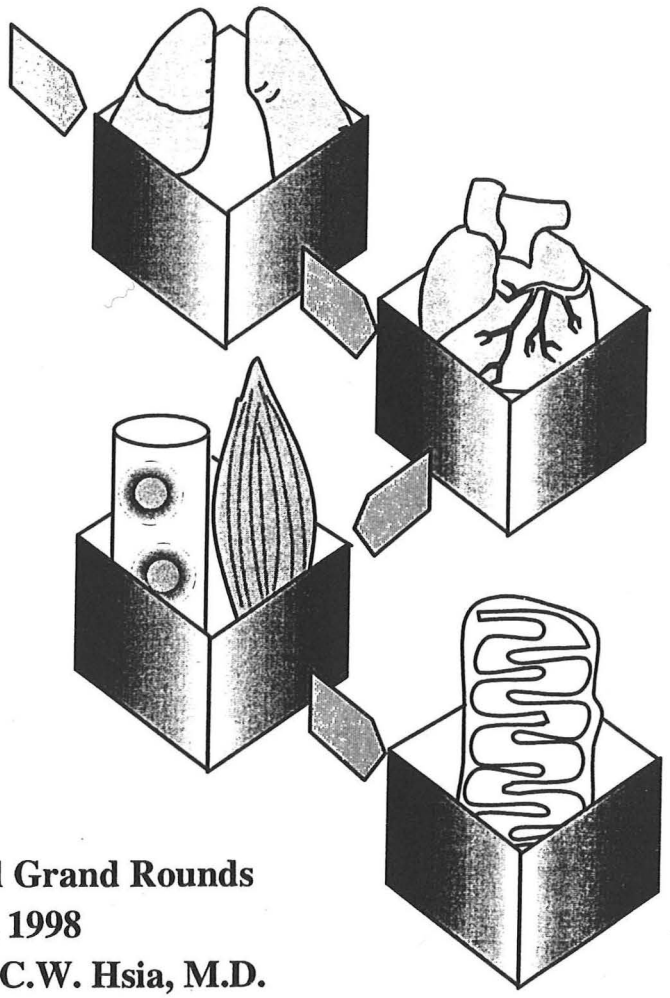
Co-adaptation in Oxygen Transport and Utilization: Matching Biological Capacities



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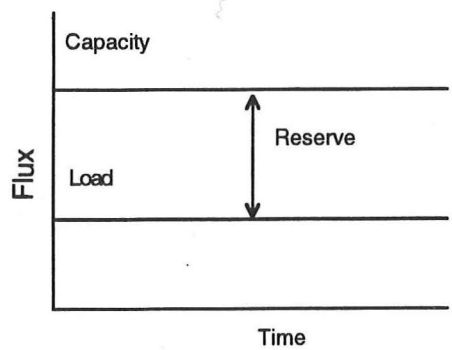
The idea that organisms evolve in a structurally and functionally integrated fashion, and that related biological processes should be matched to one another in order to optimize the efficiency of the whole organism, are as old as the science of biology itself. Charles Darwin's treatise *The Origin of Species* remains the most famous and lucid description of this evolutionary process: [1]

> *"...in order to spend on one side, nature is forced to economise on the other side."*
>
> *".....natural selection is continually trying to economise every part of the organisation. If under changed conditions of life a structure, before useful, becomes less useful, its diminution will be favoured, for it will profit the individual not to have its nutriment wasted in building up an useless structure."*

There are three fundamental types of matching in biological systems; each operative on a micro (enzymatic or molecular) or macro (whole organism and species) scale: 1) Matching capacity to load within a given system; 2) matching capacities in sequential steps along one pathway; and 3) matching capacities in parallel related pathways.

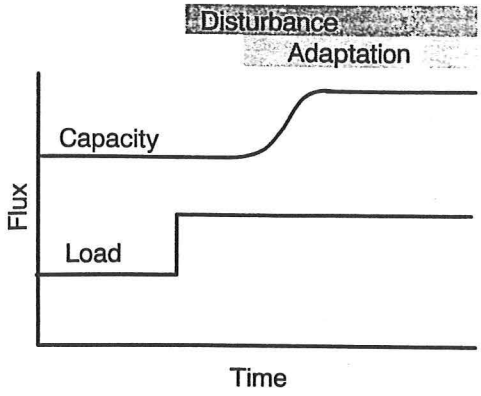
1. Matching Capacity to Load within a Given System



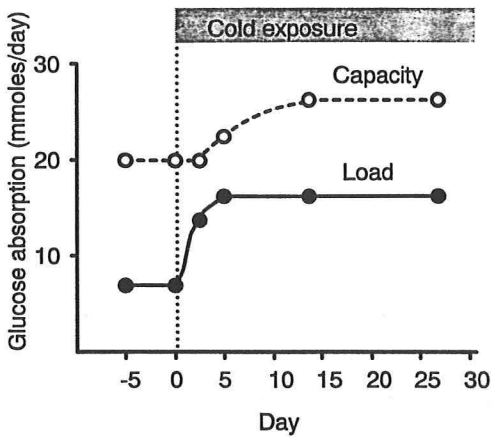
Definitions: **Load** is the flux under physiologic conditions. For an enzymatic reaction, this is the rate by which a substrate is converted to the product of the reaction. For a transport process, this is the rate by which a substance is carried from point A to point B. **Capacity** is the maximal possible load that can be achieved in a given system. **Reserve** is the difference between the load and capacity.

Across a wide range of biological parameters for a wide variety of animal species, the ratio of capacity to load has been found to be remarkably consistent, i.e., between 2 and 6; this ratio has been termed a "safety factor". [2] It appears that **matching the ratio of capacity to the load** is one of the primary goals of biological regulation. There are two ways to alter the reserve of a biological system: a) increased average daily load; and b) reduced capacity.

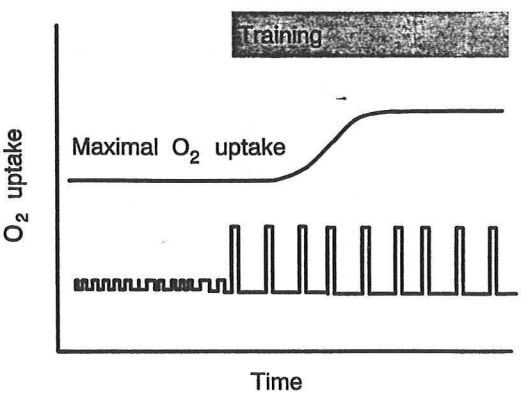
1.a. **Increased Load** There is a universal tendency for a biological system to increase its capacity in response to a sustained increase in average daily load, so as to maintain a constant ratio of capacity to load.



