NORMAL CARDIAC OUTPUT, OXYGEN DELIVERY AND OXYGEN EXTRACTION

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Abstract: The total amount of blood flow circulating through the heart, lungs and all the tissues of the body represents the cardiac output. Most individual tissues determine their own flow in proportion to their metabolic rate. The skin is a notable exception where the priority is thermal rather than metabolic. Renal blood flow and metabolic rate are related but plasma flow determines metabolic rate rather than metabolic rate determining blood flow.[1] Brain, heart, skeletal muscle and the splanchnic area all vary their blood flows according to local tissue metabolic rate. Summation of peripheral blood flows constitutes venous return and hence cardiac output. Cardiac output is therefore, largely, determined by the metabolic rate of the peripheral tissues; the heart '*from a flow standpoint, plays a "permissive" role and does not regulate its own output*'.[2] This peripheral tissue, largely metabolic, determination of cardiac output has been known for many years.[3,4]

Evidence will be presented that blood flow is scaled according to a tissue specific ratio of oxygen delivery (DO_2) to oxygen consumption (VO_2). For the brain DO_2 is approximately three times VO_2, for heart muscle DO_2 is 1.5 to 1.6 times VO_2 and is very similar for skeletal muscle for moderate exercise. Brain, heart and skeletal muscle have the ability to sustain appropriate blood flow in the face of varying blood pressure within limits – the phenomenon known as 'autoregulation'. "Autoregulation, in regard to arterial blood pressure, has been observed" also "in the kidney" and "modest autoregulation" was observed "in the intestines and liver but not in skin".[3] Guyton et al. [4] have suggested that the term 'auto-regulation' should also include variation of blood flow in proportion to metabolic rate and the compensatory changes in blood flow which occur in the face of varying arterial oxygen content (CaO_2). This article gives examples of the very precise compensation for CaO_2 change in the form of sustained tissue specific DO_2:VO_2 ratios (corresponding with tissue specific oxygen extraction, $E = VO_2/DO_2$). The adequacy of

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this adjustment for brain, exercising skeletal muscle and heart is particularly striking; skeletal muscle will, for example when CaO_2 is reduced, steal blood supply from non-exercising tissues sustaining its own oxygen delivery at normal levels.[5]

1. INTRODUCTION

For the commonest man-made circulatory systems the energy input to the pump determines the pump output. In contrast the circulation of blood in man and other animals is regulated peripherally, from adjustments made in a circulation where "both the pipe system and the fluid are able to change characteristics from time to time and thereby impose varying demands on the pump. Since the main changes in cardiac output are determined by the metabolic requirements of the body and not by voluntarily switching the pump to a higher setting, it is evident that the body sets the pace and not the pump. Thus, the heart, from a flow standpoint plays a permissive role and does not regulate its own output. So in the human circulation, the heart functions as a 'demand' pump ……".[2]

Guyton et al.[4] in their 1973 monograph quoted work dating from the early 1900s which demonstrated that:

1. "Cardiac output almost exactly parallels the level of metabolism….", and
2. "On the basis of these studies, it has now become widely recognised that the single factor most responsible for the significant linkage between metabolic rate and cardiac output is the tissue need for oxygen."

The verified specificity for oxygen is based on extensive experimentation. Guyton et al.[4] quote 21 references dating from 1922 to 1971 and at the end of the list of references comments: "… and many others."

Measurements of cardiac output prior to the use of dye dilution and the Fick method, on average, gave answers which were about 2/3 of the correct values.[4]

Below are listed the main, established features of circulatory control (other than blood pressure regulation) including metabolic and other contributions to venous return and hence cardiac output. The permissive range, mentioned in point A, is the range over which the heart will act in its, so-called, "permissive" role, simply passing on the peripherally determined venous return as cardiac output. The extra capacity for pumping above the resting value has been referred to as the "cardiac reserve" and may be 25 l min^{-1} or more for a highly trained athlete.[6]

A. The heart (in the permissive range) puts out what it receives

B. Peripheral tissues demand blood flow appropriate to:

1. Metabolic rate (VO_2): – Whole body exercise, skeletal muscle, heart, splanchnic (including the liver) and brain
2. Renal priorities (electrolyte regulation)
3. Skin (thermal priorities)
4. Bone (priorities unknown – magnitude of blood flow hard to judge)
5. Artificial shunt

C. Autoregulation – appropriate tissue blood flow

1. Flow sustained despite blood pressure change (within limits) confirming peripheral regulation.
2. The sum of all peripheral blood flows = venous return = cardiac output (within permissible range)

D. Oxygen's importance as the specific index of metabolic rate, e.g.

1. Reperfusion blood flows repay the oxygen debt for brief occlusions.[4]
2. Cardiac output is linearly related to oxygen consumption.

The features listed will be illustrated by examples from the literature.

2. EVIDENCE FROM THE LITERATURE

2.1. The Heart Puts Out What It Receives

Donald and Shepherd [7] studied exercise in two groups of dogs, one entirely normal, and the other after recovery from cardiac denervation. The results are illustrated in Figure 1.

