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Respiration Physiology 120 (2000) 1–11

www.elsevier.com/locate/resphysiol

Frontiers Review

Reduced maximal cardiac output at altitude — mechanisms and significance

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Accepted 9 November 1999

Abstract

When a lowlander ascends to altitude and acclimatizes over days to weeks, both maximal exercise capacity and maximal cardiac output are reduced compared to sea level. Of the several possible mechanisms underlying this reduction of maximal cardiac output, the available data are interpreted as supporting the simplest hypothesis — that this merely reflects the reduced requirement for muscle blood flow that results from the arterial hypoxemia of altitude (which reduces muscle O_2 availability and thus maximal muscle function). The competing hypotheses, that increased blood viscosity, reduced blood volume, autonomic nervous system changes or myocardial hypoxic dysfunction reduce maximal cardiac output, are not well supported by existing data. However, critical tests of some of these hypotheses remain to be devised and undertaken. When it comes to the question of the importance of reduced maximal cardiac output to $\dot{V}_{O_2\ MAX}$ at altitude, the available evidence suggests that cardiac output is not a major limiting variable. This is because as cardiac output rises, gains in convective flow of O_2 in the circulation are offset by losses from greater diffusion impairment of O_2 transfer in the lungs and muscles, and vice versa. However, just as with the mechanism of cardiac output reduction itself, clear-cut experimental tests of its role in limiting exercise at altitude remain to be conducted.

Keywords: Altitude, acclimatization; Cardiac output, maximum, hypoxia; Exercise, altitude, maximal O_2 uptake, cardiac output; Hypoxia, altitude, exercise; Mammals, humans; Oxygen, maximum uptake, hypoxia

1. Introduction

While it has been known since time immemorial that exercise capacity is reduced at altitude, the physiological underpinning of this impairment is not fully understood. It is certainly well known that exercise lasting more than a few seconds is

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0034-5687/00/$ - see front matter
PII: S0034-5687(99)00101-2

critically dependent upon O_2 availability to the muscle mitochondria, and that altitude of course reduces O_2 availability by virtue of reduced barometric pressure and hence inspired P_{O_2}. Accordingly, it might at first be thought that O_2 unavailability via reduced P_{O_2} transmitted down the O_2 transport system from air to mitochondria is a sufficient explanation for reduced exercise capacity, but many studies over the years have found a number of physiological effects of altitude that might, separately from a low P_{O_2}, affect O_2 availability and thus exercise capacity. Some of these would act to preserve exercise capacity, others to diminish it.

Chief amongst these is hypoxic stimulation of breathing, without which extreme altitudes, such as the 8848 m summit of Mt. Everest, could never be attained. Thus, even if on Mt. Everest the lungs were perfectly homogeneous and moreover were not subject to diffusion limitation of O_2 transport from alveoli to capillaries, the sea level arterial P_{CO_2} of 40 Torr, if unchanged at altitude, would mandate an arterial P_{O_2} of only about 3 Torr, clearly incompatible with life. Even this value would occur only if the respiratory exchange ratio was at least 1.0. Hyperventilation, therefore, acts to partly offset the effects of altitude on O_2 transport.

A second well-known, if slower, accompaniment to high altitude is increased hemoglobin concentration from erythropoietin released by hypoxic kidney cells. For a given P_{O_2} in the blood, the O_2 concentration is increased in proportion to the rise in [Hb], which by and of itself should improve O_2 transport and availability. However, high hematocrit means high blood viscosity and, as a result, the potential for reduced cardiac output (Richardson and Guyton, 1959).

A third consequence of spending time (days or weeks) at altitude is reduction in circulating plasma volume. In part, this is due to diuresis associated with the kidney's attempt to excrete HCO_3^- ions to compensate for the respiratory alkalosis induced by hypoxia; in part, this comes from increased exhaled or sweated water in a low humidity environment; in part, this could also be caused by fluid losses from gastrointestinal disturbances not uncommon in primitive and hypoxic environments. While reduced plasma volume will raise [Hb] and thus O_2 concentration in blood, cardiac filling pressures might fall and lead to reduced cardiac output and thus possibly reduced muscle blood flow. Convective O_2 delivery to the muscles may thus be compromised.

Fourthly, autonomic nervous system changes have been found to occur on ascent to altitude (Richalet et al., 1992). Changes in sympathetic (Richalet et al., 1988) and parasympathetic activity (Kacimi et al., 1993) and in myocardial adrenoceptor density (Kacimi et al., 1992; Voelkel et al., 1981) have been discovered that could affect cardiovascular function, generally in the direction that would lead to a lower maximal cardiac output.

Fifthly, hypoxia at altitude could directly impair cardiac function. Just like skeletal muscle, the heart is critically dependent on O_2 availability itself, so that at extreme altitudes such as the summit of Mt. Everest, where arterial P_{O_2} is in the range of 25–30 Torr, one could well imagine myocardial hypoxia placing limits on cardiac function and thus cardiac output.