1.a.1. Intestinal absorptive capacity in cold exposure [3]: Open circles are the maximal absorptive capacities for glucose in the intestine; closed circles represent the actual amount absorbed daily (load). When mice are exposed to cold temperature, their metabolic rate and food intake increase; intestinal glucose absorption increases accordingly. Note that the load although increased, is still way below the capacity of the system. Theoretically, the increased luminal concentration of glucose will kinetically drive faster glucose uptake and no biologic adaptation should be necessary. However, in reality when this "sub-Vmax" increase is sustained, the intestine increases its capacity to match the load. It seems that this load is too close to the capacity and what is being regulated is the reserve or the ratio between capacity and load.

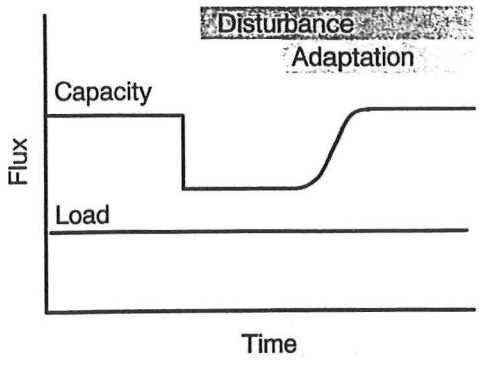


1.a.2. Maximal O_2 uptake during exercise training: Shown here is the daily average O_2 uptake and the maximal O_2 uptake in an average untrained person. As this individual undergoes physical training that imposes a regular and intermittent increase in load on O_2 transport, average daily O_2 uptake is increased but still submaximal. This load however is sufficient to elicit an increase in the maximal O_2 uptake by some 30%. In both examples above, one sees that even a submaximal increase in load triggers adaptive changes that defend and preserve the ratio of capacity to load.



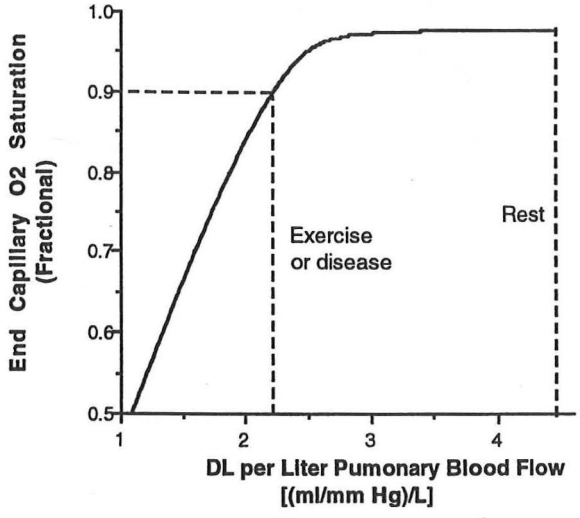
1.b. **Reduced capacity**

Below are two examples where the transport capacity is reduced but still adequate for meeting the expected loads imposed on the system: unilateral pneumonectomy and nephrectomy. Theoretically compensatory mechanisms need not occur but in fact they do.



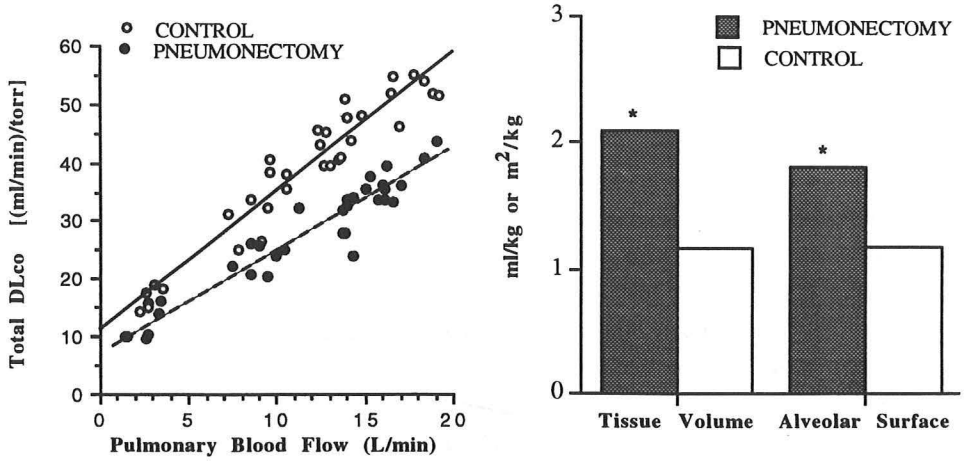
1.b.1. Unilateral Pneumonectomy.

Normally lung diffusing capacity (DL) increases proportionally as cardiac output or pulmonary blood flow increases during exercise. [4] In patients with chronic lung disease, arterial oxygen saturation does not begin to drop during exercise until DL drops below 50% of predicted for a given cardiac output. [5]

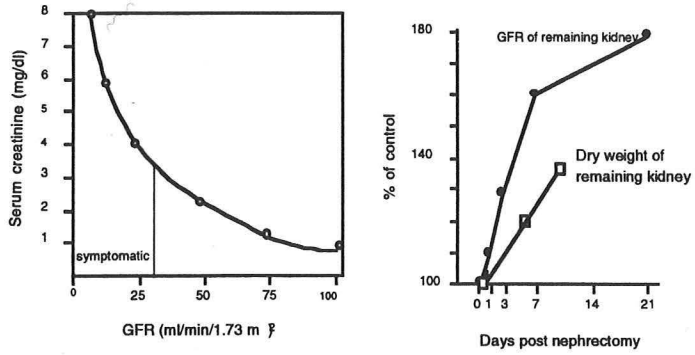


After the surgical removal of 50% of lung tissue, the entire cardiac output is directed through one lung, i.e., effective pulmonary blood flow per unit of lung is doubled at any given cardiac output. Thus in patients after pneumonectomy the reduction in DL (20 to 30%) is considerably less than expected from the fraction of alveolar tissue removed. Although alveolar-arterial O_2 tension gradient is moderately elevated, arterial O_2 saturation rarely falls below 90% even at peak exercise. [6] Hence in the postpneumonectomy patient O_2 flux during physical exertion is still below the transport capacity of the remaining lung. Yet interestingly unilateral pneumonectomy elicits a vigorous compensatory response from the remaining lung. In immature dogs there is an accelerated growth of alveolar tissue during the first 8 weeks after pneumonectomy, leading to a complete normalization of the compartmental volumes of alveolar tissue as well as gas exchange function, including a 200% increase in DL of the remaining lung from its pre-pneumonectomy

value. [7] In adult dogs after pneumonectomy, compensatory lung growth also occurs but to a limited degree, eventually restoring approximately half of the lost diffusing capacity. [8, 9]



