J Appl Physiol 100: 744–748, 2006;
doi:10.1152/japplphysiol.01395.2005.

Point: In health and in a normoxic environment, $\dot{V}O_{2\,max}$ is limited primarily by cardiac output and locomotor muscle blood flow

Starting in the 1950s, a number of experiments provided the experimental evidence supporting the original concept elaborated on by Hill and Lupton (12): in health, $\dot{V}O_{2\,max}$ in normoxia is limited primarily by cardiac output and locomotor muscle blood flow (17). The main variable accounting for the difference in $\dot{V}O_{2\,max}$ between sedentary subjects and athletes is maximal cardiac output, such that a linear relationship was observed between $\dot{V}O_{2\,max}$ and maximal cardiac output, showing that 5.9–7.5 l/min of cardiac output is needed per liter of $\dot{V}O_{2\,max}$ (5, 10, 17, 26). Part of the variability in the relationship between $\dot{V}O_{2\,max}$ and cardiac output was attributed to the variation in hemoglobin concentration, with a smaller contribution of the systemic a-v difference (5, 10, 17, 26). It was also shown that maximal exercise stroke volume was the main factor explaining the differences between subjects in maximal cardiac output (5, 10, 17, 26). A cause and effect relationship between oxygen delivery and $\dot{V}O_{2\,max}$ has been established by showing that experimental interventions increasing oxygen delivery are accompanied by an elevation of $\dot{V}O_{2\,max}$ and vice versa (6, 16).

All experimental procedures causing a reduction of maximal cardiac output are associated with a lower $\dot{V}O_{2\,max}$. Reducing blood volume is associated with lower maximal cardiac output and $\dot{V}O_{2\,max}$ (16). Bed rest studies showed that the main factor accounting for the reduction in $\dot{V}O_{2\,max}$ was the lower maximal cardiac output attained after bed rest (27), because maximal exercise O_2 fractional extraction is close to 90% after bed rest. Treatment with beta-blockers is accompanied by a reduction of maximal cardiac output and leg blood flow, which accounts for most of the reduction observed in $\dot{V}O_{2\,max}$ (21). The CaO_2 may be reduced by reducing hemoglobin concentration isovolemically and by carbon monoxide administration. These two interventions show a reduction in $\dot{V}O_{2\,max}$ that is proportional to the magnitude of the reduction achieved in CaO_2 (6, 15, 23, 30).

The influence of locomotor muscle oxygen delivery for $\dot{V}O_{2\,max}$ in trained and untrained muscles was studied in the 1970s (3, 8, 28). With the use of a one-leg training model (in the cycle ergometer), Gleser (8) reported a 16% improvement of one-leg peak $\dot{V}O_2$ that was accompanied by a 13% enhancement of the peak cardiac output during incremental exercise with the trained leg. However, neither $\dot{V}O_{2\,max}$ nor maximal cardiac output was enhanced after one-leg training when the exercise test was performed with the two legs. Thus the study by Gleser suggests that the increase in $\dot{V}O_{2\,max}$ was brought about via an enhancement of cardiac output and, likely, leg blood flow. Clausen et al. (3) reported a 10% greater peak $\dot{V}O_2$ during arm cranking after a period of endurance training with the legs in the cycle ergometer. The increase in arm $\dot{V}O_2$ was accompanied by 10 and 12% greater mean arterial pressure and peak cardiac output, also suggesting that $\dot{V}O_{2peak}$ during exercise with a small muscle mass is limited by locomotor muscle blood flow. In the study by Saltin et al. (28), the subjects that performed one-leg endurance training in the cycle ergometer improved their $\dot{V}O_{2\,max}$ by 24% during an incremental exercise to exhaustion with the trained leg. Interestingly, the contralateral leg that was not submitted to training also improved its $\dot{V}O_{2\,max}$ (6%). However, when the subjects carried out a two-legged incremental exercise the $\dot{V}O_{2\,max}$ was improved only by 11%. Thus the improvement observed during two-leg exercise was a bit less than expected if the limitation to $\dot{V}O_{2\,max}$ had been only of peripheral origin, suggesting that in that study part of the limitation to $\dot{V}O_{2\,max}$ during two-leg exercise is due to insufficient perfusion. A subsequent one-leg training study by Klausen et al. (13) adds further evidence. Their subjects trained each leg on the cycle ergometer individually. After the training, peak leg $\dot{V}O_2$ during exercise on the cycle ergometer was 16% higher during one-leg than during two-leg exercise, due to a 23% higher peak leg blood flow during one-leg maximal exercise compared with two-leg maximal exercise. In contrast, before training, peak leg $\dot{V}O_2$ was the same during one-leg cycling compared with two-leg cycling, despite the fact that leg blood flow was 8% higher during one-leg exercise. This study suggests that in the trained state, the dependency of $\dot{V}O_{2\,max}$ on oxygen delivery may be accentuated.

