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Cardiopulmonary Function

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Introduction

Unless patients have evident cardiopulmonary disease, traditional rehabilitation programs generally include therapeutic approaches to the motor control (upper limb and walking); spasticity; cognition, language and communication disorders; swallowing and nutrition; pain syndromes; bowel and bladder control; neglect and psychosocial problems.

Cardiorespiratory dysfunctions may hamper progress in the rehabilitation process, limit exercise and functional capacity, effect outcome measures and complicate present disorders. This situation, however, has been little explored in the medical literature.

An active investigation of the cardiopulmonary system should be considered in rehabilitation patients in order to plan optimal, comprehensive rehabilitation program. However, the presence of some problems including impaired body and extremity nerve function and strength, mobility limitations, sensory-perceptual dysfunctions and communication deficits has discouraged the systematic application of cardiopulmonary exercise testing to determine cardiorespiratory function in the disabled population, especially in neurological disorders.

Despite the presence of typical abnormalities in cardiorespiratory function, most disabled patients generally do not report cardiorespiratory symptoms. Many problems in these patients; such as advanced age, medications, mobility limitations and deconditioning promoting a sedentary life style usually mask cardiopulmonary impairment until increased demands appear, such as during chest infection or strenuous activity. Thus, cardiorespiratory dysfunction may be of more clinical importance in exercise tolerance for strenuous activity than in activities of daily living. Therefore, evaluation of cardiorespiratory function should be systematically included in the daily management of rehabilitation patients. Once cardiorespiratory impairment has been determined, proper cardiovascular and respiratory exercise prescription should be included in comprehensive rehabilitation programs.

Heart Rate

The frequency of contraction is an important determinant of cardiac performance (Rosse 1992, Burkhoff and Weisfeldt 2008). A normal sinus rhythm is a regular pulse between 60 and 100 beats per minute (BPM).

Normal individuls can tolerate a heart rate (HR) of approximately 30 to 180 BPM. Bradycardia is a rate less than 60 BPM. Bradycardia is often seen in athletes, sick sinus syndrome, shock, myocardial infarction (MI), heart block, junctional or ventricular escape arrhythmias, hypothyroidism, and infectious diseases such as leptospirosis, typhus and psittacosis. The use of medications like beta-blockers may also reduce the resting HR. Tachycardia is a heart rate above 100 BPM. Tachycardia is observed in fever, anemia,

thyrotoxicosis, anxiety, hypotension, dehydration, pain, myopericarditis, heart failure, arrhythmias, asthma and pneumonia (Ferguson 1992, Whiteson 2007).

The evaluation of HR can be used to estimate cardiac function during exercise. The HR increases nearly linearly with increasing workload and oxygen uptake (VO_2) as a function of exercise intensity. In other words, there is a relationship between HR and workload or power output (Franklin, Gordon, Timmis 1989, Weisman and Zeballos 1994, ATS/ACCP 2003). The maximum HR can be estimated by the equation of 220-age or 210-(age×0.65), but there is considerable variability within an age group (i.e. 10 to 15 BPM) (ATS/ACCP 2003). Increases in HR are initially mediated by a decrease in parasympathetic activity, with continued exercise by increased sympathetic activity.

Cardiac Output

Cardiac output (Q) is the product of stroke volume (SV) and HR (Sobel and Roberts 1988, Ferguson 1992, Parrillo 2008). Q can be calculated by the Fick equations: Q=SV×HR. Q is one of the measurements of overall cardiovascular performance during exercise (ATS/ACCP 2003, Burkhoff and Weisfeldt 2008). In healthy subjects, Q is a linear function of VO2 and increases in workload, from a resting value of approximately 5 l/min to a maximum of about 20l/min during upright exercise (Franklin, Gordon, Timmis 1989, Shah 2005). Initially, increases in Q accompany increases in HR and SV. At high exercise intensity, an increase in Q results from an increase in HR (Franklin, Gordon, Timmis 1989, ATS/ACCP 2003).

Blood Pressure

Systemic arterial pressure is closely releated to the product of cardiac output and systemic vascular resistance (Sobel and Roberts 1988). Hypertension is defined as a chronic elevation of arterial blood pressure. In adults blood pressure over 140/90 mm Hg is generally accepted as hypertension (Whiteson 2007, Victor 2008).

