Am J Physiol Regul Integr Comp Physiol 287: R996–R1002, 2004;
10.1152/ajpregu.00608.2003.

The following are the abstracts of the articles discussed in the subsequent letter:

Calbet JAL, Boushel R, Radegran G, Sondergaard H, Wagner PD, and Saltin B. Determinants of maximal oxygen uptake in severe acute hypoxia. *Am J Physiol Regul Integr Comp Physiol* 284: R291–R303, 2003.—To unravel the mechanisms by which maximal oxygen uptake ($\dot{V}O_{2\,max}$) is reduced with severe acute hypoxia in humans, nine Danish lowlanders performed incremental cycle ergometer exercise to exhaustion, while breathing room air (normoxia) or 10.5% O_2 in N_2 (hypoxia, ~5,300 m above sea level). With hypoxia, exercise Pa_{O_2} dropped to 31–34 mmHg and arterial O_2 content (Ca_{O_2}) was reduced by 35% ($P < 0.001$). Forty-one percent of the reduction in Ca_{O_2} was explained by the lower inspired O_2 pressure ($P_{I_{O_2}}$) in hypoxia, whereas the rest was due to the impairment of the pulmonary gas exchange, as reflected by the higher alveolar-arterial O_2 difference in hypoxia ($P < 0.05$). Hypoxia caused a 47% decrease in $\dot{V}O_{2\,max}$ (a greater fall than accountable by reduced Ca_{O_2}). Peak cardiac output decreased by 17% ($P < 0.01$), due to equal reductions in both peak heart rate and stroke volume ($P < 0.05$). Peak leg blood flow was also lower (by 22%, $P < 0.01$). Consequently, systemic and leg O_2 delivery were reduced by 43 and 47%, respectively, with hypoxia ($P < 0.001$) correlating closely with $\dot{V}O_{2\,max}$ ($r = 0.98$, $P < 0.001$). Therefore, three main mechanisms account for the reduction of $\dot{V}O_{2\,max}$ in severe acute hypoxia: *1*) reduction of $P_{I_{O_2}}$, *2*) impairment of pulmonary gas exchange, and *3*) reduction of maximal cardiac output and peak leg blood flow, each explaining about one-third of the loss in $\dot{V}O_{2\,max}$.

Calbet JAL, Boushel R, Radegran G, Sondergaard H, Wagner PD, and Saltin B. Why is the $\dot{V}O_{2\,max}$ after altitude acclimatization still reduced despite normalization of arterial O_2 content? *Am J Physiol Regul Integr Comp Physiol* 284: R304–R316, 2003.—Acute hypoxia (AH) reduces maximal O_2 consumption ($\dot{V}O_{2\,max}$), but after acclimatization, and despite increases in both hemoglobin concentration and arterial O_2 saturation that can normalize arterial O_2 concentration ($[O_2]$), $\dot{V}O_{2\,max}$ remains low. To determine why, seven lowlanders were studied at $\dot{V}O_{2\,max}$ (cycle ergometry) at sea level (SL), after 9–10 wk at 5,260 m [chronic hypoxia (CH)], and 6 mo later at SL in AH ($F_{I_{O_2}} = 0.105$) equivalent to 5,260 m. Pulmonary and leg indexes of O_2 transport were measured in each condition. Both cardiac output and leg blood flow were reduced by ~15% in both AH and CH ($P < 0.05$). At maximal exercise, arterial $[O_2]$ in AH was 31% lower than at SL ($P < 0.05$), whereas in CH it was the same as at SL due to both polycythemia and hyperventilation. O_2 extraction by the legs, however, remained at SL values in both AH and CH. Although at both SL and in AH, 76% of the cardiac output perfused the legs, in CH the legs received only 67%. Pulmonary $\dot{V}O_{2\,max}$ (4.1 ± 0.3 l/min at SL) fell to 2.2 ± 0.1 l/min in AH ($P < 0.05$) and was only 2.4 ± 0.2 l/min in CH ($P < 0.05$). These data suggest that the failure to recover $\dot{V}O_{2\,max}$ after acclimatization despite normalization of arterial $[O_2]$ is explained by two circulatory effects of altitude: *1*) failure of cardiac output to normalize and *2*) preferential redistribution of cardiac output to nonexercising tissues. Oxygen transport from blood to muscle mitochondria, on the other hand, appears unaffected by CH.

Central regulation of skeletal muscle recruitment explains the reduced maximal cardiac output during exercise in hypoxia

To the Editor: The findings of Calbet and colleagues in this (2, 3) and another journal (4) are more consistent with a physiological model in which the brain regulates exercise performance by altering the number of motor units that are recruited under different conditions (6, 7, 14, 15, 21), rather than with the traditional model that the authors prefer and that posits that exercise performance is determined by the rate of oxygen delivery to the exercising muscles (9–11, 18–20).

