



Review

Implications of exercise training in mtDNA defects—use it or lose it?

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Abstract

Whether regular exercise is beneficial or should be avoided is a question currently unsettled in patients with heteroplasmic mitochondrial DNA (mtDNA) disorders of skeletal muscle. Deleterious effects of habitual physical inactivity superimposed upon impaired mitochondrial oxidative phosphorylation may contribute to varying degrees of exercise intolerance in these patients. Endurance exercise training is widely known to improve exercise capacity in healthy subjects and various chronic-disease patient populations. Although we have shown that beneficial physiological and biochemical responses to training increase exercise tolerance in patients with mtDNA defects, knowledge of the muscle adaptive response to endurance training within the setting of mitochondrial heteroplasmy remains limited. In order to determine advisability of endurance training as therapy, it remains to be established whether potential endurance training-induced increases in mutant mtDNA levels may be offset by increases in absolute wild-type mtDNA levels, and whether chronic inactivity leads to a selective down-regulation of wild-type mtDNA. Resistance training utilizes a different adaptive exercise approach to induce the transfer of normal mitochondrial templates from satellite cells to mature muscle fibers of patients with sporadic mtDNA disorders. The efficacy and safety of this approach needs to be further established. Our current inability to clearly advise patients to “use it or lose it” underscores the immediate urgency of studying the effects of exercise on skeletal muscle of patients with heteroplasmic mtDNA defects.

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Keywords: Mitochondrial myopathy; mtDNA defect; Exercise intolerance; Treatment; Endurance and resistance training; Satellite cell**1. Introduction**

Mitochondrial electron transport chain defects due to heteroplasmic, mitochondrial DNA (mtDNA) mutations are common and becoming increasingly recognized with advances in molecular diagnostics. Exercise intolerance is a common and often disabling manifestation of muscle involvement in mitochondrial disease. With the current lack of effective treatment for mitochondrial myopathies, we have focussed on the possibility that muscle adaptation to

chronic exercise (i.e. exercise training) might improve mitochondrial respiratory chain function and hence, overall exercise capacity in adult patients with mtDNA mutations. This review will cover the rationale underlying the use of two different modes of exercise training, endurance and resistance, as treatment approaches for patients with mtDNA disorders and present studies in support of their efficacy.

Significant physiological benefits of endurance training have been detected in mitochondrial myopathy including consistent improvement in work and oxidative capacity. However, the possibility that endurance training may result in an increased proportion of mutant relative to wild-type mtDNA in patients with heteroplasmic mtDNA mutations has raised the specter that, despite significant functional improvements, training might have long-term deleterious effects [1]. This consideration, combined with a complete absence of information on the effects of physical inactivity

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upon relative levels of mutant versus wild-type mtDNA, has resulted in a management crisis for mitochondrial myopathy patients in which the basic question of whether exercise should be encouraged or avoided cannot currently be answered.

The exciting potential of physiological gene-shifting through resistance exercise training in patients with sporadic mtDNA mutations will also be reviewed. The aim in the very near future is to provide centers managing patients with mitochondrial disease with practical guidelines relating the type and degree of exercise to the nature of mtDNA mutation.

2. mtDNA mutations—effects on exercise capacity

Exercise intolerance is characterized by the development of undue fatigue at relatively low levels of exertion and can be associated with fatigue and weakness of active muscles, lactic acidosis, tachycardia, and dyspnea. Clinically, the degree of exercise intolerance in patients with mtDNA defects can vary from mild to debilitating, but in most instances, the performance of many activities of daily living (i.e. climbing stairs, grocery shopping, vacuuming, walking) is limited by low endurance. Loss of muscle mass and fixed weakness may also contribute to functional limitations in patients with mtDNA mutations.

Exercise-related symptoms may cause patients with mtDNA defects to adopt a sedentary lifestyle. Habitual physical inactivity in healthy humans results in deconditioning which is associated with decreases in mitochondrial numbers and respiratory chain activity in skeletal muscle as well as reduced cardiovascular capacity. We have postulated

that habitual inactivity in mitochondrial myopathy patients may also lead to a decrease in levels of functional mitochondria with a further restriction of the capacity of muscle for oxidative phosphorylation. Thus, habitual inactivity and resulting deconditioning could magnify functional limitations and set in motion a vicious cycle of progressively worsening exercise intolerance (Fig. 1).

3. Physiological measures of exercise capacity

The degree of exercise intolerance as well as the potential contribution of deconditioning versus mitochondrial oxidative impairment to reduced endurance can be quantified in an exercise laboratory by measuring peak oxygen utilization and the physiological components of oxygen utilization, i.e. oxygen delivery (cardiac output, Q) and oxygen extraction (systemic arterio-venous oxygen difference, $a-vO_2$ diff). Aerobic fitness is typically measured as maximal oxygen uptake (VO_2 max) and used to reflect peak capacity for aerobic energy production during dynamic exercise. According to the Fick equation, $VO_2 = Q \times a-vO_2$ difference. This signifies that VO_2 is the product of, and determined by, the cardiovascular capacity to deliver oxygen (ultimately dependent upon peak cardiac output, Q) and muscle metabolic capacity for extraction of available oxygen (dependent primarily upon muscle mitochondrial capacity for oxidative phosphorylation) [2]. In healthy individuals, maximal VO_2 and hence aerobic performance during large muscle exercise (e.g. running, cycling), is limited by the capacity of the circulation to deliver oxygen to contracting muscles. Cardiac output is tightly coupled to the level of oxygen use during exercise, normally increasing by 5 l per liter of increase in oxygen utilization. This 5:1 relationship is attributable to the fact that, assuming normal O_2 carrying capacity, arterial blood contains about 200 ml O_2 per liter of blood [3]. Thus 5 l of cardiac output corresponds to 1 l of oxygen delivery. Maximal cardiac output is dependent on the level of aerobic conditioning. Thus peak cardiac output represents an independent measure of aerobic fitness. Systemic $a-vO_2$ difference represents the level of extraction of available O_2 from arterial blood. Systemic $a-vO_2$ diff increases from 5 ml O_2 /dlQ at rest to about 15 ml O_2 /dlQ at peak exercise, with relatively minor increases as a function of aerobic fitness [4].

