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Evidence that a central governor regulates exercise performance during acute hypoxia and hyperoxia

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Summary

An enduring hypothesis in exercise physiology holds that a limiting cardiorespiratory function determines maximal exercise performance as a result of specific metabolic changes in the exercising skeletal muscle, so-called peripheral fatigue. The origins of this classical hypothesis can be traced to work undertaken by Nobel Laureate A. V. Hill and his colleagues in London between 1923 and 1925. According to their classical model, peripheral fatigue occurs only after the onset of heart fatigue or failure. Thus, correctly interpreted, the Hill hypothesis predicts that it is the heart, not the skeletal muscle, that is at risk of anaerobiosis or ischaemia during maximal exercise. To prevent myocardial damage during maximal exercise, Hill proposed the existence of a 'governor' in either the heart or brain to limit heart work when myocardial ischaemia developed. Cardiorespiratory function during maximal exercise at different altitudes or at different oxygen fractions of inspired air provides a definitive test for the presence of a governor and its function. If skeletal muscle anaerobiosis is the protected variable then, under conditions in which arterial oxygen content is reduced, maximal exercise should terminate with peak cardiovascular function to ensure maximum delivery of oxygen to the active muscle. In contrast, if the function of the heart or some other oxygen-sensitive organ is to be protected, then peak cardiovascular function will be higher during hyperoxia and reduced during hypoxia compared with normoxia. This paper reviews the evidence that peak cardiovascular function is reduced during maximal exercise in both acute and chronic hypoxia with no evidence for any primary alterations in myocardial function. Since peak skeletal muscle electromyographic activity is also reduced during hypoxia, these data support a model in which a central, neural governor constrains the cardiac output by regulating the mass of skeletal muscle that can be activated during maximal exercise in both acute and chronic hypoxia.

Key words: central governor, altitude, cardiac output, hypoxia, hyperoxia, maximal rate of oxygen uptake, muscle recruitment.

Introduction

The maximum rate of oxygen uptake ($\dot{V}_{O_2max}$) is a measure of the fastest rate at which oxygen (O_2) can be utilized by the body during severe exercise. $\dot{V}_{O_2max}$ is usually considered to be an index of cardiorespiratory, circulatory and muscular fitness. A lively debate of the definition and limiting factors for $\dot{V}_{O_2max}$ has enriched the recent literature (Bassett and Howley, 1997; Noakes, 1997; Noakes, 1998; Bassett and Howley, 2000; Noakes, 2000; Wagner, 2000a). The classical theory (Mitchell and Blomqvist, 1971) proposes that exercise is limited only after oxygen delivery to the exercising skeletal muscles becomes inadequate, inducing anaerobiosis (Bassett and Howley, 1997; Bassett and Howley, 2000). Both cardiorespiratory O_2 delivery and tissue diffusion limitation are believed to limit $\dot{V}_{O_2max}$ in normal humans during maximal exercise (Roca et al., 1989). The studies of Richardson and colleagues (Richardson et al., 1999) demonstrated reduced cytoplasmic partial pressure of O_2 (P_{O_2}) at peak $\dot{V}_{O_2}$ during single-legged exercise even when cardiac output was submaximal. These results are consistent with a supply limitation to $\dot{V}_{O_2max}$ in trained skeletal muscle, even during hyperoxia. Their data also revealed a disproportionate increase in intracellular P_{O_2} during hyperoxia, which could mean that the mitochondrial limits determining peak muscle $\dot{V}_{O_2}$ are approached even at relatively high P_{O_2} in trained skeletal muscle. Additional theories analyzing the links between O_2 delivery and utilization have also received significant attention in the recent literature (Roca et al., 1989; di Prampero and Ferretti, 1990; Wagner, 1991; Wagner, 1992; Wagner, 1995a; Wagner, 1995b; Wagner, 2000a).

An alternative theory postulates that a 'central governor', which regulates the mass of skeletal muscle that is recruited during exercise, acts to protect the heart from developing myocardial ischaemia during maximal exercise (Noakes, 1997;

Noakes, 1998; Noakes, 2000; Noakes, 2001). Thus, a logical starting point in the search for a central governor are those studies of cardiorespiratory function during acute hypoxia, since the possibility that myocardial ischaemia will develop is increased during maximal exercise in hypoxia. Studies of cardiorespiratory function during chronic hypoxia are potentially complicated by additional adaptations or maladaptations that might occur in response to sustained hypoxic stress.

Numerous studies have shown that $\dot{V}_{O_2max}$ can be modified acutely by altering one or more of the variables considered to limit this measurement. These acute changes occur before structural adaptations, normally requiring several weeks to develop, can occur. Examples of acute modifications in $\dot{V}_{O_2max}$ are its increase in response to acute increases in the partial pressure of inspired oxygen (P_{IO_2}) and, conversely, its impairment with decreasing P_{IO_2}. Altering arterial oxygen content (Ca_{O_2}), either by ascending to altitude or by descending in a deep mine to below sea level, or modifying P_{IO_2}, either in a hypobaric chamber or by breathing gas mixtures with varying oxygen fractions (F_{IO_2}), have all been reported to affect $\dot{V}_{O_2max}$ in a predictable and reproducible manner (Fagraeus et al., 1973; Welch et al., 1974; Wyndham et al., 1970). Also, $\dot{V}_{O_2max}$ increases with acute red blood cell transfusion (Gledhill, 1982; Gledhill, 1985; Spriet et al., 1986; Gledhill et al., 1999) and decreases with sympathetic blockade (Hughson and MacFarlane, 1981; Tesch, 1985; Hughson and Kowalchuk, 1991). Over a longer (chronic) period, $\dot{V}_{O_2max}$ increases with endurance training but decreases with detraining (Saltin et al., 1968a) or with prolonged exposure to high altitude (Cymerman et al., 1989; di Prampero and Ferretti, 1990; Ferretti et al., 1990; Green et al., 2000). Structural as well as functional changes in cardiorespiratory and neuromuscular function are more likely to explain these chronic changes.