The authors studied cardiovascular and respiratory function in healthy lowlanders of both genders during maximum exercise *1*) in acute hypoxia at sea level (2) and *2*) at altitude after a period of 9–10 wk of altitude acclimatization (3), which increased blood hemoglobin content and hence the potential oxygen delivery to both heart and skeletal muscle at any given cardiac output (4). In addition, the acute effect of increasing the inspired oxygen fraction at the point of exhaustion was also studied. Their key findings were the following.

Key finding 1. Peak cardiac output was reduced in subjects exposed either acutely or chronically to hypoxia, as previously shown (23–25, 27, 28). This reduction was due to decreases in both heart rate and stroke volume.

Key finding 2. However, under all conditions of hypoxia, cardiac output (2, 3, Fig. 3*A*), heart rate (2, Fig. 3*E*; 3, Fig. 3*C*), and stroke volume (2, Fig. 3C; 3, Fig. 3*E*) were entirely appropriate for the work rates at which they were measured.

Key finding 3. Cardiac output increased marginally with acclimatization to chronic hypoxia (3, Fig. 3*A*) but was still substantially below the maximum value achieved in normoxia.

Key finding 4. The increase in cardiac output during maximum exercise in hypoxia after altitude acclimatization was due to an increase in stroke volume, whereas heart rate was reduced (3, Fig. 3, *E* and *C*).

Key finding 5. Peak work rate did not increase significantly after altitude acclimatization (Ref. 3, Table 1), although measured O_2 delivery to the exercising muscles increased by 40% (~800 ml O_2/min) (3, Fig. 4*C*), two-leg oxygen consumption ($\dot{V}O_2$) by ~550 ml/min (3, Fig. 4*E*), whereas pulmonary $\dot{V}O_2$ appears to have increased by only ~280 ml/min (3, Fig. 2*D*).

Key finding 6. The substantially reduced exercise performance and the low "maximal" cardiac output measured in hypoxia were instantly reversed when the inspired O_2 concentration was increased from 10.5% to either 21% (2, see R298) or to 55% (3, Fig. 3*A*).

The authors explained these six findings accordingly.

Conclusion 1. Hypoxia limits the intrinsic pumping capacity of the heart, causing a "downregulation of maximal cardiac output" (2, see R299) perhaps as a consequence of an altered "output drive from cardiovascular nuclei in the CNS" (2, see R299).

Conclusion 2. Alternatively, the hypoxia may act peripherally to "curtail increases in (skeletal muscle) power output, which, in turn, would limit the action of the (skeletal) muscle pump and ventricular filling" (2, see R300) by reducing venous return (*conclusion 2a*). However the authors ultimately reject this conclusion: "... it is more likely that hypoxia first attenuates increases in cardiac output that limits muscle oxygen delivery and power output and, in turn, the muscle pump and ventricular filling," thereby confirming the "importance of O_2 delivery as a limiting factor for $\dot{V}O_{2\,max}$ both in normoxia and hypoxia" (2, see R302, *conclusion 2b*).

Conclusion 3. The finding that acute exposure to normoxia (2) or hyperoxia (3) immediately normalized exercise performance supported a central (cardiovascular or neural) mechanism for the action of hypoxia since "the fact that it was possible to continue the incremental exercise test with reoxygenation argues against a peripheral (muscular or metabolic) mechanism as the main cause of fatigue in severe acute hypoxia" (2, see R300).

Conclusion 4. The authors recognize that "an alternative explanation is that severe hypoxemia may have altered the capacity to fully activate motor units and thus caused a decrease in maximal exercise performance" (3, see R312) so that the "reduction in cardiac output . . . could be envisaged as a regulatory mechanism aimed at protecting either the heart itself or more importantly the CNS from hypoxic damage" (2, R299). My contention is that the authors' data do not support *conclusions 1–3*, which they in fact acknowledge, whereas *conclusion 4* is more probably correct.

