced the two-legged kicking exercise at several workloads and performed an incremental test for determination of their peak workload (WL_{peak}). On the two experimental days, two catheters were placed that were used for blood sampling and detection of the cardiogreen dye (arterial) and determination of leg blood flow (femoral vein). In addition, a catheter was placed in a vein in the arm for injection of the cardiogreen dye. The exercise consisted of dynamic contractions of the knee extensor muscles of the two legs at a rate of 1 Hz at 30 W for ~ 5 min and continued at 50% of the preestablished WL_{peak} (WL_{50}) for each condition for another 5 min. After 5–10 min of rest, the work was resumed, starting at WL_{50} for 2 min followed by 2 min at 75 and 90% of WL_{peak} . From thereon, 5-W increments were applied until the subjects achieved peak effort. Measurements of LBF, CO , and blood sampling were performed at rest, at 30 W and WL_{50} under steady-state conditions, and at peak effort close to (within ~ 1 min) exhaustion. During each exercise stage, HR, blood pressure, pulmonary $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ were recorded during the last 1–2 min. When possible, duplicate measurements of LBF and femoral a-v differences (O_2 , Lac, and K^+) were taken during the brief period of peak exercise.

Statistics. Differences in the measured variables were analyzed pairwise across the two [Hb] conditions. For multiple *t*-tests, the significance level was adjusted with the Bonferroni correction, with $P < 0.01$ being considered significant. Data are reported as means \pm SE, and often the range is also given.

RESULTS

Systemic response. Removal of whole blood reduced [Hb] from 144 ± 3.8 to 115 ± 1.9 g/l, with an individual variation of 19–38 g/l ($P < 0.01$; Table 1). This reduction in [Hb] was accompanied by a decrease in Hct from 43.5 ± 0.9 (control [Hb]) to $34.4 \pm 0.4\%$ (low [Hb]); $P < 0.01$ and a 22% (20–26%) decrease in red blood cell volume ($P < 0.01$), but BV was maintained (control [Hb], 7.06 ± 0.46 liters; low [Hb], 6.93 ± 0.48 liters; Fig. 1).

Table 1. Workload, [Hb], arterial and femoral venous oxygenation, and limb blood flow for the 2 Hb conditions

Stage	Workload, W	[Hb], g/l	PO_2 , Torr		SO_2 , %		CO_2 , ml/l		Limb Blood Flow, l/min
			Arterial	Venous	Arterial	Venous	Arterial	Venous	
<i>Control [Hb]</i>									
Rest	0 \pm 0	144.4 \pm 3.8	99.7 \pm 2.8	27.8 \pm 0.8	98.1 \pm 0.2	49.3 \pm 1.7	190.1 \pm 4.9	95.7 \pm 5.1	0.20 \pm 0.01
30 W	30 \pm 0	144.6 \pm 4.1	108.3 \pm 3.6	22.0 \pm 0.7	98.1 \pm 0.2	33.4 \pm 1.4	190.5 \pm 5.3	64.7 \pm 3.2	2.51 \pm 0.08
WL_{50}	73 \pm 6 (40–85)	146.0 \pm 4.2	109.8 \pm 2.5	22.9 \pm 0.4	97.5 \pm 0.8	29.1 \pm 1.5	191.0 \pm 5.8	56.5 \pm 1.5	4.20 \pm 0.17
WL_{peak}	143 \pm 11 (80–170)	154.4 \pm 3.6	119.2 \pm 1.2	23.6 \pm 0.8	97.7 \pm 0.7	25.6 \pm 1.1	202.5 \pm 5.1	52.8 \pm 1.3	6.50 \pm 0.40
<i>Low [Hb]</i>									
Rest	0 \pm 0	114.7 \pm 1.9*	94.9 \pm 3.4	25.0 \pm 0.7	98.1 \pm 0.4	43.2 \pm 2.8	151.1 \pm 2.5*	66.6 \pm 4.8*	0.21 \pm 0.01
30 W	30 \pm 0	116.4 \pm 1.7*	103.9 \pm 3.5	21.8 \pm 0.8	98.0 \pm 0.4	32.1 \pm 2.0	153.1 \pm 2.4*	50.2 \pm 3.4*	3.02 \pm 0.13*
WL_{50}	55 \pm 3 (40–65)	117.1 \pm 1.5*	102.8 \pm 3.0	22.2 \pm 1.2	97.8 \pm 0.3	31.1 \pm 1.6	153.8 \pm 2.2*	48.9 \pm 2.7*	4.35 \pm 0.35
WL_{peak}	118 \pm 11 (60–155)	123.3 \pm 1.0*	115.1 \pm 3.1	23.0 \pm 0.8	98.0 \pm 0.3	24.6 \pm 0.7	162.3 \pm 1.6*	40.7 \pm 1.1*	6.60 \pm 0.55