Chronic hypotension, with systolic blood pressure in the range of 85 to 110mm Hg, and without hemodynamic abnormalities such as syncope, is not pathological (Whiteson 2007, Sobel and Roberts 1988). Chronic idiopathic hypotension, vasoactive drugs, disorders of the peripheral, autonomic or central nervous system, cardiovascular deconditioning, hypovolemia, and anemia are the causes of orthostatic hypotension (Sobel and Roberts 1988).

During exercise, there is a progressive increase in the systolic pressure with an increase in VO_2. Diastolic pressure shows little change with increasing levels of exercise (Franklin, Gordon, Timmis 1989, Weisman and Zeballos 1994, ATS/ACCP 2003). If blood pressure falls as exercise intensity increases, a cardiac limitation or abnormality of sympathetic control of blood pressure such as heart failure, ischemia, aortic stenosis, pulmonary vascular disease or central venous obstruction should be suggested (ATS/ACCP 2003).

Arrhythmias

A cardiac arrhythmia is an abnormality in the timing or sequence of cardiac depolarization (Calkins 2008). Cardiac arrhythmias are generally divided into categories of disorders of impulse formation, disorders of impulse conduction or a combination of both (Bigger 1992). There are two main types of cardiac arrhythmias: tachyarrhythmia, abnormally rapid cardiac rhythm (HR above 100 BPM) and bradyarrhythmia, a slow cardiac rhythm (HR below 60 BPM) (Calkins 2008).

The consequences of arrhythmias can be palpitations, syncope, lightheadedness, chest pain, or symptoms of MI or congestive heart failure (Zipes 1988). The medical history, physical examination, electrocardiography, echocardiography, exercise tests, ambulatory monitoring and electrophsiologic studies can be used in the diagnostic approach to cardiac arrythmias (Olgin 2008).

Dyspnea

Under normal circumstances healthy people are not aware of their breathing. Dyspnea is defined as an abnormally uncomfortable awareness of breathing (Kraft 2008, Braunwald 1988, Cheville 2005). This conscious sensation of discomfort is associated with a wide variety of cardiac (coronary,valvular and myocardial) and pulmonary (stiff lungs,obstructed airways, respiratory muscle weakness) disease as well as with anemia, anxiety, obesity, and deconditioning (ATS/ACCP 2003, Braunwald 1988, Kraft 2008).

Dyspnea is experienced by normal subjects during strenuous physical exertion or by subjects unaccustomed to exercise during moderate exertion. It should be accepted as abnormal when it occurs at rest or at a mild level of physical activity not expected to cause dyspnea.

Some dyspnea scales such as the Borg Category Scale of Perceived Effort or the Linear Visual Anolog Scale, the Oxygen Cost Diagram, the Baseline and Transitional Dyspnea index, the American Thoracic Dyspnea or Chronic Respiratory Disease Questionnaire and University of California at San Diego Shortness of Breath Questionnaire have been developed to standardize assessment of the degree of dyspnea during exertion and daily living activities (ATS/ACCP 2003, ZuWallack 2000).

Breathing Pattern

The pattern of breathing refers to the respiratory frequency and regularity, the depth of breathing or tidal volume, and the relative amount of time spent during inspiration and expiration. Normal respiratory rate in adults is between 14 and 18 cycles per minute. Tidal volume of a 70-kg adult is about 500 ml per breath and the ratio of inspiratory to total time 0.4 at rest (ATS/ACCP 2003).

Both depth and frequency of breathing increase during the exercise. In normal subjects, tidal volume can reach 2.5l at high ventilatory demands (ATS/ACCP 2003). Upper limits of breathing frequency during exercise is accepted as 60 BPM (Weisman and Zeballos 1994). The ratio of inspiratory to total time increases to 0.5 to 0.55 at maximal exercise (ATS/ACCP 2003).

Ventilation

Ventilation is defined as the movement of air from outside to inside the body into the gas exchange units of the lungs. Ventilation of the lungs allows exchange of gas between blood and atmospheric air (Murray 1992).