To arrive at *conclusions 1–3*, the authors interpret their findings according to the popular model of exercise physiology that has been termed the A. V. Hill Cardiovascular/Anaerobic model (20) after its first proponent and Nobel Laureate. Hill's model, as originally described (11) but not as currently taught (19, 20), is that the development of a progressive myocardial ischemia during maximum exercise limits the maximum cardiac output. This myocardial ischemia establishes the upper limit of oxygen delivery to and use by the exercising muscles—the concept of the maximum oxygen consumption ($\dot{V}_{O_2\,max}$) (18). Above this limit and as a consequence of this ischemia, both the heart and the exercising muscles must contract anerobically, producing lactic acid according to the theory first proposed by Fletcher and Hopkins in 1907 (5). Accumulation of the lactic acid then prevents muscle relaxation because Hill believed that *1*) lactic acid was the chemical that initiated muscle contraction and *2*) its oxidative removal was necessary for complete muscle relaxation to occur (9). Anerobiosis, because it prevented the oxidative removal of lactic acid, then terminated exercising by interfering with skeletal muscle relaxation. Hence, according to this Hill model, oxygen delivery to muscle determines its function (Fig. 1). The assumption is that the two variables are causally linked; that is, that *A* (skeletal muscle blood flow/oxygen delivery) determines or causes *B* (exercise performance).

The forgotten component of this theory was Hill's belief that the heart is the organ at greatest risk of ischemic injury during maximum exercise (10, 11). But Hill surmised that myocardial ischemia could not proceed unchecked without a fatal consequence. Hence he postulated the existence of a "governor" either in the heart or the brain that would limit the pumping capacity of the heart, thereby limiting the extent of the myocardial ischemia that would develop during maximal exercise (11, p. 161–163).

Calbet et al. (2, 3) invoke this model to conclude that because hypoxia impairs exercise performance, it must act by limiting oxygen delivery to the active skeletal muscles. This effect must therefore be due to a direct effect of hypoxia on the heart, thereby limiting the maximum cardiac output that can be achieved in hypoxia (*conclusions 1*, *2b*, and *3*).

But *conclusion 4* is derived from an opposing model, which posits that exercise performance is determined by a third factor, *C* (Fig. 2), which then explains an apparently causal, but

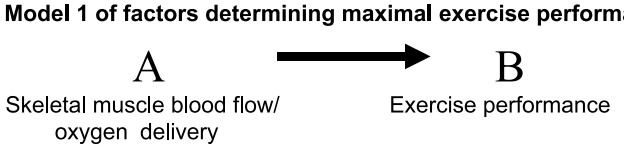

Fig. 1. *Model 1* of factors determining maximal exercise performance.

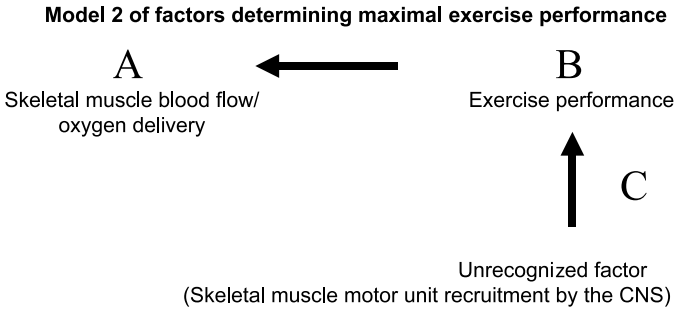

Fig. 2. *Model 2* of factors determining maximal exercise performance.

spurious, relationship between *A* and *B*. Thus, in this opposing model, the arrow of causality between *A* and *B* is reversed, because it predicts that oxygen use does not determine skeletal muscle function during exercise, but is simply the inevitable consequence of the increased skeletal muscle contractile activity during exercise (Fig. 2). This has been termed the Central Governor Model (21, 24).

Of central relevance to this debate is that *models 1* and *2* predict exactly opposite responses of the cardiac output to exercise in hypoxia. *Model 1* predicts that the cardiac output and hence muscle O_2 delivery will always be maximal in hypoxia to fully deliver all available O_2 to the "anaerobic" muscles and therefore to maximize the exercise performance (21, 23, 24). This is because in this model, the heart acts simply as the slave to the (voracious) oxygen requirements of the exercising muscles. Recall Hill's belief that such is the muscles' greed for oxygen that myocardial ischemia will develop during maximum exercise. Indeed I would argue that *model 1* is entirely incompatible with the finding of a low and submaximal cardiac output at exhaustion in persons with an intact nervous system, in any intervention that reduces the oxygen carrying capacity of the blood, be it hypoxia or anemia (4).

In contrast, *model 2* predicts that the cardiac output will be dictated purely by the work of the muscles (the exercising work rate) and that there will be no evidence for impaired cardiac function in hypoxia, because the CNS regulates the exercise performance specifically to ensure that cardiac or other damage does not occur during exercise, regardless of the environmental conditions (19–21). Thus, according to this model, any intervention that increases or decreases the work rate will cause a matching response in the cardiac output but without producing cardiac dysfunction as a result of hypoxia or ischemia. I argue that all the findings of Calbet et al. (2, 3) support this latter interpretation, disproving *model 1*.