Several studies assessing exercise capacity in mitochondrial myopathies have demonstrated that peak VO_2 is markedly low (on average about one-third of age-matched healthy sedentary individuals) [1,5,6], but the range of impaired oxygen utilization is broad. The differentiation of healthy subjects who are severely deconditioned, in whom O_2 utilization in exercise is limited by a low peak cardiac output, from patients in whom VO_2 is limited by mitochondrial function can be defined by measuring exercise cardiac output and determining peak systemic $a-vO_2$ diff. In the absence of significant cardiac disease, oxygen delivery by

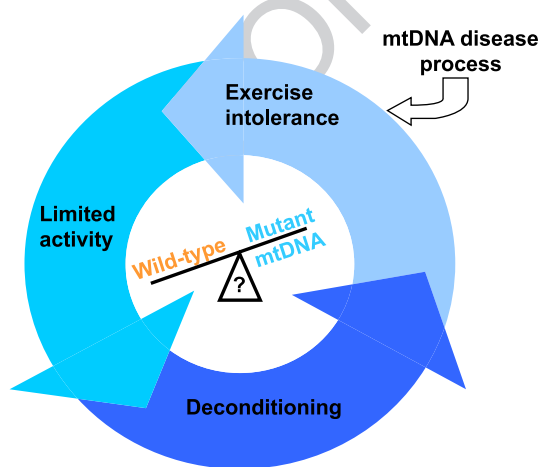


Fig. 1. Vicious cycle hypothesis of the potential contribution of deconditioning to progressive exercise intolerance in patients with mtDNA disorders. Limited exercise capacity due to mtDNA defects fosters adoption of a sedentary lifestyle leading to deconditioning and continued worsening of exercise capacity. The effects of deconditioning on mitochondrial heteroplasmy are not known, but we postulate that down-regulation of mitochondrial volume with deconditioning further restricts mitochondrial function thus worsening exercise limitations in these patients.

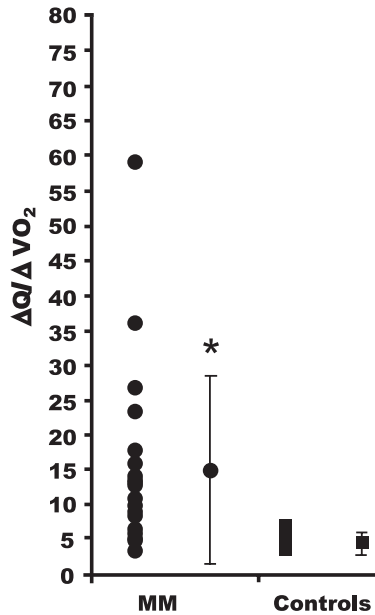


Fig. 2. In healthy individuals, the peak capacity for oxygen delivery during exercise (cardiac output, Q) is tightly coupled to the peak capacity for oxygen utilization (VO_2), where 5 l of cardiac output corresponds to a 1 l increase of oxygen utilization ($\Delta Q/\Delta VO_2 \cong 5$). In contrast, in the majority of mitochondrial myopathy patients, oxygen delivery relative to oxygen utilization is exaggerated ($\Delta Q/\Delta VO_2 \gg 5$).

135 the circulation is preserved and peak cardiac output is
 136 comparable to healthy subjects. In contrast, muscle capacity
 137 for extraction of available oxygen (systemic a- VO_2 differ-
 138 ence) is markedly limited, relating to the block in oxidative
 139 phosphorylation within skeletal muscle. In relation to
 140 oxygen utilization during exercise, O_2 delivery is high and
 141 the circulation is “hyperkinetic”, i.e. the increase in cardiac
 142 output, ΔQ , relative to the increase in oxygen uptake,
 143 ΔVO_2 , from rest to exercise is abnormally high in
 144 mitochondrial myopathy ($\Delta Q/\Delta VO_2 > 7$) compared to
 145 healthy subjects ($\Delta Q/\Delta VO_2 \sim 5$ irrespective of level of
 146 conditioning [7] (Fig. 2). Thus the hallmark of low oxygen
 147 utilization attributable to limited muscle oxidative phos-
 148 phorylation is a mismatch in oxygen delivery in relation to

utilization, reflected in low levels of oxygen extraction (low 149
 systemic a- VO_2 diff) combined with high oxygen delivery 150
 relative to VO_2 [7,8]. The measurement of cardiac output 151
 and determination of systemic a- VO_2 difference are therefore 152
 critically important in the assessment of muscle oxidative 153
 capacity in patients with suspected mitochondrial myopathy. 154

In a recent analysis of exercise tolerance in a group of 40 155
 patients with characterized mitochondrial defects, the range 156
 of exercise capacity was broad [7]. Peak VO_2 ranged from a 157
 level barely above resting metabolic rate to one comparable to 158
 healthy conditioned individuals, with the majority of patients 159
 demonstrating low aerobic fitness. Moreover, this variability 160
 correlated directly with the degree of impaired muscle 161
 extraction of available oxygen, enabling us to use systemic 162
 a- VO_2 difference as a surrogate marker of mitochondrial 163
 capacity for oxidative phosphorylation. The finding that the 164
 level of mutation (% mutant mtDNA) governed the ability of 165
 muscle to increase systemic a- VO_2 difference with exercise 166
 further supports the notion that impaired muscle oxidative 167
 phosphorylation determines the degree of exercise intoler- 168
 ance in patients with respiratory chain defects (Fig. 3). 169

