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Exercise intolerance in patients with mitochondrial myopathies: perfusive and diffusive limitations in the O_2 pathway

Simone Porcelli[1], Bruno Grassi[2], David C Poole[3] and Mauro Marzorati[1]

Mitochondrial myopathies are a heterogeneous group of disorders characterized by genetically determined defects that impair oxidative phosphorylation at the mitochondrial level. Exercise intolerance is a clinical hallmark in most of these patients, who present fatigue and dyspnoea during low levels of exertion, including moderate activities of daily living. This review aims to discuss the principal limiting factors of muscle oxidative metabolism during exercise in patients with mitochondrial myopathies, investigating the effects of perfusive and diffusive impairments along the O_2 transport pathway from ambient air to muscle mitochondria. Possible therapeutic effects of exercise training will be also highlighted.

Addresses
[1] Institute of Biomedical Technologies, National Research Council, Segrate, Italy
[2] Department of Medicine, University of Udine, Udine, Italy
[3] Departments of Kinesiology, Anatomy and Physiology, Kansas State University, Manhattan, KS, USA

Corresponding author: Porcelli, Simone (simone.porcelli@itb.cnr.it)

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Introduction

Mitochondrial disorders are a heterogeneous group of genetic diseases caused by nuclear or, more frequently, mitochondrial DNA mutations, leading to an impaired oxidative phosphorylation [8•]. These diseases are considered among the most common inherited metabolic disorders in humans, with an estimated prevalence in adults of about 1 in 5000 [8•]. Although they can affect almost any organ, mitochondrial disorders usually lead to substantial functional impairments in organs with high energy demands such as the nervous system, heart and skeletal muscle [22•]. The clinical phenotype differs considerably among patients, even when the same mutations are present [25,49]. The wide spectrum of signs and symptoms is related at least in part to differences in the ratio between mutant and normal (wild-type) mitochondrial DNA (mtDNA), which can vary among tissues, organs, cells of the same tissue, and mitochondria of the same cell, according to a phenomenon called 'heteroplasmy' [47].

Mitochondrial myopathies (MM) represent mitochondrial disorders affecting predominantly, but not exclusively, skeletal muscle function [22•] and patients with MM are primarily characterized by exercise intolerance. The current article will discuss the main limiting factors of skeletal muscle oxidative metabolism during exercise in MM patients, the effects of perfusion and diffusion impairments on O_2 conductance from ambient air to muscle fibres, and the predominant role played by the impaired mitochondrial respiratory function. The beneficial effects of exercise training programs (either aerobic or resistance) will also be briefly discussed.

Structural and functional impairments of the O_2 transport pathway in mitochondrial myopathies

Patients affected by MM suffer from symptoms such as exercise intolerance, breathlessness, fatigue and muscle weakness. As a consequence, MM patients tested by cycle ergometry evince exaggerated lactic acidosis, impaired $\dot{V}O_{2peak}$ and low peak work rate [36•]. Despite a large interindividual variability, several studies [5••,9,10,14,18,22•,29,35,44,46] quantifying exercise capacity in MM patients have reported $\dot{V}O_{2peak}$ values ranging from 10 to 20 $ml\,kg^{-1}\,min^{-1}$ (Table 1); a range compatible with class II–IV heart failure [32].

The limited aerobic power and exercise tolerance are primarily due to an impaired ability to increase muscle fractional O_2 extraction during exercise, as indicated by directly measured C(a-v)O_2 across the exercising forearm [43] and knee extensor [20] muscles, or indirectly by solving the Fick equation after measuring whole-body $\dot{V}O_2$ and $\dot{Q}$ during maximal exercise [44]. Our research group, by employing near infrared spectroscopy (NIRS), has recently confirmed these observations showing non-invasively a reduced skeletal muscle fractional O_2 extraction during cycling exercise in MM patients [10,34,35]. The functional relevance of the impaired fractional O_2 extraction at the skeletal muscle level is confirmed by the strong linear relationship between $\dot{V}O_{2peak}$ and peak fractional O_2 extraction observed in MM patients [10,12••]. This deficit in muscle O_2 extraction suggests that the principal limitation in the O_2 pathway from the lungs to the muscle mitochondria lies at the