Further evidence for a cause and effect relationship between $\dot{V}O_{2\,max}$ and locomotory muscle oxygen delivery was obtained by Harms et al. (11). They showed that if the respiratory muscles are loaded, exercise capacity and locomotory muscle blood flow and $\dot{V}O_2$ is reduced, suggesting that maneuvers redistributing part of the blood flow away from the locomotory muscles reduces exercise capacity and $\dot{V}O_{2\,max}$ (11) and vice versa. A similar conclusion was reached by Gonzalez-Alonso and Calbet (9). In their study, subjects performed constant intensity exercise to exhaustion under normothermic and hyperthermic conditions. In both conditions, fatigue was preceded by a reduction of cardiac output and leg blood flow. Moreover, we recently showed that during whole body upright exercise the combined maximal muscular vascular conductances of the limbs outweighs the pumping capacity of the heart in humans, meaning that $\dot{V}O_{2\,max}$ is limited by O_2 delivery. With the use of data from the latter, we estimated that if the human with well-trained leg and arms muscles was able to use the full potential for $\dot{V}O_2$ of the four limbs, then their $\dot{V}O_{2\,max}$ could be about 20% higher than actually measured (2).

Although $\dot{V}O_{2\,max}$ is a function of locomotor muscle blood flow, this does not exclude the possibility that other mechanisms marginally contribute to achieve $\dot{V}O_{2\,max}$ in normoxia, as, for example, exercise-induced arterial hypoxemia (4, 19), a diffusional limitation between the capillaries and the mitochondria of the active muscle fibers (24), and lower O_2 extraction capacity in some muscles (1). However, in all these conditions, peak $\dot{V}O_2$ is increased if the limitation is somehow overcome and more O_2 is made available to the mitochondria (6, 14, 22, 25). Thus the bulk of the experimental evidence accumulated during the last 80 years argues in favor of cardiac output and oxygen delivery setting the limit for maximal oxygen uptake in normoxia. All these observations also argue against theories attributing the limitation of $\dot{V}O_{2\,max}$ to brain processes as the "Central Governor Model" during exercise in normoxia carried out by healthy subjects (20). This model postulates that processes arising in the brain itself, triggered or modulated by

sensory feedback, inhibit somehow the central command, causing the exercise to terminate (20). This model has revitalized some ideas brought about more than a century ago, as reviewed by Gandevia (7). However, experimental evidence obtained during exercise with hyperthermia (18) and during exercise in chronic hypoxia (29) demonstrated that, at least during brief efforts aimed at producing a maximal leg or hand grip voluntary contraction, the ability to recruit the motor units is preserved even when measured close to exhaustion.

In summary, in healthy humans, $\dot{V}O_{2\,max}$ at sea level is limited by systemic oxygen delivery and especially by O_2 delivery to the locomotor muscles. Oxygen delivery, in turn, depends on the ability of the cardiorespiratory system (i.e., lungs, heart, and blood) to transport and distribute appropriately O_2 to the active motor units, rather than on the mitochondrial oxidative capacity, which in human skeletal muscles exceeds widely maximal O_2 supply in all known exercise models.

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Bengt Saltin
José A. L. Calbet
The Copenhagen Muscle Research Centre
Rigshospitalet
Copenhagen N, Denmark
Department of Physical Education
University of Las Palmas de Gran Canaria
Gran Canaria, Spain
e-mail: bengt.saltin@rh.hosp.dk

Counterpoint: In health and in a normoxic environment, $\dot{V}O_{2\,max}$ is not limited primarily by cardiac output and locomotor muscle blood flow

Let's begin this by being sure of the question we are addressing, because this topic is notorious for being easy to spin toward one's desired position by subtly changing the question. I would like to clear the deck of spin right from the start. So I will stipulate that without blood flow, $\dot{V}O_{2\,max}$ would be zero: Saltin 1, Wagner 0. I will also stipulate that the venerable Fick Principle, taken at its naive simplest, would tend to support my opponent: $\dot{V}O_2 = \dot{Q} \times [CaO_2 -$

Cv_{O_2}], where $\dot{Q}$ is cardiac output, Ca_{O_2} is arterial, and Cv_{O_2} mixed venous [O_2].