The foregoing clearly shows that several coexistent consequences of high altitude exposure exist, some acting to preserve and others to impair exercise capacity. Several of these have the potential of reducing cardiac output. Does this occur, what is/are the mechanism(s), and what is the consequence, if any, for exercise?

2. Cardiac output measurements at altitude

From the outset, one must separately consider acute altitude exposure, say hours to a couple of days, and chronic altitude exposure, lasting from a few days to several weeks. The latter is the focus of this review — indeed, acute altitude exposure will be discussed only briefly.

Acute exposures such as those associated with rapid (minutes to hours) ascent during altitude simulations in hypobaric chamber studies are limited to about 4500 m for safety reasons. Obviously, erythropoietin-related increases in [Hb] and significant fluid loss have not yet occurred. However, substantial hypoxic stimulation of the sym-

pathetic nervous system is seen (Grover et al., 1986). The result is that heart rate at any given $\dot{V}_{O_2}$ is elevated (although maximal heart rate is not altered). Rather, the normal (sea level) maximal heart rate is reached at lower peak work rates than at sea level (Fig. 1). Cardiac output follows heart rate under these conditions—thus, it too is elevated at any submaximal exercise intensity, but maximal cardiac output is not diminished (Wagner et al., 1986) — it, too, occurs at a lower peak work rate (Fig. 1). There is general agreement that this response is mediated by the stimulation of the sympathetic system by acute hypoxia (Hultgren, 1997; Ward et al., 1995). It is of some interest that when propanolol is used at altitude to block sympathetic β-receptors, the expected fall in heart rate at any given exercise capacity is seen, yet maximal exercise capacity (as reflected by maximal $\dot{V}_{O_2}$) is not reduced (Moore et al., 1986). Measurements have not yet been made to determine whether maximal cardiac output is reduced by this intervention. It is possible that stroke volume may increase due to longer diastolic filling times caused by the lower heart rate such that maximal cardiac output remains unaffected, but this remains to be determined under maximal exercise conditions.

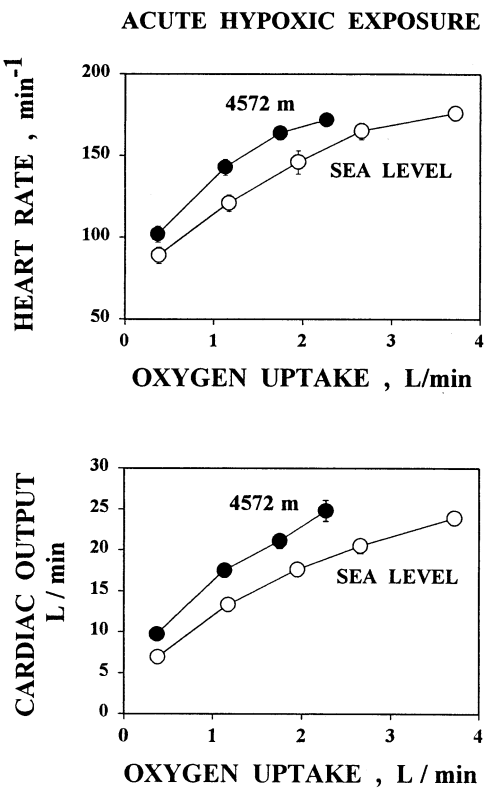

Fig. 1. Heart rate and cardiac output responses to exercise (oxygen uptake) at sea level and in a hypobaric chamber at 430 mmHg barometric pressure (equivalent to 4572 m above sea level) in eigth normal subjects. The altitude data were obtained within an hour of ascent. Both heart rate and cardiac output are greater at altitude than at sea level at any submaximal exercise level, but maximal heart rate and maximal cardiac output are the same at sea level and altitude (Wagner et al., 1986).

Exercise at high altitude in *acclimatized* lowlanders produces a different response from that seen during *acute hypoxic exposure*. In essentially all studies where cardiac output was measured at peak exercise in chronic hypoxia, cardiac output has been found to relate to O_2 consumption exactly as it does at sea level — at any given work rate, cardiac output at sea level and at altitude are the same (Pugh, 1964; Reeves et al., 1987). Heart rate remains somewhat higher at altitude than at sea level at any given work rate. A typical set of such data is shown in Fig. 2. Of course, since at altitude, maximal work rate is reduced, it is evident from Fig. 2 that maximal cardiac output is reduced as well, and that is the subject of this review. Many other data sets could have been used to illustrate this intriguing relationship — the findings are quite reproducible. The data in Fig. 2 are emphasized in Fig. 3 where a close relationship between *peak* $\dot{V}_{O_2}$ and *peak* cardiac output is evident. In other words, as altitude is gained, both maximal cardiac output and maximal $\dot{V}_{O_2}$ fall in parallel. Such data have fueled the debate on whether the reduced maximal cardiac output is even in part responsible for the reduced maximal $\dot{V}_{O_2}$, or not. Certainly at sea level, the prevailing view is that cardiac output is a key determinant of $\dot{V}_{O_2\,MAX}$ (Barclay and Stainsby, 1975; Horstman et al., 1976) so that when such large changes in maximal $\dot{Q}_T$ occur at altitudes, the possibility of a cause and effect role in $\dot{V}_{O_2\,MAX}$ must be raised.