Table 1

Summary of clinical studies reporting metabolic and cardiovascular data obtained during incremental maximal exercise on a cycle ergometer in MM patients

	n	Age (years)	Gender	Weight (kg)	W_{peak} (*W*)	$\dot{V}O_{2peak}$ (L min^{-1})	$\dot{V}O_{2peak}$ (mL kg^{-1} min^{-1})	$\dot{Q}_{peak}$ (L min^{-1})	$\Delta\dot{Q}/\Delta\dot{V}O_2$	C(a-v)O_2 (mL dL^{-1})	ΔDeoxy (Hb + Mb) %ischemia
Linderholm *et al.* [26]	7	24–43	M and F	51.7–66	75–200	0.52–0.7	10.0–11.5	11.2–20.7	~10.0	4.6–5.0	
Taivassalo *et al.* [44]	40	24–67	M and F	64.4 ± 6.2	10–224	0.35–3.3	6.0–47.0	7.1–25.8	3.3–73	2.7–17.6	
Tavassalo *et al.* [45]	8	25–60	M and F		86 ± 26	1.36 ± 0.4		14.4 ± 3.9	8.5 ± 2.1	9.7 ± 2.5	
Jeppens *et al.* (2006)	51	13–74	M and F	43–96	21–284	0.70–3.12					
Grassi *et al.* [10]	6	23–65	M and F	62.4 ± 4.1	40–255	0.76–2.91	12.9–40.4				0–78
Heinicke *et al.* [14]	5	19–60	M and F	48.0–80.0	58 ± 31	0.31–0.86	5.2–10.8	9.1–15.1	16.5–42.1	3.4–5.7	
Taivassalo *et al.* [46]	9	20–53	M and F				5.6–18.7		9.2–25.0	3.1–8.9	
Porcelli *et al.* [35]	6	23–65	M and F		72 ± 13	1.06 ± 0.2	14.7 ± 1.2	14.9 ± 1.5	11.0 ± 2.1		22.0 ± 6.7
Delaney *et al.* [5••]	12	25–58	M and F	42.7–95.5	30–150		8.0–30.0	9.0–14.0	5.0–20.0	4.5–14.6	
Nabben *et al.* [29]	10	20–72	M and F	48.9–86.0	122 ± 26	1.49 ± 0.3	21.2 ± 3.2				
Karaa *et al.* [22•]	6	42 ± 16	F	56 ± 6	57 ± 16		15.2 ± 4.3				
Fiuza-Luces *et al.* [9]	12	19–59	M and F		98 ± 11		22.1 ± 1.8				

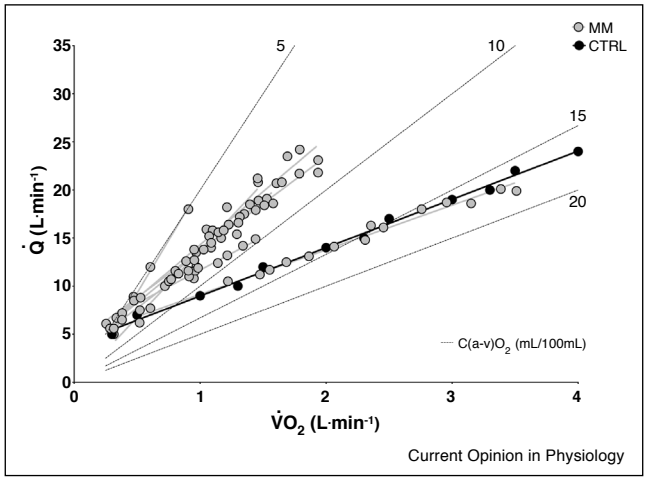
W_{peak}, peak power output; $\dot{V}O_{2peak}$, peak oxygen consumption; $\dot{Q}_{peak}$, peak cardiac output; C(a-v)O_2, arterial-venous oxygen difference; Δdeoxy(Hb + Mb), muscle fractional oxygen extraction determined by NIRS.