The purpose of the present review is to present the evidence for the possible existence of a central governor and to discuss the possible mechanisms by which this governor might limit $\dot{V}_{O_2max}$ and, hence, maximal exercise performance, certainly during hypoxia and also, perhaps, during maximal exercise at sea level.

Origin of the central governor hypothesis

Whilst preparing a rebuttal to the criticisms by Bassett and Howley (Bassett and Howle, 1997) of his previous manuscript (Noakes, 1997), Noakes (Noakes, 1998; Noakes, 2000; Noakes, 2001) rediscovered the long-forgotten central governor hypothesis as originally proposed by Hill, Long and Lupton in the 1920s (Hill et al., 1924a;. Hill et al., 1924b) In 1924, that group of classical physiologists, which included the Nobel Laureate, A. V. Hill, wrote: ‘Apparently, however, the limit to which the muscles may be driven, while breathing air, is set, not so much by the exhaustion of the muscles themselves as by the distress (cardiac and cerebral) resulting from either the rise of hydrogen-ion concentration of the blood, or its imperfect saturation with oxygen while passing rapidly through the lungs” (Hill et al., 1924b). The authors continued: “It would seem probable, and although we have no direct evidence, the indirect evidence which we are adducing makes it very probable indeed, that the heart is able to regulate its output, to some extent, in accordance with the degree of saturation of the arterial blood, either of that which reaches it through the coronary vessels or by some reflex in other organs produced by a deficient oxygen supply. From the point of view of a well coordinated mechanism, some such arrangement is eminently desirable; it would clearly be useless for the heart to make an excessive effort if by so doing it merely produced a far lower degree of saturation of the arterial blood; and we suggest that, in the body (either in the heart muscle itself or in the nervous system), there is some mechanism which causes a slowing of the circulation as soon as a serious degree of unsaturation occurs, and *vice versa*. This mechanism would tend, to some degree, to act as a ‘governor’, maintaining a reasonably high degree of saturation of the blood: the breathing of a gas mixture rich in oxygen would produce a greater degree of saturation of the blood and so allow the output to increase until the ‘governor’ stopped it again” (Hill et al., 1924b). They were also amongst the first to test this hypothesis by conducting experiments in which human athletes exercised whilst inhaling hyperoxic oxygen mixtures. They summarized the results of these experiments thus: “The use of gas mixtures containing a high pressure of oxygen enables a considerably higher oxygen intake to be attained. The increase is often so large that it cannot be due simply to more complete saturation of the blood in its passage through the lungs. It is suggested that a ‘governor’ mechanism exist, either in the heart muscle itself, or elsewhere, which tends to coordinate the output of the heart with the degree of saturation of the blood leaving it” (Hill et al., 1924b). Just as Hill and his colleagues used modified oxygen fractions in the inspired air as a tool to probe the mechanisms that regulate $\dot{V}_{O_2max}$ and exercise capacity, so in this review we choose also to concentrate on those studies of acute (immediate, 1–2 days) hypoxia and hyperoxia which, in our opinion, add support to the original hypothesis of Hill and his colleagues.

Studies of exercise under conditions of modified oxygen partial pressure (P_{IO_2})

Numerous studies show that $\dot{V}_{O_2}$ and cardiac output ($\dot{Q}$) alter in response to alterations in P_{IO_2}. During acute hypoxia, the only generally accepted finding is that $\dot{V}_{O_2max}$ is reduced whereas $\dot{V}_{O_2}$ is unaltered during submaximal exercise (Stenberg et al., 1966; Hughes et al., 1968; Hartley et al., 1973; Ekblom et al., 1975; Fulco et al., 1988; Peltonen et al., 2001). Acute hypoxia increases $\dot{Q}$, heart rate (f_H) (Asmussen and Nielsen, 1955; Stenberg et al., 1966; Wagner et al., 1986; Peltonen et al., 2001) and skeletal muscle blood flow (Calbet, 2000) at a given submaximal $\dot{V}_{O_2}$ or workload.

There is a lesser consensus of the responses of $\dot{V}_{O_2}$ to acute hyperoxia. Some studies indicate a significant increase in $\dot{V}_{O_2max}$ during hyperoxia compared with normoxia (Welch et

al., 1974; Ekblom et al., 1975; Welch, 1982; Peltonen et al., 2001), whereas others failed to measure any such increase (Hughes et al., 1968; Adams and Welch, 1980). Similarly, some studies reported a similar submaximal $\dot{V}_{O_2}$ during hyperoxia and during normoxia (Asmussen and Nielsen, 1955; Hughes et al., 1968), whereas others (Welch et al., 1974; Ekblom et al., 1975; Peltonen et al., 2001) found that the submaximal $\dot{V}_{O_2}$ was significantly higher during hyperoxia than during normoxia.

Compared with normoxia, $\dot{Q}$ is either the same (Asmussen and Nielsen, 1955; Davies and Sargeant, 1974; Peltonen et al., 2001) or reduced (Nakazono and Miyamoto, 1987) during submaximal exercise in hyperoxia. Skeletal muscle blood flow is reduced during submaximal (Welch et al., 1977) but unaltered during maximal (Knight et al., 1993) exercise in hyperoxia.