In normal adults, the resting minute ventilation (VE) of 5 to 6 l/min can be increased to as much as 150 l/min during short periods of maximal exercise (Franklin, Gordon, Timmis 1989). Increased ventilation during exercise is associated with an increase in both depth and frequency of breathing. During a low level of exercise, increases in ventilation are accomplished primarily by increases in tidal volume. As exercise progresses, both tidal volume and frequency increase until 70 to 80% of peak exercise. Further increases in

ventilation result solely from increase in frequency (ATS/ACCP 2003, Weisman and Zeballos 1994). Maximal ventilation and resting ventilation do not appear to be affected by physical training, but ventilation at submaximal loads is decreased (Levitzky 2007).

The two major patterns of abnormal ventilatory function are restrictive and obstructive patterns. A reduced FEV1 and FEF25-75% and low FEV1/FVC ratio combined with increased total lung capacity indicate obstructive ventilatory dysfunction.FVC is preserved but the time of exhalation is prolonged. In a restrictive pattern of abnormal ventilatory function both the FEV1 and FVC are reduced as is total lung capacity and the FEV1/FVC ratio is usually normal or increased (Reynolds 2008). Maximum voluntary ventilation is reduced in obstructive ventilatory pattern and is normal or low in a restrictive pattern (Reynolds 2008, Fauci et al. 2008).

Respiratory Muscle Functions

The diaphragm, external intercostals, and the parasternal part of the internal intercostals and scalene are essential muscles of respiration because these are active even during quiet breathing in normals. The sternocleidomastoid, pectoralis, trapezius, latissimus dorsi and serratus anterior muscles are accessory inspiratory muscles. They are inactive during quiet breathing in normal subjects but help to elevate the thoracic cage during strenuous circumstances (Celli 1994, De Troyer 1993).

Expiration is passive during normal quiet breathing. Active expiration occurs during exercise, speech, singing, the expiratory phase of coughing or sneezing, and in pathologic states such as chronic bronchitis. The main muscles of expiration are the muscles of the abdominal wall, including the rectus abdominis, the external and internal oblique muscles, the transversus abdominis; and the internal intercostal muscles (Levitzky 2007).

Maximum respiratory pressures (PI max, PE max) and maximal voluntary ventilation (MVV) are used for respiratory muscles evaluation. PImax and PEmax measure respiratory muscle strength. The lower limits of normal maximal inspiratory pressure is 75 cm H_2O for men and 50 cm H_2O for women. The lower limits for maximal expiratory pressure are 100cm H_2O for men and 50cm H_2O for women (ATS/ACCP 2003). MVV is often used as an index of inspiratory muscle endurance that approximates the maximal ventilation during exercise (VEmax). The reduction in MVV and in turn, VEmax may lead a ventilatory limitation to maximal oxygen transport (VO_2) and exercise capacity (Ries 1994).

Exercise Capacity

Exercise capacity is the maximum amount of physical exertion that an individual can sustain before exhaustion. Exercise performance reflects a coordinated response of cardiovascular, pulmonary, neuromuscular and musculoskeletal functions during the activity. Reduced exercise capacity may indicate dysfunction in any portion of the complex exercise response (Walker, Hall, Hurst, 1990).

Maximum oxygen uptake (VO_2) is the best index of exercise capacity and the gold standard for cardiopulmonary function or physical fitness (Franklin, Gordon, Timmis 1989, ATS/ACCP 2003, Weisman and Zeballos 1994). Genetic factors, age, gender, body size and muscle mass, habitual level of activity, and physical conditioning and training are the main determinants of normal VO2 (ATS/ACCP 2003, Franklin, Gordon, Timmis 1989). VO2 can increase from a resting value of about 3.5 ml/ minute to 30-50 ml/min/kg during exercise in normal subjects (ATS/ACCP 2003). A reduced VO_2 is a general indicator of reduced exercise

capacity and fuctional reserve capacity of the cardiovascular and respiratory systems. Exercise capacity is mainly limited by cardiovascular, respiratory and peripheral factors such as neuromuscular or musculoskeletal abnormalities (ATS/ACCP 2003, Weisman and Zeballos 1994).

