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Disparity in regional and systemic circulatory capacities: do they affect the regulation of the circulation?

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Abstract

In this review we integrate ideas about regional and systemic circulatory capacities and the balance between skeletal muscle blood flow and cardiac output during heavy exercise in humans. In the first part of the review we discuss issues related to the pumping capacity of the heart and the vasodilator capacity of skeletal muscle. The issue is that skeletal muscle has a vast capacity to vasodilate during exercise [~300 mL (100 g)$^{-1}$ min^{-1}], but the pumping capacity of the human heart is limited to 20–25 L min^{-1} in untrained subjects and ~35 L min^{-1} in elite endurance athletes. This means that when more than 7–10 kg of muscle is active during heavy exercise, perfusion of the contracting muscles must be limited or mean arterial pressure will fall. In the second part of the review we emphasize that there is an interplay between sympathetic vasoconstriction and metabolic vasodilation that limits blood flow to contracting muscles to maintain mean arterial pressure. Vasoconstriction in larger vessels continues while constriction in smaller vessels is blunted permitting total muscle blood flow to be limited but distributed more optimally. This interplay between sympathetic constriction and metabolic dilation during heavy whole-body exercise is likely responsible for the very high levels of oxygen extraction seen in contracting skeletal muscle. It also explains why infusing vasodilators in the contracting muscles does not increase oxygen uptake in the muscle. Finally, when ~80% of cardiac output is directed towards contracting skeletal muscle modest vasoconstriction in the active muscles can evoke marked changes in arterial pressure.

Keywords

cardiac output; exercise hyperaemia; sympatholysis; VO_{2max}

Overview of exercise, energy demand, muscle blood flow and cardiac output

During exercise the overall energy demand increases to sustain the contractile activity of the active skeletal muscle, the respiratory muscles and the myocardium. When exercise is performed for durations of longer than a minute or two and primarily ‘aerobic’ in nature, increases in skeletal muscle blood flow are critical to ensure the appropriate supply of O_2 to the active skeletal muscles and to remove the metabolic byproducts.

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During heavy exercise, i.e. an exercise intensity eliciting maximal oxygen uptake (VO_{2max}), which can be sustained at a constant intensity for 5–10 min, whole-body exercise capacity is, in general, limited by the maximal rate of oxidative ATP resynthesis, which depends on oxygen delivery. However, under certain circumstances, for example in hypoxia and hyperthermia, fatigue may be elicited by mechanisms originating in the central nervous system (CNS) or triggered by afferent feedback (Fitts 1994, Amann *et al*. 2009).

The hyperaemic response to exercise is initially elicited by local factors of mechanical and metabolic origin and likely adjusted depending of the degree of deoxygenation of the capillary blood, and modulated by neural mechanisms. Exercise-induced skeletal muscle hyperaemia is essentially due to the selective vasodilation of vascular units perfusing the active muscle fibres. For vasodilation to result in a significant elevation of skeletal muscle blood flow cardiac output (Q) has to increase at least to the same extent as skeletal muscle blood flow, otherwise blood pressure would fall, reducing the effectiveness of skeletal muscle vasodilation. Despite the effort made by several generations of physiologists over the last 150 years, many questions remain on the regulatory mechanisms that elicit and maintain skeletal muscle hyperaemia and how cardiac output and muscle hyperaemia are coupled during heavy exercise in humans.

Systemic and muscular oxygen delivery

Maximal systemic O_2 delivery is the product of maximal cardiac output (Q_{max}) and the arterial O_2 content (CaO_2) at peak exercise. Maximal cardiac output is determined by the stroke volume (SV) and heart rate (HR) at maximal or near-maximal exercise (Q = SV × HR), with SV playing a predominant role, inasmuch as maximal HR changes little and cannot be increased to compensate for a reduction in SV (Saltin *et al*. 1968). SV depends on the size and compliance of the heart, the preload, the afterload, myocardial contractility and the displacement of the atrioventricular (AV) plane from the base of the ventricles towards the apex in systole.

Athletic mammals have a greater heart mass when compared with non-athletic animals of similar body mass (Carew & Covell 1978, Gunn 1989). Athletic quadrupeds have almost two to threefold as much heart mass/body mass than humans (Carew & Covell 1978, Lorenz *et al*. 1999). Elite endurance human athletes have large hearts, with similarly enhanced left (35–38%) and right ventricular (RV; 37–48%) masses adjusted per body surface area and, hence, the LV/RV mass ratio (~3) is similar to that of controls (Scharhag *et al*. 2002, Perseghin *et al*. 2007). The increased heart size of the endurance athlete is due to the combination of genetic factors and the effect of training (Levine *et al*. 1991, Busjahn *et al*. 2009). That the size of the heart plays a critical role in determining maximal exercise capacity in humans is also supported by the fact that at near-maximal exercise levelling off of VO_2 with increasing exercise intensity is preceded by a levelling off of cardiac output (Mitchell *et al*. 1958, Calbet *et al*. 2007). Moreover, a number of studies using different imaging techniques have reported a correlation (r = 0.80–0.89) between VO_{2max} and left ventricular (LV) mass (Milliken *et al*. 1988, Scharhag *et al*. 2002).