Values are means \pm SE; nos. in parentheses, range. [Hb], hemoglobin concentration; SO_2 , O_2 saturation; CO_2 , O_2 content; WL_{50} , 50% of preestablished peak workload (WL_{peak}). * $P < 0.01$ compared with the same stage with control [Hb].

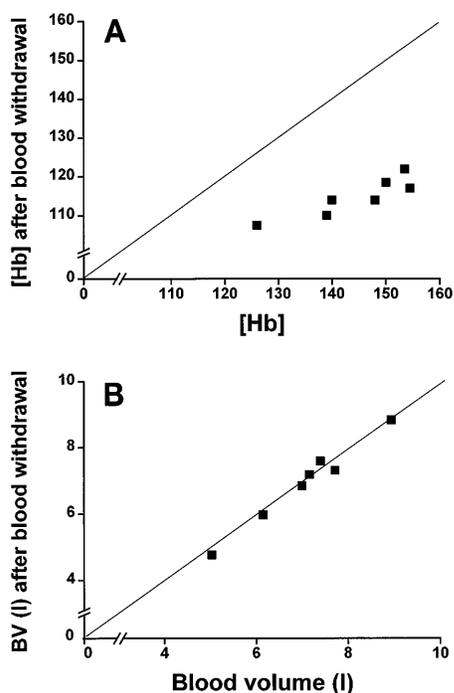


Fig. 1. Hemoglobin concentration ([Hb]; A) and blood volume (BV; B) in control condition (x-axis) and after blood withdrawal (y-axis) in 7 subjects. Solid lines, line of identity.

Mean arterial SO_2 (SO_2) was between 97 and 98% and Pa_{O_2} was >90 Torr in all conditions (Table 1). As the result of hyperventilation, Pa_{O_2} reached 119.2 ± 1.2 and 115.1 ± 3.1 Torr during peak exercise for control [Hb] and low [Hb], respectively, with a concomitant fall in arterial PCO_2 (Pa_{CO_2}) to 34.7 ± 1.2 and 35.1 ± 0.5 Torr in control [Hb] and low [Hb], respectively (Table 2). As a function of the drop in [Hb], mean Ca_{O_2} was $\sim 20\%$ lower at rest and during exercise ($P < 0.01$; Table 1). At peak effort, Ca_{O_2} was 7% higher in both conditions (not significant) as a result of an increase in Hb (~ 10 g/l).

The \dot{V}_E and Pa_{CO_2} were similar for control [Hb] and low [Hb] at rest and all exercise intensities (Fig. 2, Table 2). With submaximal exercise, $\dot{V}O_2$ was similar in the two conditions, whereas at peak effort, the mean values were lowered from 2.8 ± 0.1 (control [Hb]) to

