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Muscular, cardiac, ventilatory and metabolic dysfunction in patients with multiple sclerosis: implications for screening, clinical care and endurance and resistance exercise therapy, a scoping review.

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Abstract

In the treatment of multiple sclerosis (MS), exercise training is now considered a cornerstone. However, most clinicians tend to focus on neurologic deficits only, and thus prefer to prescribe rehabilitation programs specifically to counteract these deficits. However, the present comprehensive review shows that patients with MS (pwMS) also experience significant muscular, cardiac, ventilatory and metabolic dysfunction, which significantly contribute, next to neurologic deficits, to exercise intolerance. In addition, these anomalies also might increase the risk for frequent hospitalization ~~rate~~ and morbidity and can reduce life expectancy. Unfortunately, the impact of exercise intervention on these anomalies in pwMS are mostly unknown. Therefore, it is suggested that pwMS should be screened systematically for muscular, cardiac, ventilatory and metabolic function during exercise testing. The detection of such anomalies should lead to adaptations and optimisation of exercise training prescription and clinical care/medical treatment of pwMS. In addition, ~~F~~future studies should focus on the impact of exercise intervention on muscular, cardiac, ventilatory and metabolic (dys)function in pwMS, to contribute to improved treatment and care.

Keywords: multiple sclerosis, exercise, muscle, lung, heart, metabolism

Introduction

Multiple Sclerosis (MS) is a neurodegenerative disease of the central nervous system that predominantly affects young to middle-aged adults. The pathology of MS is characterized by myelin, oligodendrocytes and axonal loss in the brain, brain stem and spinal cord and by white matter lesions [1], resulting in heterogeneous and complex ~~symptoms~~neurological deficits, including spasticity, weakness, visual disturbances, walking and coordination impairments, tremor, ataxia, sensory problems and bladder disturbances [2]. Furthermore, "invisible" symptoms such as depression, fatigue and cognitive dysfunction are also common MS symptoms, which may occur early in the disease course [3-5]. A combination of these symptoms may eventually lead to an inactive or sedentary lifestyle [6;7], which may further exaggerate muscle weakness, fatigue, reduced functional capacity and associated health risks [8-10]. It therefore occurs very often that patients with MS (pwMS) experience impaired functional capacity and/or elevated health risks [11;12] that cannot always be explained by the disease per se, but is probably ~~mainly~~ related to altered physical activity levels.

In the treatment of MS it is nowadays commonly accepted that pwMS significantly benefit from rehabilitation/exercise therapy throughout the course of the disease. Rehabilitation is defined as "a problem solving educational process aimed at reducing disability and handicap experienced by someone as a result of disease or injury" [13]. In particular, the primary goal of clinicians in hospitals and MS rehabilitation centres is to improve the above mentioned neurological deficits, by reducing the limitations of activity and participation, to reach the highest possible level of independence, in order to maintain or even improve the quality of life of pwMS [14]. Given the heterogeneous symptoms of pwMS, a multidisciplinary approach is often warranted, including physiotherapy, occupational therapy, psychological and coping programs, cognitive rehabilitation, speech therapy and therapy to improve fatigue [15-25].

Next to the above mentioned neurological deficits, however, it has not been clearly established whether pwMS also experience MS-related muscular (at whole-muscle and cellular level), cardiac, ventilatory and metabolic dysfunction, despite the fact that these dysfunctions may contribute to the development of secondary health complications and/or internal diseases. It is commonly assumed that these dysfunctions in pwMS are simply due to physical inactivity and sedentarism (see Figure 1). Indeed, many studies have provided compelling evidence that MS often leads to an inactive lifestyle due to difficulties in engaging into physical activities [26;27]. This physical inactivity accelerates the physical deconditioning process, which in turn makes it even more difficult to engage into physical activities. As a result, a vicious cycle of physical limitation – physical inactivity – greater physical

limitation is very likely to occur in MS. ~~Due to significantly reduced physical activity levels or sedentarism, it is however very likely that such internal diseases may develop in pwMS [11].~~ In addition, these ~~impairments~~ physical limitations may contribute to greater exercise intolerance in pwMS, but may also lead to an increased risk for hospitalization and morbidity and may lower life expectancy. In other populations, physical endurance and/or resistance exercise is frequently used as the primary treatment strategy to counteract the above mentioned health complications. Interestingly, pwMS with ~~co-morbidities~~these health complications are often excluded ~~form~~ from exercise intervention studies, which might possibly explain why current exercise recommendations do not (or very limited) take this into account [28-30].