To achieve and maintain a high SV when HR is close to maximal the heart must have a very high compliance and also must be able to contract and relax very fast (Levine *et al*. 1991). Both characteristics are enhanced in endurance elite athletes and in mammals with outstanding endurance capacities (Carew & Covell 1978, Levine *et al*. 1991, Gledhill *et al*. 1994, Perseghin *et al*. 2007), and endurance training in previously untrained humans improves LV diastolic function (Shapiro & Smith 1983, Levy *et al*. 1993). In contrast, systolic function is similar in highly trained and untrained humans, and does seem to contribute to the enlarged SV of the former (Blomqvist & Saltin 1983). Therefore, the main

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factors explaining the enlarged SV of trained endurance athletes are heart size and compliance and the mechanisms that help to fill first the right and left atrium very fast (Lundback 1986) and then their corresponding ventricular cavities, and to maintain preload at peak exercise, i.e. venous return and central blood volume (Blomqvist & Saltin 1983, Dawson *et al*. 2007) when HR is high.

In 1932, Hamilton & Rompf (1932) described a relative constancy of the total heart volume during the cardiac cycle. They concluded that through the displacement of the AV plane, the heart was able to pump blood but still maintain the same volume. This concept has been confirmed with modern techniques (Lundback 1986, Carlsson *et al*. 2004). Thus, the heart is working as a normal single water pump. The valve plane, relative to the ventricles, is moved back and forth by the papillary muscles in the blood stream, pushing the blood forwards. At a high HR and cardiac output, the momentum of the blood created by the descent of the AV plane facilitates a more rapid filling of the heart decreasing the requirement of outer volume change in the surrounding tissue, reducing the energy requirements of the pumping heart (Carlsson *et al*. 2004). The motion of the AV plane represents 60% of the total SV at rest (Carlsson *et al*. 2007). During exercise at 85–90% of the maximal HR the displacement of the AV plane increased from 15.6 to 17.6 in 12 females following 8 weeks of interval training (Slordahl *et al*. 2004). It remains to be determined to what extent can the displacement of the AV plane be a limiting factor for peak SV in humans.

In most circumstances VO_{2max} is determined by systemic O_2 transport (Saltin & Calbet 2006, Wagner 2006, Levine 2008). In 1924, Hill suggested that VO_{2max} is limited by Q_{max} (Hill *et al*. 1924) and the supportive experimental evidence was obtained during the last three decades (Andersen & Saltin 1985, Calbet *et al*. 2004). This concept has been challenged by Noakes, who postulated that VO_{2max} is limited by the 'Central Governor', presumably the CNS (Noakes 1997). In his theory Noakes defends that the CNS limits the recruitment of motor units at very high exercise intensities to prevent a 'disturbance of homeostasis' and avoid catastrophic damage to heart by a 'reflex mechanism' triggered by the heart itself (Noakes 1997, Noakes & St Clair Gibson 2004, Noakes *et al*. 2004). However, this theory cannot explain why some humans with ischaemic hearts are able to perform exercise until chest pain develops or why in some circumstances exercise can be performed until collapse. Although we do not know yet what limits Q_{max}, recent experiments have shown that Q_{max} does not seem to be limited by the maximal working capacity of the heart (Brink-Elfegoun *et al*. 2007, Lundby *et al*. 2008b).

Systemic O_2 delivery also depends on CaO_2. At peak exercise at sea level CaO_2 is a little lower than at rest, due to the rightward shift in the oxygen dissociation curve of the haemoglobin caused by acidosis and hyperthermia (Nielsen *et al*. 2002), combined with some impairment in pulmonary gas exchange due to ventilation/perfusion (VA/*Q*) mismatch and diffusion limitation for O_2 at high Q_{max} (Dempsey & Wagner 1999). Increasing blood haemoglobin concentration ([Hb]) by either autotransfusion (Ekblom *et al*. 1976) or treatment with erythropoietin (Ekblom & Berglund 1991, Lundby *et al*. 2008b) increases exercise capacity and VO_{2max}, without modification of Q_{max}, peak exercise SV or HR_{max}. Conversely, isovolemic haemodilution reduces VO_{2max} during whole-body exercise (Ekblom *et al*. 1976), and also VO_2 peak during exercise with a small muscle (Koskolou *et al*. 1997) without altering peak exercise *Q*, SV or HR. Additionally, every 10% increase in [Hb] translates into an ~7% increase in VO_{2max} (Calbet *et al*. 2006a).

During exercise in acute hypoxia systemic O_2 delivery is reduced and so is VO_{2max}. Up to an inspired O_2 (F_IO_2) of 12% the main mechanism explaining the reduction in systemic O_2 delivery with acute hypoxia is the reduction in CaO_2 whilst *Q*, SV and HR are not affected, although peak HR may be slightly reduced in moderate hypoxia (Lundby *et al*. 2001). At

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higher levels of hypoxia ($F_IO_2 < 0.12$) the reduction in systemic O_2 delivery is explained by the combination of a blunted Q_{max} (with a similar contribution of SV and HR) and the reduction in CaO_2 (Calbet *et al*. 2003a). For example, with an $F_IO_2 = 0.105$ (equivalent to an altitude of 5300 m above sea level) Q_{max} is reduced by 15% compared to sea level (Calbet *et al*. 2003a). Intriguingly, increasing arterial [Hb] enhances VO_{2max} at sea level and at simulated altitudes below 4000 m, but not above 4000 m (Robach *et al*. 2008). This phenomenon is due in part to an alteration in the distribution of blood flow (Robach *et al*. 2008), but has been also attributed to a limitation in pulmonary O_2 diffusing capacity with more severe hypoxia (Calbet & Boushel 2010). In chronic hypoxia, [Hb] increases and pulmonary gas exchange improves resulting in an elevation of CaO_2 to levels similar or higher than those observed at sea level prior to the altitude exposure (Calbet *et al*. 2003b). Nevertheless, maximal exercise systemic O_2 transport remains below the sea level values due to a reduction in Q_{max} (Pugh 1964, Calbet *et al*. 2003b). Despite the fact that with altitude acclimatization systemic O_2 transport is markedly improved, VO_{2max} only increases marginally compared with the value registered in acute hypoxia. This is explained by an alteration in the distribution of blood flow, such that a lower fraction of the cardiac output is directed to the exercising muscles in chronic hypoxia (Calbet *et al*. 2003b).