1.b.2. Unilateral nephrectomy



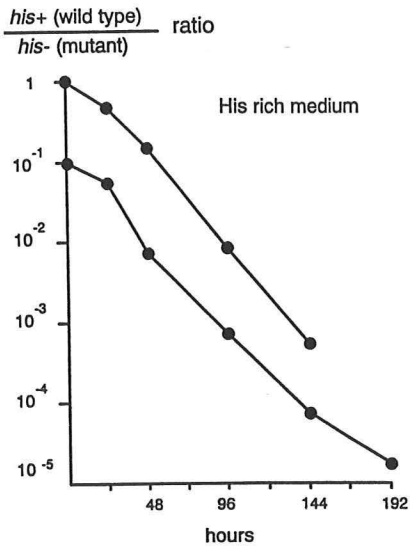
In patients with chronic renal disease, clinical symptoms of impaired renal function does not develop until the GFR falls below 30 ml/min (i.e. 15 ml/min per kidney). However, when one kidney is removed, the remaining kidney is not content to let its GFR remain at the pre-nephrectomy normal value of 50 ml/min. Within 2 to 3 weeks, GFR of the remaining kidney increases to 180% of its pre-nephrectomy value, increasing the whole organism GFR from 50 ml/min to 90 ml/min. This increase is accompanied by an increase in renal mass. [10-12]

Principles of Optimization It appears that organisms do not like to live on the edge. Maintaining an adequate reserve allows the animal to better cope with unexpected internal and external changes. Although our biological systems operate way below capacity 99% of the time, the infrequent instances where full capacity is required may well determine the difference between life and death for that organism. If this is true, then why do organisms not evolve very large reserves in all systems, such that the organism's behavior would not be limited by their bodies? [13]

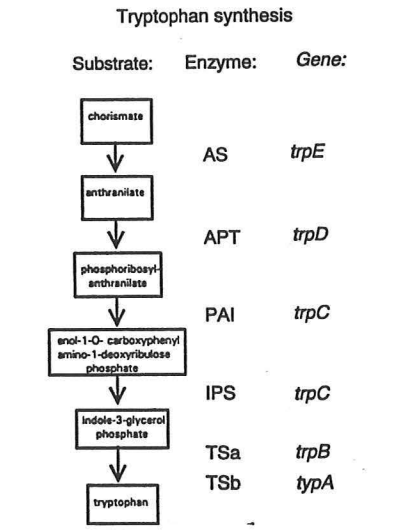
Maintenance of any biological capacity must incur costs in the form of metabolic energy or space. There are finite quantities of food, metabolic enzymes, cell membranes, cytoplasmic organelles, etc. that can be accommodated by each organism. Large reserves in one system reduces resources available to other systems and the efficiency of the whole organism. By natural selection, uneconomical animals would suffer a survival disadvantage that counterbalances the survival advantage of possessing large reserves. The atrophy and eventual loss of excessive or disused capacity by natural selection is a solid and universal phenomenon. Cave animals such as bats tend to lose their vision as they acquire sophisticated techniques of echolocation. [14] In subterranean animals such as the mole rat, eyes are not only useless but also a nuisance because of ongoing abrasion and infection during burrowing. As a result, their eyes atrophy and become covered with skin, but the vestigial organ has evolved into a circadian sensor capable of regulating the diurnal rhythm of various metabolic activities. [2] Volant birds that migrate to isolated Oceanic islands with no predators quickly lose the ability to fly. Their rudimentary wings perhaps help the animal maintain balance during walking. Beetles that live in small, windy exposed islands quickly get blown away if they try to fly; hence their wings become useless and maybe even a risk. In some species this capacity is completely eliminated. [1]

Evidence for Optimization How do we know that these examples of loss of a redundant capacity actually confers survival advantage to the organism, and that the loss did not result from simple accidental mutations which were allowed to persist because the structure had no useful function?

An interesting observation was made in a paper published in Nature (1967) by Zamenhof and Eichhorn who were searching for an evolutionary basis of parasitism. [15] They studied wild type E. coli which can synthesize histidine (his+) and a mutant E. coli which cannot synthesize histidine (his-). Phenotypically, his- E. coli will not grow in the absence of histidine in the culture medium. They inoculated his+ and his- E. coli cells in medium enriched with histidine. Theoretically, both strains should survive equally well in this medium.



In reality, the his- strain rapidly outgrew the his+ strain. The his+ to his- ratio went from 1 to 10^{-3} over 6 days or 36 generations. In fact, no matter what his+/his- ratio one starts with, in 6 days, there is a 1,000 fold reduction in his+ cells. This means that the selection is not due to production of a diffusable factor but is intricate to the cells themselves. It appears that possession of a gene encoding a capacity that is not needed becomes a liability; with passage of generations, this strain perishes. The widely accepted interpretation of this study was that of conservation of energy. Although histidine in the medium efficiently suppresses the expression of the enzymes responsible for histidine synthesis, the suppression may not be complete. So a low level of histidine synthesis is still present despite a plentiful supply in the medium which is a wasteful behavior. This metabolic energy is saved in mutants and energy conservation confers a survival advantage. Although this conclusion is clearly a testable hypothesis, no one tested it until 1978.

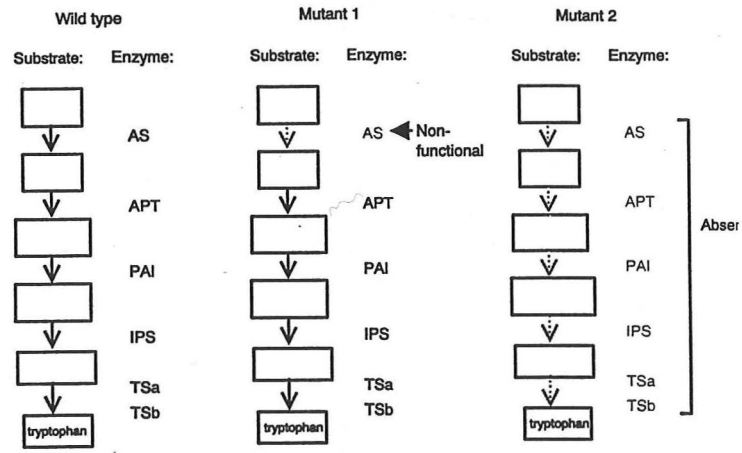


Dykhuisen [16] studied mutant E. coli that could not synthesize tryptophan. Shown here is the metabolic pathway of tryptophan synthesis. The boxes represent the metabolic intermediates. The enzymes and the genes coding for the enzymes are also shown. Tryptophan is synthesized by enzymes coded by five genes trp A to trp E. These genes exist as an operon in the genome and are all transcribed on the same mRNA.