I will even argue for him, comparing Lance Armstrong or equivalent with a sedentary normal subject each at their maximal exercise capacities, $\dot{V}_{O_2}$ would be about twice as high in LA (~80 vs. ~40 ml·kg^{-1}·min^{-1}). Ca_{O_2} in the absence of erythropoietin would be close to 20 ml/dl in each, maybe even lower in LA if he shows exercise-induced desaturation (1) plus the plasma volume expansion, common in trained athletes, that results in a reduced [Hb] (16). Cv_{O_2} would be lower in LA, perhaps as low as 2 ml/dl (i.e., 90% extraction) (5), whereas in his unfit couch potato (CP) counterpart, maximal extraction might not exceed 70% (12), with Cv_{O_2} therefore at 6 ml/dl. Thus in the Fick equation above, maximal [$Ca_{O_2} - Cv_{O_2}$] approximates 180 ml/l in LA and 140 ml/l in CP. This, in turn implies that LA's peak $\dot{Q}$ must be 32 l/min, whereas CP's is only 20 l/min (assuming both weigh ~70 kg). For LA, $\dot{Q}$ is 60% higher but [$Ca_{O_2} - Cv_{O_2}$] is only 30% higher. So Bengt would be justified in saying $\dot{Q}$ is the primary determinant of $\dot{V}_{O_2\,max}$ if the question is "what primarily explains the difference in $\dot{V}_{O_2\,max}$ between CP and LA? $\dot{Q}$ or [$Ca_{O_2} - Cv_{O_2}$]?" Saltin 1.5, Wagner 0. (I will return to LA and CP later. Bengt, watch out.)

But, this is *not* the question that we are being asked to address. The question is: "Is cardiac output (or muscle blood flow) the primary determinant of $\dot{V}_{O_2\,max}$ or not?" Stated in other words, if a normal subject is exercising at $\dot{V}_{O_2\,max}$ and you were somehow able to augment any single part of the O_2 transport and use chain, what effect would this have on $\dot{V}_{O_2\,max}$? And, would cardiac output, as one part of that chain, have the largest effect, as Bengt will argue? I hope he will not try and argue $\dot{Q}$ is the sole limiting factor, or I will blow him out of the water in rebuttal.

There is undeniable evidence that $\dot{V}_{O_2\,max}$ can be acutely altered at will in normal humans by any one of a number of interventions (8, 10, 14, 17, 21), of which altering $\dot{Q}$ is but one. Let's step down the O_2 transport pathway, examining each step in turn.

Changing $F_{I_{O_2}}$ changes $\dot{V}_{O_2\,max}$ in the same direction (5, 6). Ventilation at $\dot{V}_{O_2\,max}$ is very hard to alter in normal subjects, but published theoretical models demonstrate that maximal O_2 transport and thus $\dot{V}_{O_2\,max}$ would be affected by changes in ventilation (20). $\dot{V}_A/\dot{Q}$ inequality (2), alveolar-capillary diffusion limitation (18), and (post) pulmonary shunts (2) can and do play a small but demonstrable role in reducing arterial oxygenation and thus $\dot{V}_{O_2\,max}$, as our own editor showed many years ago (9). Cardiac output (or muscle blood flow) clearly affects $\dot{V}_{O_2\,max}$, although direct interventions to test this have been done only in animals such as dogs, for example, by pericardiectomy (3), which allows a higher cardiac output and $\dot{V}_{O_2\,max}$. Changes in [Hb] (15) and in the P_{50} of Hb (4, 11) both alter convective O_2 transport to the muscles and have been shown to affect $\dot{V}_{O_2\,max}$ in controlled studies. Skeletal muscle O_2 transport conductance (between capillaries and mitochondria), which relates closely to capillarity, has also been shown to play a significant role in setting $\dot{V}_{O_2\,max}$ (13). Finally, maximal mitochondrial rate of O_2 consumption has the power to affect $\dot{V}_{O_2\,max}$ (7).

Although the above demonstrates, beyond argument even by Bengt, that $\dot{Q}$ is by no means the only factor contributing to $\dot{V}_{O_2\,max}$, I have not yet provided the key arguments that must address the core question of sensitivity of $\dot{V}_{O_2\,max}$ to a given percent change in each of the above steps. Saltin still 1.5, Wagner still 0. Answering that question will put the nail in the $\dot{Q}$/Saltin coffin, as follows.