peripheral level where peak O_2 diffusion is low due to impaired maximal mitochondrial oxidative phosphorylation (see increased $\dot{Q}/\dot{V}O_2$ reflecting reduced fractional a-vO_2 extraction in Figure 1). The mitochondrial dysfunction in MM that expresses as impaired $\dot{V}O_2$ max due to compromised fractional O_2 extraction at maximal exercise is also associated with slowed $\dot{V}O_2$ kinetics (Figure 2).

What happens upstream at the pulmonary and cardiovascular levels?

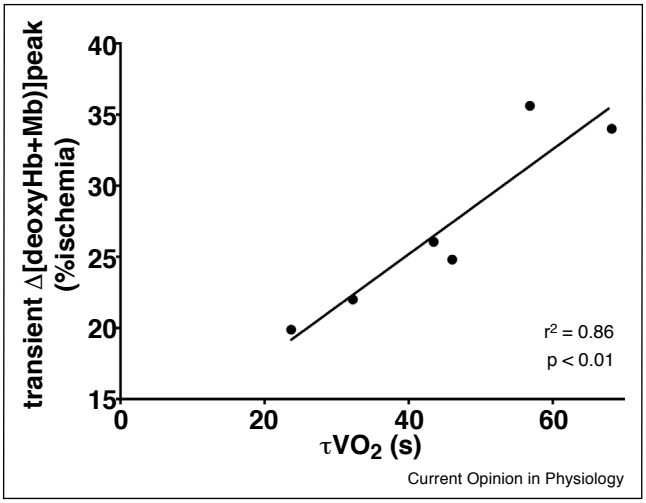
At the proximal end of the O_2 transport pathway, in the lung, patients with MM show a normal diffusing capacity (DLCO:100% of predicted value) as well as apparently intact ventilation-perfusion matching [14,23]. During exercise, MM patients may display an exaggerated ventilation relative to metabolic rate, as indicated by high $\dot{V}_E/\dot{V}O_2$ (>50 at peak exercise versus ~30 for healthy individuals – [36•]) and $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ (between 30–35 in the early phase of exercise, compared with ~25 for healthy, and >40 at peak exercise – [36•]) ratios with reduced PCO_2 and in the absence of any indication of mechanical ventilatory limitation (e.g. normal maximal and tidal flow-volume loops measured at rest and during exercise) [14,36•]. In these patients, the steep ventilatory response during exercise is likely to involve peripheral chemoreceptor (i.e. carotid body) stimulation due to dramatic increases in arterial lactate and steep declines in arterial pH. It is also thought that direct ventilatory stimulation occurs via reflexes (group III and IV muscle afferents) originating in active muscle due to metabolite accumulation and stimulation

Figure 1



Cardiac output ($\dot{Q}$, estimated by impedance cardiography) versus oxygen consumption ($\dot{V}O_2$) relationship obtained during incremental maximal exercise test performed on a cycle ergometer in 7 MM patients (grey circles) and one healthy subject (black circles). Lines of iso arterio-venous O_2 difference are also depicted (dotted lines). MM patients show a wide interindividual variability spanning from a normal response to a severe impairment (substantial incapacity to increase arterio-venous O_2 difference from resting value). (Personal observation).