At maximal whole-body exercise the active skeletal muscle mass for a 175 cm tall man can be estimated to lie in between 16 and 20 kg. A peak exercise 5–6 L min^{-1} of blood flow is required to perfuse the CNS, the coronary vessels, the respiratory muscles and other tissues apart from the active muscles, leaving 14–15 L min^{-1} for the active muscles. An elite endurance athlete with a Q_{max} of 35 L min^{-1} will be able to perfuse his active muscles with 29–30 L min^{-1} of blood flow, i.e. about twice as much as the sedentary subject. Supposing a similar active muscle mass in both cases the relative perfusion of the skeletal muscle at peak exercise should lie in between 88 and 188 mL kg^{-1} of muscle mass. However, much higher levels of relative skeletal muscle perfusion have been reported during small muscle exercise in humans (Andersen & Saltin 1985).

It should also be pointed out that there are far fewer invasive measurements in both trained and untrained women on the maximal capacities of various elements of the oxygen transport system during exercise. What can clearly be said is that VO_{2max} expressed per kg of body weight is typically about 10% lower in females than in males with comparable training histories. The likely explanations for this include the higher levels of body fat in women and slightly lower haemoglobin and haematocrit levels. In highly trained subjects VO_{2max} expressed per kg of fat free mass is similar in both sexes, suggesting that when scaled for body size and adjusted for differences in body composition there are not fundamental differences in either cardiac performance of skeletal muscle vasodilator capacity in men and women (Joyner 1993). Cardiac structural and functional adaptations to training are similar in men and women (Petersen *et al*. 2006). However, it does appear that the tendency for at least some highly trained subjects to demonstrate arterial desaturation during heavy exercise is more common in women as a result of structural differences in the their lungs (Harms *et al*. 1998, McClaran *et al*. 1998).

What are the determinants of ‘local’ exercise capacity in humans?

Local or peripheral fatigue, defined either as a task failure or a reduction in force or power generation capacity, may be elicited by a number of factors, which act by reducing the rate of ATP re-synthesis and/or by interfering with the biochemical processes involved in muscle contraction and relaxation (Fitts 1994). During sprint-like or high-intensity all-out exercise muscle fatigue appears to be independent of O_2 delivery (Weyand *et al*. 1999, Calbet *et al*. 2003c), as well as during isometric contractions (Fulco *et al*. 1994). However, the maximal power attained during incremental exercise to exhaustion (W_{max}) either with a large or a

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small muscle mass is reduced when CaO_2 is reduced either by hypoxia (Fulco *et al*. 1996, Calbet *et al*. 2009), carbon monoxide breathing (Ekblom *et al*. 1975, Gonzalez-Alonso *et al*. 2001) or isovolemic haemodilution (Ekblom *et al*. 1976, Koskolou *et al*. 1997). A tentative conclusion that can be derived from these studies is that it seems that regardless of the size of the active muscle mass, W_{max} is reduced when CaO_2 is reduced irrespective of F_IO_2.

Before the 1980s it was believed that Q_{max} could sufficiently supply the active skeletal muscles with blood flow and maintain blood pressure even during maximal whole-body exercise (Mellander & Johansson 1968). This concept was based on the observation that peak muscle blood flow was about 50–60 mL (100 g)$^{-1}$ min^{-1} (Kjellmer 1964, Grimby *et al*. 1967), implying that with a cardiac output of 20 L min^{-1} there was enough blood flow to supply ~25 kg of active muscle mass, leaving 5 L min^{-1} to supply the rest of the body. However, these pioneer measurements were carried out with xenon or venous occlusion plethysmography and both techniques underestimate muscle blood flow (Saltin 2007). In 1985, Andersen and Saltin reported values of 250 mL (100 g tissue)$^{-1}$ min^{-1} for the quadriceps muscle during one leg knee extension exercise using the continuous infusion thermodilution technique to measure femoral vein outflow (Andersen & Saltin 1985) and Doppler to measure the arterial inflow (Rådegran *et al*. 1999). Peak muscle blood flow is even higher in elite cyclists with values of ~400 mL (100 g tissue)$^{-1}$ min^{-1} reported (Richardson *et al*. 1993). The combination of these studies indicates that humans have a peak hyperaemic response which is essentially similar to that previously reported in other mammals including athletic species with very large hearts (Parks & Manohar 1983, Armstrong & Laughlin 1985, Manohar 1986, Musch *et al*. 1987).

If this magnitude of peak quadriceps muscle perfusion could be reached by other skeletal muscles then the activation of just 10 kg of muscle mass, i.e. less than during maximal exercise on the cycle ergometer, would overwhelm the pumping capacity of even the human with the highest Q_{max} causing hypotension. Regional differences in the peak hyperaemic response to exercise may exist as muscles differ in their daily use and endurance-trained muscle may have 40–60% higher hyperaemic responses than untrained muscles (Andersen & Saltin 1985, Snell *et al*. 1987, Richardson *et al*. 1993). Nevertheless, peak arm blood flow responses to exercise are lower than observed for knee extension exercise, even in arm-trained subjects (Ahlborg & Jensen-Urstad 1991, Volianitis *et al*. 2003). However, by studying elite cross-country skiers who have highly trained arm and leg muscles it was definitively shown that as initially proposed by Saltin (1985) the combined vasodilatory capacity of the arm and leg muscles exceeds the pumping capacity of the heart (Calbet *et al*. 2004) (Fig. 1). The latter finding is consistent with the idea that muscle vasodilation has to be restrained to avoid hypotension during whole-body exercise in humans.