Consequently, this ~~study~~ scoping review aimed to systematically review the literature for studies evaluating 1) muscular, cardiac, ventilatory and metabolic function in pwMS and 2) the influence of physical exercise on these parameters. Based on the literature review it is intended to evaluate the hypothesis that MS is associated with an increased prevalence of muscular, cardiac, ventilatory and metabolic dysfunction, which may lead to greater exercise intolerance. In addition, it is hypothesised that physical exercise is able to counteract these dysfunctions.

Noteworthy, future studies should challenge the above-mentioned hypothesis. For example, it is widely known that MS is associated with systemic inflammation, oxidative stress, and vitamin D depletion, to mention few systemic abnormalities in MS [31;32]. In healthy individuals and in laboratory animals, such systemic changes are known to challenge the muscular, ventilatory, cardiac, and/or metabolic functions [33-36]. It should therefore be examined whether the normalisation of these systemic anomalies would lead to improvements in muscular, ventilatory, cardiac, and metabolic functions in pwMS, even without the implementation of exercise intervention. In addition, in exercise training studies for pwMS, it should be evaluated in greater detail whether changes/improvements in muscular, ventilatory, cardiac, and metabolic functions correlate with changes in the above-mentioned systemic alterations. Such studies will provide great insights in how to improve therapy or exercise training intervention for pwMS.

Methods

This review is based on a comprehensive literature search of Pubmed, Embase, Cinahl, Pedro and Sportdiscuss by two independent reviewers (IW and DH). The database was searched by means of subject headings (e.g. MeSH terms), describing muscular, ventilatory, cardiac, and/or metabolic (dys)function in MS patients or describing the influence of exercise on these outcome measures in MS. ~~Exact search terms are~~ The search strategy is presented in Table 1.

~~Articles were searched on Pubmed, Embase, Cinahl, Pedro and Sportdiscuss up to May 2015 and the search was updated in December 2015, yielding 479 hits, of which 81 were duplicated, resulting in 398 unique publications. After screening for title and abstract, 142 papers were identified for extensive reading.~~ To be included in the present review patients with (clinician diagnosed) MS should have been studied, in which the muscular, ventilatory, cardiac, and/or metabolic (dys)function was assessed (with and without comparison to matched healthy controls). Since norm values are often based on personal characteristics (such as age and gender, for example for ventilatory, muscle and cardiac function) and because norm values for muscle function (on the cellular level) do not exist, a 'dysfunction' is considered an abnormal function, aberrant of the healthy control measurements. In addition papers investigating the influence of (acute and long term intervention) endurance and/or resistance exercise on these (dys)functions were also included in the present review. Studies applying other interventions, such as (whole body) neuromuscular electrical stimulation, balance training, pelvic floor and bladder training, home based exercise, pilates, yoga, Nintendo Wii interventions, pharmaceutical therapy or supplementation therapy in combination with exercise, aquatic exercise or exercise feasibility and reliability studies, were excluded. Furthermore, the included studies had to be peer-reviewed and had to be written in English. ~~In addition, comments, reviews and book chapters were excluded from the data extraction, as were studies regarded irrelevant to the topic of this review, resulting in 91 articles eligible for data extraction (Figure 1 and Table 2).~~

Results

Articles were searched on Pubmed, Embase, Cinahl, Pedro and Sportdiscuss up to May 2015 and the search was updated in December 2015, yielding 479 hits, of which 81 were duplicates, resulting in 398 unique publications. After screening for title and abstract, 142 papers were identified for extensive reading. In addition, comments, reviews and book chapters were excluded from the data extraction, ~~as were studies regarded irrelevant to the topic of this review,~~ resulting in 91 articles eligible for data extraction (Figure ~~1~~2 and Table 2). Furthermore, both independent reviewers agreed on the inclusion and data extraction of these studies. In general, 52 papers discussed muscular function, 20 papers cardiac function, 19 papers ventilatory function and 13 papers metabolic function. Furthermore, 50 papers described the impact of acute or long term endurance and/or resistance training on these (dys)functions. An integrative overview of muscular, ventilatory, cardiac and metabolic function is provided in Figure ~~2~~1, together with the impact of exercise training intervention.