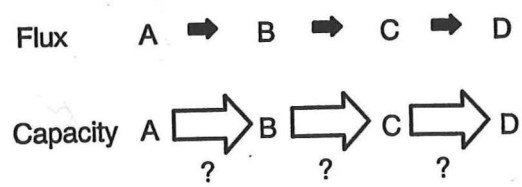
Dykhuizen studied wild type cells (trp+) and two mutants that cannot synthesize tryptophan (trp-). Mutant 1 has a missense mutation in the first enzyme of the pathway that renders this enzyme non-functional. All the subsequent enzymes are present and functionally normal. Mutant 2 has a nonsense mutation that introduced a stop codon at the beginning of the polycistronic mRNA coding for all the enzymes of the operon and the E. coli is left with absolutely no enzyme whatsoever. If the energy conservation hypothesis is correct, the following should be observed:

1. Both trp- mutants should outgrow the trp+ wild type in a trp-rich medium.

2. Mutant 1, though crippled at the first step of the pathway, still manufactures all the subsequent enzymes and in the presence of intermediates will have some obligatory constitutive trp synthesis. This capacity is energetically superfluous in the presence of ambient tryptophan. In contrast, mutant 2 is economic in two ways. First, it will not synthesize tryptophan under any circumstances. Second, it does not have to maintain the machinery for trp synthesis. Mutant 2 should be the most energy efficient in the presence of high ambient trp and should have a measurable growth advantage over mutant 1. His data showed the contrary. Whereas both mutants quickly outgrew the wild type, there was absolutely no measurable growth advantage of mutant 2 over mutant 1 in a trp-enriched medium. This lack of difference persisted despite his attempt to amplify the energy wastage on mutant 1 by providing intermediate metabolites. Thus energy cost cannot fully explain the survival advantage of the mutant strains. Space constraints may be an important selection factor but has not been formally tested.



2. Matching capacities in sequential steps along one pathway



Consider a multiple step biologic process such as sequential biochemical reactions (e.g. metabolic pathways), or transport of a substance from one region to the next within a cell, within an organ, or between organs (e.g. oxygen transport). At equilibrium in the absence of branch points, the flux (i.e. load) of each of the steps has to be equal. However, there is no *a priori* reason to assume that the capacities of all steps must be equal.

Single Step Control

$$\frac{\Delta \text{ Flux}}{\Delta \text{ Capacity}} \qquad 0 \qquad +++ \qquad 0$$

2.a. Metabolic pathways An older but still popular concept regarding metabolic enzymatic pathways is that of a rate-limiting step. Here, the idea is that most enzymes along the pathway is present in large excess and one enzyme is strategically placed at a bottleneck where the flux is near capacity. The capacity of this enzyme controls the flux across the entire reaction, whereas changes in the capacity of the other enzymes have minimal impact. Argument was made that one only has to regulate the activity at one step in order to control the entire cascade. For example, phosphofructose kinase was believed for years to be the bottleneck in glycolysis. However, this makes no economic sense because the cell is required to maintain excess capacities for all other steps all the time which is very wasteful.

Distributive Control

$$\frac{\Delta \text{ Flux}}{\Delta \text{ Capacity}} \qquad + \qquad + \qquad +$$

A notion of distributive control was pioneered by Dr. Paul Srere at the Dept. of Biochemistry as well as by others. In this concept, control is exerted at multiple points and flux across the pathway is achieved by co-regulation of individual capacities. Therefore the control of flux across the whole pathway is distributed among all the enzymes, and the capacities at individual steps are matched to one another. There is a large body of evidence supporting distributive control at the cellular level. See excellent review by Dr. Srere. [17] A few examples are given here.

Overexpression of individual enzymes

Enzyme	fold increase in activity	fold increase in glycolytic flux
Hexosekinase	14	1.1
Glucosephosphate isomerase	11	0.9
Phosphofructose kinase	4	1.0
Phosphoglyceraldehyde kinase	12	1.0
Phosphoglycerate mutase	12	1.0
Pyruvate kinase	9	1.1

Schaff et al [17] overexpressed glycolytic enzymes individually in yeast; using a lower eukaryotic cell because of the ease in manipulating its genome. The supposition is that if any one glycolytic enzyme is situated at a metabolic bottleneck, overexpression of that enzyme will increase flux across the whole pathway. They observed that overexpression of individual glycolytic enzymes by 4 to 14-fold had no impact on glycolytic flux, suggesting that there are indeed no bottlenecks in the pathway.

Niederberger et al [18] used a similar approach and overexpressed enzymes in the tryptophan synthetic pathway discussed before. Overexpression of any one or even three of these enzymes failed to increase the rate of tryptophan synthesis. Only by expressing all the enzymes can one increase flux across this synthetic pathway.

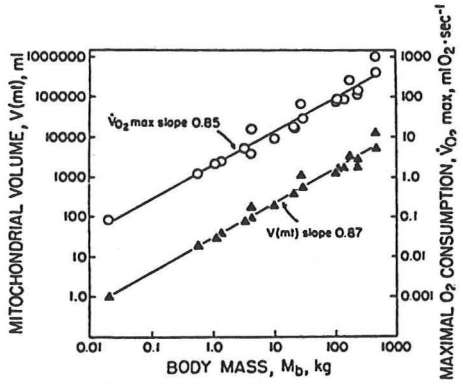
Tryptophan synthetic enzyme	Relative fold induction of activity							
	Wild type	Mutant strains						
		A	B	C	D	E	F	G
AS	1	1	1	1	1	30	27	24
APT	1	20	1	1	1	1	27	20
PAI	1	1	10	1	1	30	30	22
IPS	1	1	1	52	1	41	37	27
TS	1	1	1	1	37	1	1	24
Relative Trp synthesis	1.0	1.3	1.2	1.0	1.2	1.2	2.1	8.8

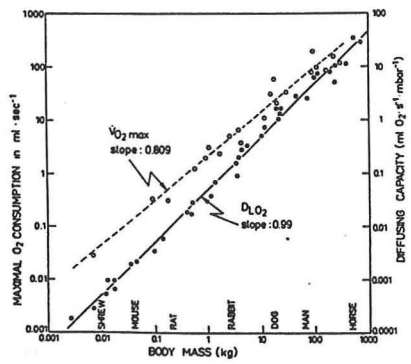
This observation is not limited to lower eukaryotes. Shown at right are the maximal velocities of a number of mitochondrial enzymes from rats that are either couch potatoes or marathon runners. [19] Every single enzyme examined was up-regulated in exercise-trained rats. These results are in keeping with the concept of distributive control or matching of sequential capacities. Examples where the amount of enzymes involved in a metabolic pathways increase or decrease coordinately include: glycolysis, TCA cycle, fatty acid synthesis, urea synthesis, nucleotide synthesis, amino acid synthesis and photosynthesis. [17]