This review will address the intertwined questions of: (1) why after acclimatization is maximal cardiac output lower at altitude; and (2) does a

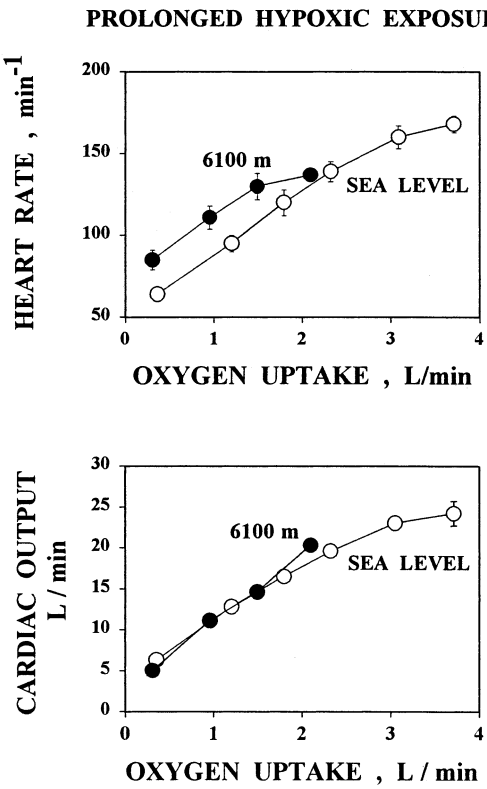

Fig. 2. Heart rate and cardiac output responses to exercise at sea level and altitude simulated in a hypobaric chamber during a prolonged hypoxic exposure. While heart rate is still somewhat elevated submaximally, maximal heart rate tends to fall along the sea level relationship. Cardiac output, on the other hand, follows the sea level relationship across the entire domain of exercise (Sutton et al., 1988).

reduced maximal cardiac output contribute to exercise limitation at altitude.

3. Potential mechanisms of reduced maximal cardiac output

The introduction laid out several possible pathways that could lead to reduced maximal cardiac output based on what might be termed pathophysiological effects of altitude:

1. Increased blood viscosity from erythrocytosis and increased hematocrit.
2. Reduced cardiac filling pressures from reduced plasma volume.
3. Autonomic changes such as increased parasympathetic or reduced sympathetic activity.
4. Hypoxic myocardial dysfunction.

There is, however, a fifth possible mechanism that does not have a pathophysiological basis: That cardiac output is dictated by exercise intensity. This hypothesis states that since skeletal muscle O_2 availability is impaired by ambient hypoxia, exercise capacity is reduced on this basis, and the requirement for cardiac output is thus correspondingly reduced. Maximal cardiac output, therefore, remains low, but appropriate to reduced metabolic needs. This hypothesis in essence refutes the four listed above and is predicated on a general mechanism in which cardiac output follows rather than leads skeletal muscle contractile function, and is not limited by impaired cardiac function for any reason. Let us now examine the existing evidence for/against each of these five hypotheses.

3.1. Increased viscosity

Clearly, viscosity increases with hematocrit (Winslow and Monge, 1987); hematocrit increases

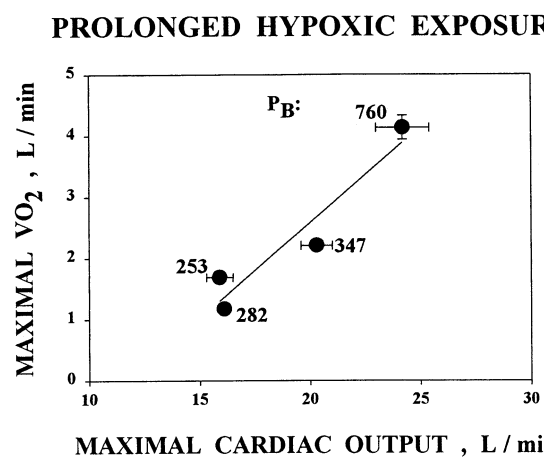

Fig. 3. Relationship between maximal oxygen consumption and maximal cardiac output during a slow ascent to the equivalent of the Everest summit in a hypobaric chamber. There is a close linear relationship, raising the question of the importance of maximal cardiac output to attaining maximal $\dot{V}_{O_2}$ at altitude (Sutton et al., 1988).