Skeletal muscle is not the only organ to which the blood flow is altered by changes in C_{aO_2}: blood flow to the heart (Hilton and Eichholtz, 1925; Baron et al., 1990; Kaijser et al., 1990; Grubbstrom et al., 1991) and brain (Jones et al., 1981) also shows considerable adaptation in response to changes in C_{aO_2}, increasing during hypoxia and falling during hyperoxia.

There is a general consensus that O_2 transport to muscle is the principal determinant limiting $\dot{V}_{O_2max}$ (Secher et al., 1977; di Prampero, 1985; Rowell, 1986; di Prampero and Ferretti, 1990; Rowell, 1993). Indeed, it is even more likely that O_2 transport is the factor limiting the $\dot{V}_{O_2max}$ of endurance-trained athletes than of normally active or sedentary subjects (Wagner, 2000a). However, as P_{IO_2} decreases, the role of the lungs in limiting $\dot{V}_{O_2max}$ increases, whereas the importance of the cardiovascular system diminishes (Ferretti and di Prampero, 1995).

Maximal cardiac function is reduced during chronic hypobaric hypoxia, with a reduction in both maximal heart rate (f_{Hmax}) and maximal stroke volume (V_{Smax}) (Vogel et al., 1974; Reeves et al., 1987). The classic explanation for the reduced $\dot{Q}_{max}$ during chronic hypoxia includes (i) increased blood viscosity from erythrocytosis causing an increased haematocrit; (ii) reduced cardiac filling pressures from reduced plasma volume; (iii) autonomic changes (either increased parasympathetic or reduced sympathetic activity); (iv) hypoxic myocardial dysfunction and (v) the possibility that hypoxia directly impairs skeletal muscle function, reducing exercise capacity so that $\dot{Q}_{max}$ is reduced in proportion to the reduced work output (Wagner, 2000b).

However, cardiac catheterization studies performed during Operation Everest II (Groves et al., 1987; Reeves et al., 1987) indicated that, although V_{Smax} decreased at altitude, the decrement was proportional to the decrease in atrial filling pressure, indicating that myocardial contractility was preserved. Reeves and colleagues (Reeves et al., 1987) concluded that a reduced maximum ventricular filling resulting from tachycardia or a reduction in plasma and blood volume or both was one possible cause of the reduced V_S. However, the point is that the proportional reduction in stroke volume and atrial filling pressure indicates that the heart was not ischaemic and that any increase in filling pressure should have produced an increase in the stroke volume and cardiac output.

Suarez et al. (Suarez et al., 1987) have concluded that: "Left ventricular systolic function is not a limiting factor in compromising the exercise capacity of normal humans on ascent to high altitude, even to the peak of Mount Everest". Similarly, Reeves et al. (Reeves et al., 1987) have concluded that "cardiac rate, cardiac output, and myocardial contractile function were preserved at extreme altitude… reduced heart rates and cardiac outputs at maximum effort were the result rather than the cause of the reduced maximal O_2 uptake".

However, it is important to stress that any reduction in $\dot{Q}_{max}$ during either acute or chronic hypoxia is paradoxical according to the classical model, which holds that the heart is simply the slave to the exercising muscles, with the unrequiting task of maximizing O_2 delivery to the exercising muscle under all conditions. Hence, for the classical model to be correct, cardiac output must always be maximal at maximal exercise regardless of P_{IO_2}, F_{IO_2} or C_{aO_2}. Hence, any intervention such as anaemia or hypoxia that reduces C_{aO_2}, thereby threatening oxygen delivery to the exercising muscles, must be countered by acute changes, the principal aim of which must be to maintain oxygen delivery to the exercising muscles. Clearly, the exact opposite holds during chronic hypobaric hypoxia. It is also of interest that the skeletal muscle blood flow is unaltered at maximal exercise during acute anaemia, even though cardiac output is submaximal (Koskolou et al., 1997).

Furthermore, the changes in left ventricular filling that are thought to cause the reduced V_{Smax} and f_{Hmax} during chronic hypoxia cannot explain why both f_{Hmax} and $\dot{Q}_{max}$ are reduced during acute hypoxia since the duration of the hypoxia is too short to alter atrial filling pressures consequent to a theoretical increase in ventilatory and urinary fluid losses.

As a result, the prevailing hypothesis is that $\dot{Q}_{max}$ should be the same during acute and chronic hypoxia so that any reduction in $\dot{V}_{O_2max}$ during acute hypoxia is due to the narrowing of the arterio-venous oxygen difference $[(a–v)_{O_2}]$ (Stenberg et al., 1966). Fig. 1 explains the basis for this belief whilst introducing another interpretation that has been overlooked.

Fig. 1 shows that any reduction in arterial P_{O_2} (P_{aO_2}) will threaten oxygen delivery to all organs in the body including the heart and brain, and not just the skeletal muscles as is the usual interpretation.

Rather, according to this model, the reduced P_{aO_2} during hypoxia will reduce potential oxygen delivery to both the skeletal muscles and the heart. Furthermore, if the heart is merely the slave to the skeletal muscles, then $\dot{Q}_{max}$ should be the same during maximal exercise in both hypoxia and normoxia since the heart's sole function is to maximize oxygen delivery to the hypoxic skeletal muscles. But if myocardial hypoxia must be prevented, then $\dot{Q}_{max}$ will fall in proportion to the reduction in P_{aO_2}.