Figure 2



The highest change (Δ) in fractional O_2 muscle extraction ([deoxy (Hb + Mb)]) in the first 120 s of exercise, suggesting a transient mistmatch between $\dot{Q}_m$-to-$\dot{V}O_{2m}$, as a function of pulmonary oxygen uptake kinetics (τ) on transition to moderate-intensity exercise. Each symbol (solid circles) represents a single MM patient. Values were obtained from data presented in Porcelli *et al.* [35]. Regression line is shown.

of peripheral mechanoreceptors linked to peripheral hyperperfusion [14]. Finally, a feedforward ventilatory drive from the co-associated cardiovascular and respiratory control centres in the ventrolateral medulla cannot be excluded. However, it should be noted that the range of respiratory manifestations vary according to age, mutations and phenotype severity. Although an impairment of pulmonary function is more typical of other metabolic myopathies (e.g. patients affected by Pompe disease – [27]), some MM patients at rest can display higher expiratory reserve and reserve volumes at the end of expiration [23]. These observations may be associated with a reduction in the forced vital capacity and forced expiratory volume in 1 s with a decrease in total lung capacity, indicative of ventilatory deficits arising from mitochondrial dysfunction crippling the diaphragm. Tragically, in these patients, exercise tolerance is so severely limited such that it is not possible for them to exercise at all.

As for the cardiovascular system, O_2 delivery to exercising muscles, in the absence of any significant cardiac involvement, is preserved in MM patients and peak cardiac output is not appreciably different from that observed in healthy subjects [44]. Moreover, MM patients present an exaggerated cardiovascular response to submaximal exercise such that, at any given submaximal $\dot{V}O_2$, heart rate (HR), cardiac output ($\dot{Q}$), and muscle blood flow ($\dot{Q}_m$) are all far higher compared with healthy subjects (e.g. Ref. [10]).

This hyperkinetic circulation during exercise has been interpreted as a functional compensation for the impairment of mitochondrial function. Indeed, this elevated perfusive O_2 delivery implies an increase in arteriolar, capillary and intramyocyte PO_2 which would be vital to achieving a given mitochondrial $\dot{V}O_2$ [20]. This notion is also consistent with structural adaptations that include a greater skeletal muscle capillarity in MM patients that would act to enhance diffusive O_2 delivery from a morphological point of view, the enhanced convective O_2 delivery is associated with a greater skeletal muscle capillarity in MM patients [46]. Interestingly, the extent of both functional and morphological adaptations is strongly correlated with the severity of mitochondrial dysfunction [10,44,46].

Notwithstanding the greater cardiovascular response, during the transition from rest to exercise in MM patients, an inadequate spatial and temporal O_2 delivery-O_2 uptake matching can be observed. In these patients, we have indeed detected a transient increase ('overshoot') of O_2 extraction by NIRS during constant work rate exercise [35], similar to that which has been described in patients with chronic heart failure [41] and, by our group, in subjects exposed to extreme deconditioning ('bed rest' studies) [33,38,39]. Although it does not actually mean that mitochondrial $\dot{V}O_2$ is necessarily impaired, this transient overshoot would have the same meaning as the 'transient' undershoot in microvascular PO_2 ($PmvO_2$) described by phosphorescence quenching in aged animals or in animals with CHF or diabetes [30,31]. Thus, it can be considered as a functional impairment of peripheral O_2 diffusion during metabolic transitions, and could be responsible, at least in part, for the slower pulmonary $\dot{V}O_2$ kinetics described in MM patients [11]. Following the approach proposed by Bowen *et al.* [3], we have re-evaluated the data originally presented in Porcelli *et al.* [35]. We calculated the peak value of fractional O_2 extraction (expressed as percentage of the value obtained during transient ischemia of the lower limb) reached in the first 120 s of exercise (transient Δ[deoxy(Hb + Mb)]) and plotted as a function of the time constant (τ) of the mono-exponential function which is usually utilized to describe the $\dot{V}O_2$ kinetics (Figure 2). Interestingly, there was a strong correlation between these two variables, suggesting that in MM patients $\dot{V}O_2$ kinetics are slowed due to a transient mismatch of $\dot{Q}_m$-to-$\dot{V}O_{2m}$ and the time necessary to attain some critical $PmvO_2$. The slower $\dot{V}O_2$ kinetics would contribute to the reduced exercise tolerance of these patients.