4. Normal physiological changes with endurance 170 training and detraining 171

Human beings are subjected to cycles of increased and 172
 decreased physical activity throughout life, and accordingly, 173
 the cardiovascular and skeletal muscle systems adapt to these 174
 changes in oxidative demand. This review is not able to 175
 address the numerous changes in physiology and metabolism 176
 that normally occur in response to endurance training and 177
 detraining, but rather, will focus on the changes most 178
 pertinent to the exercise response in patients with mtDNA 179
 disorders. 180

4.1. Use it 181

Increases in oxidative capacity are brought about through 182
 endurance exercise training, which is generally defined as 183

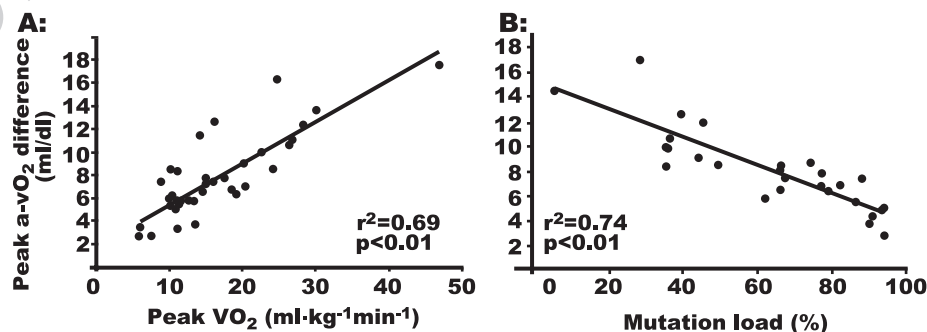


Fig. 3. (A) Peak systemic a- VO_2 difference (as determined from the Fick equation, $VO_2 = \text{cardiac output} \times \text{systemic a-}VO_2$ difference) is a surrogate marker of muscle capacity for oxidative phosphorylation in mitochondrial myopathy as indicated by the direct correlation between a- VO_2 difference and peak VO_2 in these patients. (B) Mitochondrial oxidative capacity is governed by the mutation load (% mutant mtDNA) within skeletal muscle of 26 patients with heteroplasmic mtDNA mutations, demonstrating an inverse relationship between molecular genotype and physiological phenotype.

184 any regularly performed aerobic activity involving the use
 185 of large muscle groups for sufficient intensity and duration
 186 (30 min, 50–85% VO_2 max) [2]. Endurance (or aerobic)
 187 training induces adaptations in the heart and peripheral
 188 circulation, and skeletal muscle systems that increase
 189 exercise capacity by enhancing the delivery of oxygen
 190 (O_2) to exercising muscle and by increasing muscle capacity
 191 for O_2 utilization in oxidative phosphorylation. Greater
 192 oxygen delivery is achieved through increases in cardiac
 193 output (due to increases in cardiac stroke volume rather than
 194 to changes in maximal heart rate), whereas greater oxygen
 195 extraction from blood by trained skeletal muscle (resulting
 196 in a greater $a\text{-vO}_2$ difference) is attributable to increases in
 197 capillary density, vascular conductance, and mitochondrial
 198 oxidative capacity [9]. A key feature of enhanced muscle
 199 oxidative capacity is increased mitochondrial biogenesis,
 200 which is associated with increases in respiratory chain
 201 enzyme levels, resulting in an increased capacity to generate
 202 energy via oxidative phosphorylation. Mitochondrial bi-
 203ogenesis is associated with an increase in mtDNA copy
 204 number as demonstrated by the proportionality between
 205 mtDNA content and muscle oxidative capacity [10].
 206 Increased mtDNA replication and mtDNA copy numbers
 207 support increased rates of synthesis of mitochondrially
 208 encoded proteins. This is in contrast to the increased rate of
 209 transcription of nuclear-encoded genes that occurs with
 210 mitochondrial biogenesis [11]. Endurance training is also
 211 known to promote the expression of slow type myosins,
 212 resulting in greater proportions of Type IIa and I fibers [12].
 213 These peripheral adaptive responses are local in nature,
 214 evident only in those muscles that are trained.

215 The magnitude of these physiological adaptations is
 216 dependent on duration, intensity and frequency of training
 217 as well as initial level of fitness [2]. In previously sedentary
 218 individuals, regularly performed aerobic exercise results in
 219 significant improvements in exercise capacity, whereas the
 220 development of peak exercise performance typified by
 221 competitive endurance athletes depends upon several
 222 months to years of training. Two to three months of training
 223 in sedentary individuals is known to induce moderate
 224 increases in VO_2 , muscle blood flow and capillary density
 225 (all between 15% and 20%) with greater changes in
 226 mitochondrial volume and enzyme activity (30–40%)
 227 [9,13]. Important to note is that a constant proportionality
 228 or stoichiometry is retained with respect to increases in
 229 mitochondrial respiratory chain and related enzymes, i.e.
 230 changes in nuclear encoded and mitochondrially encoded
 231 enzymes occur to the same extent. Further increases in
 232 cardiovascular and metabolic capacity accompany more
 233 prolonged periods of training.

234 Another notable training adaptation relates to the fact that
 235 trained individuals have lower blood and muscle lactate
 236 levels than untrained individuals at the same absolute level
 237 of submaximal exercise, reflecting a greater metabolic
 238 efficiency of skeletal muscle. Elevations in mitochondrial
 239 enzyme levels in trained muscle result in greater fatty acid

oxidation and reduced carbohydrate oxidation (and lactate
 production), thereby allowing oxidative metabolism to
 provide a greater contribution to the total energy demand,
 with lesser increase in ADP and decrease in phosphocrea-
 tine and reduced activation of glycolysis [14]. These
 changes in muscle oxidative capacity are thought to play a
 major role in the capacity to perform submaximal work with
 less effort and for longer durations. Furthermore, the point
 during submaximal exercise at which ventilation increases
 disproportionately to oxygen uptake (ventilatory threshold)
 is delayed with endurance training, related to the delayed
 onset of lactate accumulation within trained muscle.