A large body of evidence shows that the determinants of $\dot{Q}_{max}$ (f_{Hmax} and V_{Smax}) are both altered during maximal exercise in hypoxia. Thus, several studies found that acute

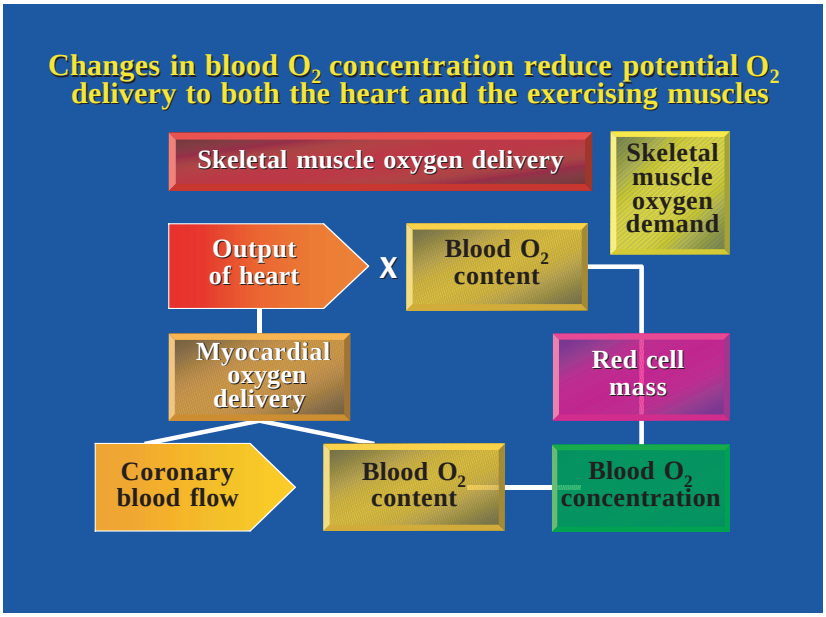

Fig. 1. Changes in blood oxygen concentration reduce the arterial oxygen supply to both the skeletal muscles and the heart. If the heart is the slave to the muscles, as predicted by the classical theory, then the output of the heart must increase during hypoxia to ensure that oxygen delivery to the skeletal muscles is maintained. In contrast, the central governor theory predicts that cardiac output will fall during hypoxia in proportion to the reduction in oxygen delivery to the heart, specifically to prevent hypoxic damage to the heart or other vital organs including, perhaps, the brain and respiratory muscles.

hypoxia decreases $f_{H_{max}}$ in both athletic and normally active men and women (Drinkwater et al., 1979; Andersen et al., 1985; Fulco et al., 1988; Lundby et al., 2001; Lundby and Olsen, 2001; Peltonen et al., 2001). Whilst these studies might indicate that the reduced $f_{H_{max}}$ is probably associated with a reduced $\dot{Q}_{max}$ during acute hypoxia, only two studies have measured a reduced $\dot{Q}_{max}$ during acute hypoxia.

Ekblom and colleagues (Ekblom et al., 1975) reported a decreased $\dot{Q}_{max}$ during carbon-monoxide-induced hypoxia (Ca_{O_2} was on average 5.1 % lower than during normoxia; $P<0.05$). The effect was due mainly to a decreased V_S. More recently, Peltonen et al. (Peltonen et al., 2001) demonstrated a reduced $\dot{Q}_{max}$ during acute hypoxia under physiological conditions (arterial desaturation caused by decreasing $F_{I_{O_2}}$, not by carbon monoxide inhalation) in endurance athletes (Table 1).

Perhaps even more interestingly, compared with findings during normoxia, peak muscle blood flow, a surrogate of $\dot{Q}_{max}$, is reduced in single-legged exercise during hypoxia and higher during hyperoxia, even though peak blood flows are well below $\dot{Q}_{max}$ in this model (Richardson et al., 1999) (Table 2). Maximal heart rates follow a similar pattern and are submaximal at exhaustion (Table 2). Furthermore, leg blood flow per heart beat, an indirect indicator of the stroke volume, rises progressively from hypoxia to normoxia to hyperoxia (Table 2). The finding that leg blood flow is not increased during single-legged exercise during hypoxia, even though the cardiac output is submaximal, parallels the finding in acute anaemia (Koskolou et al., 1997).

Clearly, in this particular exercise model, which has become a standard for studying oxygen transport limitations during exercise, fatigue develops during both normoxia and hypoxia even though there is cardiac reserve shown as submaximal $\dot{Q}$ and f_H. Even hyperoxia does not overcome some mechanism that constrains $\dot{Q}$ and f_H preventing the highest possible oxygen transport to muscle. Since neither $\dot{Q}$ nor f_H is ever maximal in that model, it is clear that something other than a limiting cardiovascular function determines the limitation in O_2 delivery that obviously limits peak muscle $\dot{V}_{O_2}$ and, hence, $\dot{V}_{O_2max}$ in single-legged exercise. Rather, the alternative conclusion must be the low $\dot{Q}_{max}$ in single-legged exercise, even during hyperoxia, is the result not the cause of the low

Table 1. *Cardiac output during maximal whole-body exercise in hypoxia*

	% Inspired O_2		
	15	21	32
$\dot{V}_{O_2max}$ (l min^{-1})	3.58±0.44*,‡	4.55±0.32	5.17±0.34*
Maximum cardiac output (l min^{-1})	25.99±3.37*,‡	28.51±2.36	30.13±2.06
Maximum heart rate (breaths min^{-1})	177±15‡	181±11	186±10
Maximum stroke volume (ml)	1.47±19‡	158±13	163±16

*Significantly different from normoxia ($P<0.05$).
‡Significantly different from hyperoxia ($P<0.05$).
From the data of Peltonen et al. (Peltonen et al., 2001).
Values are means ± S.D. (N=6).

