Coordinated Adaptation of Oxygen Transport in Cardiopulmonary Disease

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In chronic cardiopulmonary disease, functional impairment develops in all oxygen transport organs, regardless of the specific cause of the disease. Some abnormalities, such as pulmonary edema in heart failure or right ventricular failure in destructive lung disease, are direct consequences of the primary pathological process. Others, such as skeletal muscle dysfunction that cannot be fully ascribed to edema, electrolyte imbalance, or exogenous medication or fully reversed by physical training or supplemental oxygen, seem paradoxical and resemble changes during acclimatization to high altitude. To understand these secondary responses, the lung-heart muscle axis must be considered as an integrated unit. Then, it becomes apparent that oxygen transport is regulated like any other metabolic pathway, whether organized at a systemic, organ, cellular, or subcellular level, and it follows established principles of metabolic control. Of particular importance is the concept of coordinated adaptation, where a single disturbance in a multistep pathway triggers adaptation in other steps to seek new levels of functional equilibrium within the constraints imposed by the primary disorder. This article discusses (1) fundamental principles of metabolic control, (2) adaptive mechanisms in oxygen transport, (3) coordinated adaptation as a unifying concept to explain diverse secondary responses in disturbed oxygen transport and how seemingly paradoxical responses may, in fact, be beneficial if the underlying physiology is understood, and (4) clinical application of this concept to therapy.

Regulation of Physiological Reserves

In a biological system, load is the flux through the system (Figure 1A), i.e., rate of substrate conversion to the product or translocation from one point to another. Capacity is the maximum achievable load, and reserve is the difference between load and capacity. Across a wide range of systems and species, the capacity-to-load ratio is remarkably constant, suggesting a fundamental need for maintaining physiological reserves. When capacity is reduced but still adequate for the expected loads, adaptation occurs to raise the capacity of the remaining system and restore reserves (Figure 1B). For example, after unilateral nephrectomy, the glomerular filtration rate of the remaining kidney (≈50 mL/min) is still adequate for handling the usual filtration load; no compensation is needed to sustain a normal lifestyle. However, in reality, the glomerular filtration rate of the remaining kidney gradually increases by some 80%; this is accompanied by an increase in renal mass.1

Normally, lung diffusing capacity (DL) increases with pulmonary blood flow up to peak exercise without reaching an upper limit,2 indicating continued recruitment of capillary reserves, which protect arterial O2 saturation (SaO2) in lung disease until DL drops below 50% of normal. After pneumonectomy, blood flow per lung unit doubles and the remaining capillary reserves are recruited.3 Because the peak O2 flux after pneumonectomy remains below that supported by the maximal DL of one lung, no structural adaptation is needed; however, a pneumonectomy elicits compensatory growth of gas exchange tissue, which tends to normalize DL.4 Conversely, a sustained submaximal increase in load elicits adaptation that raises the capacity and restores reserves (Figure 1C). During submaximal exercise training, the average O2 uptake (load) remains far below maximal O2 uptake (Vo2 max, capacity), but this regular intermittent submaximal loading can increase Vo2 max by up to 30% over ≥8 weeks.5

These examples illustrate the regulation of physiological reserves in anticipation of potential internal or external perturbation. Although metabolic systems generally operate far below capacity, reserves protect against the infrequent scenarios when exploiting full capacity may be life-saving. However, maintaining reserves costs metabolic energy and physical space; excessive reserves divert resources and reduce the efficiency of the whole organism. Atrophy of disused capacity is a universal phenomenon in natural selection. In lower eukaryocytes, elimination of excess metabolic capacity confers a distinct competitive survival advantage within a short time span.

Regulation of Multistep Pathways

A sequential metabolic pathway may involve a biochemical reaction chain or translocation of a substrate. At equilibrium in the absence of branch points, the flux or load across all steps must be equal, but capacities need not be equal. The classic control concept is of a rate-limiting step (Figure 2), which assumes most enzymes along a pathway exist in excess whereas one enzyme is located at a bottleneck where the load is near capacity. Flux across the cascade is sensitive only to the capacity of the rate-limiting step; altering the other
capacities has minimal impact. Single-step control is inherently uneconomical because maintaining excess capacities in all steps wastes metabolic energy. Recently, Srere advanced the notion of distributive control, where flux is coordinately regulated among all steps; a corollary is that capacities of individual steps closely match one another. At the cellular level, distributive control has been demonstrated in glycolysis; the tricarboxylic acid cycle; the synthesis of fatty acids, urea, nucleotide, and amino acids; and photosynthesis. For example, the rate of tryptophan synthesis is minimally altered by selective overexpression of individual enzymes but greatly increased when all enzymes of the pathway are simultaneously overexpressed. Similarly, exercise training increases the maximal velocity of all mitochondrial enzymes simultaneously, with no apparent bottleneck.