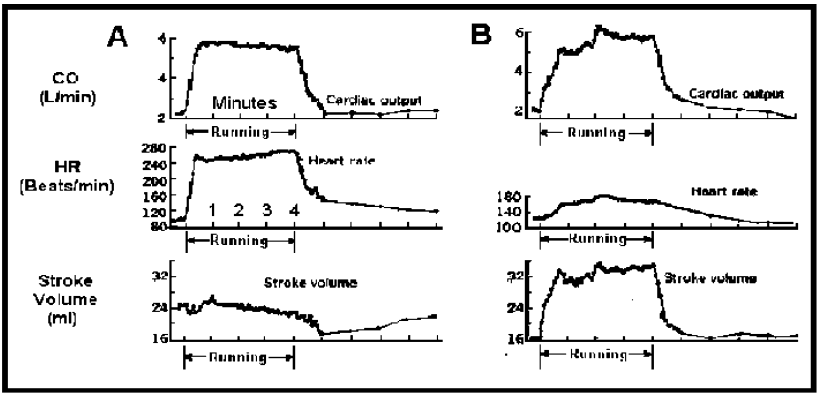

Figure 1. Results of exercise (running) in normal dogs are shown in A, where the cardiac output increase is mainly due to increased heart rate. This contrasts with the cardiac denervated dogs (B) where most of the increased cardiac output resulted from increased stroke volume. Used with permission from D. E. Donald and J. T. Shepherd, Initial cardiovascular adjustment to exercise in dogs with chronic cardiac denervation, *Am J. Physiol.* 207(6), 1325-1329 (1964).

The cardiac denervated dogs showed a cardiac output much the same as occurred in the intact dogs, largely achieved via an augmented stroke volume. This illustrates feature A above "the heart puts out what it receives".

A second example illustrating that the heart will pump out what it receives is the situation where an artificial shunt is created. Here there is no metabolic rate priority or

other control. Blood flow depends simply on the resistance to flow and arterial blood pressure; cardiac output keeps up precisely with the excess inflow unless it is so large that the cardiac reserve is insufficient.[4]

2.2. Blood Flows Related To Oxygen Consumption

2.2.1. Whole Body and Skeletal Muscle in Moderate Exercise

The linear relationship between cardiac output and oxygen consumption has been known for many years [4,6,8,9] and is illustrated in Figure 2 (left hand panel). On the right the schematic allows the deduction that if the excess cardiac output represents the blood flow to muscle then the muscle arterio-venous difference is 1/B, where B is the slope of the line.[5]

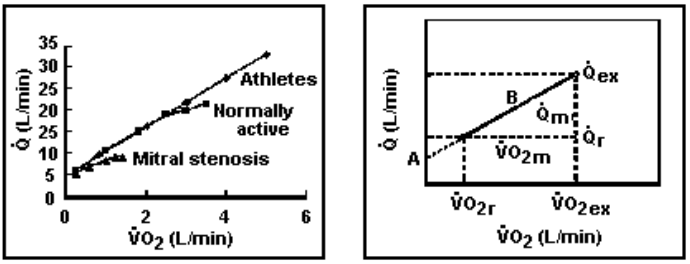

Figure 2. On the left is a classic illustration of the way cardiac output increases with oxygen consumption (after Rowell [8,9]) and on the right a hypothetical arrangement whereby the increased cardiac output above the resting value represents blood flow to the exercising muscle.[5] Key: Q, cardiac output; A, intercept; B, slope; VO_{2r} and VO_{2ex}, resting and exercising VO_2; Q_r and Q_{ex}, resting and exercising cardiac output; Q_m, muscle blood flow; VO_{2m}, muscle oxygen consumption.

Using the hypothesis illustrated in Figure 2 on the right most standard figures given for the relationship between cardiac output and oxygen consumption, dating from the early methods, gave oxygen extraction values which were too high (90% to 100% or more!). The cardiac output measurements were too low (respiratory methods). Analysis of data from Koskolou et al.,[10] where cardiac output was accurate (measured by dye dilution), allowed calculation of muscle blood flows from the Fick equation because arterial and muscle venous oxygen content were available. When the subjects had a normal arterial oxygen content (CaO_2) muscle blood flow was equal to the excess cardiac output above the resting value. Furthermore, oxygen extraction, E, was 68% (close to 2/3) for 30 watts (w) and 73w exercise. When the subjects were made normovolaemically anaemic skeletal muscle oxygen extraction was still close to 2/3; muscle blood flow had increased enough to sustain precisely the DO_2 required. However, the total cardiac output was now insufficient to supply the original resting blood flow to the non-exercising tissues – there was therefore now 'steal' of blood flow by the exercising muscle thereby supplying the required excess muscle blood flow.[5]

Figure 3 illustrates the findings; on the left exercising muscle blood flow was greater in the anaemic subjects for any given metabolic rate than in the normal subjects; this resulted in the anaemic subjects having the same oxygen delivery for any given wattage as normal subjects (middle panel). The right hand panel shows how oxygen delivery and

oxygen consumption vary with the work rate, illustrating the high oxygen extraction (similar to cardiac muscle).

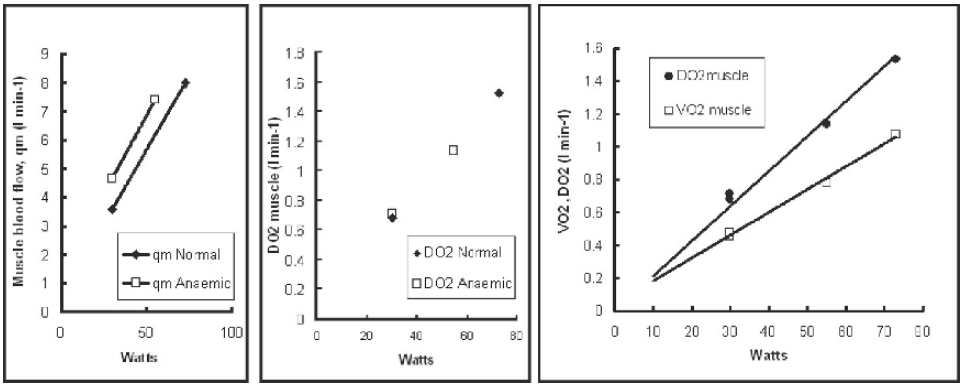

Figure 3. Exercising muscle blood flow (left panel) is greater in anaemia than normal, compensating for the reduced CaO_2 (middle panel) so that muscle oxygen delivery is the same for any given metabolic rate as it is with normal CaO_2. The right hand panel shows that DO_2 is about 1.5 times VO_2; expressed another way, oxygen extraction, E, is 2/3 of oxygen delivery. Analysis[4] of Koskolou et al. data.[10]