Perfusive and diffusive limitations to exercise tolerance

In healthy subjects, $\dot{V}O_{2max}$ (or its estimate during the incremental test, $\dot{V}O_{2peak}$) is not determined by one independent variable, but rather is the integration of several steps along the O_2 transport pathway [6,16,32,50]. Although the relative importance of the different O_2 transport pathway components depends on

factors such as environmental conditions (e.g. normoxia versus hypoxia) and exercise modality (e.g. whole-body versus small muscle mass), the movement of O_2 from ambient air to the muscle mitochondria relies on two mechanisms of O_2 transfer. Namely, convective gas-phase O_2 transport along the upper airways and the lungs, and liquid-phase along the systemic circulation to the active skeletal muscle capillary beds, and diffusive O_2 transport, from the alveolar air across the blood-gas barrier to the capillary blood in the lung, and from the muscle capillaries across the capillary endothelium, interstitial space, and, ultimately, across the sarcolemma and myoplasm to the mitochondrial reticulum [50].

Convective O_2 transport can be described mathematically by the Fick Principle of conservation of mass:

$$\dot{V}O_2 = \dot{Q} \times (CaO_2 - C\bar{v}O_2) \quad (1)$$

where $\dot{Q}$ denotes the extant cardiac output as it determines muscle blood flow and CaO_2 and $C\bar{v}O_2$ represent arterial and mixed venous O_2 contents, respectively. In this equation, limitations associated to the cardiovascular system may alter $\dot{Q}$ and O_2 transport among and within the muscle microvascular beds, whereas impairments in pulmonary function (i.e. inspired O_2 content, pulmonary diffusion limitation, $\dot{V}_A/\dot{Q}$ inequality, and shunt) could potentially alter SaO_2 and thus CaO_2.

The diffusion of O_2 from the capillary circulation to the muscle mitochondria, as described by Fick's Law of diffusion, can be mathematically represented by the following equation:

$$\dot{V}O_2 = DmO_2 \times (PcapO_2 - PmitO_2) \quad (2)$$

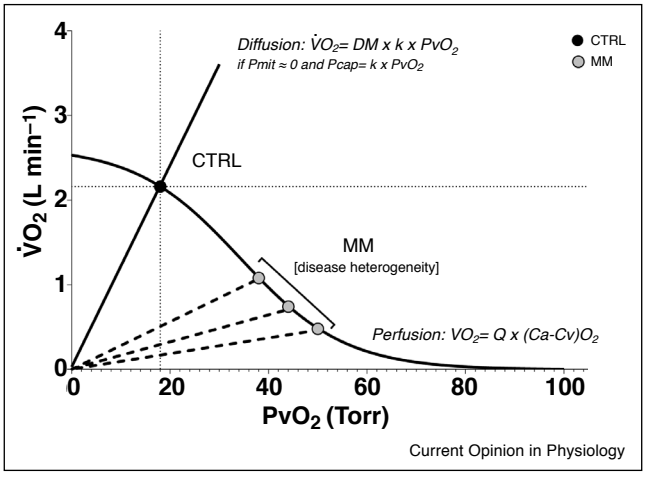
where DmO_2 represents peripheral O_2 diffusing capacity, and $PcapO_2$ and $PmitO_2$ represent mean capillary and mitochondrial PO_2, respectively. However, during maximal exercise this equation can be simplified as:

$$\dot{V}O_2 = DmO_2 \times k \times PvO_2 \quad (3)$$

because $PmitO_2$, in healthy individuals, can be assumed to be close to zero and venous PO_2 (PvO_2) is proportional to $PcapO_2$ (and calculated from the Fick Principle variables by a backwards Bohr integration, [50]).