4.2. Lose it

Inherent to the concept of training adaptation is the
 notion of training reversibility, or detraining, since the
 physiological and metabolic changes responsible for
 improved exercise capacity are not permanent. Complete
 cessation or marked reduction of endurance training leads to
 complete or partial reversal of training-induced adaptations,
 throughout the cardiopulmonary and skeletal muscle sys-
 tems that decrease maximal and submaximal exercise
 performance. Detraining leads to decreases in maximal
 work capacity, VO_2 and cardiac output that are associated
 with marked reductions in muscle capillary density, mito-
 chondrial volume and oxidative enzymes (for review, see
 Ref. [14]).

As with training gains, both the time course and
 magnitude of loss of these various adaptations are influ-
 enced by the degree and duration of detraining as well as by
 the initial fitness level of the individual before detraining
 [15]. In recently trained subjects, training-induced gains in
 VO_2 max are typically completely reversed within 4–8
 weeks of stopping training [15–17]. This loss in the
 maximal capacity for oxygen utilization is thought to be
 due to a decline in maximal cardiac output initially, with
 decreases in arterial-venous oxygen difference accounting
 for declines after more prolonged cessation of training [9].
 Rapid and progressive reductions in mitochondrial content
 and oxidative enzyme activities occur, resulting in decreased
 peak rates of mitochondrial ATP production within 3–6
 weeks. The time course of these oxidative enzymatic losses
 appears to be non-linear, with an initial rapid decline
 followed by a gradual slowing in rate of loss until a new
 steady-state is reached [18]. Declines in oxidative enzyme
 activity following detraining occur faster than decreases in
 VO_2 max, and are therefore thought not to be causally
 linked to maximal performance but rather to be of functional
 significance during submaximal exercise [19,20]. Exercise
 performed at the same absolute intensity after detraining
 results in higher lactate accumulation, increased muscle
 glycogen utilization, and carbohydrate oxidation, leading to
 reduced exercise time to fatigue. These data are taken to
 support the notion that it is the mitochondrial content of
 working muscle that is an important determinant of substrate

294 utilization during submaximal exercise. In contrast to
 295 completely stopping training, a reduction in training
 296 frequency and duration may prevent the loss of adaptation,
 297 whereas a reduction in training intensity will lead to
 298 decrements in VO₂ max and performance. Exercise intensity
 299 therefore seems to be the key variable for maintenance of
 300 training-induced adaptations [14].

301 5. Endurance training in mtDNA defects

302 Endurance training has been used to combat the effects of
 303 deconditioning in various chronically ill patient populations.
 304 However, little consideration had been given to the
 305 possibility that exercise training might be applied as therapy
 306 for muscle mitochondrial disorders.

307 5.1. Previous studies

308 Initial studies indicated that exercise training was well
 309 tolerated and improved exercise capacity in mitochondrial
 310 myopathy patients suggesting that such training had the
 311 potential to induce physiological adaptations to reverse the
 312 effects of deconditioning and ameliorate the underlying
 313 mitochondrial defect [21,22]. Although the physiological
 314 and metabolic mechanisms of improvement were not
 315 directly assessed in these studies, a particularly important
 316 question arose with respect to the normal adaptive training
 317 response of mitochondrial proliferation. In the distinctive
 318 setting of heteroplasmic muscle mtDNA disorders, would
 319 the training stimulus induce expansion of wild-type and
 320 mutant mtDNA populations equally or selectively?

321 A study was subsequently designed to assess training
 322 effects upon the overall proportion of mutant versus wild-
 323 type mtDNA as well as to more clearly define the
 324 physiological and biochemical basis of previously demon-
 325 strated improvements [1]. This study of 10 patients with

326 various heteroplasmic mtDNA defects confirmed previous
 327 findings that exercise training increased exercise capacity
 328 and improved patient assessment of quality of life: the study
 329 further showed that enhanced exercise capacity was
 330 attributable to a 20% increase in peak oxygen utilization
 331 and that the physiological basis of improved O₂ utilization
 332 was an enhanced capacity of skeletal muscle to extract
 333 available oxygen (Fig. 4) with no increase in peak O₂
 334 delivery by the circulation (which is the dominant physio-
 335 logical mechanism by which endurance training increases
 336 oxygen utilization in healthy subjects). Correspondingly,
 337 mitochondrial volume (as monitored by levels of citrate
 338 synthase) increased by 50%. In most patients, enzymatic
 339 activity of respiratory chain complexes affected by the
 340 mutation also increased albeit by lesser extent (20% on
 341 average). These muscle mitochondrial adaptations imply
 342 that the biochemical basis of improved systemic a-vO₂
 343 difference during exercise is an increased level of functional
 344 mitochondria. Interestingly, although the magnitude of
 345 increase in peak VO₂ was consistent for the training
 346 program, the increase in mitochondrial volume was approx-
 347 imately 10–20% greater than that observed in healthy,
 348 sedentary individuals undergoing similar training.