These results embody an important feature of the circulation. For this specific tissue a constant oxygen DO_2:VO_2 ratio and oxygen extraction have been maintained over a moderate range of metabolic rate both with normal and with reduced CaO_2 (in this case from anaemia). The same skeletal muscle oxygen extraction (around 2/3) was also present at 30w where CaO_2 was lowered with hypoxia, anaemia and combined hypoxia and anaemia in subjects studied by the same group.[11] Constant oxygen extraction over this metabolic rate range also means that there will be a specific rate of oxygen delivery at a particular metabolic rate.

Exercising skeletal muscle thus determines its own appropriate blood flow, so long as it is in a moderate exercise range (in heavy exercise oxygen extraction is increased) and so long as CaO_2 is above a very low value (in this case DO_2 was sustained at the lowest recorded CaO_2 – 11.47 ml per 100 ml blood, 60% of the normal value).[5,10,11]

The fact that blood flow to other organs was reduced and hence oxygen delivery to other organs (probably splanchnic) was compromised in the anaemic subjects of Koskolou et al. [10] shows that the autoregulation for exercising skeletal muscle is more powerful than for the other organs.

2.2.2. Cerebral Blood Flow and Oxygen Delivery in Hypoxia

Cerebral auto-regulation of oxygen delivery in the face of hypoxia is illustrated by an analysis of a study by Severinghaus et al.[12] The analysis examined the cerebral oxygen delivery from the Severinghaus et al. study, firstly over the first 8 hours,[13] and in a second study extending the time base to include findings at 3 days and 5 days.[14] The fall in

$PaCO_2$ was slight at 8 hrs with a maximal fall in SaO_2 at that time (Figure 4, left hand panel) and blood flow was maximal (an approximately 25% increase, middle panel).

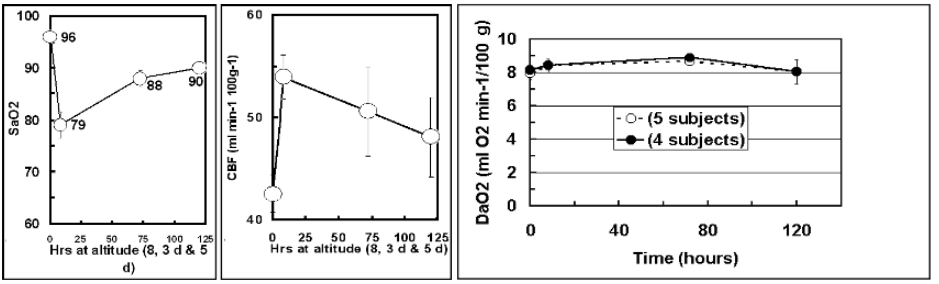

Figure 4. The left hand and middle panels show arterial saturation and cerebral blood flow (CBF) at sea level and successively after arrival at 3810 m altitude. Values are plotted for 8 hours, 3 days and five days. The large initial fall in SaO_2 is mirrored by a 25% rise in CBF. The resultant oxygen delivery (DaO_2) values are shown in the larger right hand panel. Mean values are shown for 4 subjects and for 5 subjects (values either homogeneous or not). Cerebral DaO_2 was well sustained.[13,14] Analysis of data from Severinghaus et al.[12]

With acclimatization, $PaCO_2$ fell further, SaO_2 improved and cerebral blood flow declined gradually over the next five days (Figure 4 middle panel). Oxygen delivery (right hand panel of Figure 4) was much the same as at sea level throughout the five days at altitude.[14] Hence; normal oxygen delivery was sustained throughout.

The proportion of oxygen extracted from that delivered to the brain as a whole (global oxygen extraction, E) is considerably less than for heart and skeletal muscle, about 34%, equivalent to a DO_2:VO_2 ratio of approximately 3:1.

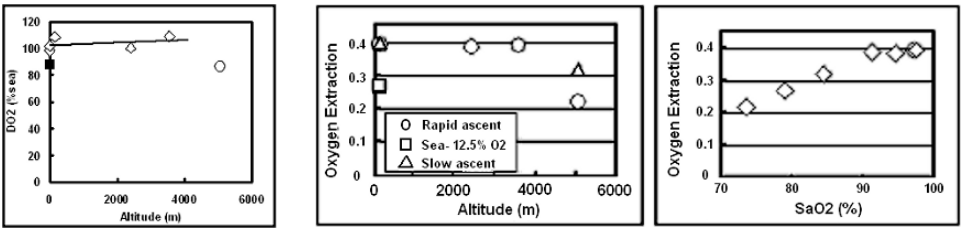

Figure 5. Cerebral oxygen delivery, as a percentage of the sea level value is shown for 2400 m, 3550 m and 5050 m (left hand panel). DO_2 is decreased at 5050 m (semi-acute ascent) but is the same as at sea level for the lower two altitudes.[18] ■ ….. Inspiration of 12.5% oxygen at sea level. The middle and right hand panel show estimates of cerebral oxygen extraction (E) for a region of frontal cortex, derived from combining near infra-red spectroscopy (NIRS) values of rSO_2 (ratio of oxygenated to total Hb) with SaO_2. The middle panel shows E against altitude and closely resembles the pattern for cerebral DO_2 with an extra point from a slow ascent to high altitude (△, 5000 m). The same values of E are shown against SaO_2 in the right hand panel.[19]