Both the timed walk test (6 or 12 min) and cardiopulmonary exercise testing (CPET) are used for evaluation of exercise capacity and functional impairment (ZuWallack 2000, Shah 2005) Oxygen uptake (VO_2), carbon dioxide exhaled (VO_2), minute ventilation (VE), heart rate (HR), electrocardiography (ECG) ,blood pressure, respiratory rate (RR), respiratory exchange ratio (RER), the ratio of physiologic dead space to tidal volume (VD/VT), oxygen saturation (SaO_2), anaerobic threshold (AT) and power output (PO) can be monitored during the CPET.

Cardiopulmonary Functions in Specific Conditions

Spinal Cord Injury

Within the past two decades, cardiopulmonary disease has emerged as the major cause of death and an important source of morbidity for aging persons with spinal cord injury (SCI) (DeVivo et al. 1993, DeVivo et al. 1999, Garshick et al. 2005, Bryce et al. 2007).

The diaphragm, external intercostals, the parasternal part of the internal intercostals and the scalene are essential muscles of respiration (Celli 1994). Injury to the cervical and upper thoracic cord disrupts the functions of the diaphragm, intercostal muscles, accessory respiratory muscles, and abdominal muscles, thereby causing reduction in spirometric and lung volume parameters and static mouth pressures (Fishburn et al. 1990, DeVivo et al. 1993, Cotton et al. 2005, Bryce et al. 2007). In patients with paraplegia, motor innervation of the diaphragm and most of the accessory muscles of breathing will be intact. However there will be partial or total paralysis of the intercostals and abdominal musculature (Liaw et al. 2000).

Spirometric and lung volume studies in patients with SCI, especially tetraplegia and high levels of paraplegia, have demonstrated restrictive dysfunction due to neuromuscular weakness characterized by significant reduction of VC, FEV1, maximal mid-expiratory flow, peak expiratory flow, total lung capacity, MVV, expiratory reserve volume, inspiratory capacity, along with a significant increase in RV, and little or no change in FRC (Bluechardt et al. 1992, Roth et al. 1995, Almenoff et al. 1995, Linn et al. 2000, Linn et al. 2001, Sutbeyaz et al. 2005). The higher level of injury, the more significantly the pulmonary function parameters are reduced (Stepp et al. 2008). Pulmonary function variables are also influenced by previous chest injury or operation, age, time since injury, obesity, and the presence of wheeze (Jain et al. 2006).

Obstructive pulmonary dysfunction is also of concern in SCI, not only because airways may collapse or be clogged by mucus, but also because they may be especially susceptible to constriction (Linn et al. 2000). Maximal mouth static respiratory pressures are reduced in SCI (Gounden 1997). Static mouth pressures have been found to correlate with level of injury in subjects with complete motor lesions, but not among those with incomplete lesions (Mateus et al.2007).

The diaphragm/upper rib cage coupling is abnormal in tetraplegia, presumably because of loss of intercostal muscle activity and increased compliance of the abdominal wall (Estenne and De Troyer 1985, De Troyer and Heilporn 1980). Rib cage paradox decreases with time after injury, possible due to the development of bony rib cage stiffness, increased strength of

cervical accessory muscles, and improved coupling of the various rib cage elements (Estenne and De Troyer 1986). Alterations in chest wall, lung and abdominal compliance in SCI are associated with an increase in the work of breathing, although overall resting oxygen uptake is lower, and may contribute to respiratory muscle fatigue (Brown et al. 2006). Cough effectiveness is reduced in patients with tetraplegia and high paraplegia due to loss of function of the major muscles of expiration including the muscles of the anterolateral wall of the abdomen, the expiratory intercostals, and the triangularis sterni (DeTroyer and Estenne 1991). Reduced expiratory pressures with ineffective cough are frequently associated with mucus plugging and atelectasis, two major causes of morbidity and mortality in SCI (Slonimski and Aguilera 2001, Schilero et al. 2009).