Thus, although the cardiac output is reduced in hypoxia, the cardiac output, heart rate, and stroke volume were entirely appropriate for the work rate under all conditions (*key finding 2*). But if the cardiac output is appropriate for the lower maximal work rate achieved in hypoxia and if it is achieved at submaximal heart rates and stroke volumes and without any evidence for cardiac dysfunction, then the cardiac output cannot determine the work rate. Rather it must be the reverse; namely that the work rate determines the cardiac output as it must if *model 2* is correct. Hence the authors' postulate that myocardial dysfunction limits the cardiac output and exercise performance in hypoxia (*conclusions 1* and *2b*) is their attempt to fit the data to the model. Indeed their data show that cardiac function was not impaired in hypoxia.

Thus their findings (*key finding 4*) that stroke volume was increased and heart rate reduced at maximal exercise in hypoxia after altitude acclimatization is the opposite of that caused by increasing myocardial hypoxia or ischemia (13, 22) and shows that cardiac functional reserve was increased at exhaustion after altitude adaptation. Thus neither myocardial ischemia nor hypoxia could have determined the exercise performance, as is required by *model 1*. Indeed the authors ultimately admit the implausibility of these two conclusions: "The possibility of an insufficient myocardial O_2 delivery in chronic hypoxia is even less plausible" (3, R311). Hence the authors do not really believe *conclusions 1* and *2b*.

This interpretation is supported by other studies showing that myocardial function is preserved during "maximal" exercise even in more severe hypoxia (25, 27, 28) and is achieved with an increased coronary blood flow (8, 12), indicating the presence of coronary reserve in maximal exercise in normoxia (further proving that ischemic myocardial dysfunction does not limit maximal exercise in normoxia as is required by Hill's original *model 1*).

Their alternate conclusion (*conclusion 2a*) that skeletal muscle hypoxia determines performance in hypoxia is disproved, as they also admit (*conclusion 2b*) by *key finding 6* that acute exposure to hyperoxia instantly improved the exercise performance, proving that a peripheral regulator such as lactic acid could not have limited exercise in hypoxia as is required by *model 1* (20). Indeed blood lactate concentrations at termination of exercise in hyperoxia were significantly higher than values measured at exercise termination in both normoxia and hypoxia (3, Table 1). This is further evidence that the (lower) venous and arterial lactate concentrations at fatigue in normoxia and hypoxia could not have limited exercise under those conditions, as is required by *model 1*.

Indeed the evidence that exercise performance in more severe hypoxia always terminates at low blood lactate concentrations, the lactate paradox, as does exercise in most disease states, provides some of the strongest evidence against *model 1* (18–20). Furthermore, after chronic adaptation to altitude, leg oxygen consumption was the same at the peak work rate in hypoxia as it was at the same work rate (~255 W) in normoxia (3, Fig. 4*E*), proving that skeletal muscle hypoxia could not have been present at exercise termination before altitude acclimatization. Indeed hypoxia has yet to be found in the exercising skeletal muscles during progressive maximum exercise to exhaustion in either normoxia (17, 26) or hypoxia (16).

Their alternate conclusion (*conclusion 2a*) that impaired venous return limits maximum exercise performance in hypoxia (as a consequence of impaired functioning of the skeletal muscle pump that assists venous return) is also disproved by the findings that stroke volume was the same (and not lower) at all work rates in hypoxia and in normoxia (3, Fig. 3*E*) and that stroke volume increased with altitude adaptation and reached the highest values in altitude-adapted subjects at exercise termination in hypoxia (3, Fig. 3*E*). This could not have occurred if venous return was impaired by hypoxia. Nor is there any other evidence that hypoxia necessarily impairs skeletal muscle function in vivo in persons exercising with an intact CNS (17).

But the most compelling evidence disproving *model 1* was their finding (*key finding 6*) that exercise performance in hypoxia did not increase after altitude acclimatization that increased blood hemoglobin concentrations, blood oxygen carrying capacity (4), and hence increased potential O_2 delivery to the heart and exercising skeletal muscles. On the basis of the slope of the $\dot{V}_{O_2}$/work rate relationship for altitude-adapted subjects exercising in hypoxia (3, Fig. 2*D*), an increase in skeletal muscle O_2 delivery of ~800 ml O_2/min should have increased the peak achieved work rate by ~120 W, which did not occur.

This summarily disproves any causal relationship between oxygen delivery and muscle function under these conditions (Fig. 1). But if these findings disprove *model 1*, do they support the theoretical basis of *model 2*, which holds that the CNS regulates exercise performance in hypoxia (*conclusion 4*)?