In general, during submaximal dynamic exercise, with either a small or large muscle mass, reductions in CaO_2 are compensated for by increases in blood flow to maintain O_2 delivery constant. Despite the fact that during maximal exercise with a small muscle mass only a fraction of Q_{max} is recruited, implying that there is substantial functional reserve, peak blood flow is not enhanced to account for the reduction in CaO_2 elicited by either lowering F_IO_2 or [Hb] (Roach *et al*. 1999). This could indicate that during small muscle mass exercise skeletal muscle blood flow is already maximal likely due to maximal vasodilation in the active regions, implying that muscle perfusion cannot be increased unless perfusion pressure is increased.

To determine if there is still some vasodilatory reserve at peak exercise in the active skeletal muscle, a vasodilator was infused intra-arterially when exercise-induced hyperaemia was maximal (Calbet *et al*. 2006b, Lundby *et al*. 2008a). During whole-body exercise (cycle ergometer exercise) at sea level, the infusion of maximal doses of ATP, i.e. the dose that

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elicits maximal vasodilation under resting conditions, increased leg vascular conductance by 17% (Calbet *et al*. 2006b). Mean arterial pressure (MAP) was not affected by the infusion of ATP into the femoral artery, due to a small (6%) but significant elevation of Q_{max}. About half of the increase in Q_{max} was directed to the ATP-infused leg which showed a trend (P = 0.08) for 0.8 L min^{-1} higher leg blood flow (LBF) (8% more than under control conditions). However, at the same time fractional O_2 extraction was reduced, indicating that the distribution of blood flow was altered by the vasodilator, and some flow went to less active muscle fibres or other vascular beds of the leg apart from the active muscle fibres. The same subjects were also studied after 8–12 days of residence at 4559 m above sea level, when their resting sympathetic nerve active should have been remarkably increased (Hansen & Sander 2003), and their resting MAP was elevated by ~20 mmHg. As expected, peak exercise Q was reduced by 19% and peak leg blood flow was 18% lower than at sea level. Thus, at maximal exercise in chronic hypoxia there was a functional reserve (about 5 L min^{-1}) to increase Q and LBF in response to the ATP infusion. Maximal exercise leg vascular conductance was increased, but not LBF because MAP was reduced with ATP. Moreover, as observed at sea level, ATP reduced O_2 extraction across the leg also indicating that ATP causes $V\dot{O}_2/Q$ mismatch. These two experiments clearly show that exercise-induced skeletal muscle hyperaemia cannot be increased without a concomitant elevation of cardiac output. This conclusion is further supported by experiments performed with a small muscle mass (one or two-legged knee extension) exercise, in which neither isovolemic anaemia (Koskolou *et al*. 1997), isovolemic anaemia combined with hypoxia (Roach *et al*. 1999) nor severe acute hypoxia (Calbet *et al*. 2009) elicited elevations in normoxic peak LBF.

In the only study where adenosine was infused at maximal doses intra-arterially during maximal knee extension exercise, adenosine was combined with hyperoxia (F_IO_2 = 1) and in the four subjects from whom maximal data were obtained peak exercise vascular conductance across the whole leg was not increased by adenosine (Barden *et al*. 2007). Although this study is in support with the concept of limited vasodilatory reserve at maximal exercise in humans, there is a limitation that precludes any definite conclusion from this study, as only the quadriceps muscle was recruited during the exercise but adenosine was infused into the common femoral artery, implying that some vasodilation may have occurred outside the working muscles.

Peak LBF and vascular conductance is increased with endurance (Roca *et al*. 1992, Mourtzakis *et al*. 2004) and high-intensity intermittent exercise training (Juel *et al*. 2004). Roca *et al*. (1992) reported a 26% higher peak LBF during semi-recumbent cycle ergometer exercise after 9 weeks of endurance training, but vascular conductance was not assessed. In another study, 5 weeks of knee extension exercise (1 h day^{-1} × 5 days week^{-1}) increased peak LBF and vascular conductance by 17% (Mourtzakis *et al*. 2004). A similar enhancement was reported by Juel *et al*. (2004) after 7–8 weeks of high-intensity intermittent training (fifteen 1 min bouts at approx. 150% of thigh maximal O_2 uptake per day, 3–5 times week^{-1}). The specific (mL kg^{-1} muscle mass) perfusion achieved after training in these studies (Juel *et al*. 2004, Mourtzakis *et al*. 2004) remains far below the high levels of skeletal muscle blood flow and vascular conductance reported in elite endurance athletes (Richardson *et al*. 1993).

Matching O_2 demand and supply during whole-body exercise

Saltin (1985) showed that the human skeletal muscle has a vasodilatory capacity that, if similar in all muscles, would require a Q_{max} two to threefold higher than actually reached to maintain MAP, it was postulated that some vasoconstriction must restrain vasodilation during whole-body exercise in humans. This concept also implies that during maximal

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whole-body exercise a competition is established between active skeletal muscles, respiratory muscles, myocardium and the CNS for a limited and ultimately insufficient amount of Q_{max}. Flow goes where the resistance is lower, but the critical questions are: how is the overall haemodynamic response to exercise integrated? How is the distribution of blood flow governed? How are perfusion priorities established? Consistent with these ideas were observations made in early 1960s that blood pressure falls during supine or head down tilt exercise in subjects who had undergone surgical sympathectomy for severe hypertension (Marshall *et al*. 1961a). Under these circumstances unchecked vasodilation in the active muscles likely contributed to the fall in blood pressure.

