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Cardiovascular control
during whole body exercise

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2. Volianitis S, Krustrup P, Dawson E, and Secher NH (2003). Arm blood flow and oxygenation on the transition from arm to combined arm and leg exercise in humans. *J Physiol* 547: 641-648
3. Volianitis S, Yoshiga CC, Nissen P, and Secher NH (2004). Effect of fitness on arm vascular and metabolic responses to upper body exercise. *Am J Physiol* 286: H1736-H1741
4. Volianitis S, Yoshiga CC, Vogelsang T, Secher NH (2004). Arterial blood pressure and carotid baroreflex function during arm and combined arm and leg exercise in humans. *Acta Physiol Scand* 181: 289-295.
5. Vogelsang TW, Yoshiga CC, Højgaard M, Kjaer A, Warberg J, Secher NH, Volianitis S (2006). The plasma atrial natriuretic peptide response to arm and leg exercise in humans: effect of posture. *Exp Physiol* 91: 765-771.
6. Volianitis S, Fabricius-Bjerre A, Overgaard A, Strømstad M, Bjarrum M, Carlson C, Petersen NT, Rasmussen P, Secher NH, and Nielsen HB (2008). The cerebral metabolic ratio is not affected by oxygen availability during maximal exercise in humans. *J Physiol* 586: 107-112
7. Volianitis S, Rasmussen P, Seifert T, Nielsen HB, and Secher NH (2011). Plasma pH does not influence the cerebral metabolic ratio during maximal whole body exercise. *J Physiol* 589: 423-429.

Contents

Preface

The work presented in this dissertation was carried out at the The Copenhagen Muscle Research Center, Department of Anaesthesiology, Rigshospitalet, University of Copenhagen, between 2002 and 2011.

I would like to thank all co-authors and those responsible for generating a positive research environment within the institutions of my employment and where the studies took place. Special thanks go to Niels H. Secher not only for valuable collaboration but for also for his support and very insightful critical comments in all stages of this thesis. Special thanks also go to Waltraut Lissau for her unconditional support in all aspects of life associated with producing a thesis.

The papers which this dissertation is based on have not been submitted previously for an academic degree.

1. **Introduction**

The recruitment of capillaries in active muscles together with a model for oxygen diffusion from the capillary to the tissue were first published in the Journal of Physiology (98, 99, 100) by August Krogh and were the basis on which he was awarded the 1920 Nobel Prize in Physiology or Medicine. These findings and evaluations set the framework for determination of muscle blood flow during exercise. Based on ideas originated by DeJager (36), Krogh (97) also presented a circulation model that describes the important role of down-regulated splanchnic blood flow during exercise for the maintenance of blood pressure. Krogh's circulation model was verified by the observation that occlusion of the dog's aorta above the superior mesenteric artery, and thereby redirecting blood volume from the capacious splanchnic region to the heart, increases cardiac output, whereas cardiac output is reduced when the occlusion is below that level (12). However, in supine humans (69), as probably in most animals (18), cardiac output is not limited by preload to the heart and may be sufficient to satisfy peripheral circulation needs, and hence redistribution of cardiac output during exercise may not be required, as shown in dogs (73).

Yet, the situation is much different in upright humans where the central blood volume is reduced (e.g., 111, 112) and accordingly sympathetic activity elevated (155). Thus, the ability to constrict high compliant vascular regions to support cardiac end-diastolic volume and consequently cardiac output is important not only for upright posture but also during exercise as demonstrated with the reduction of splanchnic (166) and kidney blood flow (63). That is the case although during exercise vasoconstriction is less relevant for the superior mesenteric artery flow (144, 42). Accordingly, the elevated cardiac output during exercise is supported by increased central blood volume (64), despite enlargement of leg (143) and cutaneous blood volume with increasing body temperature (170). These observations lead to the understanding that the blood volume available to the heart depends on the fraction of cardiac output directed to noncompliant vs. compliant regions, i.e., working muscles vs. viscera and the skin (138, 30).

The reduction in abdominal blood flow during exercise is established by an enormous increase in sympathetic vasomotor outflow, as indicated by the inverse relationship between splanchic blood flow and heart rate (172, 25) and thereby, at least indirectly, indicates sympathetic control of splanchnic blood volume. The identification of norepinephrine as the sympathetic neurotransmitter by von Euler (45), the ability to record muscle and skin sympathetic nerve activity in humans (210, 209), and perfection of the norepinephrine spillover technique by Esler et al. (44), provided insight into the activity of the sympathetic nervous system and, thus, allowed for appreciation of the sympathetic system's contribution to cardiovascular control (24).

Sympathetic activation during exercise is mediated primarily by a reflex mechanism ("the exercise pressor reflex") that arises from stimulation of both metabolically and mechanically (22) sensitive thinly myelinated and unmyelinated nerve endings within contracting skeletal muscles (89), possibly as a result of muscle ischemia (5), and the combination of increased ATP, protons, prostaglandins (119) and may be lactate (104). Also, during intense exercise the motor-neural drive elicits parallel activation of sympathetic pathways, named "central command" (118). Furthermore, the reduced central blood volume associated with upright posture enhances sympathetic activity (230), while the muscle pump during upright exercise and supine posture increases the central blood volume and reduces sympathetic activity (155). Such modulation of sympathetic vasomotor activity indicates a role for the cardiopulmonary baroreceptors in resetting the arterial baroreflex during exercise (224, 46). Yet, the sympathetic system cannot explain, or would be considered to hinder the increase in blood flow to active muscles, but their flow is secured by metabolite-induced attenuation of sympathetic vasoconstriction, named "functional sympatholysis" (156, 157, 66) and yet muscle oxygenation is not maintained during exercise (81), as confirmed in studies using near infrared spectroscopy (e.g. 23).

It is recognised that functional sympatholysis is promoting vasodilation in active muscles and thus is critical for establishing the metabolically required blood flow, nevertheless interaction between muscle blood flow and sympathetic vasoconstriction introduces a seemingly paradox: restriction of blood flow to active muscles during whole body exercise to maintain arterial pressure could be overridden by their demand for flow. This apparent paradox may reflect that sympathetically mediated restriction of blood flow is most effective in feed arteries and primary arterioles, whereas vasodilation prevails downstream in distal arterioles (206). Feed arteries are external to the muscle and therefore not exposed to vasoactive metabolites that mediate functional sympatholysis within the active muscles (213). Thus, at the level of the feed arteries sympathetic vasoconstriction could limit muscle blood flow and thereby support arterial pressure.

Yet, it has remained controversial whether during whole body exercise the increase in cardiac output is large enough to support skeletal muscle flow. Cardiovascular regulation during whole body exercise has been addressed by Rowell in a classical review (170), followed up by two famous textbooks (165, 164), Clausen (26) and recently by Laughlin et al. (103). The present review provides four lines of evidence for a flow limitation to skeletal muscles during whole body exercise. Most studies on the role of cardiac output for muscle blood flow during exercise are concerned with leg blood flow (175, 160), while this review adds the implication of cardiac output capacity for establishing arm blood flow. Furthermore, it is considered whether cardiac output influences, besides skin blood flow (30), cerebral blood flow and metabolism during whole-body exercise (188). It is argued that during exercise regional blood flow, including perfusion of active muscles, is subordinate to the control of blood pressure.

2. Skeletal muscle blood flow

The first line of evidence for a flow limitation to working skeletal muscles during whole body exercise comes from the measurement of muscle blood flow. Early use of plethysmography

reported calf blood flow during rhythmic plantar flexion up to ~30 ml/min/100 g (11). However, it was recognised that flow was probably hindered by the intensity of the muscular contractions that eliminate flow when the contraction intensity exceeds approximately 30% of maximal voluntary strength (15, 54). Thus, the immediate post-exercise value of ~80 ml/min/100 g might be more representative for calf blood flow during exercise, taking post-exercise hyperaemia as an index of flow during the relaxation phase between muscle contractions (11). Similarly, ~40 ml/min/100 g calf blood flow has been reported after running (14).

A specific measure of muscle blood flow during exercise was made possible with the [133]Xenon clearance method (102) confirming a value of ~70 ml/min/100 g, although larger values can be measured if the collimator is placed "looking away" from the direction of blood flow (189), thus minimising the absorption of [133]Xenon by intramuscular fat that slows its clearance. Considering a muscle mass of ~30 kg in males, the [133]Xenon-measured muscle blood flow demand, even when "all" muscles are engaged in exercise, would be ~21 liters/min and that is within the cardiac output capacity of both sedentary subjects (~22 liters/min; Ref. 9) and, especially athletes (~42 liters/min; Ref. 40).