**Adaptation in Oxygen Transport**

Oxygen transport is a sequential pathway involving convective delivery by ventilation and cardiac output, diffusion in lung and tissue capillaries, chemical reactions to hemoglobin and myoglobin, and mitochondrial oxidative phosphorylation. In untrained subjects at sea level, \( \dot{VO}_{2\text{max}} \) transport capacity of the heart and locomotive muscle, assessed from maximal cardiac output and \( O_2 \) extraction, is far below that of the lung assessed from maximal ventilation and \( DL \) (Figure 3).

Enhancing maximal cardiac output and \( O_2 \) extraction by physical training greatly increases \( \dot{VO}_{2\text{max}} \), but enhancing maximal ventilation or \( DL \) has a negligible effect. Up to peak exercise, \( SaO_2 \) remains normal, indicating that pulmonary gas exchange is not limiting. Breathing 100% \( O_2 \) improves \( \dot{VO}_{2\text{max}} \) without changing ventilation or cardiac output, indicating that mitochondrial \( O_2 \) use is not limiting. After bed rest, maximal cardiac output and peripheral extraction decline further but can be partially restored by physical training. Physical training increases ventilatory capacity modestly by improving respiratory muscle strength and endurance, but it has little effect on \( DL \) at a given cardiac output. Therefore, in untrained individuals, cardiac and skeletal muscles capacities are rate-limiting but \( DL \) seems excessive.

In well-trained athletes, the transport capacities of cardiac and skeletal muscles are well matched to ventilatory capacity and \( DL \). A further increase in maximal cardiac output raises \( \dot{VO}_{2\text{max}} \) only slightly but causes a precipitous fall in \( SaO_2 \). Increasing minute ventilation at peak exercise may increases \( \dot{VO}_{2\text{max}} \) further, but peak ventilation becomes constrained by the maximum expiratory flow rate. Therefore, \( \dot{VO}_{2\text{max}} \) in the athlete is equally sensitive to independent changes of

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**Figure 1.** A. Load, capacity, and reserve of a physiological system. B. Sustained reduction in capacity, even if still sufficient for meeting the usual load, triggers compensation to restore the reserve. C. Sustained increase in load elicits an adaptive increase in capacity to maintain a normal reserve.

**Figure 2.** In single-step control, maximal flux of the rate-limiting step has a smaller capacity than other steps (shaded arrow). Capacity is indicated by arrow size. Altering capacity of the rate-limiting step causes a large change in flux (\( \Delta \text{flux/} \Delta \text{capacity} = +++ \)); altering capacity of other steps has little effect on flux (\( \Delta \text{flux/} \Delta \text{capacity} = 0 \)). In distributive control, all capacities are matched; altering the capacity of one step has only a modest effect on flux (\( \Delta \text{flux/} \Delta \text{capacity} = + \)).

**Figure 3.** \( \dot{VO}_{2\text{max}} \) and capacities of \( O_2 \) transport in untrained college students, after bed rest and physical training, compared with elite Olympic athletes. Capacities of cardiac output and peripheral tissue \( O_2 \) extraction are much more malleable to physical training than ventilation or lung diffusion. In Olympic athletes, all capacities are well-matched. Data are from Saltin et al.
maximal cardiac output, ventilation, and diffusion, i.e., coordinated regulation (Figure 4). Changing any one step produces a small change in overall O₂ flux. Only by increasing all capacities simultaneously can a correspondingly large gain in maximal O₂ transport be produced. Hence, it becomes progressively more difficult to attain further performance improvement in the well-trained athlete.