Table 2. *The paradox of low cardiac output during single-legged exercise in hypoxia*

	% Inspired O_2		
	12	21	100
Quadriceps $\dot{V}_{O_2}$ ($l\,min^{-1}$)	0.86±0.1*	1.08±0.2	1.28±0.2*
Quadriceps blood flow ($l\,min^{-1}$)	6.3±0.6*	7.3±0.9	7.6±1.0
Heart rate (beats min^{-1})	145±3	140±4	136±2
Quadriceps blood flow per heart beat (ml $beat^{-1}$)	43	52	56

*Significantly different from normoxia (P<0.05).
From the data of Richardson et al. (Richardson et al., 1999).
Values are means ± S.E.M. (N=5).

work rate achieved and that both are the result of the small muscle mass that is activated in single-legged exercise.

Maximum heart rate is reduced, in a dose-dependant manner, in response to increasingly acute hypoxia, whereas maximal plasma norepinephrine and lactate concentrations are unchanged during acute hypoxia. Moreover, Lundby and Olsen (Lundby and Olsen, 2001) and Lundby et al. (Lundby et al., 2001) found that acutely changing the $F_{I_{O_2}}$ by breathing oxygen during experimentally induced acute hypoxia increased $f_{H_{max}}$ to sea-level values. A similar result has been reported during chronic hypoxia (Kayser et al., 1994; Savard et al., 1995), in which oxygen inhalation increased peak heart rate at exhaustion, although $f_{H_{max}}$ was still lower than during normoxia. To explain their findings, Lundby and Olsen (Lundby and Olsen, 2001) and Lundby et al. (Lundby et al., 2001) reported that blockade with domperidone demonstrated that hypoxic exercise in humans activates dopamine D2-receptors, which cause a reduction in circulating levels of norepinephrine. However, this mechanism does not play a major role in the hypoxia-induced reduction of $f_{H_{max}}$. The authors suggest that postganglionergic desensitization and not downregulation of cardiac adrenoreceptors is responsible for the early decrease in $f_{H_{max}}$ during hypoxia.

The reduction in $f_{H_{max}}$ and $\dot{Q}_{max}$ during acute hypoxia favours the previous theories (Hill et al., 1924a; Hill et al., 1924b; Ferretti and di Prampero, 1995; Wagner, 2000a) that, without parallel upward adjustments in both pulmonary and muscle O_2 diffusive transport conductance, a very high cardiac output would cause substantial arterial desaturation and also impair muscle O_2 extraction. Although the reduced $\dot{Q}_{max}$ during acute hypoxia would be physiologically beneficial, the response remains paradoxical according to the classical model, which holds that the heart's function is to maximize oxygen delivery to muscle rather than to protect $P_{a_{O_2}}$. Hence, the question that demands an answer is: What are the mechanisms that constrain the normal increases in $\dot{Q}$, V_S and f_H during severe exercise in acute hypoxia? As argued previously, the classical model proposed two separate mechanisms for fatigue during maximal exercise.

First was the development of myocardial hypoxia causing a progressive cardiac failure. Hence: "The enormous output of the heart of an able-bodied man, maintained for considerable periods, requires a large contemporary supply of oxygen to meet the demands for energy. When the oxygen supply becomes inadequate it is probable that the heart rapidly diminishes its output, so avoiding exhaustion" (Hill et al., 1924a; p. 443). The function of Hill's postulated governor was to reduce the work of the heart when myocardial hypoxia developed, thereby sparing the heart from damage. This concept that myocardial failure antedated the development of fatigue was included in Bainbridge's textbook, edited by the North American exercise physiologists David Dill and Arlie Bock: "The blood supply to the heart, in many men, may be the weak link in the chain of circulatory adjustments during muscular exercise, and as the intensity of muscular exertion increases, a point is probably reached in most individuals at which the supply of oxygen to the heart falls short of its demands, and the continued performance of work becomes difficult or impossible" (Bainbridge, 1931; p. 15). As a result: "The heart, as a rule, reaches the limit of its powers earlier than the skeletal muscles, and determines a man's capabilities for exertion" (Bainbridge, 1931).

Second, as a result, blood flow to the exercising muscles was reduced, inducing anaerobiosis with the production of 'lactic acid', the rising intramuscular concentrations of which ultimately caused the cessation of exercise (Hill, 1926).

Clearly, this model cannot explain the fatigue of chronic hypobaric hypoxia, including the profound muscle weakness at altitude described by Pugh (Pugh, 1958), or the inability of Peter Habeler and Reinhold Messner to walk upright to the summit of Mount Everest during their oxygen-less ascent, since (i) myocardial ischaemia does not occur during maximal exercise at extreme altitude (Reeves et al., 1987; Suarez et al., 1987) and (ii) maximum blood lactate concentrations fall in proportion to the elevation above sea level (Christensen and Forbes, 1937; West, 1986; Green et al., 1989), the so-called 'lactate paradox'. As a result "above an altitude of 7500 m, no blood lactate is predicted even for maximal exercise. If this extrapolation held good, a well-acclimatized climber who reached the summit of Mount Everest without supplementary oxygen would have no blood lactate. This is a paradox indeed, because such a climber is apparently more hypoxic during maximal exercise than in any other known situation" (West, 1986).

However the 'lactate paradox' is only paradoxical according to the classical model, which predicts that the extreme fatigue at altitude must result from abnormally elevated blood lactate concentrations despite the very low $\dot{V}_{O_2}$ and work rates when climbing at extreme altitude.

Clearly some other mechanism(s) must be operative, at least during chronic hypoxia.

Cardiovascular limitations

Although the natural temptation, according to the classical model, is to propose that myocardial hypoxaemia explains the reduced $f_{H\max}$, $V_{S\max}$ and $\dot{Q}_{\max}$ during hypoxia, the study of Blomqvist and Stenberg (Blomqvist and Stenberg, 1965) failed to reveal any electrocardiographic evidence of myocardial ischaemia during maximal exercise in acute hypoxia, as also shown during exercise in chronic hypoxia. That myocardial ischaemia does not develop even during severe exercise in either hypoxia or normoxia (Raskoff et al., 1976) is compatible with the theory of a central governor, which prevents the recruitment of so large a muscle mass that a plateau in cardiac output is reached, leading to the myocardial ischaemia predicted by the classical model (Noakes, 1998; Noakes, 2000; Noakes, 2001).