Measurements of middle cerebral artery velocity and SaO_2 made by Imray et al. during ascent to several different altitudes [15,16,17] allow calculation of values proportional to DO_2. Normal DO_2 was sustained for moderately high altitudes (2400 m and 3550 m) but was reduced to around 85% of the sea level value at 5050 metres (Figure 5, left hand panel).[18] DO_2 was reduced for acute hypoxia at sea level (black square in the figure). Cerebral DO_2 was the same as at sea level when SaO_2 values were above 90%.

Near infra-red spectroscopy (NIRS) measurements over the frontal area were also made by Imray et al. [15,16,17] The ratio of oxygenated to total blood in the sample area, rSO_2, lumps arterial and venous blood together; but analysis of the results in combination with SaO_2 suggest that oxygen extraction and the ratio of arterial to venous blood volume were unchanged over the same range as that for which middle cerebral artery DO_2 was constant.[18] This allowed derivation of oxygen extraction, E, for the region.[19] Cerebral cortical E, derived from NIRS measurement, is presented for the data from Imray et al. [15,16,17] in the middle and right hand panels of Figure 5. E plotted against altitude (middle panel) is very similar to oxygen delivery against altitude (left hand panel). The extra point (triangle, middle panel) represents the mean value for E from 14 subjects who had ascended slowly to 5000 m (taking around 17 days); E is less reduced than the value for the semi-acute ascent to much the same altitude. Adjustments are completely compensatory (constant E) for SaO_2 values above 90% (Figure 5 right hand panel) but appear to become progressively more abnormal for lower SaO_2.

In summary, cerebral oxygen delivery and extraction are sustained at the normal (sea level) value in the face of hypoxic reductions in SaO_2 above (approximately) 90%. Cerebral blood flow and DO_2 are therefore regulated by intrinsic cerebral mechanisms.

2.2.3. Myocardial Oxygen Extraction

Constancy of myocardial oxygen extraction in the face of increased cardiac output means that there is normally an increase in coronary blood flow in proportion to myocardial VO_2. Where there is also low CaO_2 (hypoxia or anaemia) the situation is more complicated. There is, nevertheless, still a priority to sustain myocardial DO_2 appropriate to the metabolic rate.

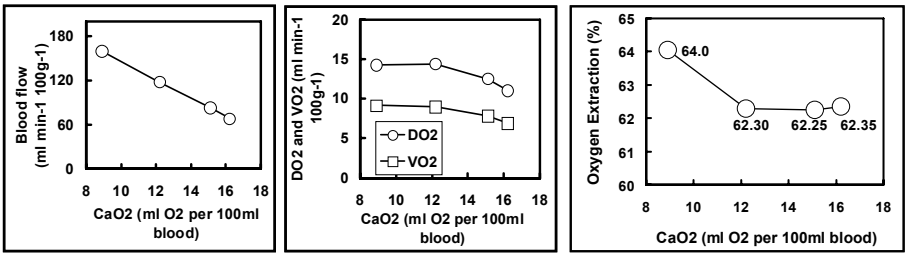

Figure 6. Myocardial (right ventricular) blood flow (left hand panel), oxygen delivery and consumption (middle panel) and oxygen extraction (right hand panel) from Martinez et al.[20] show the effect of hypoxia in dogs. Hypoxia changes myocardial blood flow partly as a result of the hypoxia and partly increased myocardial oxygen consumption due to increased cardiac output. Myocardial oxygen extraction (right hand panel) is constant for CaO_2 above 12 ml. O_2 (100 ml)$^{-1}$ blood; equivalent to a ratio of DO_2 to VO_2 of 1.6 (approx.).

Constancy of myocardial oxygen extraction in the face of changes in both metabolic rate and arterial oxygen content can be illustrated from the results of Martinez et al.[20]. The experiment consisted of hypoxic challenges in instrumented conscious dogs. Figure 6 shows blood flow values for the normal state and three hypoxic states (left hand panel).

Myocardial oxygen consumption, shown in the middle panel, is increased in hypoxia because increased cardiac output sub-serves the needs of the rest of the body (compensatory increases in blood flows elsewhere). Similarly, myocardial oxygen

delivery is increased, also shown in the middle panel. The right hand panel shows that oxygen extraction is barely changed from normal for two of the hypoxic states. Only with an arterial oxygen content of 9 ml. O_2 (100 ml)$^{-1}$ blood was there an increase in oxygen extraction.

The heart, like exercising skeletal muscle and brain, determines its own blood flow and specific DO_2:VO_2 ratio (here 1.6, oxygen extraction 62.3%) in the face of changes in myocardial oxygen consumption and arterial oxygen content. There is a lower limit for this adjustment at a CaO_2 value between 8 and 12 ml O_2 per 100 ml blood.

2.2.4. Splanchnic Oxygen Extraction

The splanchnic area (gastro-intestinal tract, pancreas, spleen and liver) drains firstly into the hepatic portal vein and then the liver (see Figure 7). In the figure 'gut' refers to gastro-intestinal tract, pancreas and spleen. The oxygen extraction and DO_2:VO_2 estimates have been made from experimental details given in the text by Folkow and Neil.[21]

Oxygen extraction is only about 16% for the portal system and 21% overall (including the liver). These correspond with DO_2:VO_2 ratios of around 20%. Blood flows in the figure are for the time between meals. After food flows increase in line with the increased metabolic rate, due to secretion, absorption and smooth muscle contraction. There are specific increases in local blood flows at the sites of increased oxygen consumption.