A fundamental teaching in muscle physiology, but which seems to have escaped the attention of many exercise physiologists, is that an increased recruitment of motor units in the active muscles is the principal mechanism by which skeletal muscle force production is modified (7, 13). Hill did not know this, explaining why his *model 1* excludes any contribution by the CNS. His presumption must have been that all the motor units in the exercising limbs are active during maximal exercise, for his model can only work if all the motor units in the active limbs are active at exhaustion so that their force production can be regulated by the action of inhibitory metabolites, principally lactic acid. Otherwise, recruitment of any quiescent motor units would allow the exercise to continue. Yet there is no evidence that all available motor units are ever recruited during any form of voluntary exercise in humans (6).

The proposal of Bigland-Ritchie and Vollestadt (1) that skeletal muscle motor unit recruitment may be reduced in hypoxia has been proven by Kayser and colleagues (14, 15). Hence skeletal muscle motor unit recruitment is submaximal in hypoxia indicating that *model 1* cannot explain why fatigue develops in hypoxia. Furthermore, if altitude adaptation fails to alter the physiological variable(s) that determine this reduced skeletal muscle motor unit recruitment in hypoxia according to *model 2* (21), then exercise performance and cardiac output will not increase, although the potential for oxygen delivery to the exercising muscles may increase substantially so that, according to *model 1*, exercise performance must increase.

Indeed, the finding that the exercise performance improves immediately the oxygen concentration in the inspired air is increased (*key finding 6*) is the single best evidence proving that the CNS regulates performance in hypoxia. For only the CNS can instantly increase the exercise performance by increasing the number of motor units that it will allow to be recruited, thereby increasing muscle force production according to the traditional teaching in muscle physiology (7, 13).

In summary, I argue that the six findings of Calbet et al. (2, 3) cannot be explained according to the traditional Hill model; in fact, they disprove that model. Rather they are entirely compatible with the Central Governor model (19–21, 23, 24). This model postulates that the extent of skeletal muscle recruitment by the CNS is the regulated variable and is determined by the need of the brain to protect itself and the body from harm (6, 18) by ensuring the maintenance of homeostasis in all bodily systems even during maximal exercise. The clear danger in hypoxia is a reduction in the arterial P_{O_2} (29). Exercise of increasing intensity in hypoxia produces a progressive reduction in arterial P_{O_2} (3, Table 1; 29). Thus it makes absolute sense that the brain should protect itself from hypoxic insult by allowing only those exercise work rates that do not reduce arterial P_{O_2} below a critical value.

The CNS ensures that this critically low arterial P_{O_2} is never reached during maximal exercise specifically by limiting the number of motor units that are recruited. The overt physiological markers of this control mechanism are the submaximal cardiac output, stroke volume, heart rate, and blood lactate concentration at peak exercise in hypoxia. The failure of altitude adaptation to normalize the arterial P_{O_2} (3; Table 1) explains why this intervention fails to enhance exercise performance, although it increases potential oxygen delivery to the exercising muscles. In contrast, inhaling oxygen-enriched air that instantly increases the arterial P_{O_2} (3; Table 1) immediately releases the brake—the "governor"—on skeletal muscle recruitment, allowing work rate and cardiac output to increase to appropriate, near maximum values (3; Table 1).

Indeed the authors correctly interpret this crucial regulatory function of the arterial P_{O_2} because they acknowledge that "the mechanism causing the reduction in the maximal cardiac output is directly related to the Pa_{O_2} and relatively independent of Ca_{O_2}" (3, R311). Yet, by interpreting their other findings according to the traditional *model 1*, they arrive at an incorrect conclusion: "The reason why the cardiovascular system does not substantially increase O_2 delivery to the exercising muscles after altitude acclimatization despite apparent function reserve remains unknown" (3, R315).

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REPLY

To the Editor: We appreciate Dr. Noakes' interest in our papers (4, 5, 7) on cardiovascular responses to exercise in hypoxia. In his letter to the Editor, Dr. Noakes carefully selects text and data from a series of our papers to support a unifying regulatory paradigm ("Central Governor Model") for limits to exercise. Fatigue is set by what he calls "Central Governor," presumably located in the central nervous system (CNS). Although we agree in some aspects, we think that Dr. Noakes' model cannot be generalized. The contradictions suggested by Dr. Noakes simply do not exist; they are the outcome of a biased interpretation of our data and selective quoting of pieces of the discussion, which, used out of context, can mislead the reader to the wrong conclusion. We wish to respond to his letter by focusing on the data and to clarify several points that appear to be misinterpreted. There are a number of points to be made that we will split into comments to the "summary of our key findings" and comments to Dr. Noakes' interpretation of our data.