To maintain myocardial oxygen consumption during hypoxia, a more complete extraction of O_2 from the coronary blood flow compensates for the reduced Ca_{O_2} compared with sea-level values. During maximal exercise, the additional compensatory mechanism of increased coronary blood flow is activated, indicating that the normal heart has a 'coronary flow reserve' that is activated only during maximal exercise in hypoxia (Kaijser et al., 1990; Grubbstrom et al., 1991). This again supports the theory that a constrainer exists specifically to terminate the exercise before myocardial ischaemia can develop.

A possible reason why stroke volume falls during hypoxia, even when only a single leg is active (Richardson et al., 1999), could be the increase in coronary flow during hypoxia since this is accompanied by an increase in coronary arterial pressure and stiffness (Templeton et al., 1972). Any increase in left ventricular stiffness would shift the end-diastolic pressure/end-diastolic volume (P_{ED}/V_{ED}) curve to the left (Janicki et al., 1996), reducing V_{ED} at the same P_{ED}, and leading to a smaller V_{ED} with a similar P_{ED} and, thus, a smaller V_S according to the Frank–Starling mechanism. However, this theoretical mechanism does not occur even during chronic hypoxia since the relationship between V_S and V_{ED} is the same during exercise at altitude and at sea level (Reeves et al., 1987). It is difficult to believe that this mechanism exists only during acute hypoxia.

Alternatively, ventricular interdependence could explain the reduced V_S during hypoxia. Acute hypoxia raises pulmonary arterial pressure (Cudkowicz, 1970) and right ventricular pressure, causing bulging of the interventricular septum towards the left ventricular cavity (Ritter et al., 1993). This, together with a decreased pulmonary capillary wedge pressure, indicating a lowered left atrial pressure and, hence, a reduced preload, lowers the driving pressure across the mitral valve and, consequently, reduces diastolic filling during the rapid phase in early diastole (Ritter et al., 1993). However, as already argued, the unaltered relationship between V_S and V_{ED} during exercise in chronic hypoxia indicates that this mechanism is not the principal factor explaining the reduced maximum cardiovascular function during chronic hypoxia.

A third explanation would be simply that the reduced peak workload during hypoxia (Peltonen et al., 2001) reduces the action of the muscle pump, thereby reducing venous return (Rowell, 1993), so that the measured cardiovascular changes are the result and not the cause of the reduced workload during hypoxia.

It has also been argued that, since pericardiectomy increases $\dot{Q}_{\max}$ in dogs (Stray-Gundersen et al., 1986), diastolic filling therefore limits maximal cardiac output in humans during maximal exercise in the upright position. Yet this logic does not follow since dogs exercise on all four legs, in which position most of their blood volume is at the level of the heart (Rowell, 1986; Rowell, 1993) such that diastolic filling pressures are optimized.

Hence, the model of exercise studied by Stray-Gundersen et al. (Stray-Gundersen et al., 1986) is the equivalent of humans exercising in the supine position in which position diastolic filling pressures are higher at $\dot{V}_{O_2\max}$ than when humans exercise in the upright position (Rowell, 1993). Thus, the conclusion must be that, during maximal exercise in the upright position in humans, the heart is not at the limit of its capacity for diastolic filling. Rather, any limitation to diastolic filling must exist 'before' the heart, as may also occur during maximal exercise in hypoxia.

Finally, an increased afterload cannot explain the reduced V_S during acute hypoxia since peripheral vascular resistance (Vogel et al., 1974) and mean arterial pressure (Wolfel et al., 1991) are unaffected during acute hypoxia (Rowell and Blackmon, 1987) and elevated only during chronic hypoxia.

Furthermore, the finding that the peak exercise heart rate is higher in silent ischaemia than in symptomatic ischaemia (Visser et al., 1990) can be interpreted as evidence that the response to the sensory signals that cause exercise to terminate with submaximal heart rates during acute hypoxia, as in ischaemia, may arise from outside the myocardium itself, possibly in the central nervous system.

In summary, direct cardiovascular factors, including myocardial dysfunction secondary to hypoxia or ischaemia, altered left ventricular diastolic function secondary to an increased coronary blood flow or an increased pulmonary arterial pressure, are unable to explain the reduced $\dot{Q}_{\max}$ during hypoxia. Nor is the reduction in $\dot{Q}_{\max}$ during hypoxia compatible with the classical model, which holds that the heart is the slave of the exercising muscles and must therefore maintain the same $\dot{Q}_{\max}$, especially when oxygen delivery to the exercising muscles is threatened by any factor that reduces Ca_{O_2}.

Central nervous system limitation

The elevated $\dot{Q}$ and f_H during acute hypoxia at a given submaximal $\dot{V}_{O_2}$ suggest an augmented sympathetic activity (Suarez et al., 1987) with increased circulating catecholamine concentrations (Cunningham et al., 1965; Manchanda et al., 1975; Escourrou et al., 1984). However, the close relationships between blood norepinephrine concentrations, heart rate and percentage $\dot{V}_{O_2\max}$ are essentially unaffected by hypoxaemia; that is, they are all changed in the same relative proportions

(Rowell, 1986). Therefore, it is interesting that $\dot{Q}_{max}$, f_{Hmax}, V_{Smax} and peak workrate (P_{max}) are each reduced during acute hypoxia, in a situation in which maximal sympathetic activity would be expected.