349 Analysis of muscle mutation load revealed an increase in
 350 the relative proportion of mutant mtDNA in muscle
 351 homogenates of six of nine patients and no change in three
 352 patients. In no case was a decrease in mutant mtDNA
 353 detected. These findings have raised concern regarding the
 354 advisability and safety of endurance training in mitochon-
 355 drial patients with heteroplasmic mutations. The particular
 356 question is, despite substantial physiological and biochemi-
 357 cal benefits, can endurance training promote a progressive
 358 expansion of mutant mtDNA with potentially long-term
 359 deleterious effects? This concern relates to the view that
 360 clinical progression of mtDNA diseases is attributable to a
 361 progressive accumulation of mutant mtDNA with resulting
 362 increases in the proportion of respiration-incompetent fibers

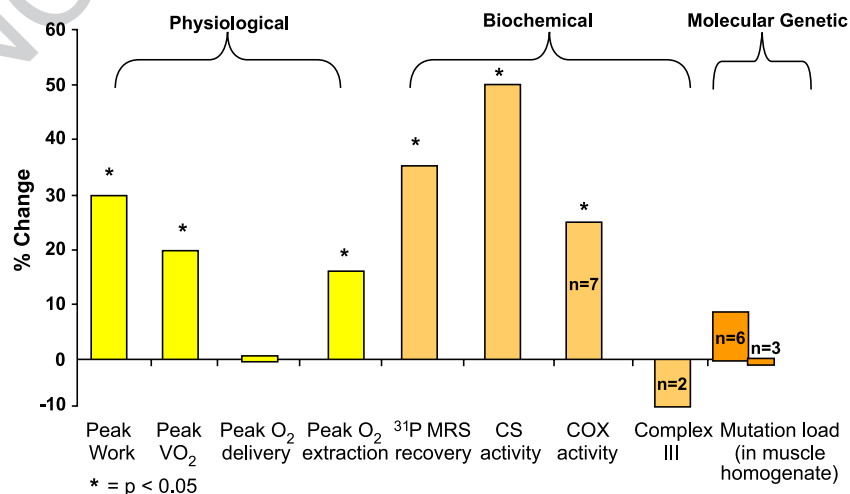


Fig. 4. Changes in physiological, biochemical and molecular genetic variables in 10 patients with mtDNA defects following 14 weeks of endurance exercise training. Adapted from Ref. [1].

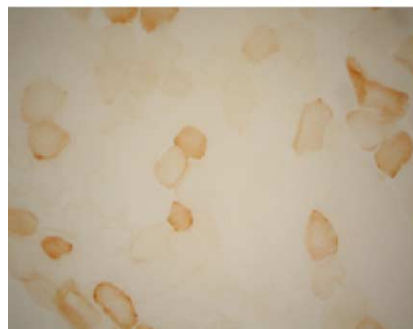
363 in clinically affected tissues [23]. Furthermore, increases in
364 skeletal muscle mutation levels over time have been
365 reported in heteroplasmic mtDNA disorders [24,25],
366 although the number of patients in whom longitudinal data
367 on mutation load are available is small. The mechanism(s)
368 responsible for accumulations of the mutation within muscle
369 fiber segments and for possible net increases in muscle
370 mutation load over time are not known. Possible mecha-
371 nisms include selective replication (replicative advantage) of
372 mutant mtDNA [26], random genetic drift of mutant
373 mtDNA [27,28] and compensatory increases in mitochon-
374 drial replication in response to biochemical deficiency [29].
375 In light of findings from this endurance training study,
376 physical activity-related preferential increases in mutant
377 mtDNA could also contribute to a drift toward higher
378 proportions of mutant mtDNA with time. Physical *inactivity*
379 and resulting deconditioning reduces mitochondrial num-
380 bers in healthy humans; and it is possible that decondi-
381 tioning could decrease wild-type relative to mutant
382 mitochondrial genomes and promote a shift toward a higher
383 percentage of mutant mtDNA.

384 The biochemical benefit of exercise training (Fig. 5) in
385 mitochondrial myopathy (i.e. increased COX activity in
386 patients with mtDNA defects that impaired COX synthesis)
387 suggests, that increases in *absolute* levels of wild-type
388 mtDNA occurred in response to training. These data imply
389 that the overall volume of wild-type mtDNA increased
390 despite a trend toward disproportionate expansion mutant
391 mtDNA. Such a response could relate to the distribution of
392 mutant and wild-type genomes within single fibers and their
393 proliferative response to metabolic feedback within normal
394 and deficient fiber segments. For example, within segments
395 that are oxidatively compromised (i.e. contain higher
396 percentages of mutant mtDNA), the exercise-related meta-
397 bolic stimulus for mitochondrial proliferation may be
398 magnified. In other words, relating to the concept of the
399 nuclear domain theory [30], the nucleus of a cytoplasmic
400 domain within a myofiber which is functionally compro-
401 mised by the presence of mutant mtDNA attempts to
402 compensate for reduced oxidative capacity and added

403 metabolic stress of training by stimulating replication of
404 mtDNA in that domain, thereby stimulating expansion of
405 mutant genomes. Alternatively, in segments containing
406 predominantly wild-type mtDNA, the training stimulus
407 would result in an increase in total numbers of wild-type
408 mtDNA. Thus both the pattern of muscle activation in
409 exercise and the distribution of mtDNA genomes within
410 active muscle may determine regional and overall patterns
411 of expansion.

412 Our inability to interpret the paradoxical molecular and
413 biochemical findings reflects our lack of knowledge of
414 factors that control copy number of wild-type and mutant
415 mtDNA molecules within skeletal muscle containing
416 heteroplasmic mitochondria. In fact, the regulatory mecha-
417 nisms controlling mitochondrial biogenesis in response to
418 contractile activity in normal muscle still remain unclear
419 [31,32]. That mitochondrial content varies to meet the
420 energy demands of the cell has been well-established, and
421 the coordinated expression of nuclear and mitochondrial
422 genes necessary for mitochondrial biogenesis makes a well-
423 orchestrated regulation of genes likely. More than 95% of
424 the genes necessary for mitochondrial biogenesis are
425 encoded in the nucleus, and regulation of these genes
426 appears to be controlled by transcriptional mechanisms [32].
427 Various nuclear-derived transcription factors regulating and
428 coordinating mitochondrial gene expression have been
429 identified: mitochondrial transcription factor A (Tfam)
430 which binds to the D-loop regulatory region of mtDNA
431 and is required for increasing mtDNA transcription and
432 copy number [33]; nuclear respiratory factor (NRF-1),
433 which transcriptionally activates Tfam, and more recently,
434 a co-activator peroxisome proliferator-activated receptor co-
435 activator-1 (PGC-1), which is being considered a potential
436 master regulator of mitochondrial biogenesis. Tfam, NRF-1,
437 and PGC-1 have been shown to be induced as part of the
438 adaptation of skeletal muscle to exercise training in healthy
439 muscle [34], and levels of Tfam have been found to
440 correlate well in increased mtDNA in ragged-red fibers
441 and decreased mtDNA levels in mtDNA-depleted cells [35].
442 The elucidation of these and other nuclear factors and