Another important clue was provided by Secher *et al*. (1977) who reported that superimposing intense arm exercise (oxygen uptake in the arms representing more than 40% of whole-body oxygen uptake) on leg exercise reduced leg blood flow and VO_2 without changes in MAP, indicating that leg blood flow was restrained by a neurogenic vasoconstricting mechanism. A similar restraint of LBF was also observed during whole-body exercise when the work of the respiratory muscles was increased (Harms *et al*. 1997, Dempsey *et al*. 2006). The same type of response, but less marked, was observed when leg cycling at 60% of VO_{2max} was superimposed on arm cranking at 80% of VO_{2max} (Volianitis & Secher 2002), causing a small reduction in arm blood flow. However, when the muscle mass recruited during the exercise was smaller, static and static-ischaemic arm exercise, causing a two to fourfold increase in muscle sympathetic nerve activity and a 15–32% increase in MAP, reduced leg vascular conductance without a net effect on LBF (Strange 1999), indicating a local autoregulatory effect in the contracting muscles when cardiac output is capable of meeting muscle blood flow demands.

More definitive evidence was obtained by studying a group of cross-country skiers in which Q_{max}, leg blood flow and arm blood flow were measured simultaneously, while skiing with different techniques (Calbet *et al*. 2004). Arm hyperaemia reached maximal levels when the skiers used the ‘double poling’ technique, in which both arms press on the poles simultaneously to propel the body. However, during maximal skiing with the diagonal technique, where arm and leg contribute to propulsion, the arm blood flow response was blunted, suggesting that during combined arm and leg exercise in the upright position the perfusing priority was given to the legs. Moreover, it was estimated that without the arm flow restriction MAP would have fallen to ~ 75 mmHg from the observed ~95 mmHg.

Several studies with patients provide evidence for the sympathetic nervous system as the main mechanism restraining muscle blood flow in the abdominal viscera and non-active skeletal muscles, and also in active skeletal muscle during heavy whole-body exercise (Lang *et al*. 1997, Dela *et al*. 2003). For example, MAP drops to values between 60 and 70 mmHg a minute or two after the onset of exercise in sympathectomized men performing exercise in both the supine position and with 15° head down tilt (Marshall *et al*. 1961b) (Fig. 2). Similarly, MAP is reduced during electrostimulation-induced exercise on the cycle ergometer in paraplegics who lack a functional sympathetic system (Dela *et al*. 2003). In patients with chronic heart failure sympathetic inhibition with clonidine results in greater vascular conductance and peak exercise blood flow in the exercising legs (Lang *et al*. 1997).

A similar response is observed in patients with idiopathic hyperhidrosis, which has been attributed to overactivity of the sympathetic fibres, in which sympathectomy increases peak forearm vascular conductance and exercise capacity during handgrip exercise (Kardos *et al*. 2000). Nevertheless, studies with patients should be interpreted with caution as adaptations other than that anticipated may have developed.

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Sympathetic vasoconstriction can be also blocked with ATP (Rosenmeier *et al*. 2004). However, ATP infusion into one femoral artery during maximal whole-body exercise in chronic hypoxia caused vasodilation without increasing leg blood flow, due to a reduction in perfusing pressure of ~20 mmHg to values that were similar to those observed at maximal exercise at sea level (Lundby *et al*. 2008a). Interestingly, in this experiment O_2 extraction was marginally increased in the contralateral leg (not ATP-infused leg) that is compatible with a reduction in leg blood flow in the contra-lateral exercising leg. Thus, it seems that there was a response to the reduction in MAP but this response was likely blunted in the ATP-infused leg while the other vascular beds were already subject to high levels of vasoconstriction.

This result together with the observation of a relatively low MAP during upright maximal cross-country skiing (Calbet *et al*. 2004) and during running uphill on the treadmill (Hermansen *et al*. 1970) indicates that a small reduction in MAP during whole-body exercise is tolerable.

As illustrated in Figure 3, LBF, leg vascular conductance and femoral venous oxygen saturation were all reduced in old compared with young subjects, during submaximal cycle ergometer exercise. These findings are consistent with the idea that there is greater sympathetic restraint of blood flow in the active muscles of the older subjects due to their more limited cardiac output and higher levels of sympathetic outflow. In agreement with this view Magnusson *et al*. (1997) showed that patients with moderate chronic heart failure can reach a peak skeletal muscle perfusion and a leg oxygen uptake comparable to that of healthy individuals when a sufficiently small muscle mass is activated. However, if the exercise involves a larger muscle mass, peak LBF, leg vascular conductance and VO_2 are markedly reduced, and these effects are accompanied by increased noradrenaline spillover (an indirect measure of sympathetic activation). Thus, in conditions with limited Q_{max}, sympathetic overactivity is even more necessary to limit exercise-induced skeletal muscle vasodilation to preserve minimal perfusion levels for the brain, heart and respiratory muscles.

Sympathetic activation is needed to maintain blood pressure while sympatholysis permits VO_2/Q matching

In the previous sections of this review, we have stressed that during whole-body exercise, VO_{2max} under most circumstances is largely dependent on factors associated with maximum oxygen delivery. In this context, a high cardiac output generally driven by a large SV is perhaps the ‘dominant’ determinant of VO_{2max}. We have also pointed out that during large muscle mass whole-body exercise the capacity of the contracting skeletal muscles to ‘demand’ blood flow via their impressive ability to vasodilate could potentially threaten blood pressure regulation in the context of a ‘limited’ cardiac output. In other words, if a sufficient mass of skeletal muscle were active, the vasodilator capacity of the contracting muscles could outstrip maximum cardiac output and blood pressure would fall. While this clearly happens in patients with autonomic failure, it does not happen in normal subjects (Marshall *et al*. 1961b, Schrage *et al*. 2004).