Muscle function

Muscle function in MS

A number of studies already investigated skeletal muscle characteristics and muscle function of pwMS. A loss of muscle mass and/or a decreased maximal muscle strength is hereby reported in pwMS, even when data were adjusted for age, body mass and fat free mass, whereas other studies reported no differences between pwMS and referent subjects [37-53]. These differences in results might be explained by the differences in age, distribution of gender and the use of different test protocols. On the level of perception of muscular effort and muscle fatigue, no differences were reported between pwMS and healthy controls [54;55]. In addition, pwMS are reported to have a significant between-leg difference in leg strength [56;57]. This asymmetry varies from 2 to 30% for maximal muscle strength [56] and results in a greater muscle volume on the more affected side of the transversus abdominis, quadratus lumborum, and the low-back extensor muscle group, suggesting a compensatory mechanism to maintain balance and posture [52;58]. Furthermore, pwMS are able to perform significantly more work with the stronger leg than the weaker leg, during submaximal single-leg fixed-load cycling and compared to healthy controls [59]. Interestingly, ~~endurance~~ isokinetic knee extensor strength and isometric knee flexor strength are reported to ~~be main predictors for~~relate best to walking capacity [60]. The mechanisms underlying the above observed strength deficits might be of muscular, via altered skeletal muscle fiber characteristics, as well as neural, via central activation, origin [37-40;43].

At the cellular level, and in accordance with the work of others [39;43;61], a smaller m. vastus lateralis type I and II skeletal muscle fibre cross sectional area (CSA) and a selective type II(a) atrophy

in pwMS were recently reported by our research group. Interestingly, muscle fibre CSA was highly correlated with muscle strength of the quadriceps (knee extension), suggesting that reduced CSA contributes to muscle weakness in pwMS and that changes in skeletal muscle characteristics in MS may affect physical function [45]. Furthermore, lower succinate dehydrogenase activity, delayed phosphocreatine resynthesis after isometric exercise (indicating impaired skeletal muscle oxidative capacity), increased basal muscle adenosine monophosphate-activated protein kinase alpha (AMPKα) and mammalian target for rapamycin (mTOR) phosphorylation (which was independently related to MS), blunted intramuscular metabolic responses during isometric exercise and complex-I deficiency in skeletal muscle mitochondria, and slowed exercise-onset oxygen uptake (VO_2) kinetics (meaning that the skeletal muscle oxidative capacity is lowered) were already reported in pwMS [39;43;62-67]. Furthermore, resting muscle oxygen consumption in m. gastrocnemius was higher in pwMS, compared with healthy controls, and was higher in patients with lower walking ability, compared to pwMS at better performance, suggesting that peripheral adaptations occurred to maintain mobility [68]. In addition, Kent-Braun et al. reported a smaller intramuscular metabolic change at the same relative exercise intensity in pwMS, compared to healthy controls, suggesting a failure of muscle activation even in mildly affected pwMS [69]. These data collectively indicate disturbed skeletal muscle cell biochemistry and composition in pwMS. ~~Although MS-associated inactivity [62] could contribute to muscle weakness, it remains an attractive hypothesis whether the biochemical skeletal muscle cell and fibre abnormalities are also related to disturbed molecular signalling pathways. For example, we have recently shown that even when physical activity is acutely restored (by an acute endurance exercise bout), muscle AMPKα and mTOR signalling (which are important for muscular mitochondrial and myofibrillar biogenesis, respectively) remained significantly disturbed [58]. The latter findings may indicate that significant anomalies in muscle biochemistry is present in pwMS, and that such dysfunction may not be related to lowered physical activity only.~~

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Muscle function and exercise in MS

Following exercise rehabilitation/therapy pwMS experienced significant improvements in muscle characteristics. In particular, improvements in muscle strength, muscle endurance, muscle mass, neuromuscular function or neural drive were reported after (progressive) resistance [70-81] or combined (resistance and endurance) exercise training [82;83]. Improvements were even higher after high-intensity exercise training, suggesting that these changes are exercise intensity related [82-84]. Furthermore, motor fatigue was significantly reduced in knee flexors and extensors among female, but not in male pwMS, after 6 months of exercise training [85]. In addition, pwMS and healthy controls showed similar physiological adjustments to exercise [50]. Loss of muscle strength

and elevated signs of fatigue were reported during fatiguing exercise [86] and after a six-minute walking test [87], whereas muscle recovery of the upper limb was similar in pwMS and healthy controls after fatiguing upper limb exercise tests [7]. At the cellular level, resistance training [61] and high intensity (interval) training [82] were reported to increase mean muscle fibre CSA and lean tissue mass. As a result, these promising data indicate that the observed abnormalities in skeletal muscle biochemistry and composition can, at least in part, be remediated by exercise training intervention in MS. ~~However, it remains to be determined whether these muscular adaptations are of similar magnitude as opposed to healthy individuals and more molecular measurements should be executed in future studies. This is of key importance to understand whether adaptations in training modalities during exercise interventions should be made in pwMS.~~

In conclusion, impairments of muscle function are present in pwMS, as indicated by a loss of muscle strength, muscle mass, disturbed skeletal muscle cell biochemistry and composition. Some of these outcomes are already reported to be able to improve after exercise intervention, although more data are needed to fully understand whether the applied exercise interventions fully remediate these abnormalities. The clinical implications of these findings will be discussed further below.