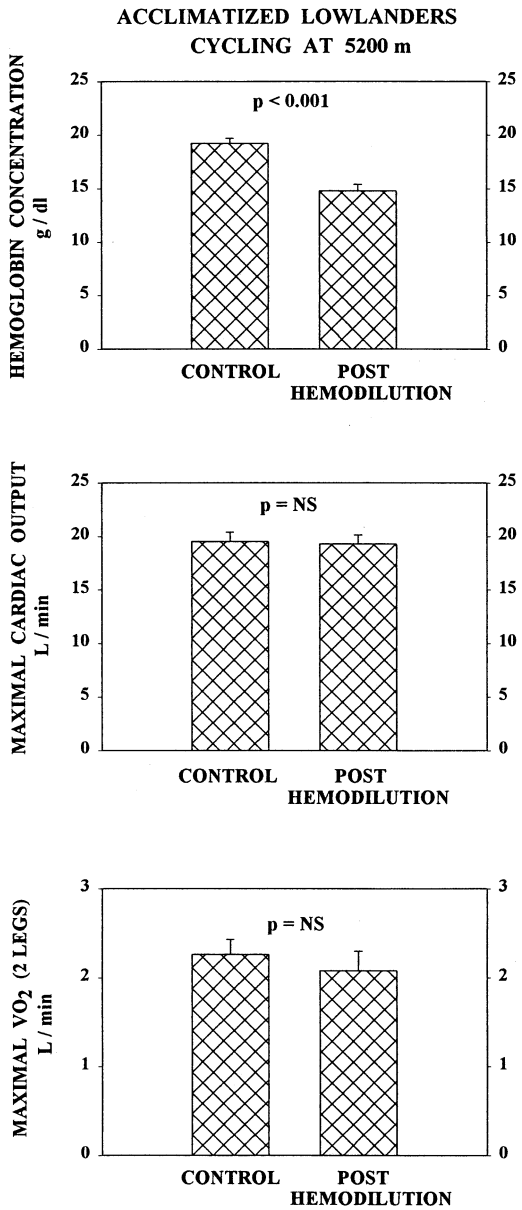

Fig. 4. Effects of isovolumic reduction in hematocrit on hemoglobin concentration, maximal cardiac output and maximal exercise capacity in acclimatized lowlanders cycling after 8 weeks of residence at 5200 m. Despite a significant reduction in hemoglobin concentration, both maximal cardiac output and maximal $\dot{V}_{O_2}$ are unaffected (Calbet et al., 1999a).

with increasing altitude, and cardiac output bears an inverse relationship to increasing hematocrit across a variety of settings that encompass levels of polycythemia similar to levels achieved during sojourns at altitude (Richardson and Guyton, 1959). Thus the stage is set for viscosity to play a role, but the above links form at best only circumstantial evidence. The critical intervention should be to reduce [Hb] isovolumically while at altitude. However, this intervention could have secondary effects that might involve other competing hypotheses — altering autonomic activity, and myocardial function in particular — that render the interpretation somewhat difficult. Fig. 4, however, shows that in those studies reporting such interventions, maximal cardiac output (or exercising muscle blood flow) is far from normalized (Horstman et al., 1980; Calbet et al., 1999a), and also that there is little or no effect on maximal exercise capacity (Sarnquist et al., 1986). In contrast, when the hypoxia of altitude is abolished acutely by giving O_2 to breathe, cardiac output can rise to (near) normal sea level values, as does $\dot{V}_{O_2}$ MAX (Pugh, 1964; Pugh et al., 1964). This occurs with no change in hematocrit. Taken together, these findings would suggest that increased viscosity is probably a minor factor in this story.

3.2. Reduced cardiac filling pressures (from reduced blood volume)

This potential explanation has been on the table for many years, without clear resolution. In part, this is because obtaining the requisite data requires right heart catheterization, something that has rarely been done at high altitude, even in chamber studies, let alone in the field.

Available data, few in number, do not lend themselves to a clear-cut answer to the question of how important cardiac filling pressures are to maintenance of cardiac output. On the one hand, such pressures do indeed appear to be lower than at sea level, but that is true submaximally as well as maximally. As Fig. 2 shows, submaximal cardiac output tracks sea level values perfectly even when filling pressures are reduced as shown in Fig. 5. One might again look to interventional studies in which blood volume has been augmented to answer the question, but this has not been done in the clear sense of increasing blood volume without reducing hematocrit. Studies ex-

panding plasma volume (and thus reducing hematocrit simultaneously) generally show little augmentation in cardiac output or exercise capacity (Grover, 1965; Hartley, 1971; Wolfel et al., 1994), but again changing several variables at once makes the interpretation difficult. Perhaps the simplest and most suggestive intervention to date is giving 50–100% O_2 and noting an immediate ability to restore cardiac output to (near) normal, with obviously no change in blood volume (Pugh, 1964; Calbet et al., 1999b). This is regarded as the best evidence that reduced filling pressures are not the principal reason for a low maximal cardiac output at altitude.