In this context, the reason it does not happen is that there is sympathetic ‘restraint’ of blood flow to contracting muscles. This restraint appears to occur *in vivo* even though there is evidence from isolated contracting skeletal muscles that sympathetic control of blood flow to contracting skeletal muscle can be abolished (functional sympatholysis).

In the early 1960s Remensnyder *et al*. (1962) used an isolated perfused hind limb preparation and showed that the rise in perfusion pressure, seen at a series of fixed flow

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rates, associated with sympathetic activation caused by carotid occlusion was lost during exercise. They reasoned that this could only have happened if the sympathetic nerves were unable to cause constriction in the hind limb. In later studies (Thomas *et al*. 1997, Thomas & Victor 1998) in isolated rat skeletal muscle, it was clearly demonstrated that nitric oxide (NO) released in association with contractions limited the ability of the sympathetic nerves to evoke vasoconstriction in active skeletal muscle. However, the role of NO in limiting the sympathetically mediated vasoconstriction in contracting human muscles is less clear, and some studies have suggested that it is and is not obligatory (Chavoshan *et al*. 2002, Dinenno & Joyner 2003).

What can be said about the sympathetic control of blood flow to contracting human muscles is that ‘sympatholysis’ is not absolute and that there is evidence from a variety of models showing at least some sympathetic control of blood flow to contracting skeletal muscles (Marshall *et al*. 1961b, Tschakovsky *et al*. 2002, Calbet *et al*. 2004). There is also evidence of ongoing sympathetic control of blood flow in contracting muscles in conscious dogs performing voluntary treadmill exercise (Ruble *et al*. 2002). In both humans and dogs, the substance or substances that limit the ability of the sympathetic nerves to cause vasoconstriction is unclear. Recently ATP release (perhaps from deoxygenated red cells) has emerged as a possible candidate (Rosenmeier *et al*. 2004, 2008, Kirby *et al*. 2008). This substance is attractive for a number of reasons but infusions of ATP or related compounds in either the contracting forearm or contracting leg can essentially eliminate sympathetic control in vasodilated limbs in a more dramatic way than is seen during exercise.

The retention of at least some sympathetic control of blood flow to contracting muscles has important implications for whole-body exercise and the regulation of blood pressure in whole-body exercise. Under these circumstances, 70–80% (or perhaps more) of cardiac output is directed towards the active muscles, and even small changes in blood flow to the contracting muscles will have a marked impact on MAP if the circulatory conditions remain unchanged in the other vascular beds. For example, if 80% of cardiac output is directed towards contracting skeletal muscles, a 20% reduction in flow to those tissues will cause a 16% increase in arterial pressure. Fortunately, this can be accomplished in most cases without limiting oxygen consumption by the contracting skeletal muscles. Along these lines, the very high muscle blood flow values observed during one-leg kicking in humans (and other forms of small muscle mass exercise) are associated with limited oxygen extraction by the active muscles (Andersen & Saltin 1985). In other words, deep venous saturation is relatively high (30–40%) in most of these models and this is in contrast to the very low deep venous oxygen saturations seen in the femoral vein during activities like heavy two-leg cycling (Proctor *et al*. 1998). This means that reductions in flow during small muscle mass exercise can be accommodated and oxygen consumption protected by increased oxygen extraction in the active muscles.

How might this increased oxygen extraction occur in a way that matches somewhat limited blood flow with the demand for oxygen? One clue comes from a study conducted by Van Teeffelen & Segal (2003) in the microcirculation of hamster skeletal muscles. As illustrated in Figure 4, these investigators showed that sympathetic control of blood flow to the smaller elements of the microcirculation was lost in contracting skeletal muscle, but retained in the larger microvessels. This finding is consistent with differing distributions of postjunctional alpha-1 and alpha-2 adrenergic receptors on the microvasculature and their differing sensitivities to metabolites and pH (there are more postjunctional alpha-2 receptors in the smallest microvessels, and their ability to constrict is limited by a number of metabolites and a fall in pH). When the findings of Van Teeffelen and Segal are extrapolated to the control of blood flow in the whole muscle it means that an increase in sympathetic outflow would constrict blood vessels that distribute flow to various regions of the contracting muscle but

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that loss of sympathetic control in the smallest vessels would tend to direct flow to the most metabolically stressed elements of the active muscle (Joyner & Thomas 2003).

This concept has important implications for whole-body exercise because it permits the minimal level of flow to support a given level of contraction to be achieved under many circumstances. In other words, the retained ability to cause vasoconstriction in the larger blood vessels would limit total flow to a muscle, and the loss of sympathetic control in the smallest vessels would direct the limited flow to the areas of the muscle where it is most needed. Together this physiological compromise would permit oxygen extraction to be maximized in a given muscle, the largest fraction of total muscle mass to receive adequate or nearly adequate blood flow, and arterial blood pressure would be regulated at the same time. Along these lines, when vasodilators are infused into contracting leg muscles oxygen consumption in the exercising leg is not augmented in a way that suggests the vasodilation is limited either to non-active or less active areas of the muscle (Calbet *et al*. 2006b). These findings are also consistent with the idea that sympathetic control is lost in the smallest vessels and that they are in fact maximally dilated.