With physical inactivity, cardiac and skeletal muscles rapidly lose their capacities but lung capacity does not diminish significantly, creating an apparent “mismatch.” The disparity stems largely from differences in the structural plasticity of muscle and lung. Skeletal muscle is metabolically active and bulky, constituting >40% of body mass and incurring a high energy cost of maintenance; large reserves are not affordable, and unused muscle structure is eliminated through remodeling. In contrast, septal lung tissue constitutes only 1% of body mass and requires comparatively little energy for maintenance; therefore, downsizing septal structure in response to changing O₂ flux is less imperative.

Charles Darwin observed that biological structures continually remodel according to changing evolutionary pressures. The hypothesis that no more structure is formed or maintained than is required to satisfy functional demands was termed “symmorphosis” by Weibel.11 Our prehistoric ancestors were presumably athletic, with well-matched O₂ transport capacities. With emerging sedentary civilization, energy conservation favors the shedding of unused muscular capacity, while the pressure to downsize lung capacity is less; the rate of remodeling may also be influenced by the differential complexity of these organs. If average physical activity continues to decline, lung structure may also eventually become downsized. Alternatively, maintaining large DL reserves may be advantageous.11 The lung is the only O₂ transport organ that interfaces with the environment and is exposed to airborne pathogens, irritants, varying temperature, humidity, and gas tension. Available data suggest that spirometry, elastic recoil, and gas exchange decline with age more rapidly than stroke volume or arteriovenous O₂ extraction in the fit subject.15,16 Large DL reserves may protect against aging and facilitate migration to a high altitude, where pulmonary diffusion is the primary factor limiting O₂ transport.

Disparate plasticity between muscle and lung allows selective manipulation to increase muscle transport capacity above that of the lung, as exemplified by the thoroughbred racehorse, a species selectively bred over centuries for superior muscle and cardiovascular capacity until these traits exceed what lung structure will support; consequently, pulmonary O₂ uptake becomes the bottleneck in O₂ transport. At peak exercise, mean pulmonary capillary transit time falls below that required for adequate O₂ loading onto hemoglobin; severe hypoxemia and pulmonary arterial hypertension develop and frank pulmonary hemorrhage is common.17 Capacity of the mechanical ventilatory pump is also exceeded, leading to CO₂ retention secondary to either a prohibitively elevated respiratory muscle energy requirement or a limit of chemoreceptor drive. Breathing supplemental O₂ significantly improves Vo₂ max, evidence that mitochondrial capacity does not limit O₂ transport.

Adaptation in Disturbed Oxygen Transport
Coordinated adaptation predicts that a sustained loss of reserves in one O₂ transport component should elicit parallel adjustments in all components toward establishing a new equilibrium of O₂ flux. Thus, chronic pulmonary diffusion impairment should induce secondary reductions in the aerobic capacities of the myocardium and skeletal muscle, whereas long-term impairment in myocardial capacity should induce reductions in the aerobic capacities of skeletal and respiratory muscle (Figure 4). These secondary responses eliminate unused structure, conserve metabolic energy, and optimize functional efficiency. Below are examples of coordinated downregulation that are beneficial.

High Altitude Acclimatization
At high altitude, diminished pulmonary O₂ uptake is the primary bottleneck in O₂ transport. Normal reserves of ventilatory capacity and DL are critical in allowing individuals to maintain adequate SaO₂. Patients with restricted lung volume or a pulmonary vascular bed who are unable to increase ventilation or recruit DL have a high morbidity and mortality at altitude. With acclimatization, other organs adjust their capacities to compensate for the reduced O₂ supply. The decline in appetite and body weight minimizes energy expenditure. Polycythemia maximizes convective O₂ delivery. Initially, maximal cardiac output and heart rate are unchanged and submaximal cardiac output at a given O₂ uptake is elevated.18 With acclimatization, maximal cardiac output, stroke volume, and heart rate decline, and submaximal cardiac output at a given O₂ uptake returns to sea level
The reduction of maximal cardiac output is counterintuitive and has been termed “maladaptive.” It is associated with parasympathetic activation, diminished responsiveness to sympathetic stimulation, and intact cardiac contractility, but it is not reversed by vagal blockade and only partially reversed by supplemental O2.19–21