Ventilatory function

~~*Ventilatroy*~~ *Ventilatory function in MS*

In the clinical evaluation of pwMS lung function anomalies are often overlooked or not closely evaluated, notwithstanding the greater likelihood for the development of severe lung complications in these patients [88]. Many pwMS may experience a reduced pulmonary/respiratory inspiratory and expiratory muscle strength and/or diffusion capacity, collectively leading to an impaired pulmonary function, even at the early onset of MS [89-94]. In addition, pwMS with a higher level of disability have lower pulmonary function and respiratory muscle strength than less disabled patients and healthy controls [91]. Such impairment in pulmonary function may lead to ineffective cough, retention of secretions and/or inability to maintain clear airways. An elevated risk for the development of atelectasis or pneumonia thus evolves [95]. ~~In the clinical care of pwMS, it is therefore important to systematically examine the pulmonary function/ventilatory system and adapt medical treatment accordingly. The latter will very likely lead to improved medical treatment.~~

In addition, such ventilatory dysfunction at rest may lead to additional limitations in exercise tolerance in pwMS (next to the neurological impairments that lead to such limitations). This has already been discovered in other chronic disease, such as obstructive chronic lung disease and heart failure [96;97]. Indeed, in pwMS significant relations are present between resting pulmonary function and exercise tolerance, thus further signifying the clinical importance of pulmonary function tests in

pwMS [98;99]. For instance, pulmonary function and respiratory muscle strength were reported to be lower in pwMS, compared to healthy controls, after a six-minute walk test [100]. It is therefore clinically relevant to further explore the ventilatory function during exercise in pwMS and unravel relationships between ventilatory anomalies and exercise intolerance in these patients.

~~*Ventilatroy*~~ *Ventilatory function and exercise in MS*

The examination of the ventilatory function during exercise can be complex in pwMS. In this respect, studies have already reported elevated carbon dioxide (VE/VCO_2) equivalents during submaximal exercise (meaning that the efficiency for ventilatory elimination of CO2 is impaired), elevated oxygen uptake (VE/VO_2) equivalents during submaximal exercise (meaning that the efficiency for ventilatory uptake of O2 is impaired), and elevated dead space ventilation (Vd/Vt ratios) during peak exercise (meaning that relatively lowered alveolar ventilation occurs) in pwMS [99;101-103]. However, in these studies elicited exercise intensities and/or subject characteristics were significantly different between pwMS and healthy controls or few ventilatory parameters were assessed. ~~In the examination of ventilatory function during exercise, however, proper matching of these factors is of key importance and a whole range of ventilatory parameters have to be assessed to be able to unravel the pathophysiology leading to ventilatory dysfunction during exercise in MS.~~

In a more recent study, a disturbed ventilatory function during endurance exercise was observed in pwMS after proper matching of subject characteristics between 37 pwMS and 15 healthy subjects and elicited exercise intensity (at 63% of predicted maximal heart rate or 3.1 mmol/l blood lactate level) [104]. Under these particular conditions, elevated dead space/tidal volume (Vd/Vt) ratios, equivalents for oxygen uptake (VE/VO_2) and carbon dioxide (VE/VCO_2) and end-tidal oxygen pressures ($PETO_2$), and lowered end-tidal pressures for carbon dioxide ($PETCO_2$) were found in pwMS. Elevated exercise $PETO_2$ and lowered exercise $PETCO_2$ in pwMS suggests elevated partial arterial O2 pressures and lowered partial arterial CO2 pressures, respectively, in pwMS.