Accordingly, as originally demonstrated by Nicolai and Zunzt (123) using X-ray evaluation of the dimensions of the heart during treadmill walking, exercise enhances the central blood volume and, as illustrated later during electrically evoked (37) or arm exercise (205) in spinal cord injured subjects, a reduction in abdominal blood volume compensates for the increase in muscle blood volume and skin blood flow required for thermoregulation (28). These observations are in support of the position that muscles have "unlimited" access to blood even during maximal whole body exercise (114).

A different view, however, came about when thermodilution (7) and ultrasound (147) blood flow methods were applied to evaluate leg flow during one-legged knee-extensor exercise.

Assuming that the measured blood flow of, e.g. 5.7 liters/min was reflecting the drainage of, or flow to, the quadriceps muscle during one-legged knee extensor exercise, with occlusion of flow to the lower leg, and by using an anthropometric estimate of the active muscle mass, a remarkable muscle perfusion of ~250 ml/min/100 g was estimated. Furthermore, even larger muscle perfusion has been determined during hypoxic exercise (~310 ml/min/100 g, Ref. 169) and in highly trained cyclists (~385 ml/min/100 g, Ref. 159).

Yet, methodological considerations regarding the magnitude of the muscle perfusion values using thermodilution during the one-legged knee extensor model need to be addressed. First, when evaluating femoral venous flow, the proximity of the artery and the vein, combined with the high diffusion coefficient of heat in the tissue may "contaminate" the thermodilution estimate of flow by prohibiting temperature equilibration within the vein and thus overestimate the flow rate (189). Furthermore, it should be considered that these studies have not addressed muscle blood flow per se but leg blood flow during exercise. The determination of flow includes also inactive muscle blood flow, eventual changes in bone blood flow and, probably more importantly, skin blood flow during exercise as body temperature increases to, e.g. 38° within a few minutes of exercise, depending on initial temperatures and the rate of heat production or exercise intensity (174, 60). Even though the estimated ~300-400 ml/min thigh skin blood flow during heat stress (178) would overestimate femoral venous flow as an indication of muscle blood flow, most likely it would not be significant since the accuracy of the thermodilution estimate is ~10%, and hence, skin blood flow would be less than the detection threshold when the leg blood flow is > 4 liters/min (178).

Another concern for the estimate of muscle perfusion is the determination of the engaged muscle volume. With the use of imaging techniques, such as magnetic resonance and computed tomography, combined with electrical muscle stimulation, it was established that during maximal knee extension exercise the quadriceps muscle is the sole contributor to the work produced (93) as

the quadriceps muscle is gradually fully recruited (154). In fact, it seems that the anthropometric muscle mass evaluation overestimates the engaged muscle volume, compared to evaluations by computed tomography, suggesting that peak muscle perfusion estimated with the use of anthropometric muscle mass evaluation may be up to ~30% larger (146).

Accepting these limitations, the magnitude of the thermodilution measurements of femoral venous blood flow has been verified by ultrasound Doppler of the femoral artery flow (147). Furthermore, these femoral venous flows are in agreement with values obtained with tracer injection such as both continuous (81) and bolus injection (143) of indocyanine green dye and with bolus injection of radio-labelled albumin (181, 95). Also, these high perfusion values are in line with reports from animal exercise models. When assessed by microspheres in the rat (8), dog (122), and horse (142), blood flow to active skeletal muscle can reach almost 400 ml/min/100 g.

Thus, if the leg muscle blood flow values during exercise are representative of all muscles in the body, there is an obvious conflict between the cardiac output that can be established (at the most ~42 liters/min, Ref. 40) and the capacity for blood flow of the muscles during maximal whole body exercise, i.e. a demand of more than 100 liters/min, expressed by Rowell's metaphor (171) when he compared the muscles to a "sleeping giant". Consequently, even if maximal blood flow capacity varies within different muscle groups, a "competition" for a share of cardiac output develops during whole body exercise, and thus the cardiac output "pie" needs to be carefully "sliced" for all the active muscles to be adequately perfused (182).

3. Competition for blood flow amongst different vascular beds during exercise

The second line of evidence for flow limitation to skeletal muscles during exercise comes by considering whether exercise with several muscle groups affects blood flow to each of these muscle groups compared to when they are working in isolation. This question has been addressed by addition of handgrip exercise on plantar flexion exercise demonstrating that "competition" for flow

between these two muscle groups attenuates the post-exercise hyperaemic response (84). Also, calf blood flow is reduced when occlusion of the active forearm increases sympathetic activity to the calf (173). However, calf blood flow is reduced only when the intensity of the added handgrip exercise exceeds about 50% of maximum voluntary contraction (86), or when exercise is performed to exhaustion (85). Similar blood flow reduction is observed when elbow-flexion exercise is added to low intensity plantar flexion exercise (84). The flow reduction seems to depend on the relative intensity of the working muscles rather than on the specific muscles involved in exercise. Also, the duration of the attenuated vascular conductance after exercise suggests that the responsible mechanism is related to a metabo-receptor mediated sympathetic activation and, therefore vasoconstriction, rather than either to central neural drive towards the muscle, or an effect of mechano-receptors (84). and points to the metabolic component of the exercise pressor reflex as the key cardiovascular regulator during exercise with several muscle groups. It seems that the addition of high-intensity fatiguing exercise of even a small muscle mass induces vasoconstriction in active small muscles.

3.1. Respiratory muscles

The consideration that the exercise pressor reflex dictates regulation of muscle blood flow during exercise has also been evaluated during whole body exercise including flow regulation to the respiratory muscles. During exercise ventilation increases exponentially with workload and the respiratory muscles need to work intensively to establish values that may exceed 260 liters/min (79, 115). Thus, considering the remarkable activation of the respiratory muscles during exercise, the role of the respiratory muscles for such "competition" for flow among different muscle groups has been of interest. Even though the metabolic requirements of the respiratory muscles are assumed to increase with ventilation, the mechanical work performed by these muscles during exercise is

probably underestimated since displacement of the heavy abdominal content and ineffective forces due to thoracic distortion are not included in the estimate (139).

The intensity of sympathetic activation elicited from fatiguing respiratory muscles (199) can reduce limb blood flow at rest (192) and implies that sympathetic activity may reduce blood flow even in large muscles during maximal exercise and, thereby, have detrimental effects on performance. A ~10% reduction of leg blood flow during cycling, when the work of the respiratory muscles increases, supports that breathing is prioritised over locomotion (67, 68). Such observations may contribute to the performance improvement that follows inspiratory muscle training (Fig. 1; 219, 59) that reduces fatigue of these muscles and therefore, at least presumably also sympathetic activation.

The reverse question has also been addressed, i.e. whether exercise affects respiratory muscle blood flow. During progressive isocapnic ventilation, intercoastal muscle blood flow increased from ~20 ml/min/100 g (as determined by indocyanine ("cardiac") green and near infrared spectroscopy) during quite breathing to ~70 ml/min/100 g at a ventilation equal to that observed during maximal exercise (215). These muscle flow values seem low, probably reflecting that evaluation by near infrared spectroscopy is influenced by skin blood flow (e.g., Ref. 198). Nevertheless, when that ventilation was established during exercise, the intercoastal muscle blood flow increased to only 80% of the maximum value observed during isocapnic ventilation, and it declined further to ~25 ml/min/100 g during maximal exercise (215). Yet, as suggested by animal studies, diaphragmatic blood flow is more resistant to sympathetic vasoconstriction than other skeletal muscles (1). If that finding applies also to humans, and considering that the different responsiveness to sympathetic stimuli between intercostal muscles and the diaphragm may be explained by a hierarchy amongst the respiratory muscles, it could be that during whole body exercise the enormous ventilation required for CO_2 elimination is prioritised over the blood flow demands of locomotor muscles.

4. Cardiac Output

The potentially limiting role of cardiac output for peripheral circulation has been evaluated in heart failure patients during one- and two-legged dynamic knee extensor exercise (106). When only one leg is engaged in dynamic work, patients with moderate CHF achieve an equally high peak muscle perfusion as healthy age-matched controls, while when both legs are engaged a lower peak muscle perfusion is established. Similarly, when in healthy subjects, the ability to increase cardiac output is constrained by administration of a β_1-adrenergic blocker (metropolol), leg blood flow is attenuated during exercise and attributed to sympathetic activation as indicated by increased norepinephrine "spillover" from the leg (143).

Thus, the third line of evidence for the limitation of cardiac output to satisfy active muscle blood flow demand is represented by evaluation of regional blood flow during exercise, where a discrepancy between flow to a muscle group working exclusively and when additional muscles are engaged exists. When either arm or leg blood flow is determined during combined arm and leg exercise, blood flow to the arms or the legs is lower than when these limbs are working exclusively, provided that during the combined exercise the additional workload represents a substantial part of the total work performed (Fig. 3, Ref. 181).