Figure 6 shows the expected relationships of SaO2 to V˙O2 max as a result of interactions among DL, maximal cardiac output, and altitude in young athletes. At a high altitude, SaO2 declines at a lower V˙O2 max than at sea level. At a given V˙O2 max, SaO2 declines as maximal cardiac output increases due to a lower pulmonary capillary transit time. At sea level, as maximal cardiac output increases from 23 to 32 L/min, there is a large gain in V˙O2 max, with minimal change in SaO2. At a high altitude, the same increase in maximal cardiac output leads to only a small gain in V˙O2 max but a precipitous drop in SaO2. Acute altitude exposure causes large decreases in SaO2 and V˙O2 max with no change in maximal cardiac output. After acclimatization, maximal cardiac output declines, resulting in a large gain in SaO2 with only a small loss in V˙O2 max; the latter loss is readily compensated for by hyperventilation. Thus, maximal cardiac output does not limit V˙O2 max at altitude; increasing maximal cardiac output exacerbates the diffusion limitation, but reducing maximal cardiac output optimizes SaO2 and lowers the myocardial O2 requirement within the constraint imposed by the lower O2 uptake across the lung.

With acclimatization, muscle fiber diameter, mitochondrial volume, and oxidative enzymatic capacity decrease.22 Exercise at a high altitude induces enzymes of glycolysis but not the citric acid cycle, respiratory chain, fatty acid oxidation, or ketone body use.23 Muscle morphology superficially resembles disuse atrophy, but capillary density is increased and mitochondria are closer to capillaries, which minimize diffusive resistance to O2 uptake. Downregulation of muscle mass results in just enough aerobic capacity to match pulmonary O2 uptake, so overall metabolic energy wastage is minimized.

Chronic Lung Disease

In moderate-to-severe chronic obstructive pulmonary disease (COPD), maximal cardiac output is reduced; skeletal and respiratory muscle dysfunction develops even in the absence of overt hypoxemia, resting pulmonary hypertension, or exogenous steroid administration.24,25 Some consider COPD a multisystem disease.26 The reduction in maximal cardiac output, attributed to deconditioning, impaired venous return due to elevated intrathoracic pressure, and pulmonary arterial hypertension, resembles the response to altitude exposure. In addition, diaphragm weight and thickness correlate inversely with the histological severity of emphysema,27 a seemingly “paradoxical” response. Because the work of breathing is grossly elevated in COPD and respiratory muscles must work harder, one expects the diaphragm to hypertrophy rather than atrophy. The normal diaphragm is dome-shaped, with muscle fibers mostly oriented vertically. Muscle contraction causes the dome to descend like a piston drawing air into the lung. Lung hyperinflation in COPD depresses and reduces the radius of curvature of the diaphragm, causing its fibers to
shorten and orient more horizontally; shortened fibers are mechanically disadvantaged and generate less tension for a given neural input. Chronic fiber shortening reduces muscle mass via a reduction in the number of sarcomeres arranged in series; consequently, the remaining sarcomeres lengthen, partially restoring the tension generated but reducing contractile fiber shortening for a given neural input. Contractile shortening of the flattened diaphragm is, in fact, counterproductive because it pulls the ribcage inward and reduces inspiratory thoracic volume. Thus, “atrophy” of the flattened diaphragm preserves the contractile efficiency of the remaining fibers and minimizes the detrimental mechanical effects of hyperinflation. Although mechanical disadvantage seems to be the major reason favoring diaphragm atrophy in moderate COPD, chronic hypoxemia, physical deconditioning, and malnutrition in severe COPD further contribute to diaphragm weakness.

Skeletal muscle weakness and atrophy is common in COPD and directly related to the decline in flow rates; the main symptom limiting exercise is often leg fatigue instead of dyspnea. On exercise, muscle metabolism is marked by depleted high-energy phosphate stores, impaired oxidative enzymatic capacity, and early onset of glycolysis; changes correlate with reductions in vital capacity, handgrip strength, and skeletal muscle mass. Muscle protein concentration and slow-twitch oxidative fibers are reduced while glycolytic enzymes are elevated. Abnormalities are not responsive to slow-twitch oxidative fibers are reduced while glycolytic enzymes are elevated. Abnormalities are not responsive to exercise training and only partially alleviated by exercise training. One potential explanation for skeletal muscle weakness is the excessive O₂ cost of breathing, causing respiratory muscles to compete with locomotive muscles for a finite O₂ delivery, shown by an inverse relationship between work of breathing and leg muscle blood flow in normal subjects during exercise even as total body O₂ uptake continues to increase. In restrictive lung disease, nearly 50% of any further increment in O₂ delivery near peak exercise is required by respiratory muscles just to sustain the ventilatory pump; exercise may be curtailed by insufficient O₂ delivery to locomotive muscles, causing combined peripheral and respiratory muscle fatigue. Long-term depression of muscle activity leads to fiber atrophy, and muscle capacity is downsized to match the diseased lung.