Comments to the "summary of our key findings". Reading Dr. Noakes letter it seems that it was already known that

maximal cardiac output is decreased in acute hypoxia. In this regard, Dr. Noakes cites a study by Peltonen et al. (25) published in *Eur J Appl Physiol* in 2001 and Peltonen's PhD Thesis (2002; see Ref. 24 of Dr. Noakes' letter). The level of acute hypoxia used by Peltonen et al. ($F_{I_{O_2}} = 0.15$) is too low to elicit an 8.8% reduction in maximal cardiac output as they reported. In fact, during whole body exercise with moderate hypoxia ($F_{I_{O_2}} \sim 0.12$), maximal cardiac output has been repeatedly found to be similar to that attained during normoxic exercise (16, 18, 28). In the same study (25) it is reported that normoxic maximal cardiac output tended to be 5.7% and $\dot{V}_{O_2\,max}$ 14% greater with mild hyperoxia ($F_{I_{O_2}} = 0.32$) when it is more commonly found that normoxic maximal cardiac output is not altered by hyperoxia (5, 7, 12) and that to achieve a 14% enhancement of $\dot{V}_{O_2\,max}$ with hyperoxia, the $F_{I_{O_2}}$ should be over 0.5 and close to 1.0 (1, 19, 22, 24, 26). Thus, the study by Peltonen et al. is not an appropriate reference to state that it was already known that maximal cardiac output is decreased with acute hypoxia. In addition, Dr. Noakes is overlooking previous publications from our group showing a small decrease of maximal cardiac output during two-leg knee extension with a slightly greater level of hypoxia ($F_{I_{O_2}} = 0.11$) (20). Our control experiments for the Chacaltaya Expedition showed that in acute hypoxia of greater severity (equivalent to 5,300 m of altitude), maximal cardiac output is decreased by ~15%. More importantly, by analyzing the impact of hypoxia on pulmonary gas exchange and systemic and muscular O_2 transport we were able to determine that the reduction of maximal cardiac output (and the corresponding decrease in peak leg blood flow) explained one-third of the loss in $\dot{V}_{O_2\,max}$ observed during exercise in severe acute hypoxia.

In contrast with Dr. Noakes' statement, we did not find that "cardiac output increased marginally with altitude acclimatization due to enhanced stroke volume." On page R307 (5), we explicitly mention that cardiac output values were similarly reduced by ~15% in acute and chronic hypoxia. There was no significant increase of cardiac output with acclimatization. The enhancement of maximal exercise stroke volume with altitude acclimatization was accounted for by increased parasympathetic tone in chronic hypoxia (2) and does not reflect increased contractility or venous return.

In *key finding 4*, Dr. Noakes states that the peak power output did not increase despite marked improvement in systemic and leg O_2 delivery. Mean peak power output showed a trend to be 12% greater after acclimatization ($P = 0.16$). In this case, we had a type II error, because when we combined all the data obtained in the 16 subjects who participated in experiments during the Chacaltaya Expedition, peak power output was significantly improved with altitude acclimatization (27). Moreover acclimatization resulted in a significant increase of 13% in $\dot{V}_{O_2\,max}$, lessening the difference between normoxia and acute hypoxia by one-third (5).

Comments on Dr. Noakes interpretation of our data. First of all, it is important to remark that in our papers (4, 5, 7, 9) we analyzed the role that each step in the O_2 transport chain may play in the reduction of $\dot{V}_{O_2\,max}$ caused by acute and chronic hypoxia. In addition, we attempted to determine why maximal cardiac output is reduced in chronic hypoxia. Sometimes Dr. Noakes subtly mixes arguments and interpretations that we made in regard to the regulation of maximal cardiac output, applying them to the limitation of $\dot{V}_{O_2\,max}$ and exercise capacity, misleading the reader to the conclusion that we contradict ourselves. For example, see the following.

Conclusion 1. Contrary to Dr. Noakes' selective representation of our discussion on the regulation of maximal cardiac output in hypoxia, we appropriately discussed the possibility of several contributory mechanisms. Least support was given to limited "intrinsic pumping capacity of the heart." We state clearly (4, p. R300) that there was no evidence to support such a mechanism in our study and argue against this mechanism just as does Dr. Noakes. We postulate that severe hypoxemia (low arterial P_{O_2}) per se (directly or indirectly) could blunt neural output from cardiovascular nuclei in the CNS, causing a reduction of maximal cardiac output, to preserve arterial P_{O_2} when pulmonary gas exchange is seriously impaired. This hypothesis is based on the fact that desaturation in well-trained athletes during maximal exercise at sea level has been associated with, among other factors, a very high cardiac output (11). Due to the sigmoid shape of the O_2 dissociation curve of hemoglobin, a minimal reduction of lung mean transit time during hypoxia when arterial O_2 saturation lies on the steep position of the O_2 dissociation curve, as occurred during maximal exercise in acute hypoxia (66% Sa_{O_2}), could cause a substantial decrease of Pa_{O_2} and of Sa_{O_2}. It has been shown that lung mean transit time is reduced as cardiac output increases (17). Under these circumstances, a further elevation in cardiac output might result in no increase or, even worse, a deterioration of systemic O_2 supply. If this hypothesis is true, maximal O_2 delivery in acute hypoxia will be attained at a lower maximal cardiac output than in normoxia. Our studies support this concept but do not provide definitive experimental evidence for a downregulation of maximal cardiac output by hypoxia. Although we do not know how the pumping activity of the heart might be regulated by hypoxia, we offered some plausible mechanisms, summarized by Dr Noakes in *conclusion 2*).