A: Pre-Training



B: Post-Training



Fig. 5. Immunohistochemical micrograph of cytochrome oxidase (COX) activity in muscle of a patient with a mtDNA defect before and after 14 weeks of endurance training. Biochemically determined COX activity in this patient increased by 20% with training.

443 associated molecular mechanisms involved in exercise-
444 induced mitochondrial biogenesis may shed light on the
445 proliferative response of mutant mtDNA.

446 5.2. Current status of endurance training in mtDNA 447 disorders

448 At present, we are unable to provide definitive recom-
449 mendation *for* or *against* endurance training for patients
450 with mtDNA defects. Whether endurance training expands
451 mutant genomes preferentially needs to be resolved before
452 precluding patients from experiencing the numerous,
453 established benefits of training. Also, given the likely
454 deleterious effects of physical inactivity, we believe it
455 would be a mistake to conclude that exercise should be
456 entirely avoided. However, the effects of deconditioning on
457 mitochondrial volume and mutant levels within muscle are
458 directly relevant to the recommendation of endurance
459 training for these patients, particularly as not all patients
460 will continue training should they undertake an exercise
461 training program. Physicians and patients routinely seek
462 advice regarding endurance training as a treatment option,
463 underscoring the immediate urgency to address its safe
464 prescription for patients with mtDNA defects.

465 We believe a key to resolving the safety of endurance
466 training is to determine the effect of cycles of training and
467 detraining upon wild-type mtDNA copy number and that
468 increases in wild-type copy number are responsible for
469 improved mitochondrial oxidative capacity, exercise per-
470 formance and quality of life in patients with heteroplasmic
471 mtDNA mutations. This may be addressed by investigation
472 of the proportion and distribution of mutant and wild-type
473 mtDNA copies within individual muscle cells and correlat-
474 ing changes in wild-type mtDNA copy number with
475 changes in biochemical enzyme activity. Single-fiber
476 analysis techniques provide greater resolution at the cellular
477 level than analysis of muscle homogenates (the outcome
478 measure in Ref. [1]) and will be particularly informative
479 with respect to the effects of training-induced proliferation
480 and detraining-induced losses on the focal distribution of the
481 two genomes within individual fibers containing differing
482 levels of biochemical impairment. Given the data, perhaps
483 the question could be re-phrased: could life-long physical
484 activity prevent further progression of mutant mtDNA
485 accumulation over time which has been documented thus
486 far?

487 6. mtDNA mutation—effects on muscle strength

488 Myopathic weakness (defined as the inability to generate
489 normal muscle contractile force) may be present with or
490 without exercise intolerance. Apart from extraocular muscle
491 involvement, fixed weakness usually affects predominantly
492 proximal hip and shoulder girdle musculature and is
493 generally mild. Weakness may be more pronounced when

combined with sustained or repeated muscle contractions 494
(i.e. with superimposed fatigable weakness). The patho- 495
physiology of muscle weakness in patients with mtDNA 496
defects is unclear but presumably involves mitochondrial- 497
dependent effects upon muscle cell integrity and viability. In 498
addition, muscle disuse related to habitual physical inactiv- 499
ity may play a role. 500

Assessment of muscle strength is most reliably done 501
using quantitative measures of contractile force and muscle 502
performance rather than qualitative assessment of strength 503
obtained with manual strength testing. Computerized 504
dynamometry, permits measurement of peak isometric and 505
isokinetic (eccentric and concentric contraction) muscle 506
torque, to supplement information gained from measure- 507
ment of isometric strength. Studies relating the degree of 508
muscle oxidative impairment to muscle weakness in 509
mtDNA defects are few [36], and to our knowledge, there 510
have been no trials assessing effects of resistive strength 511
training in patients with mitochondrial myopathies. 512

7. Normal physiological changes with resistance training 513 and detraining 514

Resistance exercise demands low volume, highly intense 515
contractions of muscle fibers. The lifting of weights to yield 516
such muscle overload typically involves an eccentric 517
component (lengthening of fiber during contraction) and a 518
concentric component (shortening of fibers during contrac- 519
tion). Chronic resistance training induces physiological 520
adaptations that completely differ from those of endurance 521
training and leads primarily to an increase in muscle 522
strength. Although both neural and muscular factors modify 523
the expression of human strength, enhanced neural facili- 524
tation predominates in the early phase of training, followed 525
by physiological adaptation within skeletal muscle [37]. 526

7.1. Use it 527

The most fundamental biologic adaptation to resistance 528
training is an increase in muscle fiber cross-sectional area, 529
allowing for increased muscular force. This is brought about 530
by fiber hypertrophy, where increased net synthesis of 531
myofibrillar protein is associated with enlargement of all 532
three major fiber types, with largest increases occurring in 533
Type II fibers [38]. A transformation in myosin heavy chain 534
isoform expression occurs, resulting primarily in fast fiber 535
type conversion (Type IIx→IIa) [12]. Although increases in 536
certain glycolytic enzyme activities, such as lactate dehy- 537
drogenase and phosphofructokinase have been reported, this 538
does not seem to be a consistent finding [39]. Furthermore, 539
these changes are not of the same magnitude as the increases 540
in oxidative enzymes observed after endurance training. The 541
increases in total contractile protein generally occur without 542
parallel increases in capillarization, total volume of mito- 543
chondria, or mitochondrial enzymes within the trained 544

545 muscle fibers [13]. Thus, with pure resistance training, the
546 ratio of mitochondrial volume and enzyme concentration to
547 muscle contractile protein is actually reduced. Resistance
548 training alone does not lead to improvements in cardiovas-
549 cular function or VO_2 max.