The peak VO_2 and power output (PO) values are reported to be lower in SCI subjects than those in healthy controls due to reduced active muscle mass and increased adipose tissue in SCI (Flandrois et al. 1986, Hooker et al. 1993, Vinet et al. 1997, Schilero et al. 2009). Greater muscular strength is associated with greater aerobic power and endurance (Zoeller et al. 2005). Cardiac output, stroke volume and mean exercise systolic and diastolic blood pressures are low in SCI patients. These lower physiologic responses are due to the loss of central sympathetic vasomotor outflow and the loss of a muscle pump below the level of injury, inducing a venous pooling of the blood (Coutts et al. 1983, Van Loan et al. 1987, Davis et al. 1988, Hooker et al. 1993, Vinet et al. 1997, Lassau-Wray and Ward 2000).

The major cardiovascular concerns associated with SCI are higher prevelance of cardiovascular disease, greater morbidity and mortality from cardiovascular causes, heightened cardiovascular risk factors, blood pressure abnormalities (orthostatic hypotension, autonomic dysreflexia), deep vein thrombosis, thromboembolic events and rhythm disturbances (bradyarrhythmias, reduced heart rate variability) (Myers et al. 2007).

Morbidity from cardiovascular causes, particularly coronary artery disease (CAD) tends to occur earlier in SCI individuals than among ambulatory populations (Philips et al. 1988, DeVivo et al. 1992, Garshick et al. 2005). The risk of developing cardiovascular disease (CVD) is associated with both the level and extent of injury (Groah et al. 2001). A major contributor to the heightened risk of CVD in SCI is the fact that risk factors, including hyperlipidemia, obesity, and diabetes, are comparatively high among individuals with SCI (Philips et al. 1988, Yekutiel 1989, Bauman et al. 1999, Demirel et al. 2001). An additional contributing factor to the high cardiovascular morbidity and mortality in SCI is the sedentary lifestyle and reduced physical function associated with loss of motor function (Bauman et al. 1999, Jacobs and Nash 2004).

Stroke

Cardiorespiratory complications and recurrent stroke are leading causes of mortality in the stroke population (Gordon et al 2004).

Stroke patients have partial or total weakness of the diaphragm, and intercostal and abdominal muscles on the affected side (Annoni et al. 1990, Roth and Noll 1994, Similowski et al. 1996, Lanini et al. 2003). The major function of expiratory muscles is to generate a forceful and effective cough. Expiratory muscle weakness results in an ineffective cough, retention of secretions, and inability to maintain a clear airway. This may lead to pneumonia and microatelectasis. Pneumonia is estimated to occur in about one third of stroke patients and is a major cause of morbidity and mortality in these subjects (Harvey et al. 2007). Weakness of the respiratory muscles results in changes in the mechanics of the lungs and thorax, such as a

reduction in lung compliance and a severe restrictive ventilatory impairment. Restrictive ventilatory impairment may lead to hypoventilation and hypoxemia (Sezer et al. 2004). Both decreased motion and paradoxical motion of the affected half of the rib cage have been described in patients with stroke (Fugl-Meyer and Grimy 1984). Furthermore, the efficiency of the unaffected muscles may be decreased due to instability of the chest wall and an inactive lifestyle. A larger hemidiaphragmatic excursion on the unaffected side was observed in these patients (Khedr et al. 2000).

Respiratory dysfunction, due to reduced VC, IC, TLC, FEV1, FVC, FEF25-75%, MVV, PEF, and ERV, has been reported after stroke (Roth and Noll 1994, Annoni et al. 1990, Khedr et al. 2000, Sezer et al. 2004). A significant relationship has been shown between respiratory dysfunction and motor disability scores (Annoni et al. 1990, Khedr et al. 2000).