	Vmax	
	Sedentary rats	Trained rats
Citrate Synthase	26	52
Isocitrate Dehydrogenase	2.2	4.1
α-Ketoglutarate Dehydrogenase	1.1	1.8
Glutamate Dehydrogenase	1.9	2.5
Succinate Dehydrogenase	4.2	8.4
Malate Dehydrogenase	312	459
Cytochrome c	8.8	18

2.b. Oxygen Transport Zooming out from a microscopic level to the whole organism, one example of co-ordinated regulation is O_2 transport and utilization, in which the sequential steps fall into four categories: convective transport (ventilation to the alveolus, cardiovascular delivery to the periphery); diffusive transport (across alveolar-capillary barrier, across capillary-tissue barrier); chemical reaction with carriers (hemoglobin or myoglobin); and oxidative phosphorylation within the mitochondria.

2.b.1. Are the different capacities matched? Taylor & Weibel proposed the term "symmorphosis" to describe the principle of matching biological structural capacities to functional demand in an economical fashion [20]. They compared physiologic and structural studies from a large number of animals of different sizes and habitual activity levels. Athletic species (e.g. dog and horse) possess larger specific lung diffusing capacity, heart mass, skeletal muscle mass and mitochondrial volume than related sedentary species of similar size (e.g. goat and cow, respectively). Across the animal kingdom, maximal O_2 uptake ($\dot{V}O_2max$), diffusing capacity (DLO_2) and muscle mitochondrial volume [V(mt)] in the heart and diaphragm all increase with body mass in a log linear fashion. The slopes of the increase in $\dot{V}O_2max$ and muscle mitochondrial volumes are similar. However the slope of the increase in DLO_2 with respect to body mass is significantly greater. [21, 22]

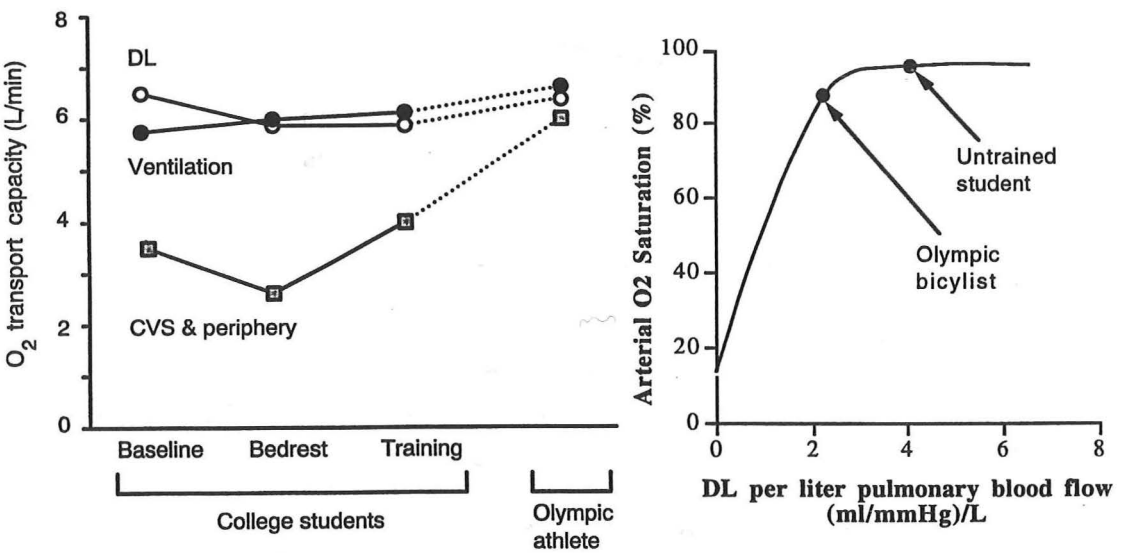




From these data Taylor and Weibel conclude that, at least for larger animals, the lungs possess excessive capacity whereas the other steps of O_2 transport are well matched to the maximal O_2 uptake of the animal [2]. For semantic, conceptual as well as technical reasons, their data and interpretation remain controversial. Physiological studies have not been able to directly demonstrate any "excess" or "redundant" lung capacity. Instead these studies show a co-ordinated regulation of O_2 flux across all steps consistent with a distributive control model as explained below.

2.b.2. What limits oxygen transport during exercise?

Other than pulmonary diffusing capacity, the steps of O_2 transport are malleable and lose their capacities quickly when physical fitness is not maintained. In contrast, pulmonary diffusive uptake does not become deconditioned, thus providing some reserve for adaptation to hypoxic environments, allowing organisms to migrate up to an altitude of 10,000 - 12,000 feet. In the average sedentary human subject at sea level, cardiac and peripheral skeletal muscle constitute the major bottleneck limiting exercise, i.e. maximal stroke volume and maximal O_2 extraction by muscle are relatively low. Arterial O_2 saturation remains normal up to maximal O_2 uptake, indicating that pulmonary diffusion is not limiting. Increasing inspired O_2 to 100% improves maximal O_2 uptake without increasing cardiac output, indicating that mitochondrial O_2 utilization is not a limiting factor.



Adapted from Saltin et al. [23]

2.b.3. Effects of Physical Training

Regular physical training enhances maximal O_2 uptake as well as the capacity for cardiovascular O_2 delivery, peripheral O_2 utilization and maximal sustained ventilation, but does not alter DL. Hence with training, capacities of all the transport steps become better matched. In

the untrained person a 40% increase in maximal cardiac output causes a 40% increase in maximal O_2 uptake with a negligible effect on arterial O_2 saturation. In the athlete a 40% increase in maximal cardiac output will cause a large fall in arterial O_2 saturation and less than a 10% increase in maximal O_2 uptake. [24, 25] Increasing minute ventilation at peak exercise by adding a mild expiratory flow resistive load increases the tidal volume and maximal O_2 uptake. [26] This is because in the athlete there is no longer any bottleneck; maximal O_2 uptake is equally sensitive to independent changes in maximal cardiac output, ventilation and diffusing capacity. Altering the capacity at each step alters the flux of the entire system.