One possible explanation for the reduced $\dot{Q}_{max}$ and P_{max} during hypoxia is that the limitation originates centrally in the brain. If the level of sympathetic activity at a given heart rate is the same under normoxic and hypoxic conditions (Rowell, 1986), then the lower f_{Hmax} values during hypoxia could indicate a lesser sympathetic stimulation.

However, the finding that plasma norepinephrine and lactate concentrations were similar to normoxic values after maximal exercise during acute hypoxia, despite a lower f_{Hmax} with increasing altitude (Lundby et al., 2001), suggests that sympathetic activity *per se* was not reduced but that the response of the heart to sympathetic stimulation was blunted.

These authors (Lundby et al., 2001) concluded that postganglionic desensitization and not a reduction in cardiac adrenoreceptor numbers is responsible for the early decrease in f_{Hmax} during maximal exercise in hypoxia. In accordance with this interpretation, Manchanda et al. (Manchanda et al., 1975) reported that acute hypoxia reduced the stimulatory effects of catecholamines on cardiac function even during submaximal exercise. They found that, although cardiac performance increased in proportion to the rise in plasma catecholamine concentrations during normoxia, the response was blunted during acute hypoxia even though plasma catecholamine concentrations were elevated. They postulated that the depressant effect of increased hypoxaemia and acidosis during moderately heavy exercise in acute hypoxia may override the cardiostimulatory effects of elevated circulating catecholamine concentrations.

There are, however, studies to indicate that the central nervous system itself may act as a ‘central governor’ during maximal exercise in hypoxia. First, the typical signs of peripheral neuromuscular fatigue, i.e. an increase in the integrated electromyogram signal (IEMG) are absent during chronic (Kayser et al., 1994) and acute (Peltonen et al., 1997) hypoxia. Rather, IEMG activity is reduced at peak exercise but increases with oxygen administration at altitude (Kayser et al., 1994). Hence, Kayser et al. (1994) conclude that: “during chronic hypobaric hypoxia, the central nervous system may play a primary role in limiting exhaustive exercise and maximum accumulation of lactate in blood”. Second, blunting of afferent sensory signals from the working muscles does not diminish the hypoxia-induced cardiovascular adaptations to acute hypoxia, suggesting that the limitations in exercise performance are of central origin (Kjaer et al., 1999). Third, vasomotor depression on exposure to acute hypoxia is induced by central hypoxia in non-acclimatized subjects (Koller et al., 1991). Fourth, the animal experiments of Jones et al. (Jones et al., 1981) have shown that, as Ca_{O_2} falls, regardless of whether this is due to a reduction in P_{O_2} or in haematocrit or both, there is a reciprocal increase in cerebral blood flow such that cerebral O_2 delivery remains constant. This indicates that the brain has the ability to sense acute hypoxia and to increase blood flow in response. The finding that the extent of the cerebral microvasculature increases with chronic exposure to hypoxia (Harik et al., 1996) further indicates the capacity of the central nervous system to sense, and to respond to, hypoxia. Moreover, hypoxia has a tendency to increase both overall and respiratory perceptions of effort for a given absolute $\dot{V}_{O_2}$ (Shephard et al., 1992).

All these findings, but most especially those of Kayser et al. (Kayser et al., 1994), support the original central governor hypothesis of Hill and colleagues (Hill et al., 1924a; Hill et al., 1924b), as modified by Noakes (Noakes, 1998; Noakes, 2000; Noakes, 2001), that skeletal muscle recruitment during severe exercise is regulated by a central governor specifically to prevent the development of progressive arterial desaturation leading to myocardial ischaemia or cerebral hypoxia. Thus, reduced $\dot{Q}_{max}$ and $\dot{V}_{O_2max}$ during acute hypoxia might be the result rather than the cause of the reduced skeletal muscle recruitment (Peltonen et al., 2001). The postulated pathways for this effect are presented in Fig. 2.

Further evidence for the existence of a central governor is provided by an analysis of the theories of the relationship between $\dot{V}_{O_2max}$ and exercise performance and how these predict the responses of both to either hypoxia or hyperoxia. Two different interpretations exist: one favours the belief that $\dot{V}_{O_2max}$ directly determines the maximal workload that can be achieved; the other that $\dot{V}_{O_2max}$ is the effect rather than the cause of the measured exercise performance. If $\dot{V}_{O_2max}$ determines maximal exercise performance, then $\dot{V}_{O_2max}$ and exercise performance should change in direct and equal proportion during acute hypoxia and hyperoxia compared with values measured during normoxia. However, this is not the case: all the earlier and modern studies show a greater change in $\dot{V}_{O_2max}$ than in maximal performance both during hypoxia and hyperoxia (Saltin et al., 1968b; Drinkwater et al., 1979; Maresh et al., 1983; Fulco et al., 1988; Roca et al., 1989; Knight et al., 1993; Peltonen et al., 1995; Gore et al., 1997; Nielsen et al., 1998; Peltonen et al., 2001). Furthermore, the change in exercise duration at a constant workload during either hypoxia or hyperoxia exceeds the measured changes in $\dot{V}_{O_2max}$ under those conditions (Fagraeus et al., 1973; Adams and Welch, 1980).

Although exercise performance and $\dot{V}_{O_2max}$ do not change equally with changes in F_{IO_2}, an interesting finding is the strongly positive correlation between changes in maximal workload and $\dot{Q}_{max}$ during both hypoxia and hyperoxia (Peltonen et al., 2001), supporting the theoretical existence of a central governor linking cardiac function and exercise performance (Fig. 2).