A reduced ventilatory gas exchange efficiency in pwMS during exercise (elevated VE/VO2 and VE/VCO2) can point towards a ventilation-perfusion mismatch [104]. An abnormal diffusion capacity can be thought to contribute to such ventilation-perfusion mismatch. In accordance, a significantly lower diffusion capacity has been observed in pwMS [89;90]. A compromised gas exchange during exercise leads to elevations in VE/VCO_2 and VE/VO_2, and altered $PETO_2$ and $PETCO_2$ [104]. Correlations between elicited exercise intensity (exercise blood lactate content) and VE/VO_2 ($r=0.42$), $PETO_2$ ($r=0.37$) ($p<0.05$) have been found in pwMS [104]. It seems that an impaired O_2 uptake efficiency, which is specifically present in MS, is related to anaerobic metabolism during exercise. Cardiovascular dysfunction might also lead to ventilation-perfusion inequalities in pwMS: this will be explained in the next section. Some other studies also report diaphragmatic dysfunction or disturbed

respiratory coordination: this can also contribute to ventilation-perfusion mismatch during exercise in pwMS [105;106]. A severe ventilation-perfusion mismatch could trigger an increased ventilatory drive, but also cause desaturation (significant reduction in SaO2%, due to hypoxamie), during exercise [99]). In final, it is important to mention that correlations have been described between ratings of perceived exertion and VE/VO2 (r=0.32), VE/VCO2 (r=0.35) and PETCO2 (r=-0.28) during exercise in pwMS [104]. These data thus further confirm that ventilatory dysfunction during exercise not only correlates with exercise tolerance, but also with sensations of fatigue during exercise in pwMS. ~~As a result, it is fair to conclude that improvements in ventilatory function during exercise should be strived in pwMS to improve exercise tolerance.~~

Interestingly, some studies showed that expiratory muscle strength training is able to enhance the strength of the respiratory muscle, increasing maximal expiratory pressure [92;93;107;108], whereas one study reported improvements in forced vital capacity after 4 weeks of aerobic exercise [109]. ~~In addition~~However, a ventilation-perfusion mismatch or ventilatory dysfunction during endurance exercise in pwMS is not remediated by a 6-month training intervention (combination of strength and endurance training exercises) [104]. Despite significant improvements in exercise tolerance (as reflected by decreases in exercise blood lactate level and heart rate at a similar workload) and lower exercise ratings of perceived exertion, ventilatory anomalies remain present.

In conclusion, impaired pulmonary function (as compared to healthy controls) and significant ventilatory dysfunction during exercise is present in pwMS, as indicated by alterations in VE/VO2, VE/VCO2, Vd/Vt ratio, SaO2%, PETO2 and/or PETCO2. This dysfunction correlated significantly with exercise tolerance and sensations of exercise in pwMS, and is not easily remediated by exercise training intervention. On the other hand, specific respiratory muscle training may be a more promising intervention to counteract pulmonary dysfunction in pwMS. The clinical implications of these findings will be discussed further below.

Cardiac function

Cardiac function in MS

Patients with MS are prone to a greater risk for the development of ischemic heart disease and heart failure [11], but also at greater risk for premature cardiovascular death and hence a lowered life expectancy [110]. ~~In pwMS cardiac and cardiovascular function should thus be screened much more often in clinical practice as currently being executed.~~ It is currently speculated that the increased incidence of these cardiac diseases in pwMS is related to physical inactivity, inflammatory processes, and/or higher prevalence of smoking and obesity [11]. When the cardiac function in pwMS is

evaluated, two major abnormalities can be discovered more often than in healthy counterparts: impaired left ventricular function and a disturbed cardiac autonomic control.

The cardiac function has been studied in pwMS by echocardiography, magnetic resonance imaging, or radionuclide angiography at rest. Most studies have detected significant left and right ventricular dysfunction in pwMS [111-114]. This cardiac dysfunction is characterized by a reduction in cardiomyocyte high-energy phosphate content [112], a reduction in left and right ventricular ejection fraction [111;113;114], impaired left ventricular relaxation [111], lowered cardiac stroke volume [114], and/or abnormalities in ventricular dimensions (i.e. wall hypertrophy) [111]. It is hypothesized that these abnormalities in cardiac function at rest are mainly due to cardiac autonomic dysfunction [111;114], although the contribution of the intake of anticholinergic, α-blocking, and/or tricyclic antidepressant drugs also seems significant [111]. Anomalies in the cardiac autonomic function in pwMS can be observed by measuring heart rate (HR) and/or blood pressure responses to Valsalva manoeuvre, deep breathing and active changes in posture, and/or changes in blood pressure during sustained handgrip [115-118]. It is currently thought that cardiac autonomic dysfunction results from demyelinating plaques that damage the vasomotor centres in the brainstem and/or interfere with autonomous nervous system descending fibers in the spinal cord [115-118].