Effects of Training

	Structural & Biochemical Effect	**Physiologic Effect**
Lung		Δ ventilatory pattern ↑ Ventilatory capacity ↔ DL
CVS	↑ heart size and myocardial mass	↑ stroke volume ↓ heart rate
Muscle	↑ muscle mass and capillary density ↑ slow twitch oxidative fibers ↑ mitochondrial volume ↑ activity of oxidative enzymes ↑ glycogen content ↑ fat utilization	↑ muscle strength ↑ muscle endurance

The **thoroughbred race horse** is an example where the species has been selectively bred for superior muscle strength and cardiovascular capacity out of proportion to what their lung structure will support, i.e. a mismatch develops. At maximal exercise pulmonary O_2 transport becomes a major limiting factor because a) the rapidly increasing cardiac output exceeds the capacity of the pulmonary capillary bed for oxygenation; and b) the requisite ventilation for maintaining adequate arterial O_2 saturation exceeds the capacity of the respiratory pump. At peak exercise, their arterial O_2 saturation drops to below 80%, CO_2 retention develops, and mean pulmonary artery pressure rises to nearly 100 mmHg. [27] Under such hyperdynamic conditions, stress failure of the alveolar-capillary barrier may develop [28, 29] and frank exercise-induced pulmonary hemorrhage is common. Treatment with furosemide attenuates the exercise-induced rise in pulmonary vascular pressures [30] and improves racing performance but does not prevent the occurrence of pulmonary hemorrhage. [31]

2.b.4. Effects of aging Maximal O_2 uptake declines with age, associated with parallel declines in maximal alveolar ventilation, pulmonary diffusing capacity, heart rate, stroke volume, oxygen extraction, limb muscle mass and oxidative capacity. [25, 32] In highly

trained elderly subjects the decline is attenuated but again, all components of O_2 transport decline at similar rates with no single limiting step.

3. Matching capacities in parallel related pathways

The utilization of O_2 occurs in parallel with that of substrates for energy production. It takes approximately 30 s from the onset of exercise before heart rate and stroke volume increase sufficiently to deliver enough O_2 to sustain aerobic metabolism. During this transient period locomotive power output is generated from the rapidly available energy stores in skeletal muscle. ATP is generated anerobically via the high energy phosphocreatine (PCr) pool and glycolysis. During short burst exercise (e.g. 100 m dash) no oxygen is utilized; in fact runners hold their breath during the period of maximum effort. These short term stores are rapidly replenished after exercise. During intermediate duration exercise (1500 to 5000 m race), performance depends primarily on the rate of O_2 transport to exercising muscles, the coupled CO_2 transport and the rate at which glucose can enter tissue from blood. For long distance marathon (e.g 26 miles), circulatory transport of oxygen and glucose are still important, but increasingly the muscle must utilize its glycogen and fat stores to supply the substrates for oxidation. When these substrate stores are exhausted, fatigue develops. After exercise muscle energy stores are replenished slowly from caloric intake.

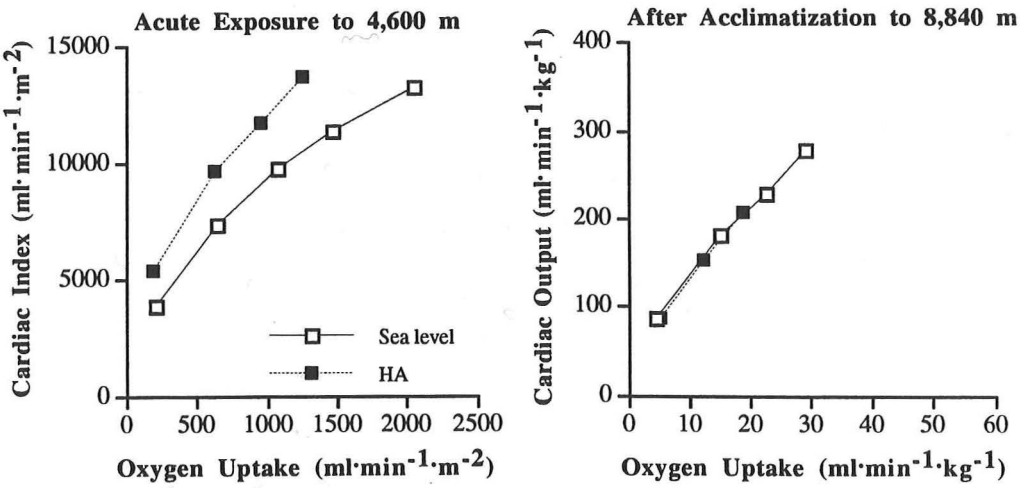
During extreme endurance loads, e.g. Tour de France cycle race (22 days, 2,400 miles), metabolic rate can increase 10 fold from rest. However, even if these exertional loads are intermittent, muscle energy stores must be replenished and waste products eliminated during periods of rest; hence average resting metabolic rate increases. The Tour de France racers gorge themselves each evening and consume 7,000 kcal/day which is enough to maintain a constant body weight during the race. Their average metabolic rate is 4 to 6 times basal metabolic rate [33]. Jared Diamond [33, 34] compared the highest sustainable metabolic rate during endurance activities in a large number of animals and found similar ratios, suggesting an upper limit to sustainable metabolic rate. Why can't the endurance racers eat more calories, or achieve a higher average metabolic rate since they have access to unlimited food? It may be that capacity for meeting long term endurance loads is dependent not just on delivery and utilization of O_2 and substrates, but also on the absorptive capacity of the small intestine, the hepatic capacity for synthesizing glycogen stores, and the filtration capacity of the kidney for eliminating wastes. In animals, these organs hypertrophy in response to increased daily metabolic activity brought on by chronic cold exposure [3]. The Tour de France athletes likely reached the limits of intestinal and hepatic capacities for delivery substrates and renal capacity for eliminating wastes.

4. Mismatched Biological Capacities

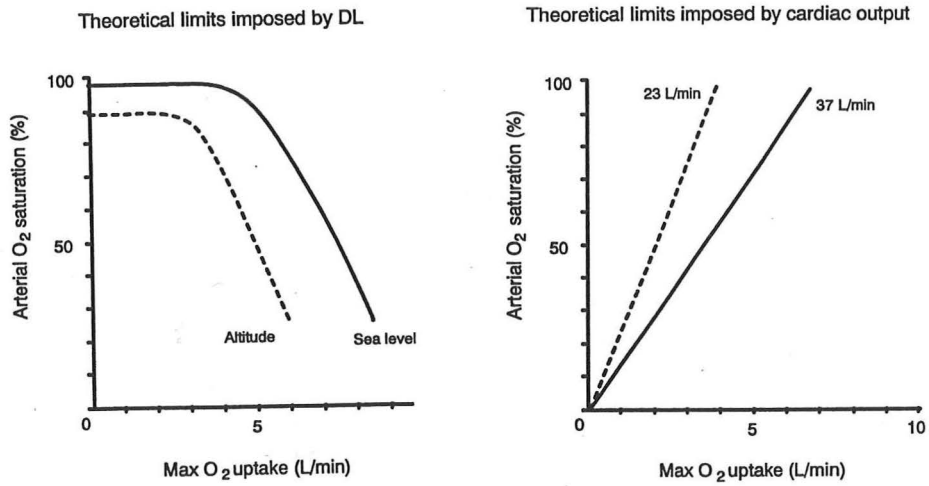
Mismatches in biological systems are created by: a) external factors (selective breeding, environmental change); and b) internal factors (disease). One would expect the organism to adjust the capacities of related processes accordingly in order to re-establish an equilibrium. Illustrated here are two examples of apparently paradoxical physiological responses which, when interpreted in light of the optimization principle, become perfectly sensible.