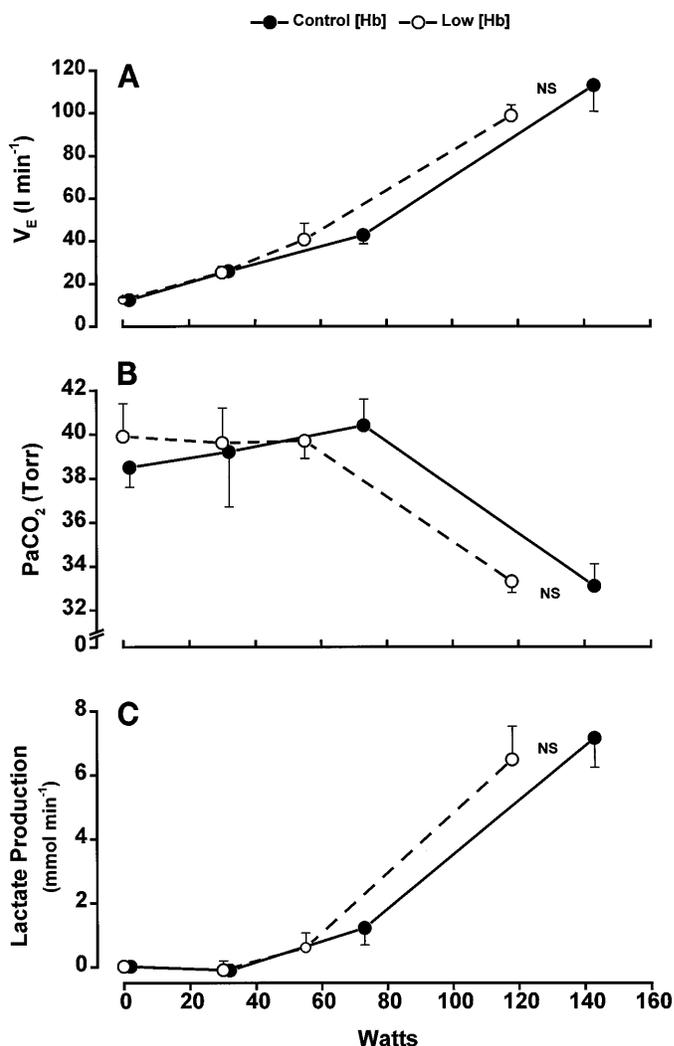


Fig. 2. Pulmonary ventilation (\dot{V}_E ; A), arterial PCO_2 (Pa_{CO_2} ; B) and lactate production (C) for control and low [Hb] conditions at rest and during submaximal and peak exercise. Values are means \pm SE. Significance was tested by comparing control [Hb] and low [Hb] at rest and exercise stages without taking into account the absolute workload at 50% of the preestablished peak workload and that at peak effort. NS, not significant.

Table 2. Arterial and femoral venous values for [Lac], PCO_2 , pH, and K^+ for the 2 Hb conditions

Stage	[Lac], mmol/l		PCO_2 , Torr		pH		K^+ , mmol/l	
	Arterial	Venous	Arterial	Venous	Arterial	Venous	Arterial	Venous
<i>Control [Hb]</i>								
Rest	0.9 ± 0.1	0.9 ± 0.1	38.5 ± 0.9	46.6 ± 1.6	7.37 ± 0.01	7.34 ± 0.01	4.2 ± 0.1	4.1 ± 0.1
30 W	0.8 ± 0.1	0.8 ± 0.1	39.6 ± 2.6	55.2 ± 2.7	7.38 ± 0.02	7.30 ± 0.01	4.5 ± 0.1	4.5 ± 0.1
WL ₅₀	1.3 ± 0.1	1.6 ± 0.2	42.5 ± 1.1	61.4 ± 1.7	7.34 ± 0.01	7.27 ± 0.01	4.8 ± 0.1	4.7 ± 0.0
WL _{peak}	4.9 ± 0.2	6.0 ± 0.3	34.7 ± 1.2	69.2 ± 1.2	7.32 ± 0.01	7.17 ± 0.01	6.0 ± 0.2	6.2 ± 0.2
<i>Low [Hb]</i>								
Rest	0.9 ± 0.1	0.9 ± 0.1	40.0 ± 1.3	48.0 ± 0.8	7.39 ± 0.01	7.34 ± 0.01	4.3 ± 0.1	4.2 ± 0.1
30 W	1.2 ± 0.3	1.2 ± 0.3	40.2 ± 1.6	54.7 ± 1.9	7.38 ± 0.01	7.31 ± 0.01	4.5 ± 0.1	4.5 ± 0.2
WL ₅₀	1.6 ± 0.6	1.8 ± 0.7	40.9 ± 0.8	58.0 ± 2.2	7.36 ± 0.01	7.28 ± 0.02	4.6 ± 0.1	4.5 ± 0.1
WL _{peak}	5.7 ± 1.2	6.7 ± 1.1	35.1 ± 0.5	69.7 ± 2.1	7.33 ± 0.01	7.16 ± 0.02	5.7 ± 0.3	6.0 ± 0.3

Values are means \pm SE. [Lac], lactate concentration.