As demonstrated by Roca *et al.* [37] the Fick Principle can be conflated with Fick's Law when $\dot{V}O_{2peak}$ ($\dot{V}O_2$ plotted on the ordinate) and PvO_2 (abscissa) are known (see also Ref. [50]). Since the relationship between O_2 saturation and PO_2 occurs via the sigmoidally shaped O_2-Hb dissociation curve, the Fick Principle relationship is plotted as a curved line (mirror image of the O_2-Hb dissociation curve) for a given $\dot{Q}$, haemoglobin concentration ([Hb]), and SaO_2, as a function of P_vO_2. Fick's Law of Diffusion is represented by a straight line from the origin, in which the slope is equal to $DmO_2 \times k$. $\dot{V}O_{2peak}$ is the point of intersection between the two functions, that satisfies both relationships simultaneously (Figure 3) [50].

Figure 3



Graphical representation depicting the equations for diffusive [straight lines from origin] and convective [curved line] oxygen transport in the muscle. Maximal $\dot{V}O_2$ occurs where the two relationship intersect. Note that in MM patients (grey circles) the reduced VO_{2peak} is attributable to a diffusive impairment and a wide variability between patients exists, likely due to disease heterogeneity. Reference curves (solid lines) for healthy subjects ($\dot{V}O_2$ max black circle) are also shown. See text for details (based on data reported by Linderholm *et al.* [26], Taivassalo *et al.* [45] and Porcelli *et al.* [35]).

In this diagram (proposed by Ref. [50]), the diffusive component is drawn as a straight line based on the assumption that mitochondrial oxidative function is normal [15] and $PmitO_2$ can be neglected since it is very close to zero [50].

What happens to convective O_2 transport and peripheral O_2 diffusion in MM patients? How can this diagram be constructed for MM patients?

As discussed above and with the exception of respiratory problems, lung function appears well preserved in MM patients and CaO_2 is defended from small decreases of PO_2, should they occur, by the end-pulmonary-capillary blood residing normally on the flat upper portion of the oxy-haemoglobin dissociation curve. Moreover, $\dot{Q}_{peak}$ is usually similar in MM and healthy control subjects (e.g. Ref. [45]).

As for O_2 diffusion, in MM patients $PmitO_2$ cannot be assumed to be equal to zero, considering the mitochondrial respiration impairment, and the fact that PO_2 in venous blood draining from the muscles is

characteristically elevated (38–50 mmHg according to Ref. [26]), as a consequence of the impaired capacity to increase fractional O_2 extraction. In MM patients, therefore, peripheral O_2 diffusion is significantly lower than in healthy subjects. If we approach the problem as an equivalent to Ohm's law, there are two principal resistances to peripheral O_2 diffusion: specifically, in addition to the resistance provided by the capillary–interstitium–myocyte interface, as in normal subjects, there is an additional, more distal component within the intramyocyte compartment that arises from the impaired mitochondrial respiratory chain function. Thus, if we analyze peripheral O_2 diffusion in MM patients as a multi-step system with at least two important in-series resistances [6]:

$$\dot{V}O_2 = (PcapO_2 - PiO_2)/R_{bm} + (PiO_2 - PmitO_2)/R_{mit} \quad (4)$$

where PiO_2 is the intramiocite PO_2, and R_{bm} and R_{mit} are the blood-myocyte resistance and the 'mitochondrial' resistance, respectively [6]. R_{bm} is proportional to the exchange surface occupied by red blood cells and inversely related to the distance between red blood cells within a given capillary [7,13]. This resistance will therefore decrease with increased capillarity and volume of red blood cells within those capillaries. R_{mit} is a function of the overall capacity of the mitochondria to consume O_2 (ATPox) and it is regulated by PiO_2, [ADP], [Pi], [NADH], and [H^+] [17,24].