First, suppose maximal mitochondrial O_2 consumption is *less* than maximal O_2 available by transport from the air to the mitochondria. Further raising O_2 transport by increasing cardiac output (or for that matter any of the other above O_2 pathway steps) will have no effect on $\dot{V}_{O_2\,max}$ because it is by definition O_2 supply independent. Saltin 1.5, Wagner 1.0.

But suppose things are turned the other way around: maximal mitochondrial O_2 use potential now *exceeds* O_2 availability. Then, according to the evidence presented above, augmenting each and every step in O_2 transport should have a positive effect on $\dot{V}_{O_2\,max}$, and it does. Suppose each component is augmented by 20% of its value, one at a time. Integrated physiological models incorporating all pathway steps (20) and Fig. 1 show that a 20% increase in $F_{I_{O_2}}$ raises $\dot{V}_{O_2\,max}$ by only 5.0%, due to the flat O_2-Hb dissociation curve in the normal range. Increasing ventilation 20% will also lead to a small (1.3%) increase, again because P_{O_2} is on the flat part of the curve, and raising P_{O_2} has little effect on Ca_{O_2}. Increase lung diffusing capacity 20% in an athlete who has *mild* hypoxemia due to diffusion limitation and $\dot{V}_{O_2\,max}$ will increase by 2.9%. Increasing diffusing capacity in a subject without diffusion limitation obviously cannot improve $\dot{V}_{O_2\,max}$. If skeletal muscle O_2 diffusional conductance is increased by 20%, $\dot{V}_{O_2\,max}$ will be 5.0% higher. Increase [Hb] by 20% and $\dot{V}_{O_2\,max}$ increases by only 3.9%. Finally, increase $\dot{Q}$ by 20%, and $\dot{V}_{O_2\,max}$ increases by only 2.6%, *half that when muscle O_2 conductance is raised equally*. Why? Because muscle O_2 conductance has only one significant effect—to increase O_2 flux from blood to cells. But raising $\dot{Q}$ has opposing effects (19). First, it *increases* convective O_2 transport by the circulation as predicted by both Bengt and the Fick principle. But the higher $\dot{Q}$ simultaneously reduces transit time in both lung

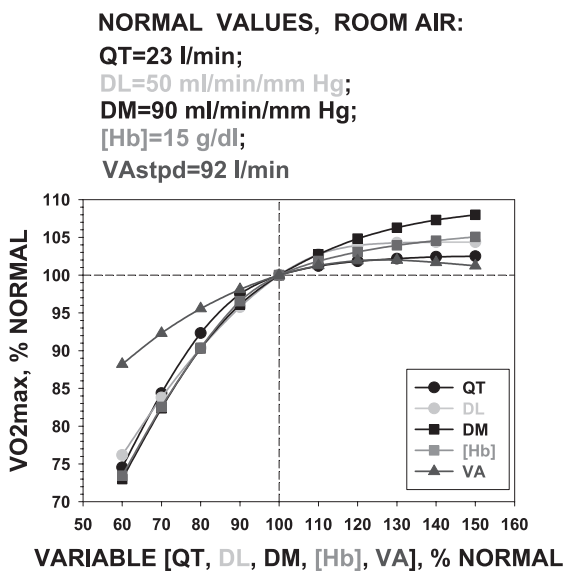

Fig. 1. Calculated effects of individual changes in key O_2 transport variables on $\dot{V}_{O_2\,max}$. Data reflect typical normal sea level values. Calculations use the model are described in Ref. 20. Note that all variables affect $\dot{V}_{O_2}$, and that $\dot{Q}_T$ is by no means the most important factor.

and muscle capillaries and this *worsens* diffusion limitation, significantly opposing this convective gain.

This brings me back to LA and CP as promised. If LA did not have a superior muscle O_2 conductance to facilitate O_2 transport to cells, the 32 l/min $\dot{Q}$ would simply limit O_2 extraction due to rapid red cell transit. *The only way LA can get to 80 ml/min $\dot{V}O_{2\,max}$ is by having both an exceptional $\dot{Q}$ and a matching, exceptional muscle capillary-to-mitochondrion O_2 transport system to permit almost full O_2 extraction from the rapidly flowing blood.* Thus, even if Bengt argues from the Fick Principle, as in my opening paragraph, the untold story is that muscle O_2 conductance must also be extraordinary, every bit as important as $\dot{Q}$, or O_2 extraction could not possible reach 90%. I rest my case, Bengt: Saltin 1.5, Wagner 10.