2.3 ± 0.1 l/min (low [Hb]; Fig. 3) as a result of attainable peak power output being reduced 17% (range 9–25%; from 143 to 118 W; $P < 0.01$). The CO tended to be higher at a given $\dot{V}O_2$ in low [Hb] compared with control [Hb]. The difference amounted to 1.2–1.7 l/min higher CO per liter per minute of $\dot{V}O_2$ at the three exercise levels. The difference in mean values for CO at a given absolute workload was similar to the difference in leg blood flow, resulting in similar estimated blood flows to the noncontracting tissues. This was also the case at peak effort in the two conditions. CO reached 20–21 l/min, and contracting muscle blood flow averaged 15–16 l/min (see DISCUSSION), leaving close to 5 l/min of blood flow for noncontracting tissues. The HR tended to be higher in low [Hb] compared with control [Hb] during exercise, reaching 155 beats/min at peak effort. Stroke volume was unaffected by [Hb].

Regional response. With low [Hb], LBF was unchanged at rest but higher when exercising at 30 W (Fig. 3). At peak effort, LBF reached the same level in both conditions (~ 13 l/min for two legs); as a result, O_2 delivery was reduced (18%; $P < 0.01$) in low [Hb]. Two-legged blood flow at peak effort amounted to 63 and 65% of CO in control [Hb] and low [Hb], respec-

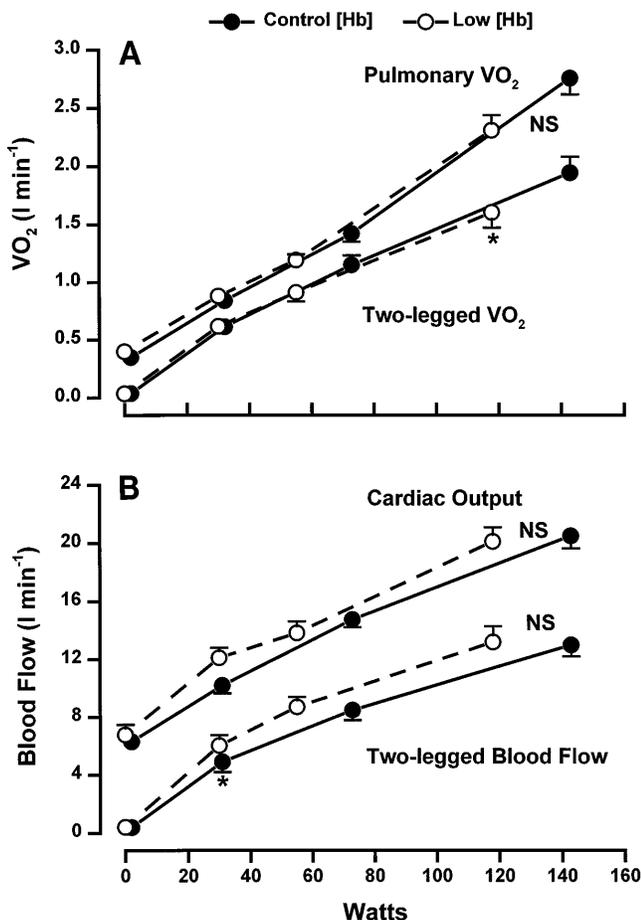


Fig. 3. Pulmonary and limb (for 2 legs) O_2 uptake ($\dot{V}O_2$) at rest and during submaximal and peak exercise (A) and cardiac output and limb blood flow (for 2 legs) at rest and during exercise (B). Values are means \pm SE. For statistics, see Fig. 2. *Significantly different from same stage with control [Hb], $P < 0.01$.