Although several subsequent studies failed to reproduce these findings (179, 161, 158, 10, 203), when the results from these studies are summarised, an ∼10% reduction is revealed (221, 218), or when the blood flow reduction is large enough to reach statistical significance with a small sample size, a 20-30% reduction is reported (22). Similarly, during ergometer cycling leg blood flow is attenuated compared to the value achieved during one-legged knee extension (121), illustrating the restrain placed on the peripheral circulation when increased active muscle mass is competing for the available cardiac output. Furthermore, the competition for flow between different vascular beds, both between the two legs (95) and upper and lower body (223, Fig. 5A) is manifested even

following endurance training. This observation suggests that both the enhanced cardiac output and central and local structural changes that accompany endurance training, including cardiac hypertrophy (e.g., 34, 116) and number of capillaries in the muscles (e.g.,72, 94), facilitate peak muscle perfusion, nevertheless, cannot satisfy the peripheral blood flow demands during maximal whole body exercise.

Yet, muscle blood flow depends not only on metabolism and thereby vasodilation in the vessels feeding the muscle but also on mechanical factors such as the duration of contraction relative to relaxation (duty cycle) and the effective pressure head, i.e. the perfusion pressure (50). Thus, by virtue of the height difference between arms and legs in an upright posture, arm blood flow is expected to be smaller than leg blood flow when related to the estimated muscle mass.

Arm blood flow is influenced both by the lower perfusion pressure that the arms are subjected to when they work together with the legs (181, 224) and possibly sympathetically mediated vasoconstriction, as indicated by increased norepinephrine "spillover" over the arms when leg exercise is added (Fig. 2; 221). The resultant lower arm blood flow is thus provoking a larger arterial to venous oxygen difference to meet the oxygen demands of the working arms (Fig. 4, Refs. 181, 221, 218, 223). Furthermore, when during running the legs are swung back and forth, leg blood flow is promoted (193) while a similar "gravitational swing" may not be established for the arms, suggesting that perfusion pressure, and thus limb blood flow depends not only on body position but also on the angular velocities of the specific movement.

Accordingly during arm cranking, arm blood flow does not increase to a comparable level as leg flow at an equal power (3, 4) indicating that the arms are not as perfused as the legs (21). When arm blood flow during maximal exercise is related to the active muscle mass, a perfusion of ~140 ml/min/100 g in non-arm trained subjects and ~185 ml/min/100 g in rowers is revealed (Fig. 5, Ref. 223) when the engaged muscle mass is evaluated by X-ray Absorptiometry (DXA). Even though

computerised tomography and magnetic resonance imaging are standards for measuring skeletal muscle mass, the availability and the minimal exposure to radiation makes DXA an attractive alternative (226). The DXA approach provides skeletal muscle estimates that agree closely with measurements by computerised tomography, although DXA tends to overestimate total body skeletal muscle by ~5% (226), and thus peak arm perfusion may be ~5% larger. However, even if these arm perfusion values (about 160 ml/min/100 g) are corrected for the DXA overestimation of muscle mass, they are well below the maximal leg blood flow reported (159).

Since blood flow for a given oxygen uptake is higher during contraction in a muscle comprised predominantly with slow twitch (ST) fibres (soleus) compared to a muscle with primarily fast twitch (FT) fibres (white gastrocnemius) in anaesthetized rats (113, 48), it could be considered that the differences in blood flow capacity between arms and legs may be due to different fibre-type composition between arms and legs. However, this explanation is unlikely as there is on average 50/50% fiber type distribution in all human muscles, with the triceps having little more FT fibres and the soleus little more ST fibres (41).

Yet, if the arm-derived muscle blood flow values are applied to a hypothetical total body muscle mass of ~30 kg (78), the cardiac output capacity (regardless of training status) would still be surpassed during whole body dynamic exercise. Taken together, the view is that muscle blood flow represents a balance between metabolically-mediated vasodilation and sympathetically-induced vasoconstriction. While engaging only a small muscle mass sympatholysis secures a large muscle blood flow but with co-activation of multiple muscle groups, or with a restrain on cardiac output (f.x., by lower body negative pressure, Ref. 201), there is insufficient sympatholysis on the exercising vasculature and, thus, muscle blood flow is limited by the ensuing vasoconstriction.

4.1. Skin blood flow

Limited cardiac output may also affect skin blood flow during exercise. With skin blood flow that can reach 7-8 liters/min, or about 300 to 400 ml/min/100 g during passive heating (168), the flow capacity of the cutaneous circulation is comparable to that of skeletal muscles. Thus, it has been considered that during exercise in hyperthermia the elevated skin blood flow, besides the implication for left ventricular pressure and end-diastolic volume, according to Krogh's model when a large fraction of cardiac output is distributed to a compliant region like skin, can reduce blood flow to the active muscles in favour of the elevated skin circulation to serve thermoregulatory homeostasis (170). During prolonged exercise in a hot environment, skin blood flow increases gradually and may amount to ~3 liters/min, as estimated from forearm skin values (80). This additional skin blood flow demand cannot be satisfied by the further ~20% reduction of splanchnic (167) or renal (148) blood flows, which are already reduced by approximately 75% during exercise, as indicated by the reduction in venous oxygenation (216). Considering that splanchnic and renal circulations, combined with the modest vasoconstriction in inactive skeletal muscles, can contribute to the systemic circulation at most a total of ~1 liter/min (170), it is deemed that active limb muscles are needed as a circulatory "donor" (80).

However, blood flow to active limb muscles and tissues is either maintained or increased when heat stress is superimposed upon light to moderate intensity prolonged exercise (178, 125, 124, 126). Using positron emission tomography Heinonen et al. (70) demonstrated that heat increases muscle blood flow as evaluated by the partitioning of blood flow between muscle and skin under passive heat stress. The implication is that when the metabolic heat production is substantial during prolonged or high intensity exercise, an increase in muscle blood flow may compromise skin blood flow. In support, the cutaneous circulatory demand has a ceiling as skin blood flow plateaus at ~ 55% of maximal level when core temperature reaches ~38 C˚ (17). This plateau manifests by a restrain

of active vasodilation, as shown by selective local blockade of noradrenergic vasoconstrictor nerves (90), implying that oxygen delivery to active skeletal muscles is prioritized over skin blood flow with adverse consequence for thermoregulation (61). Support for that postulate comes from the increased risk for death in the elderly associated with a heat wave (190), probably reflecting the limited capacity of the elderly to increase cardiac output and thus, skin blood flow and thereby their predisposition to hyperthermia.

4.2. Cerebral blood flow and metabolism

4.2.1. Cerebral blood flow

Whole body exercise poses not only a circulatory challenge to splanchnic, muscle, and cutaneous vascular beds but, seemingly, also to the brain, with potential metabolic consequences and implication for performance. Cerebral activation and thus cerebral metabolism during exercise is heterogeneous (i.e., brain area specific, Ref. 101) that provokes a differential blood flow response, depending on the type of mental activity. Moreover, regional specificity of cerebral blood flow (CBF) combined with the different measuring methods used, have led to contrasting observations that fuelled a controversy as to whether CBF increases during exercise (77, 183). However, considering that regional CBF is more sensitive than the global CBF to brain activation during small muscle exercise with no increase in global CBF, e.g. handgrip (136, 51, 52, 185), it is now accepted that whole body exercise provokes a marked increase in CBF (207, 82, 83, 177), e.g. by ~35% during cycling (from 58 to 79 ml/min/100 g, Ref. 188).

Similarly with the peripheral vasculature, however, CBF and O_2 delivery to the brain may be attenuated with a restricted cardiac output either because of administration of a β_1-adrenergic blocking agent (75, 187), heat stress (131, 132, 229), or because of cardiac disease (74). For example, heart failure patients show a normal increase in middle cerebral artery mean flow velocity during one-legged exercise, but that increase is lowered during two-legged exercise (71).

Additionally, with the marked hyperventilation associated with maximal exercise, $PaCO_2$ tension is lowered and that reduces CBF (207, 82, 83, 105, 187, 228), although this effect does not seem to manifest in the posterior cerebral vasculature (176). Together with the possible hypoxemia developed during maximal whole-body exercise (38) and especially rowing (149, 222), the reduction in CBF may provoke a decrease in cerebral oxygenation by 10% (127). Such a reduction in cerebral oxygenation appears to affect performance, i.e. elicits so-called central fatigue as supported by the effect of hypoxia on the ability to perform repeated handgrip exercise rather than rapid contraction as exemplified by computer "mouse click" (150). In support, when oxygen is added to the inspired air during whole body exercise and thereby hinders the reduction in cerebral oxygenation, performance is enhanced by ~5% (127, 6) with no effect on muscle oxygenation (127). Although the enhancement is not always statistically significant in single studies (130, 218, Fig. 6), when these results are summarised an average performance enhancement of ~ 3.5% is revealed (effect size Glass' $\Delta = 1.4$, Ref. 196).