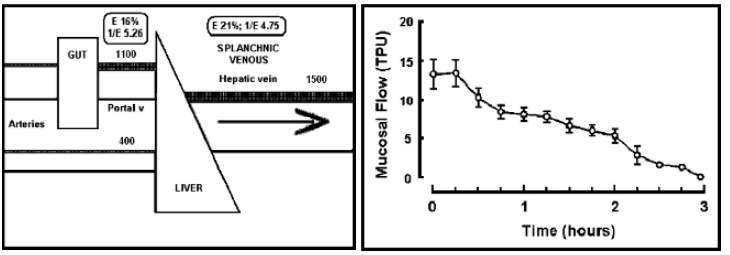

Figure 7. Left hand panel: schematic diagram of the splanchnic blood flow and arterial and venous oxygen content values (clear, oxygenated blood; dark stippled, de-oxygenated blood), with blood flow and oxygen extraction estimates (derived from Folkow and Neil [21]). Portal oxygen extraction is less than overall splanchnic oxygen extraction. Normal splanchnic function is associated with low oxygen extraction (a high oxygen delivery to consumption ratio – around 5). The portal blood flow (1100 ml min^{-1}) and hepatic vein blood flow (1500 ml min^{-1}) will be greater after meals. Right hand panel: Ileal mucosal blood flow in dogs subject to controlled haemorrhage – 5 ml kg^{-1} every 15 minutes. The fall in blood flow after the first increment is very early and occurs with very little overall haemo-dynamic change. Intestinal mucosal autoregulation is far less robust than for brain, heart and skeletal muscle.[22]

The "modest auto-regulation" observed "in the intestines and liver" to quote Green et al.[3] can be illustrated by the right hand panel of Figure 7. The modest increments of controlled haemorrhage (5 ml kg^{-1} every 15 minutes) caused a fall in mucosal blood flow very early, after only the second increment. [22]

The splanchnic area, with high DO_2:VO_2 ratios is another example of blood flows related to oxygen consumption but appears to be vulnerable to requirements for blood flow elsewhere. Details of the response of blood flow to reductions in CaO_2 are not readily available but it is anticipated that the 'steal' observed with modest exercise in

subjects with reduced CaO_2 will mean that the tolerable range of CaO_2 reduction will be less than for skeletal muscle or brain.

2.3. Oxygen Consumption Related to Blood Flow – The Kidney

Experimental reductions in renal blood flow cause a proportional reduction in renal oxygen consumption and hence no change in oxygen extraction.[1] The metabolic rate depends on sodium absorption which depends on blood flow, in particular, plasma flow. Quoted values for renal oxygen extraction are low; approximately 1/6 appears to be a consensus (16-17%) so the DO_2:VO_2 ratio is normally about 6:1. When the oxygen content of the arterial blood is reduced there is little change in renal plasma flow so the renal oxygen consumption remains much the same. Oxygen delivery is now lower for any given plasma flow than with normal CaO_2. Hence, oxygen extraction is increased and erythropoietin is produced.

There is still a correlation between blood flow and metabolic rate for the kidney in normal subjects (normal CaO_2), so the correlation for the whole body still holds good. For the kidney however the causal relationship (flow determines VO_2) is the reverse of that found in the other major organs – skeletal muscle, heart, brain and the splanchnic area.

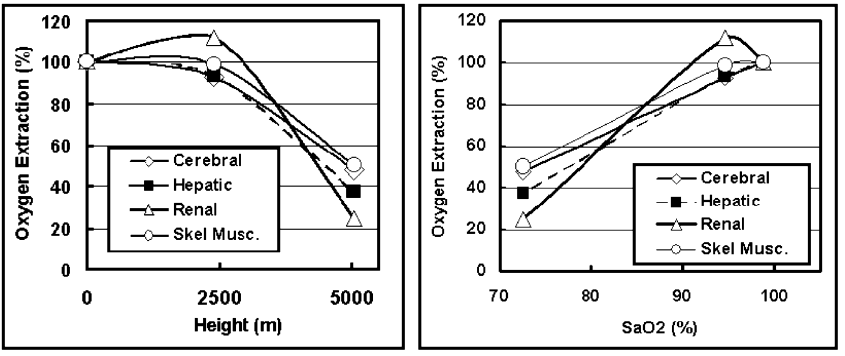

Figure 8. Oxygen extraction values (E) are shown for brain, liver, skeletal muscle and kidney in resting subjects at sea level, 2400 meters and 5050 meters altitude after moderately rapid ascent. E was derived from NIRS measurement (rSO_2, oxygenated/total Hb) and SaO_2: $E = 1.39x(1 - rSO_2/SaO_2)$. Only the renal value of E is increased at 2400 meters – left hand panel. The right hand panel shows the same values for oxygen extraction plotted against arterial oxygen saturation. All values were reduced at 5050 meters. After Wolff et al.[19]

The effect of hypoxia on renal oxygen extraction, E, is illustrated in Figure 8, where E has been calculated from rSO_2 and SaO_2 for brain, liver, skeletal muscle and kidney at rest. The NIRS measurements made by Imray et al.[15,16,17] included rSO_2 over these organs with calculation according to $E = 1.39x(1 - rSO_2/SaO_2)$ [19] to give values at sea level, 2400 metres and 5050 metres; measurements were made after a moderately rapid ascent. Figure 8 shows that E for brain, liver and resting skeletal muscle was unchanged at 2400 meters but renal oxygen extraction was increased. All E values were reduced at 5050 meters.