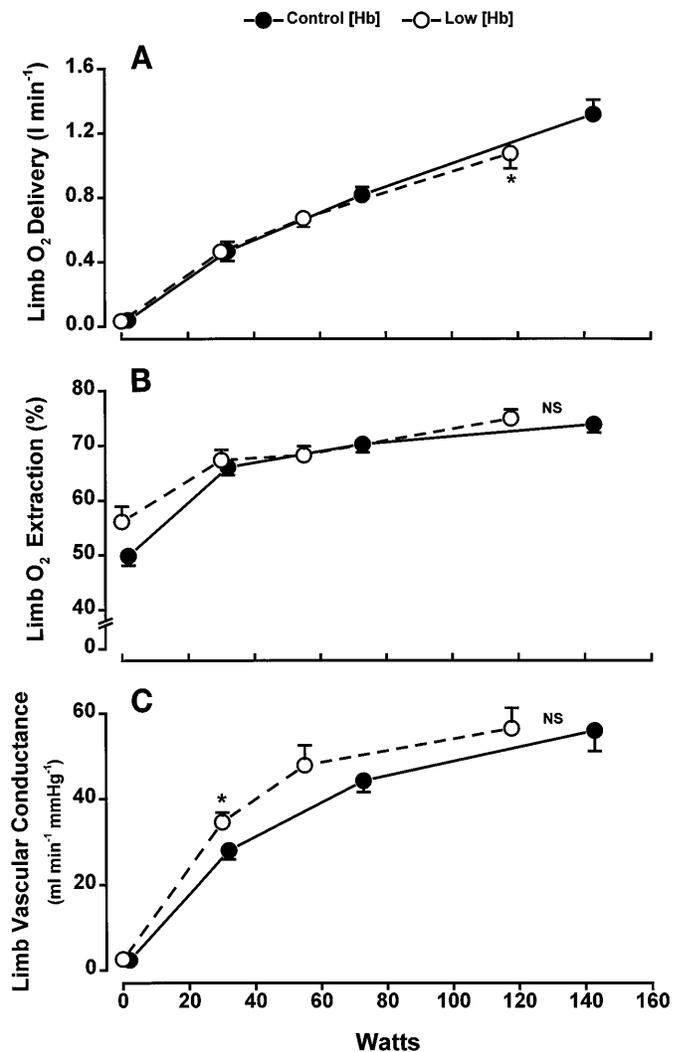


Fig. 4. O_2 delivery (A), O_2 extraction (B), and vascular conductance (C) in working leg muscles at rest and submaximal and peak exercise. Values are means \pm SE. For statistics, see Fig. 2. *Significantly different from same stage with control [Hb], $P < 0.01$.

tively. Of note is that when expressing LBF relative to the workload (two-legged blood flow/W), the difference was 0.02 l \cdot min⁻¹ \cdot W⁻¹ ($P < 0.01$), resulting in the same O_2 delivery in control [Hb] and low [Hb] (Fig. 4). Moreover, with an unaltered systemic blood pressure, limb vascular conductance was lower at a given absolute workload.

Femoral venous SO_2 (Sfv_{O_2}) was barely affected by the lowering of [Hb] at rest or at submaximal exercise. This is also the case at peak effort when Sfv_{O_2} reached 25.6 and 24.6% in the control and low [Hb] conditions, respectively (Table 1). Also, femoral venous PO_2 (Pfv_{O_2}) was only moderately and nonsignificantly lower, reaching at peak effort 23–24 Torr in both conditions (Table 1). The femoral venous O_2 content (Cfv_{O_2}) was reduced at rest and all exercise intensities ($P < 0.01$) when [Hb] was lowered but not to the extent of Ca_{O_2} (Table 1). The femoral a-v O_2 difference was then reduced ($\sim 20\%$) at all exercise levels ($P < 0.01$). The O_2 extraction by the working muscle expressed in relation to O_2 delivery

was similar in the two [Hb] conditions, increasing with exercise intensity and reaching ~75% at peak effort (Fig. 4).

Leg $\dot{V}O_2$ was identical in the two conditions at rest (0.02 l/min) and at 30 W (0.3 l/min; Fig. 5). At peak effort, leg $\dot{V}O_2$ was lower with low [Hb] (~20%; $P < 0.01$). Leg $\dot{V}O_2$ -to-workload ratios, however, were the same regardless of [Hb] and exercise level. The elevation in leg $\dot{V}O_2$ during submaximal exercise was accounted for fully by the observed increase in LBF in both conditions (Fig. 5). Going from submaximal to peak effort, leg $\dot{V}O_2$ only contributed 55–60% of the pulmonary $\dot{V}O_2$, reflecting that additional muscle became engaged in the exercise.