The opposite view has however also been advanced. Since $PaCO_2$ influences CBF, it has been evaluated whether addition of CO_2 to inspired air would improve the reduced work capacity in hypoxia. At altitude, cerebral oxygen delivery is reduced, both by the hypoxia-induced arterial haemoglobin desaturation and the attenuation of CBF, as a result of hypoxia-stimulated hyperventilation and the consequent hypocapnia (204, 137, 194, 47). However, even when CBF and cerebral oxygenation are restored with the addition of CO_2 to the inspired air, performance is not improved. An explanation for the absence of performance improvement by addition of CO_2 to the inspired air could be that the elevated ventilation in response to the additional $PaCO_2$ limits muscle blood flow (67) and, hence, under these circumstances performance is limited by "peripheral" rather than "central" fatigue. However with addition of CO_2 to inspired air, ventilation is increased only

during submaximal exercise in hypoxia and, therefore, a possible "competition" for flow between the brain and the respiratory muscles during maximal exercise would be considered to be similar.

On the other hand, during exercise with bicarbonate infusion that reduces ventilation by approximately 12 liters/min despite an increase in $PaCO_2$ and therefore presumably in CBF, performance is enhanced by approximately 5% (Fig. 7, Refs. 128, 220,), while the NIRS determined muscle oxygenation is not different compared to the control trial (128).

Considering that bicarbonate administration restores muscle pH during exercise (129), it seems that the performance enhancement during exercise with bicarbonate administration is effected by both a "central" ergogenic effect of enhanced CBF and attenuation of "peripheral" fatigue, as a consequence of reduced ventilation (67) and may be a direct effect of pH on muscle metabolism. Thus, an explanation for the absence of performance enhancement with CO_2 supplementation during exercise in hypoxia may be related to "peripheral" fatigue outweighing an eventual ergogenic effect of enhanced CBF.

While attenuated increase in cardiac output during exercise may affect CBF, it remains unsettled how that restrain is established. Cholinergic vasodilatation has been considered with regard to the cerebral perfusion response to both handgrip and cycling exercise (185) but has not been substantiated with magnetic resonance scanning during moderate handgrip exercise (163). Alternatively, a likely candidate to restrain flow to the brain is increased sympathetic activity, similar to findings for exercising muscles (143, 221). Even though it remains debated whether sympathetic activity influences CBF in humans (202, 212), sympathetic influence on CBF in humans during exercise is illustrated during stellate ganglion blockade that hinders the restriction in CBF on the blocked side during exercise with reduced ability to increase cardiac output following administration of a beta-adrenergic blocking agent (76). Furthermore, sympathetic nerve activity of the cerebral vasculature is assessed by transcranial plasma noradrenaline spillover. Specifically, by

modifying sympathetic nerve firing (with trimethaphan or clonidine infusion) and neuronal

noradrenaline uptake (with desipramine infusion) in healthy and autonomic failure subjects, the

possibility of sympathetically-mediated cerebral vasoconstriction is substantiated (117). It follows

that when the increase in cardiac output is small or absent during exercise sympathetic

vasoconstriction may explain the lack of exercise-induced increase in CBF (188), but this

possibility has not been evaluated during exercise (or orthostasis) with restrained cardiac output.

4.2.2. Cerebral metabolism

The sympathetic activation associated with intense whole body exercise could influence

cerebral metabolism, expressed as the cerebral metabolic rate of O_2 ($CMRO_2$) and the ratio of

oxygen to carbohydrate uptake of the brain, known as the cerebral metabolic ratio (CMR) and in

turn affect performance (188). Cerebral carbohydrate metabolism is stimulated by

sympathomimetic drugs such as amphetamine, ritalin, and ephedrine (225), and activation of the

sympathetic nervous system during stressful conditions relevant to exercise (e.g. hypoxia or

hypoglycaemia, Refs. 20, 92).

During progressive whole body exercise there is an intensity dependent ~30% increase in

$CMRO_2$ (62,187, 186, 16, 151, 208). On the other hand, with the intense sympathetic activation

associated with whole body exercise CMR declines (33) reaching its lowest recorded value of 1.7

during ergometer rowing (Fig. 8, refs. 217, 220). Furthermore, even when oxygen delivery is

enhanced with hyperoxic breathing during maximal exercise, CMR remains reduced (217)

suggesting that CMR is not affected by cerebral oxygenation and that non-oxidative carbohydrate

consumption for the brain is independent of oxygen availability.

Thus, if the decrease in CMR during intense exercise does not depend on oxygen availability,

the decrease must depend on an increased cerebral uptake of carbohydrate and only lactate and

glucose seem to be important in that regard (152). Cerebral glucose uptake decreases (91), or is

maintained (76, 31, 32, 217, 220), during intense exercise and the reduction in CMR is dominated

by cerebral lactate uptake. Lactate transport across the blood-brain barrier dependents on the arterial

concentration (76, 211). Yet, this reduction in CMR takes place also with little, or no, increase in

plasma lactate as during prolonged exercise when it becomes a challenge to continue the work (132),

related to, e.g., a decrease in muscle (88), or may be also brain glycogen (110, 109), and an increase

in brain temperature (132).

It may be that the brain's choice of lactate as substrate is a consequence of enhanced

metabolism (188) as known from skeletal muscles (19). Further, it could be that the reduction in

CBF because of the reduction in $PaCO_2$, and may be also inadequate cardiac output, would require

brain lactate production to supplement aerobic metabolism. In fact, lactate is produced by the brain

at the same time as lactate is taken up, f.x., lactate release from the brain increases during exercise

(211) and more so under hypoxic conditions as demonstrated both in the rat (195) as in humans

(140). Irrespective of whether brain lactate production is a consequence of enhanced metabolism

and/or limited oxygen availability, it may account for about 10% of the brain's metabolism (195,

140).

At a CMR of 1.7 less than one third of the amount of carbohydrate taken up by the brain can

be accounted for by the concomitant uptake of oxygen and even though the explanation for such

gross metabolic imbalance in the activated brain remains unknown, it may be coupled to an

adrenergic mechanism (186, 184). Infusion of epinephrine, but not of norepinephrine, is associated

with a reduced CMR (184) and the decline in CMR is blunted with administration of a non-selective

β-adrenergic blocking agent (180, 187, 58), while a $β^1$- adrenergic agent is without such an effect

(31). Taken together it seems that a $beta^2$-adrenergic mechanism contributes, if not dictates, the

decrease in the CMR with activation of the brain. On the other hand, a meta-analysis (153) suggests

that cerebral lactate uptake may not be directly related to adrenergic activity within the brain but

rather by increasing arterial lactate concentration, as adrenergic activity modulates whole-body glycolysis (162), and thus increases cerebral lactate uptake.

Lactate transport across the blood-brain barrier has been thought to be pH dependent (134) but although bicarbonate infusion increases exercise performance by ~2%, brain lactate metabolism is unaffected by the higher pH and CMR is similar to the control trial (220). However at least following high intensity exercise, brain lactate metabolism is not determined only by the arterial lactate concentration, as cerebral lactate uptake is reduced while arterial lactate concentration is peaking (220) but, perhaps, follows the cerebral energy requirements that decrease abruptly with exercise cessation (227).

Taken together, neither compromised cerebral oxygenation nor a change in cerebral metabolism, possibly linked to cerebral glycogen depletion (109) are the only factors that affect central fatigue as, e.g., the limited ability of the brain to eliminate the consequences of its high metabolic rate may increase brain temperature and contribute to central fatigue (132). It seems that the reduction in CMR does not depend on oxygen delivery but rather on sympathetic activation (188), but it is enhanced by hypoxia (140).

5. Arterial and cardiopulmonary Baroreflex

The fourth line of evidence for restricted muscle blood flow during whole body exercise is derived from consideration of blood pressure regulation. The maintenance, or increase, of blood pressure during dynamic exercise requires that the increase in cardiac output matches the elevated skeletal muscle vascular conductance. Since with administration of a plasma expander (87) cardiac output during exercise increases, it can be argued that it is not the pumping capacity of the heart but rather venous return that is limiting cardiac output capacity (120). In support, only patients with ischemic heart disease develop chest pain during exercise.

But how is blood pressure controlled when there is limited cardiac output to distribute to the tissues? In 1972, Guyton et al. presented a model that provided basis for the understanding of long-term blood pressure control. The model links blood pressure and sodium balance, where imbalance between salt intake and renal excretion leads to alteration in filling of the vascular system and thus influences blood pressure. The critical role of the kidney in Guyton's model of long-term blood pressure control is relevant to exercise. The increased sympathetic activity elicited when exercise intensity approaches ~75% VO_2max (55) provokes not only release of arginine vasopressin, to promote water reabsorption and increase blood pressure, but reduces renal blood flow in proportion to exercise intensity (63).