In healthy subjects, R_{mit} would be substantially negligible and R_{bm} would represent the main resistance that influences O_2 diffusion. By contrast, in MM patients both R_{bm} and R_{mit} would affect peripheral O_2 diffusion. More specifically, R_{bm} should be lower, in accordance with the MM-associated increased capillarization and, presumably, an elevated total microvascular red blood cell volume within the muscle [2,46]. In contrast, the apparent R_{mit} will be substantial due to the impaired mitochondrial respiratory function. In order to sustain peripheral O_2 diffusion, and thus any given O_2 flux in MM patients, the increased $PmitO_2$ would have to be compensated for by an equivalent increase in $PcapO_2$ in combination with a reduced R_{bm} This scenario would be accomplished, at least in part, by the increased microvascular O_2 delivery, secondary to the exaggerated cardiovascular response, and the elevated capillarity, respectively. This hypothesis is consistent with the increased maximal ATP synthesis rate observed in MM patients breathing hyperoxic gas compared to their healthy counterparts [48].

Glycolytic products ([ADP], [Pi], [NADH] and [H^+]) drive mitochondrial function at the expense of still greater glycolysis. In MM patients, early glycolytic activation may be an adaptation necessary to reduce R_{mit}. It is pertinent that MM patients demonstrate a high blood lactate concentration even during low intensity exercise [10] as well as greater [ADP] and [H^+] [48].

Returning to the 'Wagner' diagram, in healthy subjects it is possible to find the unique solution where Eqs. (1) and (2) yield the same $\dot{V}O_2$ and PvO_2 based on two important approximations: i) mitochondrial PO_2 is taken to be zero; ii) $PcapO_2$ can be replaced by PvO_2, multiplying by a constant, k [50]. Moreover, in this diagram the values for the independent variables ($\dot{Q}$, Dm, [Hb]) are those determined at maximal exercise, with arterial O_2 concentration being maintained close to resting values in most healthy individuals who have adequate lung diffusing capacity and ventilation. Our MM patients do not satisfy some of these assumptions intrinsic to the 'Wagner diagram' as it is evident that mitochondria PO_2 cannot be close to zero even at maximal exercise intensity, and that the value of k would have to be different. If we consider that the elevated intramyocyte PO_2 does represent a high 'O_2 diffusion resistance' at the mitochondrial level, as a first approximation, the diffusion line for MM patients can be represented by a straight line with a far lower slope (impaired O_2 diffusion) than that of healthy subjects. Figure 3, constructs the Wagner diagram for MM patients (versus healthy controls) by utilizing the data obtained in a group of patients by Linderholm *et al.* [26]. PvO_2 values were calculated from venous O_2 saturation and pH data [40]. The convective O_2 delivery curve was drawn to reflect the data from Taivassalo *et al.* [44] and Porcelli *et al.* [35] that demonstrates no differences between MM patients and healthy subjects. MM patients demonstrate heterogeneous physiological responses, even in the presence of an unchanged maximal O_2 delivery (upper curve). The higher PvO_2 values demonstrate the lower capacity to increase fractional O_2 extraction which, in-and-of-itself is the product of the lower diffusing capacity (DmO_2) that predicates the limited level to which $\dot{V}O_{2peak}$ can rise.

Benefits from exercise training to O_2 transport pathway

There is no cure yet for mitochondrial myopathies, nor is there any pharmacological treatment capable of stalling disease progression [1]. Although new therapeutic strategies have recently shown some potential efficacy at the pre-clinical level [51] and also in a small group of patients [21,22•], therapeutic options still remain focused on supportive interventions aimed at relieving complications. Specifically, antioxidants including vitamin E, alpha lipoic acid, and Coenzyme Q_{10} are the most frequently used treatments for MM patients in clinical practice to combat augmented reactive oxygen species production. However, no systematic large-scale study has ever shown any effect of such treatment [1].