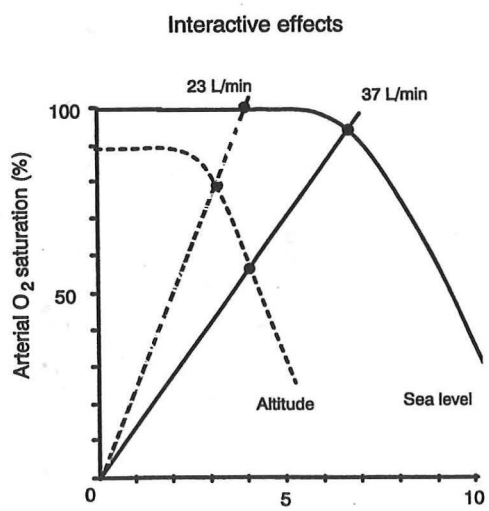
a. changes in cardiac and skeletal muscle function during acclimatization to high altitude;
b. cardiac and skeletal muscle dysfunction in chronic lung disease.

4.a. High Altitude Upon exposure to high altitude pulmonary O_2 uptake becomes the primary bottleneck in O_2 transport. Normal reserves in ventilatory capacity and DL allow individuals to maintain adequate arterial O_2 saturation for prolonged stay up to 12,000 ft. This is why patients with restricted lung volume or vascular bed have a high morbidity and mortality at high altitude. With time other organs of O_2 transport adjust their capacities to match the reduced O_2 supply; this is the process of acclimatization. For example, appetite declines and weight loss may be an adaptive process that minimizes energy expenditure. Polycythemia develops to restore arterial O_2 content. After an initial increase in submaximal cardiac output (left panel below) [35], maximal cardiac output decreases below sea level baseline (right panel below) [36-38]; this decline is independent of changes in hematocrit and is due to a lower maximal heart rate and a lower stroke volume. [39]



The decline in maximal cardiac output is only partially reversed by breathing an oxygen-enriched atmosphere [37] and may be related to activation of the parasympathetic system or diminished responsiveness to sympathetic stimulation [40]. There is no evidence of an intrinsic hypoxic depression of cardiac contractility [36]. The decline in maximal cardiac output appears counter-intuitive in the presence of hypoxia and sympathetic activation, and has been described as maladaptive. An examination of the interaction between pulmonary diffusion and cardiac output reveals that when pulmonary diffusion is the bottleneck, a decline in maximal cardiac output actually optimizes arterial O_2 saturation and O_2 delivery, as shown below.



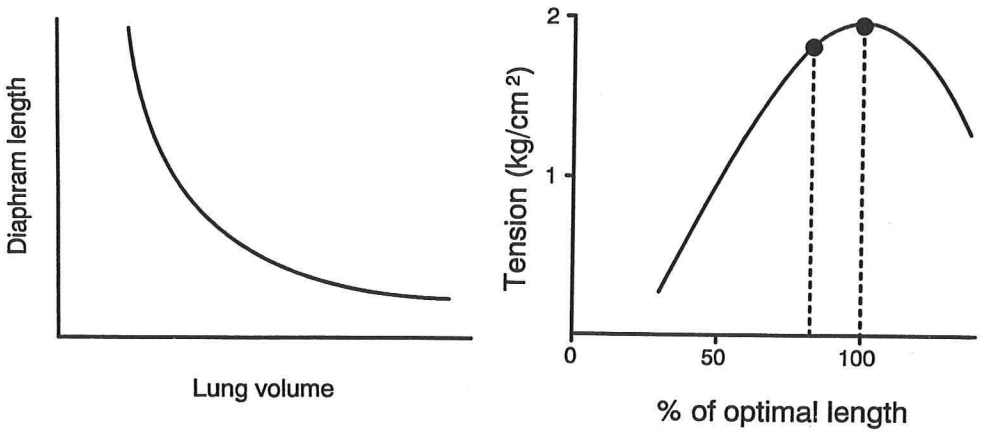


Left panel: For a given DL, arterial O_2 saturation is lower at altitude (PAO_2 = 60 mmHg) than at sea level (PAO_2 = 110 mmHg) and declines earlier as maximal O_2 uptake ($\dot{V}_{O2max}$) increases. *Middle panel*: For a given maximal cardiac output, the higher the $\dot{V}_{O2max}$, the higher the saturation. As maximal cardiac output increases the same $\dot{V}_{O2max}$ will lead to a lower saturation because of a reduction in pulmonary capillary transit time. *Right panel*: The points of intersection represent the interactive effects between DL, $\dot{V}_{O2max}$ and maximal cardiac output. A reduction in maximal cardiac output from 37 to 23 L/min at high altitude is associated with a small reduction in $\dot{V}_{O2max}$ but a large increase in arterial O_2 saturation.

With chronic high altitude exposure skeletal muscle fiber diameter decreases, capillary density increases and the mitochondria polarize next to the capillaries. These changes minimize the diffusive resistance for O_2 uptake. Volume of muscle mitochondria is reduced, indicating a loss of oxidative capacity. [41] Exercise at high altitude induces glycolytic enzyme activity but decreases enzyme activities involved in the citric acid cycle, respiratory chain, fatty acid oxidation and ketone body utilization. [42] These changes of acclimatization are not due to disuse. Reduction of muscle O_2 transport capacity may seem a paradoxical response to ambient hypoxia, but in fact these changes preserve overall metabolic efficiency by maintaining just enough muscle structural capacity to match the reduced O_2 uptake from the lungs.