The importance of renal vasoconstriction during exercise does not only relate to the conservation of sodium and water, which is trivial when compared to the loss by sweating, or to the redistribution of blood from the kidneys to active muscle, which is ~300 ml and it is trivial compared to ~20-25 liters/min cardiac output increase during exercise. Rather, renal vasoconstriction during exercise contributes towards the increase of total peripheral resistance and thus maintenance of arterial pressure (170). The intense renal vasoconstriction contributes to offset the vasodilatation seen in active skeletal muscle, and thus prevents a dramatic fall in total peripheral resistance that could compromise the arterial pressure. In support, patients with autonomic failure who have compromised capacity for sympathetic vasoconstriction show a pronounced fall in blood pressure with exercise (108).

Even though the role of the kidney is important for long term blood pressure regulation, the shorts term regulation (i.e., during exercise) is manifested by the baroreceptors. During exercise, the main contributor to peripheral resistance comes from constraining the extent of peripheral hyperaemia through the arterial baroreflex, which includes both the carotid bifurcation and the

aortic arch and is stimulated by feedback from stretch sensing unencapsulated free nerve endings located at the medial–adventitial border (191).

The quantitative approaches available for evaluation of arterial baroreflex function in humans (49) are: a) elevations or reductions of arterial pressure with infusion of vasoactive drugs (the "Oxford method", Ref. 197), b) the Valsalva manoeuvre, using voluntary increase of intrathoracic and abdominal pressure through straining, c) the variable pressure neck-chamber technique, which allows selective activation/deactivation of the carotid baroreceptors by application of a negative/positive pressure to the anterior neck region (43), and d) two methods based on the analysis of spontaneous oscillations of systolic arterial pressure and R-R interval: (i) the sequence method, that analyses the relationship between spontaneous increasing/decreasing ramps of blood pressure and related increasing and decreasing R-R interval through linear regression (53) and (ii) spectral methods (35), that assesses the relationship (in terms of gain) between oscillatory components of the two signals. Among these methods the variable pressure neck-chamber method is of special interest because it allows for non-invasive, non-pharmacological and selective evaluation of the carotid baroreflex (i.e., void from the contributions of the aortic and cardiopulmonary baroreceptors to the blood pressure responses) by altering carotid sinus intramural pressure.

First, it was thought that the arterial baroreflex is "deactivated" and does not regulate blood pressure during exercise as deducted from the fact that both heart rate and blood pressure rise during exercise, an observation that is in direct opposition to the inverse relationship between heart rate and blood pressure, the essential characteristic of the arterial baroreflex (107). An explanation for the parallel increase of heart rate and blood pressure during exercise was found to be a "resetting" of the arterial baroreflex that continues to regulate both heart rate and blood pressure with the same sensitivity at the higher levels established during exercise (Fig. 9, Refs. 145, 46). Support for that

explanation comes from the reflex responses in heart rate and blood pressure with the same magnitude as at rest, when using a variable pressure neck chamber to the carotid baroreceptors during exercise (13) by influence from both central command (56) and the exercise pressor reflex (141, 57). Thus, the baroreflex tonically opposes vasodilation by imposing sympathetic vasoconstriction to active muscles and, thereby, increasing peripheral resistance in order to support blood pressure (171), as has been shown both in humans (133) and dogs during exercise (135, 27).

In addition, the hemodynamic response to whole body exercise is influenced by cardiopulmonary baroreceptors. Higher heart rate and blood pressure during sitting compared to supine exercise at comparable level of VO_2 (200) has hinted to the contribution of cardiopulmonary baroreceptors to the blood pressure response during exercise. Importantly, the cardiopulmonary baroreceptors not only contribute in establishing the prevailing blood pressure but are also involved in the resetting of the arterial baroreflex (224). Specifically, increasing the load of the cardiopulmonary baroreceptors by assuming the supine position resets the operating point of the arterial baroreflex to a lower blood pressure during exercise (Fig. 9). Furthermore, the increased load to the cardiopulmonary baroreceptors in the supine posture is established by enhanced venous return as implied by plasma atrial natriuretic peptide that is released in response atrial stretch (Fig. 10, Ref. 214). Thus, variation in the central blood volume may explain the lower blood pressure during combined arm and leg exercise than when the arms are working alone (181, 221, 218, 223) by concomitant adjustment of the arterial baroreflex function (224, 46).

6. Conclusion

The blood flow capacity of the arms is lower than that of the legs. However, during intense whole body exercise, even with the values estimated for the arms the blood flow demand of active muscles presents a challenge to the capacity of the heart to provide sufficient cardiac output. Even though cardiac output is supported by an increase in venous return, mediated by the muscle pump of

primarily the lower legs, the blood flow demand surpasses venous return and, hence, cardiac output redistribution is necessary in order to preserve systemic blood pressure. The arterial barorereflex is critical in the cardiac output redistribution during exercise as it provokes sympathetic vasoconstriction, in order to regulate systemic resistance, not only to the abdominal organs (and inactive vascular beds) but also to active muscles and the skin, and perhaps equally importantly, may be also to the brain. Therefore, it is argued that blood pressure is the primary regulated variable during exercise that challenges regional blood flow especially during whole-body exercise.

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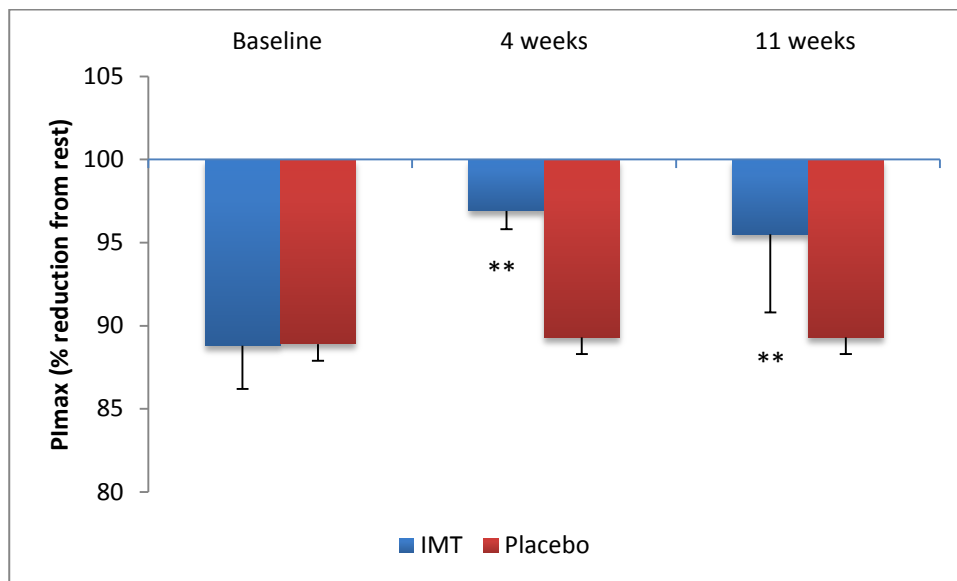
Figures