550 The magnitude and time course of muscle strength gain,
551 fiber hypertrophy and fiber type conversion depend on
552 training volume (intensity, frequency and duration) and
553 level of fitness. In studies assessing muscle adaptation to 9–
554 10 weeks of resistance training in previously untrained
555 individuals, increases of 20–30% in muscle strength and
556 10–20% in fiber cross-sectional area are typical [40,41]; how-
557 ever, much greater increases in cross-sectional area (100%
558 of pre-training values) have also been reported [15]. As the
559 muscle adapts, a progressive overload is required to
560 continue improvements.

561 A vital role in the muscle adaptation process to overload
562 is activation of muscle satellite cells, which are mono-
563 nucleated, committed muscle precursor cells that are derived
564 from the initial population of embryonic myogenic cells
565 [42,43]. In adult muscle, they remain undifferentiated and
566 dormant beneath the basal lamina of skeletal muscle fibers
567 until evoked by various stimuli to re-enter the cell cycle to
568 undergo mitotic division, proliferation and fusion. In
569 response to muscle overload and hypertrophy, satellite cells
570 contribute their nuclei and cytoplasmic contents (including
571 mitochondria and mtDNA) to the existing myofiber in order
572 to maintain the ratio of nuclear material to other cellular
573 components at a constant level. As mature skeletal muscle is
574 post-mitotic and multi-nucleated, the addition of these
575 satellite cell-derived nuclei is believed to be a prerequisite
576 for the maintenance of enlarging myofibers.

577 In addition to overload, acute myotrauma is a stimulus
578 for satellite cell induction. Satellite cells typically withstand
579 damaging influences and undergo activation, migration, and
580 fusion and, depending on the intensity of damage, they
581 participate in the repair of existing fibers or form new
582 myofibers through a process equivalent to muscle histo-
583 genesis in the embryo [43]. Overload in the form of
584 eccentric exercise, which can result in extensive muscle
585 damage attributable to mechanical injury affecting the
586 sarcolemma and cytoskeleton, has been proposed to
587 stimulate satellite cell proliferation. An increase in the
588 number of satellite cells has been reported to follow
589 eccentric exercise in human muscle [44].

590 At present, the biology of satellite cells is better-
591 characterized in animals than in humans, however, given
592 their stem cell-like behavior and relevance to various
593 disease states, the response of satellite cells to muscle
594 contraction and injury is emerging as an important field of
595 study [42]. The effects of both acute and chronic overload
596 induced by unaccustomed or strenuous exercise, particularly
597 damaging eccentric muscle contractions, on satellite cell
598 activation in rats have been well described. In humans, the
599 stimulus intensity and time course for satellite cell activation
600 and proliferation through acute resistance overload is

virtually unknown [44]. Studies of the effects of resistance
training on satellite cell proportions in healthy humans is
limited [41,45,46]. These studies employed high-intensity
resistance exercise combining concentric and eccentric
muscle contractions over a period of 8–16 weeks and
demonstrated increases semi-quantitatively in the proportion
of activated satellite cells within muscle after training. The
authors concluded that the smaller than anticipated satellite
cell response was due to the fact that peak satellite cell
activation likely occurred earlier in the training period and
that after 8 weeks of training, substantial differentiation of
cells had already occurred.

7.2. *Lose it*

The cessation of resistance training inevitably leads to
loss of muscle strength and hypertrophy, however, the time
course for the rates of loss is variable. Muscle cross-
sectional area declines more rapidly than strength perform-
ance which can be maintained for up to 4 weeks of
inactivity [12,15]. Muscle strength has been found to remain
above pre-training values after 12 weeks of training
cessation [47]. Furthermore, a reversal in fiber type
distribution with re-expression of the fast type IIx myosin
heavy chain isoform accompanies cessation of resistance
training.

8. “Gene-shifting” in mtDNA defects

The absence of mutant mtDNA in skeletal muscle
satellite cells, despite high levels of mutant mtDNA in
mature myofibers, has been demonstrated in patients with
sporadic large-scale deletions and sporadic point mutations
of mtDNA [48,49], in contrast to maternally inherited
mtDNA defects where the mutation is present in mitotic
tissue. This unanticipated finding led to the hypothesis that
activation of these typically quiescent myogenic cells
could result in the shifting of normal mitochondrial
templates from satellite cells to mature muscle and hence,
decrease the proportion of mutant mtDNA in muscle
below threshold for phenotypic disease expression by
restoring oxidative capacity. The feasibility of this mito-
chondrial gene-shifting approach has been reported in two
cases of patients harboring sporadic tRNA mutations of
mtDNA, both using models of muscle injury to induce
satellite cell activation. Clark et al. [48] used a myotoxic
agent, bupivacaine, to induce muscle fiber necrosis and
found that the regenerating fibers contained undetectable
levels of mutated mtDNA and were respiratory competent.
Shoubridge et al. [50] described the complete restoration
of wild-type mtDNA in muscle fibers regenerating from
traumatic injury induced by a previous biopsy. Both
groups attributed normalization of the mtDNA genotype
to induction of satellite cells in the focus of regenerating
muscle.