Renal perfusion depends, not on metabolic rate, but on electrolyte priorities. Oxygen extraction however is normally sustained at a low value and "auto-regulation in regard to

arterial blood pressure has been observed in the kidney".[3] Although perfusion is not dependent on the metabolic rate the constancy of blood flow in the face of blood pressure changes suggests peripheral control, in this case dependent on electrolyte regulation.

3. DISCUSSION

3.1. Tolerable range for constant oxygen extraction is CaO_2 dependent

From the exercising muscle study (section 3.2.1) it appears that the sustained muscle DO_2:VO_2 ratio (and oxygen extraction) is specifically related to CaO_2 rather than to PO_2 or Hb. The values of oxygen tension in the exercising muscle venous blood were all very similar for normal and anaemic states but those for 30-watt exercise in hypoxia were reduced as seen in Figure 9.

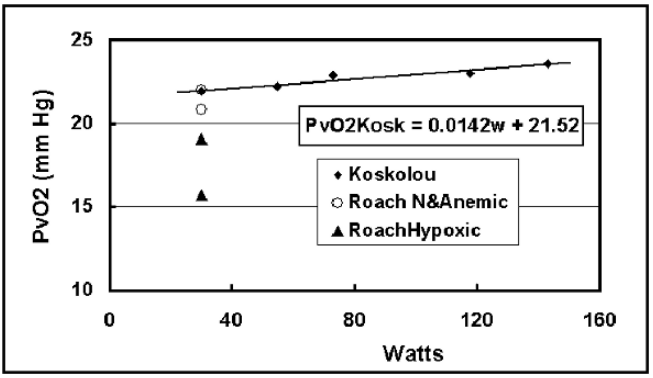

Figure 9. Exercising muscle venous PO_2 (P_vO_2) for the normal and anaemic subjects of Koskolou et al.[10] were all on a shallow line whereas the hypoxic values from Roach et al.[11] were well below the anaemic ones.

The dependence of constant oxygen extraction (and DO_2:VO_2 ratio) on CaO_2 rather than PO_2 or Hb suggests the importance of maintaining an oxygen supply. However, the mechanism driving the oxygen into the mitochondria depends upon PO_2 and the diffusion rate will depend on distance as well as the diffusion coefficient for oxygen. Krogh's work showed very large changes in inter-capillary distances across a range of skeletal muscle metabolic rates which allow adequate diffusion rates.[23] The diffusion coefficient for oxygen is probably constant, though some augmentation of the diffusion coefficient above that for water has been shown to occur with artificial dextran solutions.[24] A feature of the diffusion of oxygen suggested by this is the possibility that there could be augmentation of the diffusion coefficient from alterations in tissue polymer changes. Also important is the suggestion that diffusion of oxygen starts at arteriolar level as this may allow local tissue signalling.[25]

3.2. Possible reduction of resting tissue VO_2 when CaO_2 is excessively low

The finding that there is both reduced oxygen delivery and extraction in brain at SaO_2 values below 90% (section 3.2.2) is either an artefact of the calculation or means that

there is reduced oxygen consumption. This should be testable by modern methods and would be of considerable interest. This appears to apply also to liver, kidney and resting skeletal muscle (section 3.3, Figure 8). It is possible that lowering of VO_2 occurs when tissue self-regulation is beyond the range where adequate oxygen delivery can be sustained in tissues not being driven to higher metabolic rates. Very high oxygen extraction values are known to occur in exercising skeletal muscle where the metabolic rate is driven to high and maximal levels. Here the metabolic rate is driven to the high levels in contrast to resting tissues.

3.3. Effects on mechanisms sustaining blood flow adjustments

The impaired intestinal perfusion in haemorrhage in dogs (illustrated in Figure 7; section 3.2.4) was improved significantly by the administration of a dopamine-1 agonist (Figure 10, left hand panel). Guzman et al.[22] found no difference in VO_2 suggesting an improved DO_2:VO_2 ratio. This is compatible with E,control at baseline of 0.24 and E,drug of 0.21 (DO_2:VO_2 ratios: 4.2 and 4.8, respectively).

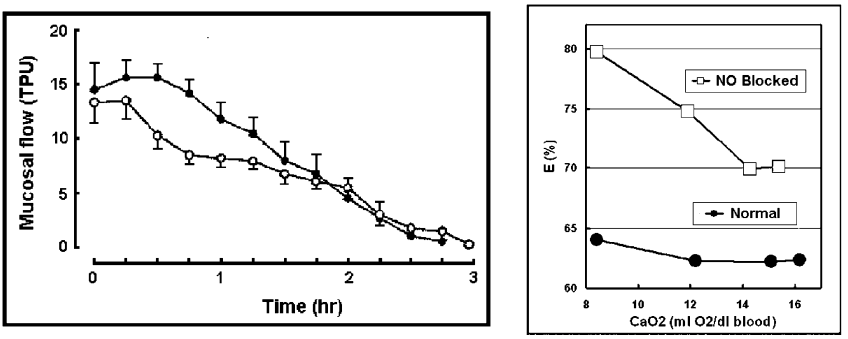

Figure 10. The left hand panel here shows improved intestinal mucosal blood flow in dogs, haemorrhaged 5 ml Kg^{-1} every 15 minutes, on a Dopamine-1 (DA-1) receptor agonist (●). With no drug blood flow is significantly worse for the first 6 bleeding episodes. TPU …. Tissue perfusion units. There was no change in mucosal VO_2.[22] In the right hand panel the normal, well-sustained cardiac oxygen extraction (Figure 6) is grossly modified by NO blockade. Oxygen extraction is greater and increases over most of the hypoxic range.