In summary, sympathetic control of blood flow to contracting muscles is critical for the regulation of arterial pressure in humans. This restraint of flow is especially evident during whole-body exercise like cross-country skiing or in older humans who have age-related reductions in maximum cardiac output (Proctor *et al*. 1998, Calbet *et al*. 2004). The mechanisms responsible for generating and targeting the sympathetic outflow required to ‘manage’ this competition between systemic cardiac output and local vasodilation are unclear and while there is some evidence that baroreflexes and baroreflex resetting play an important role in this phenomenon, there are still a number of questions about this topic (Ogoh *et al*. 2003, Joyner 2006). Additionally, the substances released by the active muscles, which limit the ability of the sympathetic nerves to cause vasoconstriction in the active muscles, are also incompletely understood with ATP recently emerging as an important candidate substance that could explain most of this phenomenon. More importantly, observations in the microcirculation are now consistent with observations in the macrocirculation and provide a unifying framework (Fig. 5) for both systemic blood pressure regulation and blood flow ‘management’ to skeletal muscle during heavy exercise in humans.

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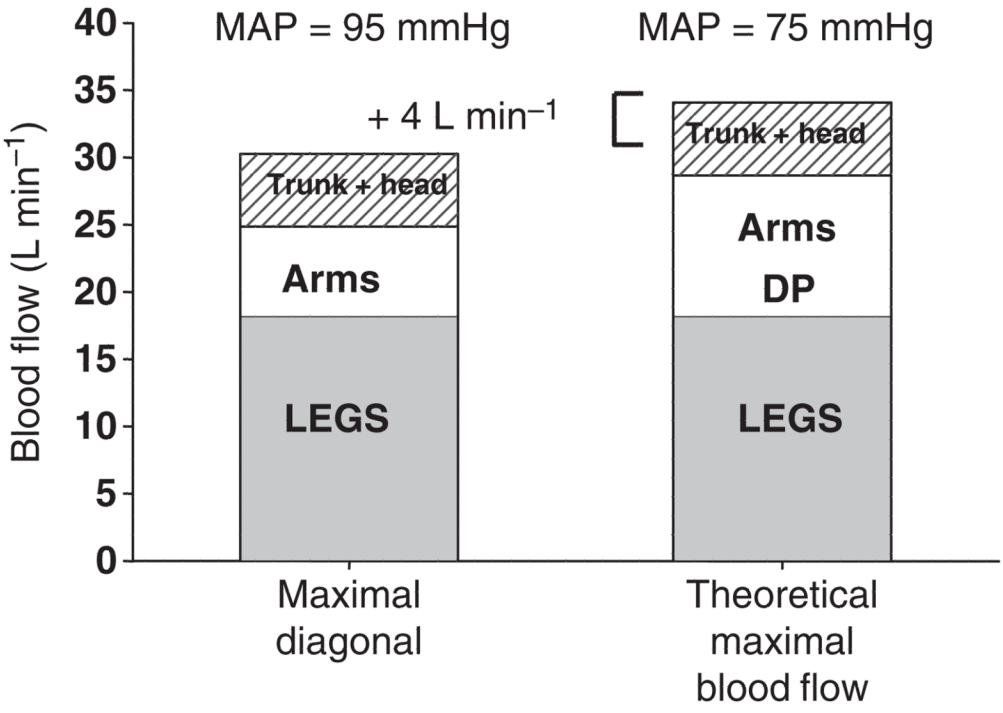

Figure 1.

The combined vasodilatory capacity of the arm and leg muscles exceeds the pumping capacity of the heart (Calbet *et al*. 2004). Cross-country skiers were studied during sub-maximal (76% VO_{2max}) skiing while using arm and legs (diagonal technique), only arm (double poling technique) and leg skiing (like skating). They were also studied during maximal exercise with the diagonal technique. Trunk and head perfusion at maximal diagonal was calculated by subtracting peak leg and arm blood flows from peak cardiac output. The maximal theoretical cardiac output was calculated by adding the maximal values observed for leg blood flow (during maximal diagonal), the peak arm blood flow (observed during double poling) and the 5 L min^{-1} of blood flow necessary to perfuse the head and trunk. The latter gave 4 L min^{-1} more cardiac output than actually measured, implying that in humans with well trained arm and leg muscles the combined peak perfusion of the head trunk and arm muscles exceeds the pumping capacity of the heart. This also implies that during maximal upright arm and leg combined exercise muscle vasodilation must be restrained to avoid hypotension (Calbet *et al*. 2004).

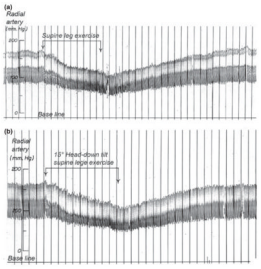

Figure 2.
Original record of arterial pressure during supine and head down tilt leg exercise in a 44-year-old male who had undergone thoracolumbar sympathectomy for the treatment of severe hypertension. The patient had normal autonomic innervation of the heart and could increase his heart rate and cardiac output. Thus, the fall in blood pressure during exercise seen in this figure is some of the first evidence that the sympathetic nerves must restrain blood flow to active muscles to regulate arterial pressure during exercise. Note that even the head down position used to maximize cardiac filling does not prevent the fall in arterial pressure during exercise. Figure from Marshall *et al*. (1961b).