Conclusion 3. Here again we disagree with Dr. Noakes. On reoxygenation in acute hypoxia and also when breathing 55% O_2 at altitude, the subjects (almost exhausted at the end of both incremental exercises with low $P_{I_{O_2}}$) were able to continue exercise, increase their work capacity, and also oxygen uptake. What we were referring to was that "local" muscle fatigue was likely not responsible for limiting work output during cycling exercise in hypoxia as, for example, would be the case during exercise with small muscle mass (handgrip, knee-extension exercise, one-leg cycling) in either normoxia or hypoxia (3). We cannot rule out, however, some degree of peripheral fatigue when the subjects were breathing hypoxic gas, and that is why we cautiously wrote "the fact that it was possible to continue the incremental exercise test with reoxygenation argues against a peripheral (muscular or metabolic) mechanism as the main cause of fatigue in severe acute hypoxia." The fact that the subjects were able to continue the exercise with reoxygenation means that fatigue, if present, was rapidly counteracted by increased aerobic ATP resynthesis. This should be possible if fatigue is particularly linked to accumulation of inorganic phosphate (10, 29) rather than to the accumulation of H^+ (6). With greater O_2 availability, the rate of ATP resynthesis through oxidative phosphorylation is increased and fatigue would be easily counteracted. What was clear about the ability to increase workload and $\dot{V}_{O_2}$ with acute restoration of normoxia was the rapid, immediate increase of oxygen delivery to the legs. No doubt, in acute hypoxia O_2 delivery was insufficient to maintain power output at exhaustion, as indi-

cated by the strong activation of anaerobic metabolism and the lower muscular $\dot{V}_{O_2}$, compared with normoxic conditions. These are experimental facts.

Dr. Noakes uses some of the data from the paper "Why is $\dot{V}_{O_2\,max}$ after altitude acclimatization still reduced despite normalization of arterial O_2 content?" (5) to argue that O_2 delivery is not limiting maximal power output at altitude. He bases this on the fact that with acclimatization we found a 54% increase in systemic oxygen delivery and only a 13% increase in $\dot{V}_{O_2\,max}$. What he overlooked in his letter was that there was a proportional increase in O_2 delivery and O_2 uptake in the legs during cycling with acclimatization. Elevated Hb concentration and a similar cardiac output elicited a higher systemic O_2 delivery, but part of the increase in systemic O_2 delivery was distributed away from the active muscles. During exercise in acute and chronic hypoxia, fatigue occurred before subjects attained their maximal oxidative potential, so in absence of metabolic blockade they were able to increase aerobic energy provision as soon as O_2 delivery was increased. Without the increase in O_2 delivery to exercising muscle with reoxygenation $\dot{V}_{O_2}$ would not have increased further and fatigue would certainly not have been overcome. This is the reason why we emphasized the dependence on oxygen delivery for maximal oxygen uptake in acute and chronic hypoxia. Another issue is what mechanisms account for the attenuation of maximal cardiac output at altitude. We proposed (and this is only a working hypothesis that needs to be experimentally tested) that when a certain level of arterial P_{O_2} is reached, the CNS blunts the increase of cardiac output and fatigue occurs. So, during maximal exercise in acute or chronic hypoxia with a large muscle mass, fatigue may be caused by a depression of motor drive, a mismatch between O_2 delivery and O_2 demand in the active muscles, or a combination of both mechanisms.