Finally, it is of interest to speculate about the site of the oxygen sensor that appears to link cardiovascular function and exercise performance during hypoxia and hyperoxia. Noakes’ original suggestion was that the oxygen tension in the coronary vascular bed would be the monitored variable to prevent the development of a progressive myocardial ischaemia (Noakes, 1998; Noakes, 2000; Noakes, 2001; Fig. 2).

Alternatively, other studies suggesting that a central governor limits exercise during hypoxia or at altitude (Koller

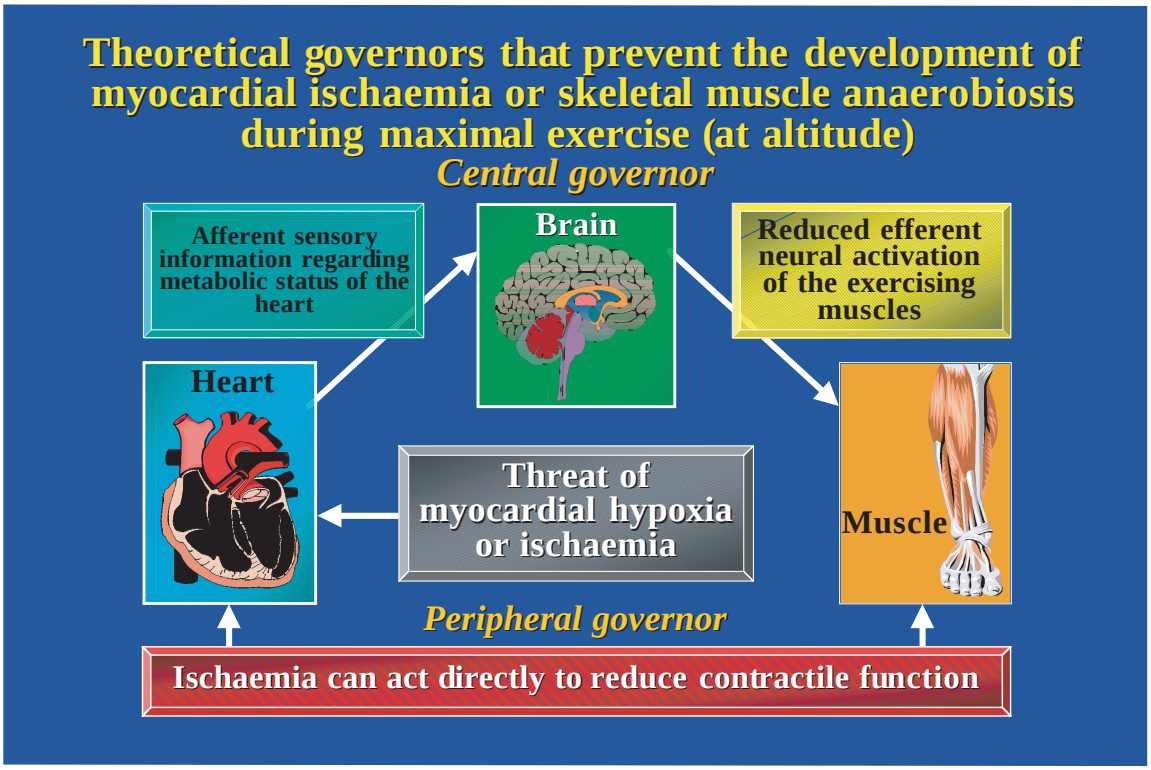

Fig. 2. The central governor theory proposes that afferent sensory information from the heart, but also perhaps from the brain and respiratory muscles, informs the brain of any threat that hypoxia or ischaemia may develop in those organs. In response, the central governor acts *via* the motor cortex to reduce the efferent neural activation of the exercising muscles, thereby reducing the mass of muscle that can be recruited and, hence, reducing the exercise intensity that can be sustained. The existence of peripheral governors in skeletal muscle and heart is proved by the rapidly deleterious effects of ischaemia on contractile function of both the heart and skeletal muscles and the existence of the condition of myocardial hibernation (Noakes, 2001).

et al., 1991; Kayser et al., 1994; Harik et al., 1996; Peltonen et al., 1997; Kjaer et al., 1999) can be interpreted to show that the efferent information to the central governor (Fig. 2), and which terminates exercise at a lower $f_{H\max}$, $V_{S\max}$ and $\dot{Q}_{\max}$, may arise not in the coronary vessels or myocardium but possibly in the central nervous system itself.

For example, the evidence presented here can be interpreted as indicating that skeletal muscle has the potential to increase its blood flow and oxygen utilization up to the point at which a short mean capillary transit time causes a peripheral oxygen diffusion limitation to develop. However, if a similar diffusion limitation exists in the central nervous system, this would also offer a possible explanation for the observed reductions in $\dot{Q}$, f_H, exercise performance and electromyographic activity during acute hypoxia since all would slow the transit time in the cerebral capillaries, thereby preventing the development of cerebral hypoxia. However, the same model would also explain how the central governor would prevent the development of myocardial ischaemia.

Concluding remarks

The arguments presented in this review are compatible with the theory that the reduced $f_{H\max}$, $V_{S\max}$ and $\dot{Q}_{\max}$ during acute and chronic hypoxia are due to central regulation, the goal of which is to prevent the development of hypoxia in one or more of the vital organs including the brain, heart or perhaps the respiratory muscles. The action of this central governor is to regulate the mass of muscle that can be recruited during exercise under conditions in which the oxygen delivery to these vital organs is threatened. By limiting the muscle mass that can be activated, the central governor limits the peripheral peak $\dot{V}_{O_2}$ to a level that will not induce hypoxia in any of the vital organs.

If this model is correct, it suggests that a search for the possible factors limiting maximal exercise performance should include studies of the central nervous system, since such studies might uncover the possible existence and mode of action of the proposed central governor.

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