Cardiac function and exercise in MS

These abnormalities in cardiac function and cardiac autonomic control affect cardiac function during exercise in pwMS. A higher resting heart rate, a higher exercise heart rate and significantly lower oxygen pulse (VO2/HR) during exercise is commonly observed in pwMS, indicating a lowered stroke volume and/or peripheral oxygen extraction capacity [100;102;103;119], whereas one other study reported no differences between heart at rest and after exercise between pwMS and healthy controls [50]. In other populations, such impaired left ventricular function during exercise could lead to arterial pulmonary hypertension that would further elevate VE/VCO_2 and alter $PETCO_2$ during exercise and thus mimic ventilatory dysfunction [120]. As a result, cardiac dysfunction during endurance exercise can be detected by abnormalities in ventilatory parameters. Moreover, a lowered cardiac stroke will lead to a decreased cardiac output (in case of similar or decreased HR): such lowered cardiovascular reserve will definitely lead to severe exercise intolerance. The early (within the first 20 seconds) HR increase at initiation of endurance exercise is significantly slowed in pwMS, and this impairment in HR increase speed correlates significantly (r=0.64) with walking capacity in pwMS [119]. The finding of a slower 20-second HR increase in pwMS is in support for a specific disturbance of the autonomic cardiac control [119]. Other studies also reported an attenuated HR increase during onset of endurance exercise in pwMS [118;121] or suggested an abnormal dissociation between HR and pressor response to static work (isometric handgrip exercise)

[122]. In general, at onset of exercise, the rapid HR increase relies on the withdrawal of the tonic vagal activity [123]. A smaller early exercise-onset HR increase is thus speculated to be mainly related to a reduced withdrawal of the vagal tone, which is linked to a disturbed central command and/or metabo/tetanoreflex mechanisms that precede such withdrawal. In addition, primary pulmonary arterial hypertension could be present in pwMS, especially when receiving interferon beta therapy [124]. The latter will also lead to abnormalities in cardiac and/or ventilatory function and thus limit exercise performance capacity in pwMS.

Whether exercise training intervention is capable of remediating the observed abnormalities in cardiac function in pwMS remains unknown. It remains to be studied whether cardiac function, assessed by echocardiography or other medical imaging techniques, can be improved by exercise training in pwMS. A recent study examined the impact of six months of combined endurance/strength training in pwMS, and it was observed that the slowed HR increase at onset of endurance exercise (indicative for dysfunction in cardiac autonomic control) remained present, even though exercise tolerance improved significantly (as evidenced by reductions in blood lactate content at similar absolute workloads) [125]. These data thus seem to indicate that cardiac autonomic dysfunction during exercise in pwMS is not easily remediated by exercise training in pwMS. It is hypothesized that brain lesions that lead to dysfunction in cardiac autonomic dysfunction are permanent in pwMS, and thus persist after participation into a long-term exercise intervention.

In conclusion, significant cardiac dysfunction and abnormalities in cardiac autonomic control during endurance exercise is present in pwMS, as indicated by alterations in VO2/HR and slowed HR increase at onset of exercise. This dysfunction correlated significantly with exercise tolerance in pwMS, and is not easily remediated by exercise training intervention. The clinical implications of these findings will be discussed further below.

Metabolic function

Metabolic function in MS

Whether pwMS suffer more often from metabolic abnormalities (disturbances in blood lipid profile, glucose tolerance, body composition) remains a topic of intense debate [10;11;126;127]. However, evidence is accumulating that pwMS more often suffer from glucose intolerance and a disturbed glycemic control, as compared to healthy persons [126]. In addition, glucose tracer ([18F]-fluorodeoxyglucose) uptake in knee ~~en~~ and hip flexors is reported to be higher in pwMS compared to healthy controls and [18F]-FDG uptake was lower in the weaker knee flexors of pwMS, indicating a

greater metabolic cost during physical activity [57]. It therefore becomes clinically relevant to examine whether metabolic dysfunctions or anomalies are also present during exercise in pwMS.