Figure 1
Reduction in inspiratory muscle strength (PImax, maximum inspiratory mouth pressure) after 6 min maximal ergometer rowing, percent from resting PImax during 11 weeks of inspiratory muscle training (IMT) in the training and placebo group. Values are mean ± SD, ** $P < 0.01$ difference between groups (Redrawn from ref. 219).
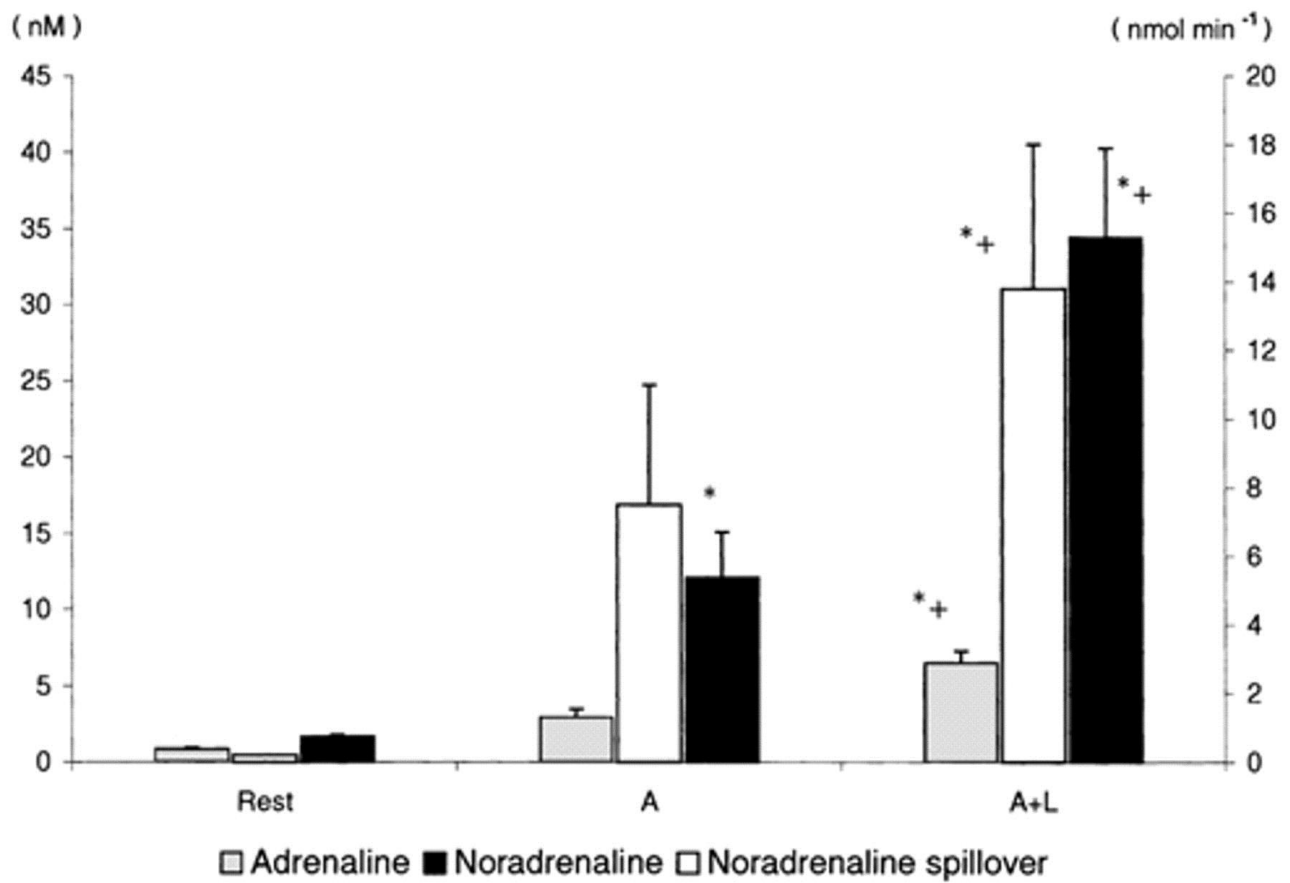
Figure 2
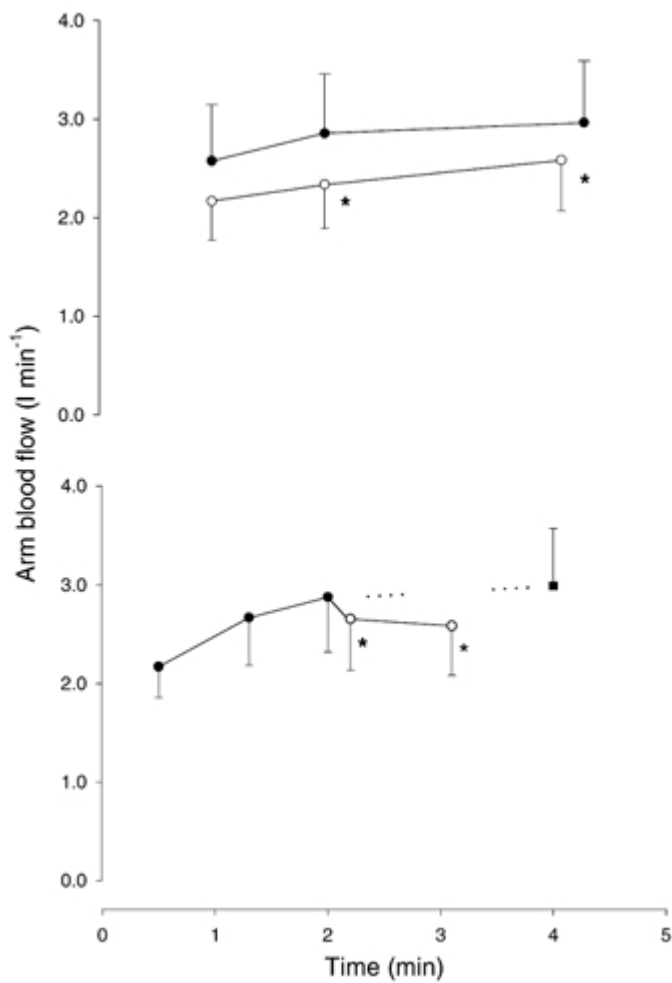Catecholamines and noradrenaline spillover at rest and during arm (A) and combined arm and leg (A + L) exercise (Ref. 221).

Figure 3

Arm blood flow during arm (A, •), arm and leg (A+L, ○; upper) and the transition (lower) from A to A+L trials. Measurements were taken at 60, 120 and 270 s during the independent trials and at 30, 60, 110 and 180 s during the transition trial. The projected value (■) is from the data during the A and A+ L independent trials. Values are means ± SE, $n=7$, * different from A, $P < 0.05$ (Ref. 218).
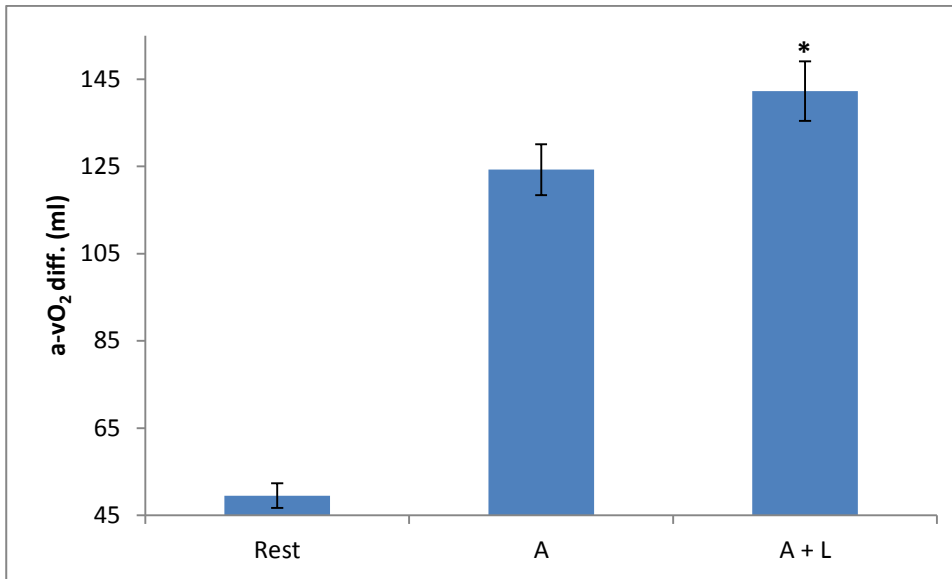
Figure 4