Exercise training, known to boost the biogenesis and function of mitochondria in healthy people, has been suggested to reduce symptoms in MM patients by

Figure 4

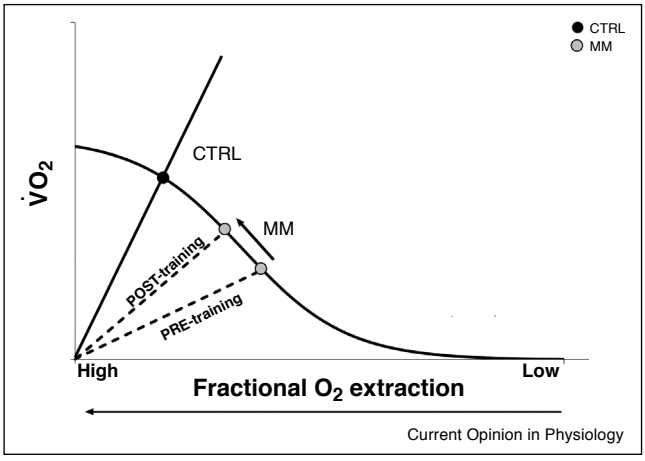


Illustration of the effects of 12–14 weeks of aerobic exercise training on the determinants of $\dot{V}O_{2peak}$ in MM patients (grey circle). After training no change in the convective oxygen delivery curve is shown with VO_{2peak} improvement due exclusively to an enhanced diffusive component (steeper slope of the dashed line). Reference lines (solid lines) for healthy subjects (black circles) are also shown. See text for further details (based on data reported by Taivassalo *et al.* [45] and Porcelli *et al.* [35]).

increasing the size and function of the normal mitochondrial reticulum in myocytes. Indeed, several studies have demonstrated the benefits of aerobic [4,19,35,42,45], resistance [28], and combined resistance and aerobic [9] exercise training on skeletal muscle oxidative capacity and quality of life in MM patients. More specifically, Taivassalo *et al.* [45] and Jeppesen *et al.* [19] demonstrated that 12–14 wk of moderate exercise training, in MM with single large-scale mitochondrial DNA (mtDNA) mutations, increased $\dot{V}O_{2peak}$ and work capacity about 15%, and mitochondrial respiratory chain enzymatic activities. Although an early study found that the level of mutant mtDNA in the muscle increased with training [42], this finding was not confirmed by more recent studies, suggesting that physical training for up to 12 months is not contraindicated in patients with common mtDNA mutations [19,28,45]. Interestingly, the increased $\dot{V}O_{2peak}$ was associated with an enhanced peak systemic arterio-venous O_2 difference [45] or a greater NIRS-derived skeletal muscle fractional O_2 extraction [35] whereas systemic oxygen delivery ($\dot{Q}$) was not significantly affected by training in either study. Thus, in MM patients the principal impact of physical training (increased capacity for oxygen extraction) is quite different from that usually observed in healthy individuals (i.e. a robust increase of O_2 delivery by the cardiovascular system combined with a modest widening of the arterio-venous O_2 difference, Ref. [36•]). A schematic representation of training effects on perfusive and diffusive components of $\dot{V}O_{2peak}$ in MM patients is shown (Figure 4). No changes in the convective O_2 delivery curve are assumed in accordance to unchanged cardiac output and arterial O_2 content [35,45] whereas a diffusive straight line with steeper slope demonstrates improved diffusing capacity (DmO_2), consistent with the higher capacity to increase fractional O_2 extraction after training observed by our group [35].

Conclusions

MM patients are characterized by exercise intolerance that can limit everyday life activities and impair quality of life. The pathophysiological basis of this limited exercise capacity lies at the peripheral level within skeletal muscle where a reduced capacity to increase fractional O_2 extraction during exercise causes a reduced peripheral O_2 diffusion and leads to a reduced maximal aerobic power ($\dot{V}O_{2max}$). Among the several promising therapeutic approaches investigated, it seems that exercise training can be a valid strategy to counteract limitations in the O_2 transport pathway from the lungs to muscle and hence improve patient exercise tolerance and quality of life.

Conflict of interest statement

Nothing declared.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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