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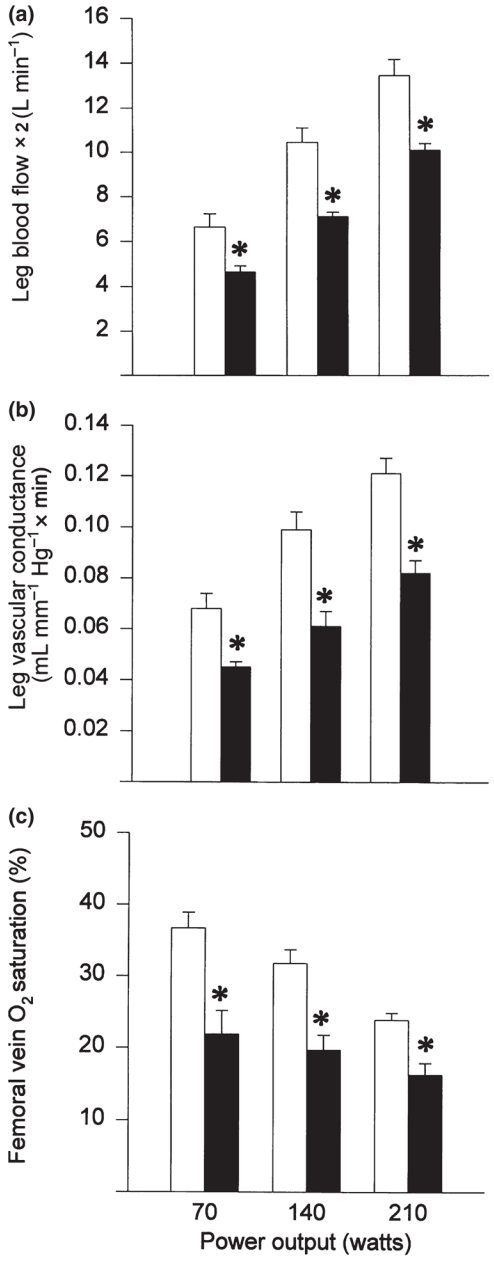

Figure 3.

Estimates of two leg blood flow made using thermodilution in trained younger (open bars) and older (filled bars) subjects during cycle exercise. Leg blood flow, vascular conductance and femoral venous oxygen saturation were all reduced in the older subjects. These findings are consistent with the idea that there is greater sympathetic restraint of blood flow in the active muscles of the older subjects due to their more limited cardiac output and higher levels of sympathetic outflow. The reduced venous oxygen saturation in the older subjects indicates that oxygen consumption is maintained by greater extraction. These data are also consistent with emerging ideas about sympathetic regulation of arterial blood pressure during exercise and physiological ‘strategies’ that facilitate high levels of oxygen uptake even when total blood flow is limited. Figure from Proctor *et al*. (2003). *$P < 0.05$ compared to young subjects.

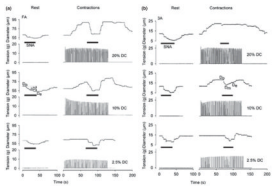

Figure 4.
Individual records of the responses of a feed artery (FA panel a, left) and a 3A arteriole (panel b, right) to sympathetic stimulation at rest and during contractions caused by three levels of direct current stimulation in hamster retractor muscle. In the feed artery sympathetic stimulation (SNA) caused a reduction in vessel diameter at rest and during all levels of contraction showing that contraction did not inhibit sympathetic vasoconstriction. In the 3A arteriole the ability of sympathetic stimulation to reduce vessel diameter was lost during the highest level of contraction. When concepts arising from this paper are applied to whole-body exercise in humans, they suggest that continued sympathetic control of larger arteries during exercise might regulate or restrain total muscle blood flow. However, loss of sympathetic control in the smaller vessels would optimize the distribution of flow within the active muscles. Such a mechanism would also direct the limited flow to the most metabolically active areas in the contracting muscles and likely enhance oxygen extraction. Figure from Van Teeffelen & Segal (2003).

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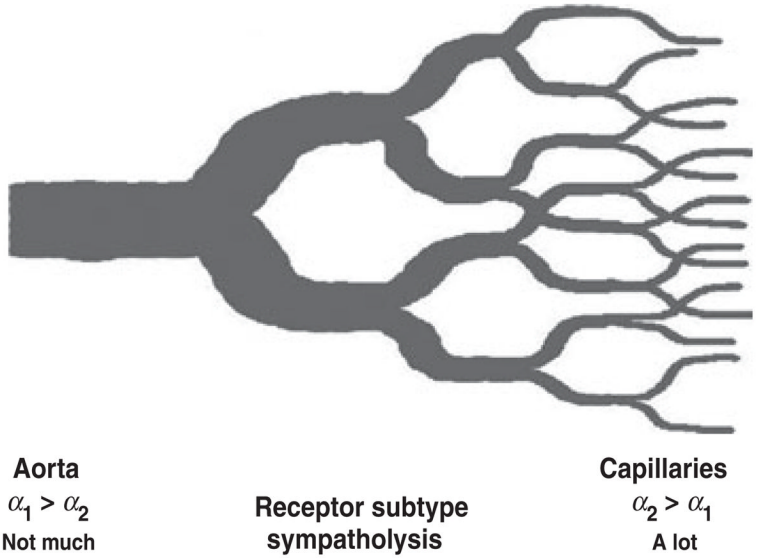

Figure 5.

Ideas about how blood flow and metabolism are matched. There is a progressive increase in sympatholysis from conducting blood vessels to the capillaries in skeletal muscle. This tends to eliminate sympathetic restraint of blood flow to the most active areas within a contracting muscle but permits total flow to that muscle to be regulated upstream. Such a scheme would explain the almost total extraction of O_2 across active skeletal muscle vascular beds during heavy large muscle mass exercise in humans. It would also permit relatively more total muscle to be perfused in the context of the 'limited' cardiac output seen in humans. Data from animal models suggest that differences in alpha-adrenergic receptor subtype distribution from large to small blood vessels might contribute to this phenomenon, but this idea is unproved in humans.