Peak oxygen consumption VO_2, the criterion measure for exercise capacity, is poor in the stroke population (Potempa 1996, Arsura 2005, Pang et al. 2005, Rimmer and Wang 2005, MacKay et al. 2005, Macko et al. 2005, Pang et al. 2006, Courban et al. 2006). Peak VO_2 in individuals with stroke has been shown to be as low as 50-70% of that age and gender matched in value to sedentary individuals (Mackay-Lyons and Makrides 2004, Eng et al. 2004, Gordon et al. 2004). The impairment in cardiorespiratory fitness is related to a combination of physiologic and environmental factors (Kelly et al. 2003). Physiologic factors include the loss of strength and coordination, resulting in a reduction in the number of recruitable motor units, and diminished capacity for oxidative metabolism in paretic muscle tissue (Potempa et al. 1996). Enviromental factors that may contribute to impairment in fitness include bedrest and physical inactivity after the stroke (Mackey et al. 1996). HR is increased at low work rates in stroke patients (Sezer et al. 2004). Decresased cardiovascular fitness, disuse atrophy, weakness, and respiratory dysfunction in stroke patients may be responsible for this condition (Sezer et al. 2004). Low exercise capacity has been related to an increased risk of various forms of cardiovascular disease in these individuals (Pang et al. 2006). Poor cardiorespiratory fitness has also been linked to a higher risk of stroke and stroke mortality (Arsura 2005, Pang et al. 2005).

Stroke is associated with cardiac complications such as cardiac arrhythmias and ischemic heart damage (Katz-Leurer et al. 2003, Harvey et al. 2007). Cardiac disease has been reported to occur in up to 75% of stroke survivors (Roth 1993). Both coronary artery disease (CAD) and ischemic stroke, share links to many of the same predisposing, potentially modifiable risk factors such as hypertension, abnormal blood lipids and lipoproteins, cigarette smoking, physical inactivity, obesity, and diabetes mellitus (Roth 1993, Gordon et al. 1998, Pearson et al. 2002, Goldstein et al. 2006). Many patients with clinically apparent or silent myocardial ischemia have coexistent cerebrovascular disesae. Conversely, many patients with cerebrovascular disease have varying degrees of CAD (Sirna et al. 1990). Accordingly, recurrent stroke and cardiac disease are the leading causes of mortality in stroke survivors (Gordon et al. 2004).

Multiple Sclerosis

Respiratory complications are a major cause of morbidity and mortality in patients with multiple sclerosis (MS) (Sadovnick et al. 1991, Midgard et al. 1996 Gosselink et al. 1999). The causes of respiratory dysfunction have been divided into five categories; respiratory muscle weakness, bulbar dysfunction, obstructive sleep apnoea, abnormalities of respiratory control and paroxysmal hyperventilation. In most cases there is more than one cause (Howard et al. 1992, Carter and Noseworthy 1994).

Most studies observed only slightly abnormal pulmonary function tests in patients with mild MS (Smeltzer et al. 1992, Buyse et al. 1997, Karpatkin 2008). Spirometric values (VC, FEV1) were essentially normal in ambulatory patients, but were reduced in wheelchair-bound and particularly in bedridden patients (Smeltzer et al. 1988, Smeltzer et al. 1992, Foglio et al. 1994, Buyse et al. 1997, Altintas et al. 2007). FVC and MVV were found to correlate best with the level of disability as assessed with the Kurtze Expanded Disability Status Scale (EDSS) score (Smeltzer et al. 1988, Smeltzer et al. 1992, Foglio et al. 1994, Buyse et al. 1997). The Tiffenau index (FEV1/FVC) was unaffected by disability level, indicating a restrictive patern of pulmonary dysfunction (Smeltzer et al. 1988, Smeltzer et al. 1992, Buyse et al. 1997). TLC and RV were almost normal and independent from the EDSS (Smeltzer et al. 1992, Foglio et al. 1994, Buyse et al. 1997). Restrictive ventilatory impairment may lead to hypoventilation and hypoxemia in patients with MS (Koseoglu et al. 2006). Many patients with MS do not have dyspnea (Smeltzer et al. 1992).