3.3. Autonomic nervous system changes

There is a large body of work, much from the laboratories of Jean-Paul Richalet and of Jack Reeves and their associates demonstrating that in chronic hypoxia there are measurable changes in the autonomic nervous system (Voelkel et al., 1981; Richalet et al., 1988, 1992; Kacimi et al., 1992, 1993). In man, Richalet's group reports diminished heart rate response to isoproterenol (Richalet et al., 1988), evidence of reduced cardiac β-adrenergic receptor activity (Kacimi et al., 1992), and evidence of increased muscarinic receptor activity (Kacimi et al., 1993). Each of these changes could in theory contribute to a lower maximal heart rate in chronic hypoxia. Interestingly, plasma norepinephrine levels at rest and during exercise are found to be higher at altitude than at sea level, consistent with higher observed resting and submaximal exercise heart rates (Antezana et al., 1994). The changes in β-receptor activity measured in man are small, about 16% (Kacimi et al., 1992), yet maximal heart rate is generally found to be considerably reduced even in the face of higher circulating catecholamine levels. While these studies collectively show some autonomic effect of chronic hypoxia, they have not answered the question of whether these effects are responsible wholly or even in part for the reduced maximal heart rate (let alone cardiac output) in chronic hypoxia. Indeed, the immediate reversibility of reduced maximal heart rate with 100% O_2 breathing (Pugh, 1964; Calbet et al., 1999b) coupled to the very different maximal heart rate responses to acute versus chronic hypoxia (yet similar effects of infused isoproterenol under the two conditions) rather argues against autonomic changes as playing a significant role in the reduced maximal cardiac output at altitude.

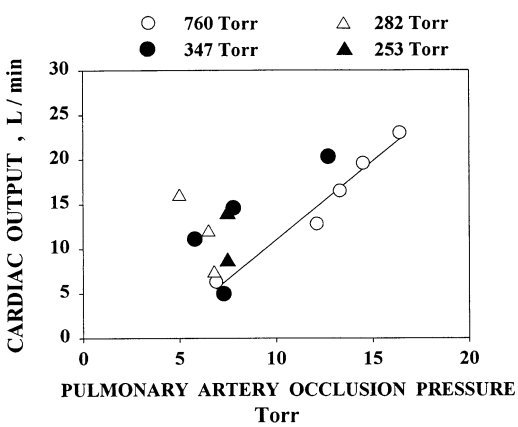

Fig. 5. Relationship between cardiac output and pulmonary artery occlusion pressures at sea level and altitude during a slow simulated ascent of Mt. Everest. If anything, cardiac output is increased at any given filling pressure at altitude compared to sea level (Reeves et al., 1987).

Direct interventions appear to offer the chance of examining the role of the autonomics in regulating maximal cardiac output. Sympathetic blockade with propanolol has no effect on maximal $\dot{V}_{O_2}$ (Moore et al., 1986), but cardiac output at peak exercise remains to be measured under these conditions. Hartley (1971) found atropine increased maximal heart rate at altitude but not at sea level but did not measure cardiac output nor the atropine effect at sea level at the same low work rate corresponding to maximal at altitude. Parasympathetic blockade with glycopyrrolate raises maximal heart rate essentially to normal sea level maximal values while at altitude, but has no effect on cardiac output or exercise capacity (Boushel et al., 1999, Fig. 6). The full range of necessary studies have not yet been performed, but currently available data suggest little or no role for autonomic alterations (which do occur) on the issue at hand — reduced maximal cardiac output. Thus, the literature suggests that removing sympathetic or parasympathetic influences