If ventilatory or gas exchange capacity is the bottleneck, enhancing skeletal muscle O₂ transport should have no effect on V̇O₂max. However, exercise training in COPD increases V̇O₂max modestly but significantly (12% to 14%) without improving ventilatory capacity or DL. In postpneumonectomy patients, V̇O₂max, ventilatory capacity, and cardiac output are all reduced by 50%. Exercise training has little effect on V̇O₂max only due to improved peripheral O₂ extraction and leg blood flow, associated with reduced muscle lactate production but no change in maximal cardiac output.

Selective respiratory muscle training in CHF relieves dyspnea and improves respiratory muscle strength and endurance by 40% to 50%, whereas V̇O₂max increases modestly by 14%. A similar myopathic spectrum is seen in chronic renal failure; exercise training in hemodialysis patients significantly improves submaximal exercise tolerance with a small increase in V̇O₂max in half of the patients attributable entirely to improved peripheral O₂ extraction without enhancement of cardiovascular O₂ delivery. This response pattern transcends specific disease cause and supports coordinated adaptation as a unifying homeostatic principle.

**Concept and Practical Application**

Capacities of all O₂ transport components are coordinately regulated to maintain adequate but not excessive functional reserves. Cardiac and skeletal muscles are metabolically costly and highly malleable to physical conditioning. Lung structure is inexpensive to maintain and need not be as malleable; nonetheless, respiratory function is modulated in other ways. For example, enhancing maximal cardiac output by physical training can secondarily increase peak DL via recruitment of capillary reserves not used by the sedentary individual; it also improves respiratory muscle perfusion and facilitates ventilation-perfusion matching. Respiratory muscle training can reduce the blood flow requirements of respiratory muscles and secondarily increase available blood flow to locomotive muscles.

Environmental hypoxia and cardiopulmonary disease selectively reduce O₂ transport reserves, triggering coordinated structural remodeling that downregulates muscle aerobic capacity. For example, it makes little sense for an athlete who develops CHF to carry the extra weight of highly oxidative muscle that can no longer be used. Thus, seemingly “mal-
adaptive” responses may actually optimize the efficiency of the system at a lower functional level. In stable chronic cardiopulmonary disease and acclimatized highlanders, O2 transport can potentially be as well-matched as in the Olympic athlete at sea level; maximal O2 flux is determined not just by the primary disorder but by all steps of the pathway. Enhancing any individual capacity raises VO2max only modestly; all capacities must be simultaneously enhanced before a proportionally large increase in VO2max can be achieved. Even correction of the primary disorder will only partially normalize O2 transport unless all other steps are addressed equally. Indeed, after heart or lung transplantation, VO2max remains at 50% to 60% of normal; significant long-term functional, histological, and biochemical impairment persists in skeletal muscles. Immunosuppressive therapy, deconditioning, and possible irreversible end-organ destruction complicates the data interpretation; however, they do not contradict the basic tenet of coordinated adaptation. Within this framework, general therapeutic measures that maximize the aerobic capacity of each transport component (muscular conditioning, nutrition, correction of anemia) are as important as specific treatment (inducing bronchodilation in COPD or reducing afterload in CHF). In practice, coordinated adaptation provides rational support for routine prescription of long-term physical training in chronic cardiopulmonary disease. The inability to dramatically increase VO2max with training in patients is expected and should not be construed as failure of the training regimen. Physical training enhances submaximal endurance as well as the feeling of well-being, even if large improvement of VO2max does not occur. In addition, patients are often disproportionately debilitated due to fear of symptoms; consequently, VO2max is impaired more than expected from the reduction in maximal DL, cardiac output, or ventricular ejection fraction. Maintaining long-term fitness ensures that all O2 transport steps are matched within the constraints of the primary disorder and that the entire metabolic cascade is as efficient as possible; optimization is critical because patients can ill afford metabolic energy wastage. Optimization also ensures that patients are poised to realize the maximum benefit from any specific therapy aimed at correcting the underlying disorder.

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References

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