It can be seen in Figure 10 (right hand panel) that the well-sustained myocardial oxygen extraction in hypoxia (Figure 6 right hand panel and lower section above) is radically altered by nitric oxide (NO) blockade. Oxygen extraction is higher and not well-sustained. If NO is basic to the control of blood flow for other metabolic dependent tissues this will be a combination of effects on peripheral tissues as well as the heart.

3.4. Arterial blood pressure control

To quote Guyton et al.[4] "If each local tissue is to control its own blood flow by dilating or constricting its blood vessels, then it is essential that the arterial pressure be maintained at a pressure high enough to supply the blood demanded by the tissues." And, " it is often thought that nervous control of arterial pressure is effected almost entirely by changing the resistance to blood flow through the small tissue blood vessels. However, an increase in resistance would decrease blood flow through the tissues. Therefore, when a tissue

demands additional quantities of blood flow because of its local needs, vasoconstriction of its arterioles to maintain the arterial pressure would be very detrimental to the tissue's own needs. Fortunately, the local vasodilating effect caused by increased metabolism usually prevails over the vaso-constricting effect of the nervous signals, and the net result is decreased vascular resistance rather than increased resistance. Yet, how can the nervous system maintain arterial pressure in the face of the decreasing vascular resistance? The answer is: by increasing the filling pressure of the circulation. Strong sympathetic stimulation of the large vessels, particularly the veins, can increase this pressure, called the *mean systemic pressure,*[1] from a normal value of 7 mm Hg up to 18 to 21 mm Hg, almost a three fold increase. This is essentially the same effect as increasing the pressures in all the peripheral vascular reservoirs by an average of three fold, which greatly increases venous return and cardiac output. Therefore, the arterial pressure is maintained by an increase in cardiac output and not by an increase in peripheral resistance." As an example he quotes experimental work where heavy exercise in the sympathectomized-vagotomised dog led to a gross fall in blood pressure, whereas in the intact animal there was an increase in blood pressure.

3.5. Overview

Determination of blood flows to specific organs and the overall (whole body) proportional relationship of cardiac output to metabolic rate confirms that it is tissue requirements, not cardiac function per se which determine cardiac output.

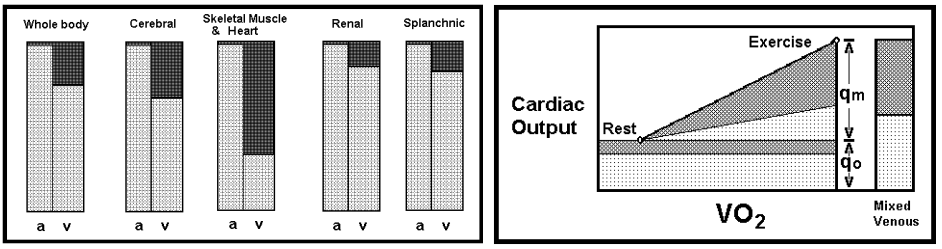

Figure 11. The panel on the left shows normal arterial and venous oxygenation for the body as a whole, for the brain, skeletal muscle and heart, the kidney and the splanchnic area. The venous oxygenation for the whole body is as shown at rest, approximately ¼ oxygen extraction, cerebral 1/3, skeletal muscle and heart approximately 2/3, kidney about 1/6 and the splanchnic area around 1/5. In moderate exercise skeletal muscle removes 2/3 of arterial oxygen but the rest of the body still removes ¼ as illustrated in the panel on the right. This depicts venous oxygenation for muscle (blood flow qm) and the rest of the body (blood flow qo). These will mix to give a combined, mixed venous blood with progressively lower oxygen saturation as exercise intensity increases.

Figure 11 illustrates the oxygen extraction status for the various major organ systems and also for the whole body at rest in the left hand panel. The venous value for the whole body at rest, representing the total of all tissue blood flows is approximately ¼ desaturated. In exercise the exercising muscle venous drainage, with 2/3 desaturation, is

[1] 'mean systemic pressure' is the effective mean pressure which would obtain if blood flow was stopped and the blood volume distribution had reached equilibrium.

added in progressively higher proportion (with heavy exercise desaturation is even greater). The right hand panel illustrates admixture of the 2/3 desaturated muscle venous blood to the ¼-desaturated blood from the rest of the body. The mixed venous saturation, SvO_2 = (qm x 1/3 + qo x ¾) / Cardiac output, for the modest exercise range.

In summary, blood flows are largely determined at tissue level and normally sustain a tissue specific oxygen extraction. This tissue specific oxygen extraction is sustainable within limits of arterial blood pressure (autoregulation), metabolic rate and arterial oxygen content. The CaO_2 range over which a normal oxygen extraction can be sustained varies from one tissue group to another; skeletal muscle and heart sustain normal extraction (approximately 2/3, DO_2:VO_2 of 1.5 to 1.6) down to an oxygen content at least as low as 60% of normal, cerebral oxygen extraction 1/3 (DO_2:VO2 of 3) above 90% or so for hypoxia, the limit for anaemia may well be at the same CaO_2. For the kidney and splanchnic areas oxygen extraction is much lower (1/6 to 1/5, DO_2:VO_2 ratio of 5 or 6) and the splanchnic area does not appear to be able to stand low CaO_2 or blood pressure. Limits for the kidney are not yet clear but it extracts more oxygen when CaO_2 is low rather than sustaining a constant value.