Metabolic function and exercise in MS

Unfortunately, the metabolic function (blood lipids, glucose and endocrine hormones) during exercise is poorly understood or studied in pwMS and should thus deserve greater attention in the near future. Recently, our research group reported that combined (resistance and endurance) exercise is able to improve glucose (in)tolerance in pwMS, in an exercise intensity dependent manner [83;128]. In addition, leisure time physical activity is reported to be associated with lower waist circumference, triglyceride levels and glucose concentrations, contributing to important health-related benefits [129], whereas resistance training was only able to decrease triglyceride levels, but body-weight, blood pressure, serum glucose, total cholesterol and high-density lipoprotein cholesterol remained unchanged [81]. Furthermore, Heesen et al. (2003) studied the impact of 30 min of cycling at 60% of peak oxygen uptake (VO_{2peak}) in pwMS vs. healthy controls on blood cytokine and endocrine hormone concentrations. Changes in blood (nor)epinephrine, adrenocorticotropic hormone (ACTH), cortisol, β-endorphin, interferon gamma (IFNγ), tumor necrosis factor alpha (TNFα) and interleukin 10 (IL-10) content were normal in pwMS during such exercise bout, although a trend for a hyporeactive cytokine response emerged in pwMS [130]. It was thus concluded that metabolic dysfunction, as evidenced by these blood parameters, was not present in pwMS. In a subsequent study the impact of an 8-week endurance training program on changes in these blood parameters during acute endurance exercise was studied in pwMS [131]. No significant changes in these blood parameters during acute endurance exercise were found when following such exercise intervention in pwMS [131]. However, another study highlighted a significant abnormality in the lipolytic response to endurance exercise in pwMS: due to autonomic dysfunction pwMS are less capable of triggering fat mobilization during an exercise bout [48]. In accordance, muscle fat oxidation (as indicated by respiratory gas exchange ratio (RER) in this study) is reduced accordingly in this particular condition [48].

In conclusion, although data are presently scarce, some metabolic dysfunction is present in pwMS, as indicated by a suppressed lipolytic response (by elevated RER). Whether this metabolic dysfunction correlates significantly with exercise tolerance, and whether this metabolic dysfunction can be remediated by exercise intervention, remains to be addressed in pwMS. The clinical implications of these findings will be discussed further below.

Discussion

~~*Are the observed muscular, ventilatory, cardiac, and metabolic abnormalities (during exercise) simply due to physical inactivity in MS?*~~

~~It is commonly assumed that the above-mentioned anomalies in pwMS are simply due to physical inactivity and sedentarism (see Figure 1). Indeed, many studies have provided compelling evidence that MS often leads to an inactive lifestyle due to difficulties in engaging into physical activities [125;126]. This physical inactivity accelerates the physical deconditioning process, which in turn makes it even more difficult to engage into physical activities. As a result, a vicious cycle of physical limitation – physical inactivity – greater physical limitation is very likely to occur in MS. However, future studies should challenge the above-mentioned hypothesis. For example, it is widely known that MS is associated with systemic inflammation, oxidative stress, and vitamin D depletion, to mention few systemic abnormalities in MS [127;128]. In healthy individuals and in laboratory animals, such systemic changes are known to challenge the muscular, ventilatory, cardiac, and/or metabolic functions [129-132]. It should therefore be examined whether the normalisation of these systemic anomalies would lead to improvements in muscular, ventilatory, cardiac, and metabolic functions in pwMS, even without the implementation of exercise intervention. In addition, in exercise training studies for pwMS, it should be evaluated in greater detail whether changes/improvements in muscular, ventilatory, cardiac, and metabolic functions correlate with changes in the above-mentioned systemic alterations. Such studies will provide great insights in how to improve therapy or exercise training intervention for pwMS.~~

Implications for screening, clinical care and exercise therapy prescription

From the previous sections, it has become evident that significant muscular, ventilatory, cardiac and metabolic dysfunction may occur in pwMS. In this section, the clinical implications of these findings are discussed.

Muscular dysfunction. A disturbed muscle function is present in pwMS, as indicated by a loss of muscle strength, muscle mass, disturbed skeletal muscle cell biochemistry and composition. Since some of these outcomes are already reported to be able to improve after exercise, it is important and clinically relevant to develop exercise programs that are able to counteract reduced muscle strength, loss of muscle mass and disturbed skeletal muscle characteristics, enhancing muscle function in pwMS. Since abnormalities for muscle fiber size as well as for muscle oxidative capacity have been found in pwMS, is may be suggested to offer endurance and resistance training to counteract both anomalies. In addition, in order to develop individually optimized rehabilitation programs, pwMS should be screened properly on muscle function, and training modalities should be