Respiratory muscle weakness has been observed in a number of studies in patients with MS (Smeltzer et al. 1988, Smeltzer et al. 1992, Foglio et al. 1994, Tantucci et al. 1994, Buyse et al. 1997 Koseoglu et al. 2006). Expiratory muscles presented more severe weakness than inspiratory muscles in most studies whereas others found inspiratory and expiratory muscles to be equally affected (Smeltzer et al. 1988, Smeltzer et al. 1992, Foglio et al. 1994, Tantucci et al. 1994, Buyse et al. 1997 Koseoglu et al. 2006). When expiratory muscle weakness is severe, it can lead to a weak, ineffective cough and inability to clear airways, which in turn leads to respiratory complications that are a common causes of morbidity and mortality in MS (Altintas et al. 2007). The studies have demonstrated that ambulatory MS patients were unlikely to have significant respiratory muscle dysfunction, whereas wheelchair-bound patients, especially those with upper extremity weakness, often had severely compromised respiratory muscle function (Smeltzer et al. 1988, Smeltzer et al. 1992).

Patients with MS show a poor exercise tolerance and reduced physical, recreational and social activities (Petajan et al. 1996, Romberg et al. 2004, Motl et al. 2005, Koseoglu et al. 2006, Rampello et al. 2007). Peripheral as well as central factors may be involved in the pathogenesis of the reduced exercise tolerance and fatigue in patients with MS (Foglio et al. 1994, Schubert et al. 1998, Comi and Leocani 2002, Chetta et al. 2004). Neurological deficits promoting a sedantary lifestyle may lead to a decline in cardiovascular fitness, exercise capacity, disuse atrophy and weakness in MS patients (Koseoglu et al. 2006). Reduced respiratory muscle function has also been cited as a possible explanation for the documented reduction in exercise capacity in patients with MS (Koseoglu et al. 2006).

Cardiovascular autonomic dysfunction has been reported in 25-75% of patients with MS (Acevedo et al. 2000, Morrison et al. 2008). Moderate abnormalities in HR and blood pressure have been demonstrated at rest (Sutherland and Andersen 2001). In MS patients, the HR response to graded exercise testing is generally linear with respect to work rate, but it is blunted compared with healthy controls. This attenuation of exercise HR may result from cardiovascular dysautonomia (White and Dressendorfer 2004). Cardiovascular dysautonomia is also associated with an attenuated rise in blood pressure during exercise. Inadequate rise in systolic pressure during exercise may lead to insufficient perfusion of the brain or muscles and the premature development of exertional symptoms such as light-headedness or muscle fatigue (White and Dressendorfer 2004).

Parkinson's Disease

Respiratory dysfunction has been recognized as a cause of morbidity and mortality in patients with Parkinson's disease (PD) (Vincken et al. 1984, Vincken et al, 1989, Vercueil et al. 1999). A variety of respiratory problems such as aspiration pneumonia, respiratory dysrhythmias whether or not associated with levodopa therapy, chronic or recurrent airflow limitation, acute respiratory failure and lung infection have been reported. Additionally, obstructive and restrictive ventilatory defects, upper-airway and intercostal muscle involvement have been documented (Hovestadt et al. 1989, Zupnick et al. 1990, Brown 1994, Izquierdo-Alonso et al. 1994, Sabaté et al. 1996a, Koseoglu et al. 1997, Herer et al. 2001, Weiner et al. 2002, Polatli et al. 2002, De Pandis et al. 2002).

Different possible mechanisms such as involvement of the upper airway striated muscles, decreased arterial PO_2, L-dopa induced dyskinesias, and systemic defect in mitochondrial function have been postulated to explain the respiratory dysfunction in PD (Koseoglu and Ordu-Gokkaya 2006).

Obstructive airway changes (FEV1/FVC less than 80%, PEF and FEF 25-75% less than 75%), have frequently been reported most frequently in the literature (Hovestadt et al. 1989, De Bruin et al, 1993, Sabaté et al. 1996a, Koseoglu et al. 1997, Polatli et al. 2002, Sathyaprabha et al. 2005), but restrictive changes (VC less than %80 and FEV1/FVC higher than 80%) can also occur in PD (Izquierdo-Alonso et al. 1994, Koseoglu et al. 1997). Weakness of the respiratory muscles has been identified in PD (De Bruin et al, 1993, Sabaté et al. 1996b), the weakness of these muscles increases with disease progression (De Bruin et al, 1993, Sabaté et al. 1996a, Sabaté et al. 1996b, Weiner et al. 2002, Haas et al. 2004, Sathyaprabha et al. 2005). Although dyspnea is not a frequent complaint among patients with PD, it is well documented that the intensity of dyspnea is related to the activity and the strength of the respiratory muscles (Weiner et al. 2002).