4.b. Chronic lung disease Patients suffering from moderate to severe chronic respiratory impairment commonly show derangement of cardiac and peripheral muscle function. For example, cardiac output during exercise is reduced in patients with COPD even in the absence of overt pulmonary hypertension, due to combined factors including: deconditioning, impaired venous return from a high average intrathoracic pressure, and an elevated pulmonary artery pressure. Muscle weakness is a common finding in patients with stable moderate to severe COPD, and involves both respiratory and non-respiratory skeletal muscle. The main symptom that limits exercise is often leg fatigue and not dyspnea. [43] Upon exercise, oxidative metabolism of the skeletal muscles, assessed by ^{31}P-NMR, is abnormal in patients compared with normal subjects. [44] Patients show a marked decrease in cellular pH, phosphocreatine (PCr) and ATP contents of muscle at rest and during exercise in contrast to control subjects, suggesting progressive depletion of muscle high energy phosphates, impaired oxidative metabolism and earlier occurrence of anaerobic glycolysis. The depletion of PCr correlates with the reduction in vital capacity, maximum hand grip strength and muscle mass. Muscle protein concentration is lower. The percentage of type I slow twitch oxidative muscle fibers is reduced. The activity of glycolytic enzymes are elevated while activities of oxidative enzymes are

reduced. [45, 46] Abnormalities in enzyme activities are not responsive to long-term O_2 therapy [45] and are only partially alleviated by intensive exercise training [47, 48].

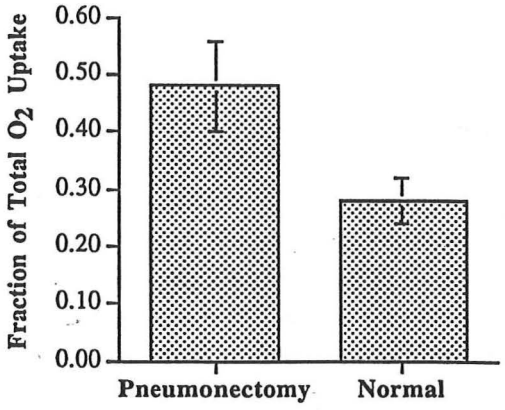


There is an inverse correlation between histological severity of emphysema and diaphragm weight and thickness in patients with COPD. [49-51] The loss of respiratory muscle mass is again counter-intuitive, since work of breathing is abnormally elevated in COPD and respiratory muscles are working harder than normal. One might expect to find respiratory muscle hypertrophy, not atrophy. Diaphragm atrophy can develop even in the absence of overt hypoxemia or malnutrition. A mechanical disadvantage of respiratory muscles is perhaps the most important cause in patients with moderate disease, while chronic hypoxemia, deconditioning and malnutrition further contribute to muscle weakness in patients with severe disease. Thoracic over-expansion causes the inspiratory muscles to become shortened. The diaphragm loses its normal dome shape and cannot descend or expand the rib cage during contraction. The shortened sarcomeres are at a mechanical disadvantage and cannot generate a normal tension during contraction. [52] In response the muscle gradually loses sarcomeres in series so the remaining sarcomeres are lengthened, thus partially restoring the tension that can be developed but reducing the shortening during contraction for a given level of neural input. [52] Hence the loss of diaphragm muscle mass in COPD actually counteracts the detrimental effects of thoracic over-expansion and helps to preserve contractile efficiency.

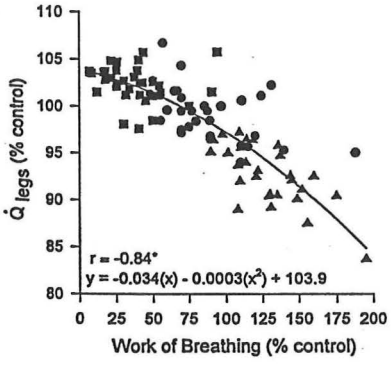
Competition between respiratory and non-respiratory muscle for the available cardiac output is an important cause of peripheral muscle dysfunction in patients with lung disease (e.g. after pneumonectomy, below left). As a result of the excessively high O_2 cost of

breathing in these patients, blood flow requirement of respiratory muscles is elevated. During heavy exercise, a disproportionately high fraction of cardiac output must be diverted to sustain the metabolic needs of the respiratory muscles. Consequently, O_2 delivery to leg muscles may not be sufficient to sustain the demands of locomotion, and lactate is produced by muscle even during light exercise. Buffering of lactate by bicarbonate leads to enhanced CO_2 production and stimulation of ventilation, further increasing the power and metabolic requirement of respiratory muscles out of proportion to the work being performed, and exacerbating the sensation of dyspnea [53]. The higher the work of breathing during exercise, the lower the blood flow ($\dot{Q}$) to leg muscles. [54]

Oxygen Requirement of Respiratory Muscles



Blood flow to Leg Muscles (From [54])



Eventually, exercise stops because of muscle fatigue as well as dyspnea; the excessive metabolic demands of respiratory muscles and the reduced maximal cardiac output leave little O_2 for muscles of locomotion. [55] Chronic deprivation of blood flow to skeletal muscles can lead to atrophic changes described above. In patients with severe end-stage lung disease, the excessively high O_2 cost of breathing during simple daily activities may constitute a major fraction of total body O_2 uptake that the metabolic demands of the GI tract cannot be adequately met, leading to reduced food intake and malnutrition, which further aggravates muscle atrophy as well as loss of muscle glycogen store and enzymatic capacity.

These secondary changes in muscle are not generally considered beneficial; however, the principles of optimization would suggest that it is wasteful to maintain the respiratory muscles at a ventilatory capacity higher than airway or parenchymal function would allow. Similarly, it is wasteful to maintain cardiac and peripheral O_2 transport capacities in excess to what the lung

will support; hence respiratory and non-respiratory skeletal muscles co-adapt to match their capacities to that of the limiting step. The end result is that in patients with chronic stable lung disease, distributive control of O_2 transport is eventually re-established. Exercise is limited not just by the primary pulmonary pathology, but also by respiratory muscle energetics, cardiac and peripheral O_2 transport. Improvement in any of these factors, e.g. by exercise training, can enhance maximal O_2 uptake in the absence of any improvement in airway or parenchymal function.

Summary

Matching related capacities is a fundamental principle of biological regulation. In a given system, various compensatory mechanisms defend the physiological reserve with exceptional precision. In complex metabolic pathways the capacity of each component is tightly regulated to match that of other components. Matching is affected by the malleability of a component and the interaction among components. For the O_2 transport system, the myocardium and skeletal muscle are the most malleable by physical training and thus have diminished capacity in the sedentary individual. Lung structure is the least malleable and hence appears to have a greater capacity relative to the heart and muscle. In elite athletes the capacities of all components are optimized and fully exploited; control of O_2 flux is distributed along all components and there is no single step that is excessive or rate-limiting. Environmental hypoxia and lung disease can impose a bottleneck, i.e., a primary pulmonary limitation to O_2 transport. Co-adaptation occurs through pulmonary-cardiac-peripheral interactions, and eventually restores functional equilibrium whereby the capacities of the lung, heart and muscle are again matched.

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