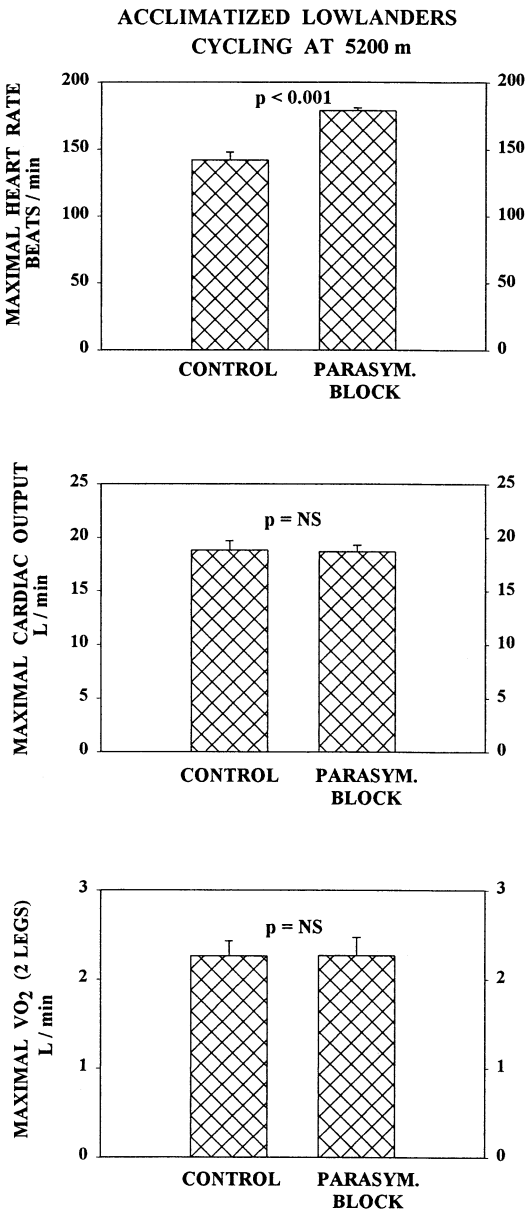

Fig. 6. Effects of parasympathetic blockade on maximal heart rate, cardiac output and exercise capacity in acclimatized lowlanders cycling after 8 weeks of residence at 5200 m. Parasympathetic blockade essentially normalizes maximal heart rate (which is less than 150 beats/min under control conditions). However, neither cardiac output nor exercise capacity are improved (Boushel et al., 1999).

leads to compensatory effects that leave overall blood flow and exercise capacity not measurably altered.

3.4. Hypoxic myocardial dysfunction

The hypothesis that the myocardium self-limits its own pumping function to avoid potentially disastrous ischemia has been advanced more than once (Alexander et al., 1967), most recently by Noakes (1997, 1998). The idea here is that some signal related to O_2 availability shuts down exercise prior to the heart's becoming overtly hypoxic. While this idea has its teleological appeal, evidence in its support is difficult to identify. Perhaps most closely studied in Operation Everest II, the heart seems to perform admirably even at the equivalent of the Everest summit (Reeves et al., 1987; Suarez et al., 1987). Data come from several types of measurement: There is no EKG evidence of ischemia, no clinically evident angina. There is no evidence of reduced contractility of heart muscle from echocardiography, ejection fraction, or the filling pressure/cardiac output relationship. There is no evidence of hypoxic depression of maximal heart rate, although this is difficult to state with certainty in the face of altered autonomic function mentioned above. Perhaps one might argue that the necessary tools do not exist (or have not been applied) to detect a protective signal, but the observation that cardiac output tracks $\dot{V}_{O_2}$ exactly as at sea level (Fig. 2) all the way to maximal effort suggests that if impending myocardial hypoxia is the basis for cardiac output ceilings at altitude, the signal must be very subtle — there is no fall-off in overall function at maximal effort as Fig. 2 shows. The direct intervention to test this hypothesis — perfuse the coronary arteries with fully oxygenated blood while keeping all other systems ambiently hypoxic at altitude — will be very difficult to carry out even in animals, let alone man. Together with the complementary experiment of perfusing the exercising muscles with fully oxygenated blood while keeping the heart ambiently hypoxic, one would elegantly address the problem rather definitively.

3.5. Maximal cardiac output is dictated by maximal skeletal muscle $\dot{V}_{O_2}$ (which is O_2-limited at altitude) and is thus reduced in proportion to reduced $\dot{V}_{O_2\ MAX}$

This is the 'passive' hypothesis which states that none of the above four pathophysiological hypotheses — increased viscosity, reduced blood volume, autonomic changes, or myocardial hypoxia — are responsible for the low maximal cardiac output of acclimatized subjects at altitude. Rather, at any given power output there is an associated requisite level of cardiac output. This level would be signaled from events possibly within the skeletal muscles in a way similar to that at sea level. So, if the muscles cannot do as much work at altitude, due to arterial hypoxemia, the signals driving cardiac output are correspondingly less. In support of this hypothesis is the observation that *immediately* — within seconds — of eliminating ambient hypoxia at altitude by the intervention of 100% O_2 breathing, maximal cardiac output (and $\dot{V}_{O_2}$ and power output) are essentially restored to sea level values (Pugh, 1964). This happens with no change in viscosity or blood volume, and is such a rapid response that structural changes in the autonomic system, such as receptor numbers, cannot be expected to normalize and explain the changes. On the other hand, it is clear that the myocardial hypoxic dysfunction hypothesis cannot be excluded by the acute effect of 100% O_2. Additional more correlative evidence supporting the 'passive' hypothesis is: (1) the similarity of the sea level and altitude heart rate and cardiac output responses to exercise typified in Fig. 2, and (2) the close relationship between $\dot{V}_{O_2}$ and cardiac output shown in Fig. 3. That this is compatible with this hypothesis is evident if the *x* and *y* axes are interchanged: maximal cardiac output could be determined by maximal $\dot{V}_{O_2}$. It is otherwise difficult to suggest a critical experiment that would allow us to conclude it is the correct hypothesis. It may have to be accepted or rejected on the basis of stronger evidence against the preceding four hypotheses.