652 **9. Resistance training in mtDNA defects**

653 Resistance training could provide a more physiological
654 means of mitochondrial gene-shifting than myotoxin injec-
655 tion or surgical trauma. In a single case report, a decrease in
656 the proportion of mutant relative to wild-type mtDNA and
657 an increase in respiratory-competent fibers was detected in
658 muscle after resistance training [51]. These findings
659 suggested that satellite cell incorporation was the basis of
660 muscle metabolic improvement, effects of resistance train-
661 ing on muscle strength was not addressed, nor was the
662 mechanism of mitochondrial gene transfer. A subsequent
663 pilot study in a small group of patients with sporadic
664 mtDNA mutations demonstrated improvements in muscle
665 strength with unilateral leg training and demonstrated
666 variable changes in mutation load and enzymatic activity
667 assessed in muscle homogenates (Fig. 6) [52]. Analysis of
668 wild-type and mutant mtDNA copy number in single cells,
669 along with quantitation of satellite cell activation and
670 proliferation may more clearly illuminate the effects of
671 muscle overload on mitochondrial gene shifting.

672 Further study is essential to establish the practicality,
673 efficacy and safety of resistance training as a non-invasive
674 method of inducing the transfer of normal mitochondrial
675 templates from satellite cells to mature muscle. In particular,
676 the type of muscle contraction required to maximally induce
677 satellite cell activation needs to be resolved. Theoretically,
678 eccentric (damaging) exercise may provide a more potent
679 stimulus than concentric (hypertrophy-inducing) muscle
680 contractions, however, performing eccentric-only contrac-
681 tions is less practical for the patient. Also, although satellite
682 cells demonstrate the capacity for self-renewal, the effect of
683 such eccentric exercise training on the satellite cell pool is
684 unknown. This question relates to the notion that a decrease
685 in satellite cell number and proliferative capacity may
686 account for impaired skeletal muscle regeneration with
687 aging [43] and limited capacity for regeneration in

dystrophic muscle [53]. Knowledge of the appropriate
stimulus intensity for satellite cell activation is imperative,
but we feel that heavy intensity muscle contractions would
not compare to the constant degenerative and regenerative
processes occurring in dystrophic muscle. Nevertheless, the
question of whether a lifetime of intense resistance exercise
(i.e. body building) depletes the satellite cell pool and
influences the regenerative capacity of muscle is unresolved.

In addition to the potential therapeutic effect of resistance
training on the mitochondrial disease process, normal
adaptive processes increasing muscle strength are likely to
occur, particularly for muscles that are weak due to disuse
atrophy. Moreover, we believe that training of a large
muscle mass (i.e. quadriceps) also has the potential to show
a physiologically detectable effect on exercise tolerance. By
improving mitochondrial oxidative metabolism in muscle
groups used for daily activities (i.e. walking), resistance
training may be a functionally significant approach to
therapy for mitochondrial myopathy patients.

10. Conclusion

Physical activity induces numerous beneficial physio-
logical adaptations in skeletal muscle; the lack of muscle
“use” has the opposite effect in both health and disease. The
effects of exercise training in mtDNA disorders are
incompletely understood. Endurance training-induced mitoch-
ondrial biogenesis may increase both mutant and wild-
type mitochondrial genomes within skeletal muscle; which
increase is functionally dominant will determine the safety
of this treatment approach. Resistance training-induced
transfer of normal mitochondrial templates from satellite
cells to mature muscle may lower the mutation level below
phenotypic expression. Ultimately, should both endurance
and resistance exercise training approaches prove to be safe
and effective in inducing increases in muscle wild-type

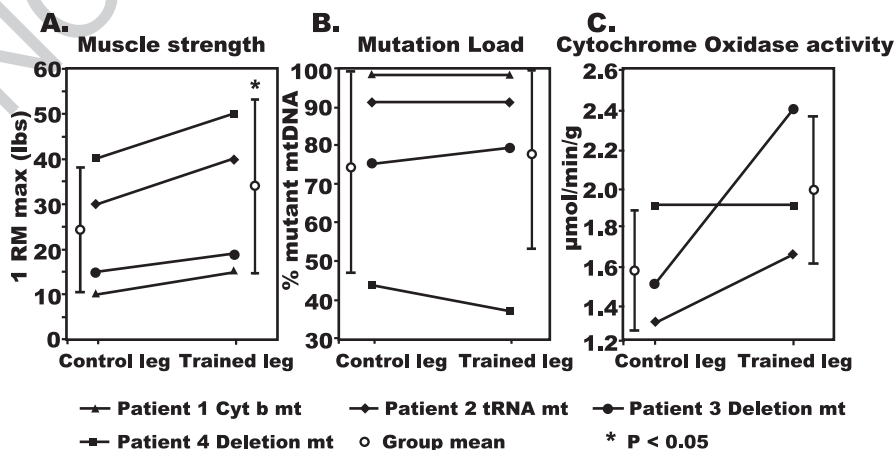


Fig. 6. Changes in physiological, molecular genetic and biochemical variables in four patients with sporadic mtDNA defects following 10 weeks of unilateral dynamic resistance training of upper leg (quadriceps muscles). Muscle strength increased in all patients (A), while changes in mutation load (B) were variable but was unchanged or decreased in three of four patients. The activities of cytochrome oxidase (C) are shown for the three patients in whom the mutation affected this enzyme (the fourth patient harbored a mutation in cytochrome *b*).

722 mtDNA levels, both treatment strategies may be used in
723 combination and in succession. A paradigm of short-term
724 heavy resistance training to initiate incorporation of wild-
725 type mtDNA from satellite cells to mature muscle followed
726 by longer-term endurance training to increase and maintain
727 their numbers may be efficacious.

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733 aimed at resolving the safety and efficacy of exercise
734 training in mitochondrial disorders.

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