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Peter D. Wagner
University of California, San Diego
La Jolla, California
e-mail: pdwagner@ucsd.edu

REBUTTAL FROM DRS. SALTIN AND CALBET

The diffusional limitation theory is based primarily on one study (8) where an extraordinary elevation of leg $\dot{V}O_{2peak}$ (39%) and whole body (WB) $\dot{V}O_{2\,max}$ (35%) was observed after 6 wk of training (Ref. 8, p. 1070), whereas maximal exercise intensity was only enhanced by 9%. Leg $\dot{V}O_2$ only accounted for 53–55% of WB $\dot{V}O_2$ at maximal exercise (before-after training), i.e., far below the normal 75–85% (5). These low leg peak $\dot{V}O_2$ values were likely caused by underestimation of peak leg blood flow (BF; which was only 5–6 l/min). Because during WB exercise, systemic a-v difference is never higher than leg a-v difference, peak cardiac output should have been >19 l/min before training and >23 l/min after training (+20%), leaving 9–10 l/min of BF for the rest of the body, which is too high a figure (5). Because DO_2 (oxygen conductance) is calculated as peak leg $\dot{V}O_2$/mean capillary Po_2 ($PmcO_2$) (10), it is likely that DO_2 was also underestimated (8).

Could a "couch potato" (CP) enhance his $\dot{V}O_{2\,max}$ by increasing his cardiac output and BF? CP should be able to achieve an arm BF of ~2.5–3 l/min with an O_2 extraction a bit lower in the arms than the legs during maximal exercise (1–3, 7). This means that the $\dot{V}O_{2peak}$ of CP arms could reach 0.6–0.7 l/min. To perform maximal exercise with the four extremities, CP will need to increase his maximal cardiac output from 20 to 24 l/min. With the extra perfusion, CP could achieve a $\dot{V}O_{2\,max}$ 20% greater, even when assuming a lower muscle diffusing capacity in the arms than in the legs (2). CP could also increase his $\dot{V}O_{2\,max}$ after blood transfusion or treatment with EPO. After this intervention, $PmcO_2$ will be similar or a bit higher (6), meaning that the increase of $\dot{V}O_{2\,max}$ requires an increase of DO_2 after transfusion or EPO. If for a given $PmcO_2$, DO_2 is enhanced when [Hb] is increased, it implies that $\dot{V}O_{2\,max}$ is not limited by a structural resistance to diffusion in the skeletal muscle of healthy humans, i.e., what Roughton and Forster called membrane component of the oxygen conductance (9). Thus, for DO_2 to be the key limiting factor for $\dot{V}O_{2\,max}$, first the evidence that DO_2 actually represents the maximal attainable oxygen diffusing capacity in skeletal muscles should be provided. However, we agree that a diffusion limitation theoretically is a possibility but functionally it is a very minor player in healthy humans (4).

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REBUTTAL FROM DR. WAGNER

My good friends Bengt and Jose have done a wonderful job of making my case and my rebuttal easy, because we clearly agree on several points. We agree that cardiac output/muscle blood flow is *one* determinant of maximal $\dot{V}O_2$. We agree that *one* major difference between an athlete and a couch potato is in maximal cardiac output. However, we surprisingly agree that other factors contribute substantially to maximal $\dot{V}O_2$. Bengt and Jose say this in *paragraph 2* referring to the role of CaO_2, which is *not* blood flow and restate this in their concluding paragraph, agreeing that lungs, heart, and blood are all important, just as I have argued. But they cannot use this to advance their own argument because the topic was *not* about O_2 delivery, it was about blood flow.

I must also remind my friends that the topic includes the word *primarily*. They provided *no* evidence that per unit of change in the responsible variable, blood flow is the primary factor, more important than any other conductances in the O_2 transport chain. They have failed to realize that for a high cardiac output to allow a high $\dot{V}O_{2\,max}$, the diffusing capacities in both the lungs and muscles *must* be correspondingly high, or pulmonary O_2 loading and tissue unloading *must* be compromised, as pointed out many years ago by Piiper et al. (1, 2). They have assigned primary importance to one variable (flow) without assessing all other pertinent variables. How can you compare the roles of each variable when not all are addressed? Suppose you ask which is the fastest way to get from *point A* to *B*? By car, bicycle, or plane, and don't even study other alternatives such as by train or on foot. You simply cannot conclude that by train or on foot are not faster ways to get there. By looking at only part of the story, they have presented only part of the answer.

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