4. REFERENCES

1. H. Valtin, *Renal Function: Mechanisms Preserving Fluid and Solute Balance in Health and Disease.* Ch 6 Renal Hemodynamics and Oxygen Consumption. (Little, Brown and Company, Boston, 1973), pp 177-196.
2. A. J. Carlson and V. Johnson, *The Machinery of the body*, Third edition. (The University of Chicago Press, Chicago, 1948).
3. H. D. Green, C. E. Rapela and M. C. Conrad, Resistance (conductance) and capacitance phenomena in terminal vascular beds. In, *Handbook of Physiology*, *Circulation,* (Am. Physiol. Soc., Washington D.C, sect. 2, vol. II, chapter. 28, 1963), pp. 935-960.
4. A. C. Guyton, C. E. Jones and T. G. Coleman, *Circulatory Physiology: Cardiac Output and its Regulation,* (W. B. Saunders Company, Philadelphia, 1973).
5. C. B. Wolff. Cardiac output, oxygen consumption and muscle oxygen delivery in submaximal exercise: normal and low O_2 states, *Adv. Exp. Med. Biol.* **510**: 279-284 (2003).
6. A. C. Guyton, Integrated dynamics of the circulation and body fluids. Ch 6, In, *Pathologic Physiology: Mechanisms of Disease*, edited by W. A. Sodeman and T. M. Sodeman, (W. B. Saunders Co., Philadelphia and London, 1979), pp 169-197
7. D. E. Donald and J. T. Shepherd, Initial cardiovascular adjustment to exercise in dogs with chronic cardiac denervation, *Am J. Physiol.* **207**(6), 1325-1329 (1964).
8. L. B. Rowell, *Human Circulation: Regulation During Physical Stress* (OUP *Oxford,*. 1986).
9. L. B. Rowell, *Human Cardiovascular Control* (OUP Oxford., 1993).
10. M. D. Koskolou, R. C. Roach, J. A. Calbet, G. Rådegran, and B. Saltin, Cardiovascular responses to dynamic exercise with acute anemia in humans, *Am. J. Physiol.* **273**, H1787-H1793 (1997).
11. R. C. Roach, M. D. Koskolou, J. A. L. Calbet, and B. Saltin, Arterial O_2 content and tension in regulation of cardiac output and leg blood flow during exercise in humans, *Am. J. Physiol.* **276**, H438-H445 (1999).
12. J. W. Severinghaus, H. Chiodi, E. I. Eger, B. Brandstater, and T. F. Hornbein, Cerebral blood flow in man at high altitude, *Circulation Res.* **19**, 274-282 (1966).
13. C. B. Wolff, Cerebral blood flow and oxygen delivery at high altitude, *High Altitude Medicine and Biology* **1**(1), 33-38 (2000).
14. C. B. Wolff, P. Barry and D. J. Collier, Cardiovascular and respiratory adjustments at altitude sustain cerebral oxygen delivery – Severinghaus revisited, *Comp. Bioch. and Physiol. Part A* **132**, 221-229 (2002).
15. C. H. E. Imray, A. W. Wright, C. Chan, A. R. Bradwell and the Birmingham Medical Research and Expeditionary Society (BMRES), 3% carbon dioxide increases cerebral oxygen delivery when breathing hypoxic gas mixtures, *High Altitude Med. Biol.* **3**(1), p106 A31 2002 (abstract).

16. C. H. E. Imray, S. Walsh, T. Clarke, H. Hoar, T. C. Harvey, C. W. M. Chan, P. J. G. Forster and the BMRES, 3% Carbon dioxide increases cerebral oxygen delivery at 150m & 3549m, *High Altitude Med. Biol.* **3**(1), p106 A32 (2002) (abstract).
17. C. H. E. Imray, H. Hoar, A. D. Wright, A. R. Bradwell C. Chan, and the BMRES, Cerebral oxygen delivery falls with voluntary forced hyperventilation at altitude, *High Altitude Med. Biol.* **3**(1), p106 A33 (2002) (abstract).
18. C. B. Wolff, and C. H. E. Imray, Partitioning of arterial and venous volumes in the brain under hypoxic conditions, *Adv. Exp. Med. Biol.* **540,** 19-23 (2004).
19. C. B. Wolff, N. Richardson, O. Kemp, A. Kuttler, R. McMorrow, N. Hart and C. H. E. Imray, Near infra-red spectroscopy and arterial oxygen extraction at altitude, Adv. Exp. Med. Biol., **599,** 183-189.
20. R. R. Martinez, S. Setty, P. Zong, J. D. Tune and H. F. Downey, Nitric oxide contributes to right coronary vasodilatation during systemic hypoxia, *Am. J. Physiol.* **288**(3), H1139-H1146 (2005).
21. B. Folkow and E. Neil, *Circulation* (Oxford University Press, London, Toronto, 1971).
22. J. A. Guzman, A. E. Rosado and J. A. Kruse, Dopamine-1 receptor stimulation impairs intestinal oxygen utilization during critical hypoperfusion, *Am. J. Physiol.* **284**, H668-H675 (2003).
23. A. Krogh, *The Anatomy and Physiology of Capillaries* (Hafner Publishing Co., New York, 1959).
24. M. McCabe and D. J. Maguire, The measurement of the diffusion coefficient of oxygen through small volumes of viscous solution: implications for the flux of oxygen through tissues, *Adv. Exp. Med. Biol.* **316**, 467-473 (1992).
25. B. R. Duling and R. M. Berne, Longitudinal gradients in periarteriolar oxygen tension. A possible mechanism for the participation of oxygen in local regulation of blood flow, *Circulation Res.* **27**, 669-678 (1970).