adjusted accordingly. Moreover, it may be speculated to experiment with nutritional support in adjunct to resistance exercise training. For example, it remains to be examined whether the supplementation of amino acids during resistance training would lead to greater clinical benefits in pwMS. To improve skeletal muscle oxidative capacity, it is an appealing hypothesis to offer high-intensity exercise training sessions in pwMS. Indeed, when high-intensity interval training programmes are followed by pwMS, markers for muscle oxidative capacity will increase with significantly greater magnitude, as opposed to the commonly applied low-to-moderate intense endurance training programmes [82]. Although MS-associated inactivity [132] could contribute to muscle weakness, it remains an attractive hypothesis whether the biochemical skeletal muscle cell and fibre abnormalities are also related to disturbed molecular signalling pathways. For example, we have recently shown that even when physical activity is acutely restored (by an acute endurance exercise bout), muscle AMPKα and mTOR signalling (which are important for muscular mitochondrial and myofibrillar biogenesis, respectively) remained significantly disturbed [66]. The latter findings may indicate that significant anomalies in muscle biochemistry is present in pwMS, and that such dysfunction may not be related to lowered physical activity only. Finally, it remains to be determined whether muscular adaptations, as a result of exercise intervention, are of similar magnitude as opposed to healthy individuals and more molecular measurements should be executed in future studies. This is of key importance to understand whether further adaptations in training modalities during exercise interventions should be made in pwMS.

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Ventilatory dysfunction. A significantly disturbed ventilatory function during exercise is present in pwMS, and this disturbance is not remediated by endurance/strength training only [104]. First, it is thus important to systematically screen the ventilatory function in pwMS, and adapt medical treatment accordingly, when possible. Second, in exercise interventions other training methodologies may be used to aim to counteract this ventilatory dysfunction in pwMS. For example, inspiratory and expiratory muscle training (inspiratory muscle training against low-to-moderate inspiratory resistance, or expiratory muscle training against low-to-high expiratory resistance, or breathing exercises combined with certain upper body movements) significantly improves pulmonary function at rest in pwMS [108;133;134]. Therefore, is~~t~~ can be concluded that such specific exercises should be added in rehabilitation programs for pwMS to maximize the clinical benefits. However, it is not yet studied whether such specific exercise affects the ventilatory function during exercise as in pwMS. ~~As a result, it is fair to conclude that~~Furthermore, improvements in ventilatory function during exercise should be strived in pwMS to improve exercise tolerance. However, as long as the aetiology of a ventilation-perfusion mismatch during exercise in pwMS remains elusive, it is difficult to propose effective treatments. It thus follows that the aetiology for ventilation-perfusion mismatch

during exercise in pwMS should be examined in greater detail so new or novel therapies can be studied or implemented. The latter will certainly lead to significant improvements in the treatment of MS.

Cardiac dysfunction. A significantly disturbed cardiac function and cardiac autonomic control during endurance exercise is present in pwMS. Considering the significant impact of such dysfunctions on exercise tolerance in pwMS, it is evident that clinicians should systematically examine the cardiovascular system as well. It remains to be examined in greater detail whether such cardiac dysfunction can be remediated by exercise training intervention or whether such remediation only occurs after the selection of specific training modalities/methodologies. Due to the lack of such data, we are currently significantly limited to provide optimal cardiac care to pwMS by exercise intervention.

Metabolic dysfunction. During endurance exercise, the lipolytic response, and hence muscle fat oxidation, is significantly suppressed in pwMS. This will very likely affect the respiratory gas exchange ratio (RER) during exercise. Because the RER can be used to determine whether a maximal exercise test is executed in cardiopulmonary exercise tests, caution is warranted in the use of this methodology in pwMS. It must however be studied further whether a reduced lipolytic response affects muscle glycogen stores (greater depletion) during exercise and elicits early peripheral muscle fatigue in pwMS. On the other hand, to improve fat oxidation capacity endurance exercise training should preferentially be prescribed to pwMS (resistance training is much less effective). In other populations (such as obesity and/or type 2 diabetes patients) such intervention leads to improvements in fat oxidation capacity [135]. The latter then also contributes to improvements in insulin sensitivity and, hence, glycemic control. Furthermore, given the elevated likelihood to develop impaired glucose tolerance in pwMS, it may be argued to add resistance training on top of endurance training, to exercise as frequently as possible or to prolong the exercise programma. Such adaptations are instrumentals in greater improvements in glycemic control, at least in type II diabetes patients [136].

Conclusion

This ~~systematic~~ scoping review indicates that MS is associated with significant muscular, cardiac, ventilatory and metabolic dysfunction. These anomalies contribute significantly to exercise intolerance in pwMS and can lead to increased risk for the development of cardiometabolic disease, increased hospitalization frequency and/or reduced life expectancy. Consequently, pwMS should be

screened systematically for muscular, cardiac, ventilatory and metabolic function, before and during exercise. To further optimize rehabilitation/exercise therapy, training modalities (training duration and intensity) should be adapted accordingly and the impact of nutritional support should be examined.

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