Conclusion 4. We mention the possibility of hypoxia-induced depression of motor drive as a possible mechanism that could limit power output and in turn the muscle pump, venous return, and ultimately cardiac output. This regulatory schema may operate during maximal exercise with a large muscle mass in severe hypoxia, and thus be consistent with the argument of central regulation. However, there are multiple exercise conditions where this paradigm simply bears no support. During maximal exercise with a small muscle mass (knee-extension exercise), maximal cardiac output, peak power output, and leg blood flow are similar in normoxia and acute hypoxia ($F_{I_{O_2}} = 0.105$), despite the fact that arterial P_{O_2} was reduced to 38 ± 1 mmHg in acute hypoxia (i.e., only 4 mmHg higher than during maximal hypoxic exercise on the cycle ergometer; not published). So no sign of cardiovascular or motor drive depression during single knee-extension exercise was seen in severe acute hypoxia. Is there conclusive evidence to state that central motor drive, power output, and motor activation are blunted during maximal dynamic exercise in hypoxia? Some clues to answer this question were given by Savard et al. (26a) during exercise after prolonged hypoxia. More recently it has been shown that maximal power output during supramaximal all-out exercise (Wingate test) is not impaired in severe acute hypoxia, despite a marked reduction of the oxidative contribution to energy turnover (6). Similarly, there is no evidence of central mechanisms limiting small muscle mass exercise in hypoxia as shown by Fulco and colleagues (13, 14, 23, 31). During the Copenhagen Muscle Research Centre expedition to La Paz (year 2000) we studied the effect of acute and chronic hypoxia on peak isometric knee extension force. During this expedition we used the twitch-interpolation technique to find out if there was deficit of neural activation during maximal voluntary isometric contractions of the quadriceps femoris. In agreement with previous reports (13, 14, 23, 31) neither acute hypoxia (equivalent to 4,100 m) nor 8 wk of sojourn at this altitude had any effect on peak isometric force or magnitude of neural activation (M. Zacho, unpublished observations).

Although Dr. Noakes' concept in Fig. 2 has little support, it may have some basis in particular conditions, as, for example, during exercise with a large muscle mass in severe acute hypoxia, but should not be generalized. For example, during normoxic maximal exercise with isovolemic anemia, maximal cardiac output is not blunted, despite a marked reduction of arterial O_2 content and exercise capacity (21, 30). It is difficult to isolate "the factor" (see Noakes' Fig. 2) responsible for this cardiovascular response in the intact human. Although it seems that this mechanism could explain fatigue in acute hypoxia, it is clearly insufficient to explain fatigue in chronic hypoxia, where not only is cardiac output blunted, but also is the distribution of cardiac output. In fact, fatigue occurred at a higher arterial P_{O_2} during exercise in chronic hypoxia (34 ± 1 vs. 45 ± 1 mmHg, in acute and chronic hypoxia, respectively, $P < 0.05$). Moreover, during submaximal exercise in acute hypoxia, the subjects attained an even lower arterial P_{O_2} (31 ± 1 mmHg, $P < 0.05$) and exercise was maintained during 10 min. Would this response have been possible in the face of a progressive derecruitment of motor units according to the "Central Governor Model"? Muscular activation results from the combined effect of motor unit recruitment and firing rate; will firing rate be also reduced according to the "Central Governor Model"? A recent paper by Gonzalez-Alonso and Calbet (15) provided further support to the classical paradigm rejected by Dr. Noakes. In that study, subjects performed constant intensity exercise to exhaustion at 356 W (an intensity just above $\dot{V}_{O_2\,max}$, which elicited exhaustion within 5–10 min), under normothermic and hyperthermic conditions. In both conditions, fatigue was preceded by a reduction of cardiac output and leg blood flow, i.e., O_2 delivery; however, the reduction of O_2 delivery occurred sooner during the hyperthermic than during the normothermic condition. Consequently, subjects fatigued sooner during the hyperthermic condition. However, Dr. Noakes would likely prefer an alternative interpretation: a "fatigue factor" (in this case should be a signal other than arterial P_{O_2}) acting somewhere in CNS interferes with the motor drive during supramaximal exercise at constant power output. Moreover, we recently showed that during whole body upright exercise, the combined maximal muscular vascular conductances of the limbs outweigh the pumping capacity of the heart in humans, meaning that $\dot{V}_{O_2\,max}$ is limited by O_2 delivery even at sea level (8).

Peak oxygen uptake and power output are likely regulated by complex integration of feed-forward and feedback signals. For this reason, in our papers we have chosen to broadly discuss potential contributing mechanisms, recognizing the complexities of the integrated response and at the same time drawing conclusions based on the data within the context of the experimental design. Dr. Noakes' selective quoting of our various results and their interpretation is lamentable because it may lead readers to believe that we are self-contradictory and

unable to interpret our own findings. What emerges clearly from our work taken overall is that oxygen uptake and peak power output during dynamic exercise in normoxia and acute hypoxia depends on oxygen delivery. There are experimental models that could be applied to determine whether a central signal is more important than oxygen delivery for peak work capacity during dynamic exercise. So we encourage Dr. Noakes to carry out such experiments to support the "Central Governor Model," because the bulk of our data do not give much experimental support to it.

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