Low [Hb] had little effect on the [Lac] response (Table 2). The release of [Lac] from the contracting muscles resulted in similar arterial and venous [Lac] levels at the same workloads in both conditions. Arterial and venous pH corresponded to the femoral venous P_{CO_2} and [Lac] (Table 2). Also, the K^+ concentration increased with exercise, reaching 6.0–6.2 mmol/l in the femoral vein at peak effort in the two conditions (Table 2).

DISCUSSION

The major finding of this study was that during submaximal work LBF was elevated and matched by

an increase in CO, compensating for the reduction in Ca_{O_2} caused by a 20% decrease in [Hb]. It is of note that blood pressure was identical in the two conditions, which means that the larger LBF was due to local vasodilatation and not to an increased perfusion pressure. However, neither LBF, CO, nor O_2 extraction compensated for a low [Hb] at peak effort.

The lack of a compensatory elevation in LBF with low [Hb] at peak effort is puzzling, at least in view of the finding by Sproule et al. (15) of a CO of 23 l/min in chronically anemic patients, resulting in only 1.8 l/min $\dot{V}O_{2max}$. An explanation of the present findings could then be that the pump capacity of the heart may have set a limit. This is hardly the case. Peak LBF was close to 7 l/min in both conditions, putting a demand for the two legs at 13 l/min. The heart pumped an additional 7 l/min, of which 2 l/min can be estimated to have perfused contracting skeletal muscle in the hip region, not accounted for in the measurements over the legs, and the respiratory muscles. This leaves ~5 l/min to the remaining body, which is a high value considering that the exercise effort is maximal. In ordinary two-legged exercise, blood flow to the noncontracting tissues is reduced at the onset of exercise in relation to the relative exercise intensity, being as low as ~3 l/min at exhaustive exercise (12). From the perspective of the performing muscle, especially in the low [Hb] condition of the present study, an additional 1 l/min of blood flow to each leg would have been enough to compensate for the low Ca_{O_2} . This amount would have been available if noncontracting tissue blood had been reduced as in ordinary two-legged exercise (12).

Another and very critical finding is that the C_{fvO_2} is high not only at normoxia and submaximal exercise but also at peak effort with low [Hb], when it is 41.3 ml/l with a P_{fvO_2} of 23 Torr. This is quite different from observations by Sproule et al. (15). They found a low C_{fvO_2} of 13.5 ml/l with a P_{fvO_2} of 23 Torr, which is explained by a shift to the right of the O_2 dissociation curve (Fig. 6), which is not observed in acute anemia. Thus the leg a-v O_2 differences constitute 86% in chronically and severely anemic patients compared with 75% in acute anemia (low [Hb] in present study), with no difference in the latter study compared with control [Hb]. The findings of the present study point to a diffusion limitation in the contracting muscle that can be due to 1) a short MTT, 2) limited mitochondrial respiration, 3) restricted off-loading of the O_2 from the Hb molecule, and 4) capillary red blood cell spacing and heterogeneity in flow. The number of capillaries varied among subjects, as expected, considering the large range in $\dot{V}O_{2max}$. The higher degree of capillarization in the trained subjects matched their larger muscle perfusion, giving a similar estimated MTT of 525 ms. Although there was a tendency for the subjects in the upper range of MTT (600–650 ms) to have a slightly larger femoral a-v O_2 difference, it is questionable whether the MTT explains the low O_2 extraction because the femoral a-v O_2 difference is less in the low [Hb] condition despite an unchanged MTT. It could possibly be explained by an enlarged spacing of red