Collectively, however, this writer sees the sum of the evidence as supporting the fifth, 'passive' hypothesis based upon what was described above. However, a number of critical interventional experiments will have to be performed to put the matter to rest.

4. Does the low maximal cardiac output at altitude contribute to the corresponding reduction in $\dot{V}_{O_2\ MAX}$?

Even at sea level, one of the oldest and most contentious questions in the context of exercise continues to be "What determines maximal $\dot{V}_{O_2}$?" To cut to the quick, the traditional view holds that cardiac output is 'the' critical limiting factor (Barclay and Stainsby, 1975; Horstman et al., 1976). Thus, it is argued, O_2 transport depends on the product of cardiac output, [Hb] and O_2 saturation of Hb. Furthermore, comparing athletes to non-athletes, there is no systematic or at least quantitatively significant difference in either [Hb] or O_2 saturation between the two. Indeed, due to plasma volume expansion, [Hb] may be lower in the athlete and due to higher cardiac output, arterial O_2 saturation may also be lower due to development of alveolar–capillary diffusion limitation. Clearly the difference in maximal exercise capacity between athletes and non-athletes lies in their differences in maximal cardiac output.

In the context described, this conclusion is inescapable, but there is much evidence to point out that even at sea level, other elements of the O_2 transport chain can independently affect maximal $\dot{V}_{O_2}$. Thus, hypoxemia (Roca et al., 1989) and anemia (Hogan et al., 1991) themselves are known to reduce $\dot{V}_{O_2\ MAX}$ independently of cardiac output, just as hyperoxia (Welch, 1983) and increased [Hb] (Gledhill, 1982) will raise maximal $\dot{V}_{O_2}$. The O_2 transport system can be described in terms of the key conductances at each step. In health, the principal variables are: (a) ventilation; (b) pulmonary diffusing capacity, (c) cardiac output (or muscle blood flow), (d) hemoglobin concentration, and (e) muscle O_2 transport conductance. The latter is the functional equivalent of diffusing capacity in the lung, and includes the real diffusional conductance from the muscle microcirculatory red cell to the mitochondria plus the functional consequences of any non-uniformity in

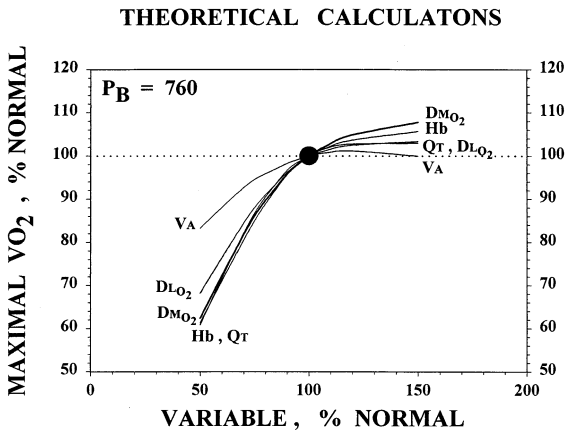

Fig. 7. Theoretical calculations for sea level conditions showing the sensitivity of maximal $\dot{V}_{O_2}$ to several different independent variables associated with oxygen transport ($\dot{V}A$ = alveolar ventilation, $D_{L_{O_2}}$ = lung diffusing capacity, $D_{M_{O_2}}$ = muscle diffusing capacity, Hb = hemoglobin concentration, $\dot{Q}T$ = cardiac output). These calculations show how each of these variables independently affects maximal oxygen consumption in a model of the lungs, circulation and muscle. Except for ventilation, all variables produce very similar quantitative results (Wagner, 1996).