Arterial–axillary venous O_2 difference (a-vO_2 diff.) at rest and during arm (A) and combined arm and leg (A + L) exercise (average mean data ± SE from refs. 181, 221, 218, 223; *n*=31, * different from A, $P < 0.05$).
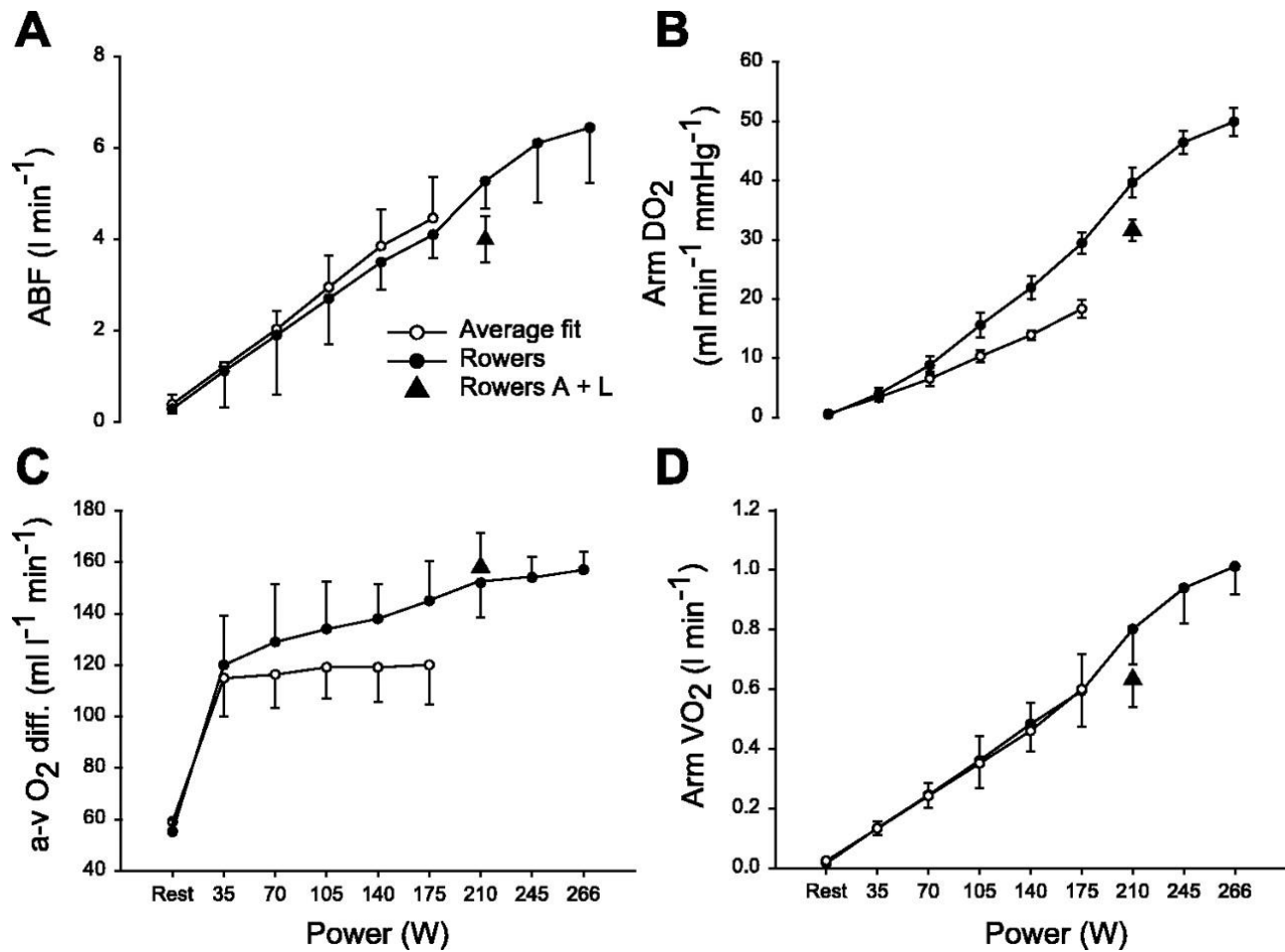
Figure 5

Peripheral circulatory variables during arm cranking to exhaustion in rowers and average, fit

subjects. ABF, arm blood flow (A); DO_2, diffusional O_2 conductance (B); a-v O_2 diff, arteriovenous

O_2 difference (C); $\dot{V}O_2$, oxygen uptake (D); A + L, addition of leg exercise to arm cranking in the

rowers. Values are means ± SE for 8 average fit subjects and 7 rowers. Redrawn from ref. 223.
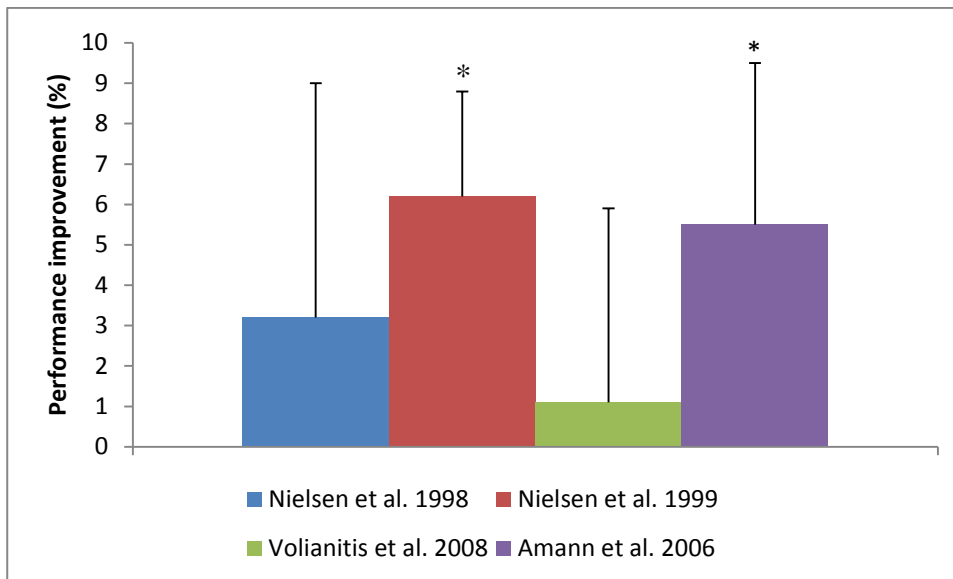
Figure 6

Performance improvement in maximal ergometer rowing (percent of power) with 0.28 - 0.30 O_2 supplementation in the inspired air. Mean data $\pm$ SE from refs. 130, 127, 6, 217. * different from normoxic trial, $P < 0.05$.
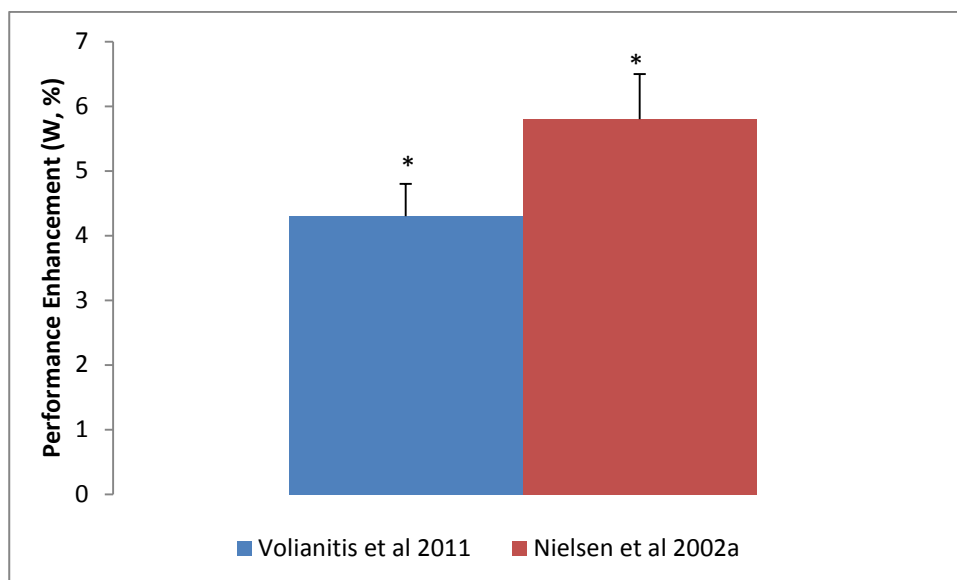
Figure 7

Performance improvement in maximal ergometer rowing (percent of power) with bicarbonate infusion. Mean data ± SE from refs. 128, 220. * different from saline trial, $P < 0.05$
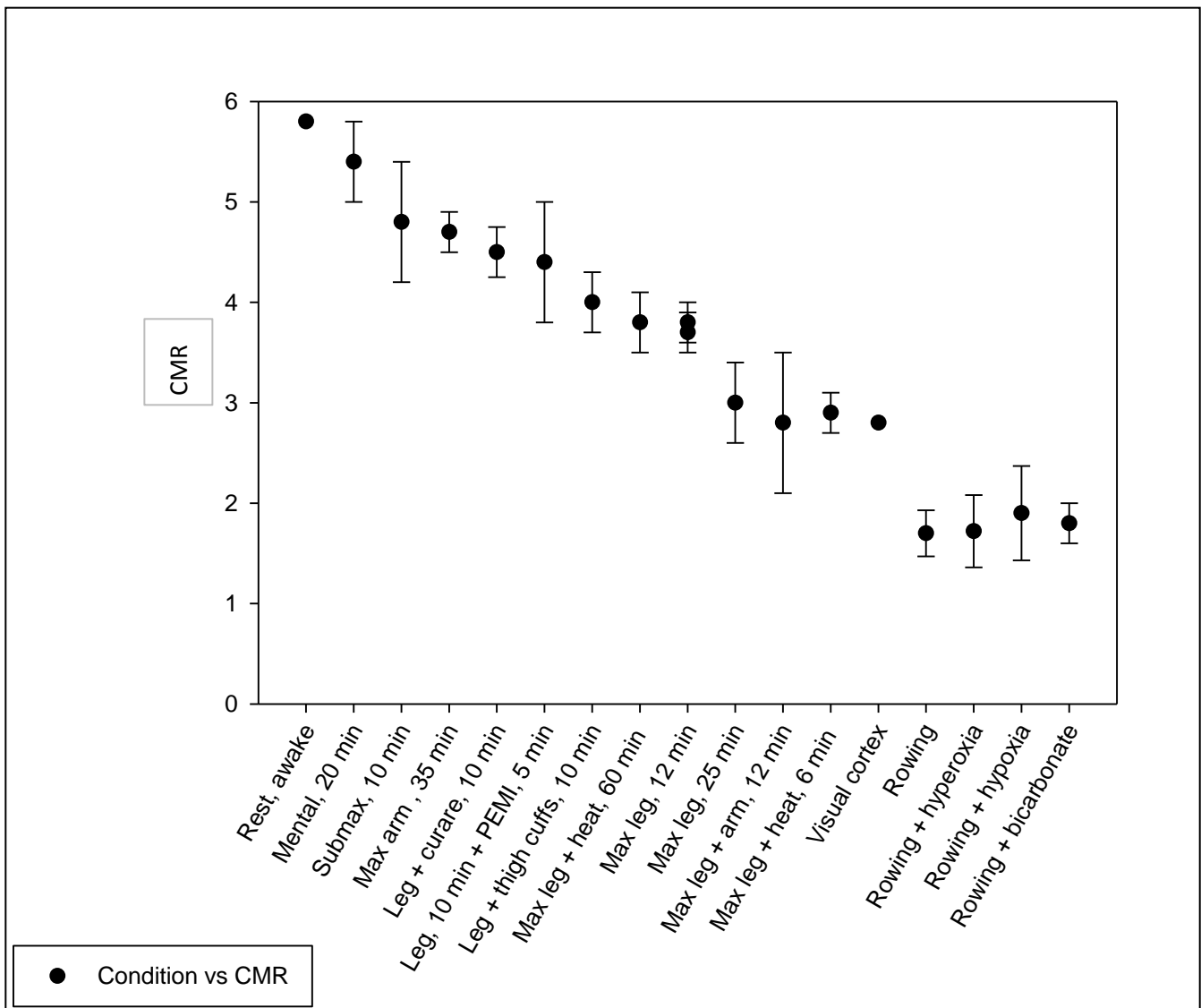
Figure 8