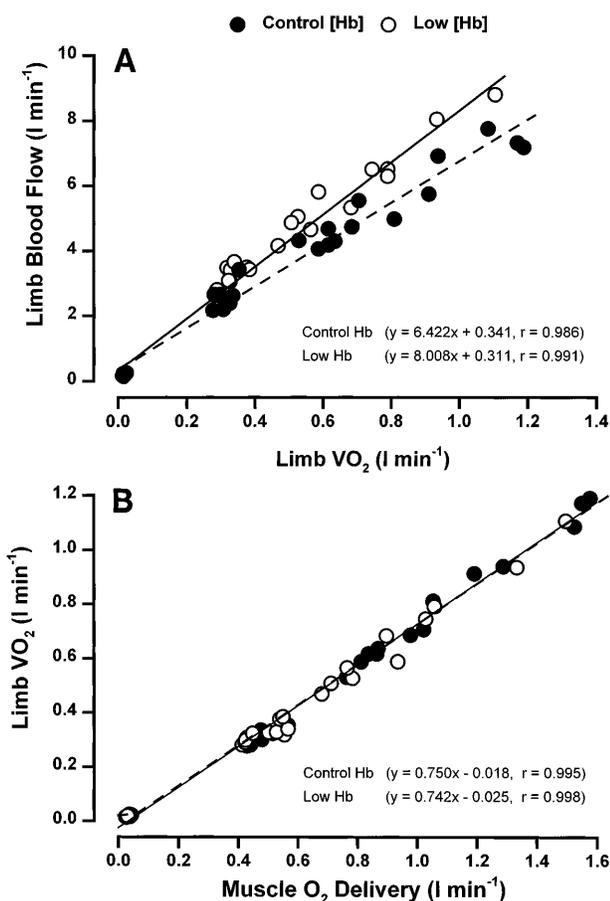


Fig. 5. Individual values for limb blood flow (A) and O_2 delivery to working muscles (B) vs. limb $\dot{V}O_2$ at rest and during submaximal and peak exercise.

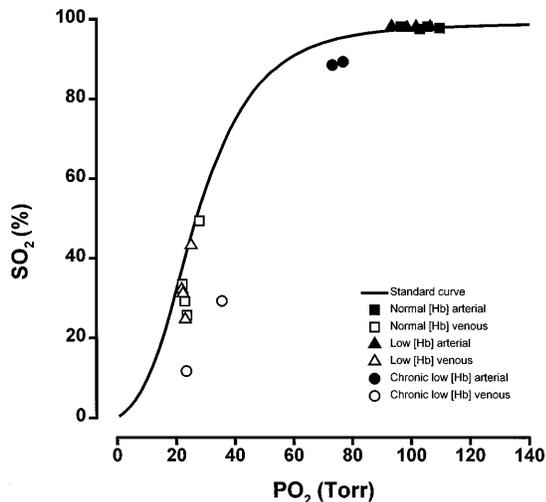


Fig. 6. Standard O₂ dissociation curve (drawn from data in Ref. 13) with mean arterial and venous values at rest and exercise from acute anemia in present study and right-shifted values from patients with chronic, severe anemia (14). SO₂, O₂ saturation.

blood cells in the capillary with a low Hct (2). On the other hand, the blood flow distribution within the capillary beds of contracting skeletal muscles may be improved with low Hct or [Hb] (8). Moreover, although Ca_{O₂} is lower with low [Hb], the pressure gradient for O₂ diffusion into the cell was maintained, which should favor a larger O₂ flux to the contracting muscles. The limitation could be in the capacity for mitochondrial respiration, which, however, is unlikely because the peak V_{O₂} with low [Hb] is lower than with control [Hb]. When the control [Hb] is compared with the low [Hb] in regard to Pfv_{O₂}, they are almost identical in the corresponding conditions, which may be a reflection of Pfv_{O₂} and Cfv_{O₂} being regulated variables. Of note is that almost as low a Pfv_{O₂} is observed during the submaximal exercises as at peak effort, but O₂ extraction is elevated as Sfv_{O₂} is gradually lowered with increasing exercise intensity. The lower Sfv_{O₂} with increasing exercise intensity is a function of the acidification of the blood. It is of note that a lowering of Ca_{O₂} to 150–160 ml/l by lowering the [Hb] and maintaining Pa_{O₂} at a normal level does not affect the submaximal and maximal lactate responses. With [Lac] and P_{CO₂} levels being the same in the two conditions, pH is reduced in an identical manner in control and low [Hb]. Taken together, the Pa_{O₂}, Sa_{O₂}, and pH data point to the off-loading of O₂ from Hb as possibly limiting O₂ extraction.