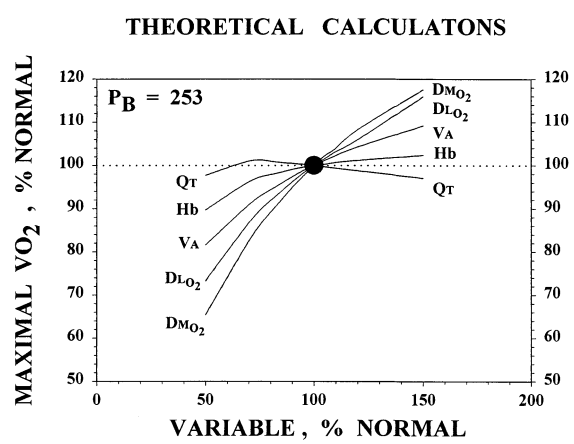

Fig. 8. Corresponding theoretical calculations to those shown in Fig. 7, but for a barometric pressure of 253 Torr, equivalent to that on the summit of Mt. Everest. Symbols are as for Fig. 7. Note now that cardiac output can be varied over an enormous range with negligible effects on maximal $\dot{V}_{O_2}$. On the other hand, muscle and lung diffusional conductances are more important quantitatively than at sea level. See text for explanation (Wagner, 1996).

the distribution of muscle blood flow with respect to local metabolic rate. Why these two phenomena are linked into a single conductance parameter reflects our current inability to separate the two experimentally. What the accumulated literature shows is that all five of the above variables (a)–(e) are each capable of altering maximal $\dot{V}_{O_2}$ in a very complex manner that, while technically independent of the other four, will have quantitative effects that depend on the values of all of these variables. Such effects will also change according to altitude due to the non-linear nature of the O_2 Hb dissociation curve. Integrated models of the O_2 transport system encompassing all five transport variables show that each affects $\dot{V}_{O_2}$ MAX independently, although in different ways quantitatively. Thus, while the magnitude of the cardiac output is clearly important, calculations show that at sea level the lung and muscle O_2 transport conductances and blood [Hb] all have very similar quantitative effects to that of cardiac output (Wagner, 1996). On the other hand, ventilation is of little importance to O_2 transport at sea level (Fig. 7).

At high altitudes, O_2 exchange takes place on the steep region of the O_2Hb dissociation curve. This creates a distinct disadvantage for processes based on diffusion of O_2 (in the lung and muscle) (Wagner, 1977) This in turn means that maximal O_2 transport becomes more sensitive to the magnitude of these conductances than at sea level (Wagner, 1996) (Fig. 8).

But what of cardiac output at altitude, the principal subject of this review? The same model and calculations that confirm an important role for cardiac output in contributing to limits to $\dot{V}_{O_2}$ MAX at sea level show an ever lessening role for cardiac output as altitude is progressively increased. At the Everest summit equivalent, these calculations show that over a very wide range, variation in cardiac output will have *no measurable effect on maximal* $\dot{V}_{O_2}$ (Wagner, 1996) (Fig. 8). How can this at first sight remarkable prediction be explained? On the interplay between convective and diffusive transport processes in the overall O_2 transport system. Put simply, if cardiac output were to increase, convective transport of O_2 around the body would increase in proportion, other factors equal. But other factors are not

equal: the higher cardiac output reduces capillary transit time in both the lungs and muscles and impairs O_2 transport accordingly — diffusion limitation is more in evidence. The negative effects of greater diffusion limitation offset the positive effects of greater convective transport, and the net result is a wash — no effect on maximal $\dot{V}_{O_2}$.

Theoretical calculations are fun and permit the formulation of experimental paradigms to test hypotheses, but they are, of course, not themselves proof of correctness. What experimental evidence exists to support or refute this prediction that the reduced maximal cardiac output plays no role in limiting $\dot{V}_{O_2\,MAX}$ at extreme altitude? And a small role only at intermediate altitude? Very little direct evidence exists, mostly because the obvious test of the hypothesis has turned out to be difficult to perform. A manipulated increase in cardiac output acutely and in a manner that affected no other component of the O_2 transport and utilization system is currently unachievable, it would seem. Thus, accelerating the low maximal heart rate with parasympathetic blockade simply results in a reduced stroke volume and no change in maximal cardiac output or $\dot{V}_{O_2}$ (Boushel et al., 1999). So too, plasma volume expansion has led to such small changes in cardiac output that the hypothesis has not been completely tested (Calbet et al., 1999a). Less direct, but evidence nonetheless is in the β-adrenergic blockade studies of Moore et al. (1986) showing on Pikes peak (altitude 4110 m) no reduction in $\dot{V}_{O_2\,MAX}$ (although maximal cardiac output was never measured). Other evidence includes the lack of change in $\dot{V}_{O_2\,MAX}$ in subjects over time at a given altitude despite reduction in maximal cardiac output with acclimatization (Bender et al., 1988). Direct experimental evidence wherein large changes in maximal cardiac output alone are acutely produced has not been obtained.

Perhaps an esoteric study of an athletic animal given a mechanical heart whose output can be varied at the touch of a button (and in whom exercise studies are performed after acclimatization to substantial altitude) will be required to settle the issue. Until then, conclusions should be tentative, but what theoretical and experimental evidence exists suggests that, especially at extreme altitude, the low maximal cardiac output is not a disadvantage since it appears not to be an important variable in setting the limits to maximal O_2 transport.

Acknowledgements

Supported by NIH HL17731.

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