The cerebral metabolic ratio (CMR, brain uptake of oxygen relative to that of carbohydrate; glucose+1⁄2 lactate) at rest and during various types of brain activation including several types of exercise with intense whole body exercise (ergometer rowing) demonstrating the largest deviation from the resting value of 6 (Redrawn with data from refs. 217, 220, 222).
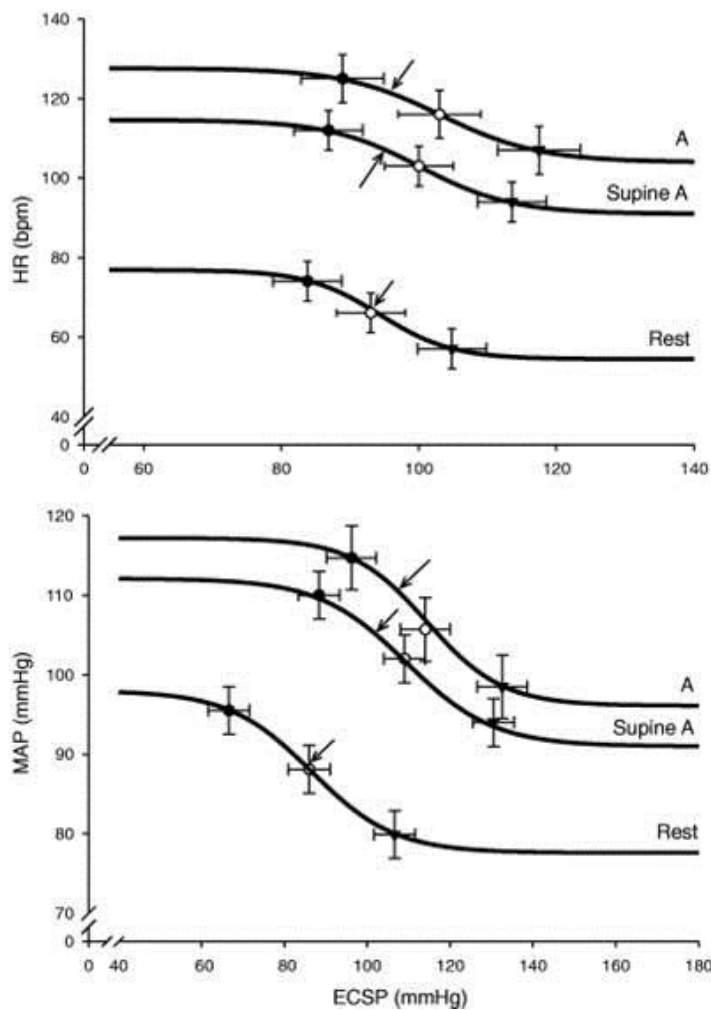
Figure 9

The carotid-cardiac (upper) and carotid-vasomotor (lower) reflex response during upright and supine arm exercise (A). Reflex responses in heart rate (HR) and mean arterial pressure (MAP) after stimulation of carotid sinus baroreceptors at rest during upright and supine arm exercise. Data represent mean ± SE. Lines are the mean fit of data from individual subjects. Arrows indicate the position of MAP for the given exercise modality. In each line the threshold (left), centering (middle) and saturation (right) of the baroreflex function are shown (Redrawn from ref. 224).
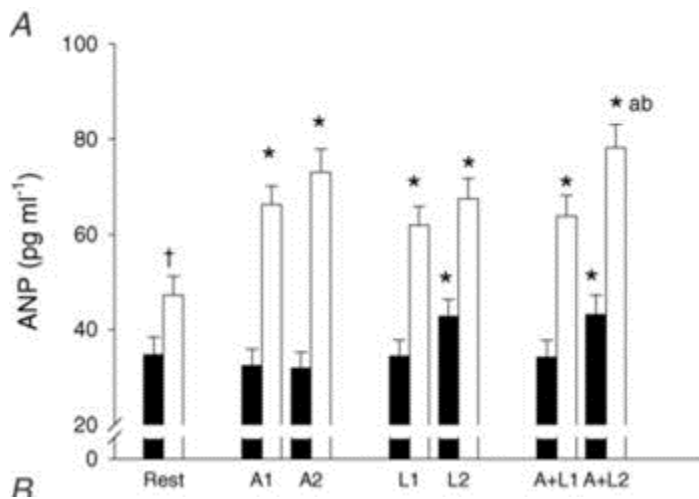
Figure 10

Plasma atrial natriuretic peptide (ANP), A) at rest and during arm (A), leg (L) and combined A and

L (A + L) exercise in upright seated (filled bars) and supine exercise (open bars)

Blood samples were taken at the first (1) and the last minute of exercise (2). Values are means ±

S.D., $n = 11$, ∗ Different from rest; † different from upright posture; a different from A, b different

from L; all at $P < 0.05$ (redrawn from ref. 214).

Summary

It is controversial whether during whole body exercise the increase in cardiac output is large enough to support skeletal muscle blood flow. This review addresses four lines of evidence for a flow limitation to skeletal muscles during whole body exercise. First, even though during exercise the blood flow achieved by the arms is lower than that achieved by the legs (160 vs. 385 ml min-1 100 g-1), the muscle mass that can be perfused with such flow is limited by the capacity to increase cardiac output (42 L min-1, highest recorded value). Secondly, activation of the exercise pressor reflex during fatiguing work with one muscle group limits flow to other muscle groups. Another line of evidence comes from evaluation of regional blood flow during exercise, where there is a discrepancy between flow to a muscle group when it is working exclusively and when it works together with other muscles. Finally, regulation of peripheral resistance by sympathetic vasoconstriction in active muscles by the arterial baroreflex is critical for blood pressure regulation during exercise. Together these findings indicate that during whole body exercise muscle blood flow is subordinate to the control of blood pressure.

Dansk Resumé

Om øgningen af hjertets minutvolumen under helkropstræning er stor nok til at forsyne musklerne med blod er uklart. Denne oversigt giver fire argumenter for en begrænsning i blodforsyningen til musklerne under helkropsarbejde. Et argument er, at selvom perfusionen til armene er lavere end for benene (160 vs. 385 ml/min/100 g), er den muskelmasse, der kan forsynes af en sådan gennemstrømning begrænset af hjertets kapacitet til at øge dets minutvolumen (42 l/min, højest målte værdi). Det andet argument er, at aktiveringen af pressor reflekser under udtrættende arbejde af en muskelgruppe begrænser blodgennemstrømningen til andre muskelgrupper. Således er er der en diskrepans mellem blodgennemstrømning til en muskelgruppe, når den arbejder isoleret, og når den arbejder sammen med andre muskelgrupper. Endeligt medfører den arterielle baroreflex regulering af den perifere modstand, som også omfatter aktive muskler. Disse observationer indikerer, at blodgennemstrømningen til skeletmuskulaturen er underordnet kontrol af blodtrykket.