The mechanisms for elevating V_E, CO, and LBF in hypoxia are understood because there are sensors for alterations in Pa_{O₂} (9). In contrast, a sensor for Ca_{O₂} located centrally or in the peripheral tissues has been sought, but none has yet been identified. Novel proposals for Ca_{O₂} to have a regulatory function have been put forward by Ellsworth et al. (4) and Jia et al. (5). The former authors suggest that there is a release of ATP from the red blood cells when they pass through peripheral vascular beds that is related to the number

of occupied O₂ binding sites on the Hb molecules. The other possibility as proposed by Jia et al. is that the Hb molecule functions as a scavenger of nitric oxide (NO) in the peripheral vascular bed, with low [Hb] causing more NO to be available to induce vasodilatation. An attractive feature with these two proposals is that they take into consideration a role for the variable amount of [Hb], a key to explain our findings. We are left then with the phenomenon that acute lowering of Ca_{O₂}, either by low [Hb] or hypoxia, elevates LBF and CO during submaximal exercise, but how it is brought about in the low [Hb] condition is unknown.

When Ca_{O₂} is lowered by inhaling hypoxic gas, the usual response is an increase in ventilation regulated by increased peripheral chemosensor activation. Although the aortic peripheral chemosensor is capable of sensing changing Ca_{O₂} (9), it makes a negligible contribution to the overall ventilatory response. This is apparent in the present study by the lack of an increase in V_E even though Ca_{O₂} was decreased 20% in the low [Hb] condition. For example, at 30 W, V_E was nearly identical between the two conditions despite a difference in Ca_{O₂} of ~40 ml/l. The increase in [Lac] and fall in pH during exercise were also similar between conditions and thus provided no extra central drive to breathe. The lack of increase in peripheral chemoreceptor stimulation is explained in the present study by the nearly identical Pa_{O₂} values in the two conditions at rest and exercise. In comparison, in a recent study, Koskolou et al. (7) showed that when Ca_{O₂} was lowered by breathing hypoxic gas, the same magnitude of drop in Ca_{O₂} caused by a decrease in inspired PO₂ resulted at 30-W exercise in a 10 l/min higher V_E and a 5 Torr lower Pa_{CO₂}. The function of the heart measured as stroke volume is also differentially affected by hypoxia and low [Hb]. In hypoxia, stroke volume is reduced (7), whereas this is not the case in acute (present study) or severe, chronic anemia (15).

The present study was performed in the morning 12–18 h after reduction of [Hb], which allowed for fluid adjustments but hardly any adaptation on a cellular level including the red blood cells, which may occur with slowly developing chronic anemia. In this respect, it is of interest to note that in the few cases studied (13), it appears that their LBF elevation at submaximal work is similar to the one found in the present study. At peak exercise, however, chronically anemic subjects had a 1 l/min higher LBF than that observed in our subjects with low [Hb] despite a slightly higher Ca_{O₂} (172 vs. 162 ml/l). On the other hand, the femoral a-v O₂ difference was slightly smaller (7 ml/l) in the chronically anemic subjects. This resulted in a similar relationship between O₂ delivery to the exercising limb and leg V_{O₂} in acute and chronic anemia, but at peak exercise, it was brought about by a higher blood flow in the chronically anemic subjects (13, 15).

In summary, this study has demonstrated that O₂ delivery to exercising muscles and V_{O₂} were well maintained at the submaximal level even though [Hb] was 20% lower. This was accomplished by a compensatory elevation in LBF and CO. Equally clear is that at peak

exercise, LBF and CO did not increase with low [Hb], resulting in a reduced peak O₂ delivery and V̇O₂. This lack of compensation, either by increasing the blood flow or O₂ extraction, is surprising because 1) only a limited fraction of the muscle mass was engaged in the exercise, 2) the subjects' maximal CO was not reached, and 3) the venous blood draining the contracting muscles still contained ample amounts of O₂. This being the case, it is of interest that, even with low [Hb], the previously well-documented tight coupling among O₂ delivery to the exercising limbs, performed work, and V̇O₂ still exists (Fig. 4).

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