Deconditioning and decreased endurance in the individual with PD have been discussed in many studies (Protas et al. 1996, Canning et al. 1997, Stanley et al. 1999, Bergen et al. 2002). The peak VO_2 and the peak HR reached during exercise are used to define the level of cardiovascular conditioning and to prescribe exercise. By interfering with the exercise movement, the PD-asssociated movement disorders of rigidity and bradykinesia can increase cardiovascular requirements, metabolic responses and ventilatory requirements for submaximal exercise (Koseoglu and Tomruk 2001).

Autonomic dysfunction occurs frequently in individuals with PD, but usually in the later stages of the disease. The most frequent symptom of cardiovascular autonomic dysfunction is orthostatic hypotension (Peralta et al. 2007, Robertson 2008). About 50% of PD patients especially in the advanced disease stage complain about general symptoms of orthostatic hypotension (Ziemssen and Reichmann 2009). In addition to orthostatic hypotension, cardiovagal and baroreflex dysfunctions are reported in patients with PD (Goldstein 2003, Okubadejo and Danesi 2004, Friedrich et al. 2008, Schmidt et al. 2009). It is also demonstrated that HR and blood pressure at peak exercise, are lower than healthy subjects in patients with PD (DiFrancisco-Donoghue et al. 2009).

Ankylosing Spondylitis

Ankylosing spondylitis (AS) affects the joints primarily but also has extra-articular manifestations, and in some patients these features may contribute significantly to morbidity and mortality (Quismorio 2006).

A wide spectrum of pulmonary manifestations have been reported in AS, including upper lobe fibrosis, interstitial lung disease, pleural thickening, pleural effusion and restricted pulmonary functions (Quismorio 2006). Pulmonary function tests in AS have displayed a high prevalence of restrictive pattern, characterized by low FVC frequently associated with low thoracic expansibility (Feltelius et al. 1986, Franssen et al. 1986, Vanderschueren et al. 1989, Fisher et al. 1990, Baser et al. 2006, Sampaio-Barros et al. 2007, Dincer et al. 2007).

It is reported that the respiratory muscle strength, measured by MIP, MEP and endurance (MVV), were significantly lower in AS compared with matched healthy controls. The respiratory muscle strength correlated with diminished chest expansion (Vanderschueren et al. 1989, Sahin et al. 2004, Sahin et al. 2006). Therefore, patients with AS rarely develop respiratory failure or complain of dyspnoea (Fisher et al. 1990).

Exercise capacity is reduced in patients with AS. Several explanations are proposed for the reduction in exercise capacity, such as pulmonary function impairment, chest wall restriction, poor respiratory muscle performance, peripheral muscle weakness and deconditioning (Eliott et al. 1985, Feltelius et al. 1986, Fisher et al. 1990, Casserly et al. 1997, Carter et al. 1999, Koseoglu et al. 1998, Seckin et al. 2000, Cerrahoglu et al. 2002, Van der Esch et al.2004, Dincer et al. 2007).

Patients with AS have a reduced life expectancy compared with the general population and this seems mainly to be due to excess CVD mortality (Peters et al. 2004). The classical CVD associated with AS includes aortic valve incompetence, which is said to affect 10% of cases, although its prevalence increases in patients with longer disease duration and more severe AS disease (Goodson and Solomon 2006). Other CVD observed in AS include; conduction defects, arrhythmias, left ventricular dilatation and diastolic ventricular dysfunction (Peters et al. 2004, O'Neill and Bresnihan 1992). Pericardial involvement is rare in AS (Goodson and Solomon 2006).

Rheumatoid Arthritis

Pulmonary involvement contributes significantly to morbidity and mortality of patients with rheumatoid arthritis (RA) and is the second most common cause of death after infections (Anaya et al. 1995). A variety of respiratory tract lesions are thought to be associated with RA. These include pleural involvement, rheumatoid nodulosis, interstitial involvement, Caplan's syndrome, airway involvement, pulmonary vasculitis and drug-induced lung diseases (Banks et al. 1992, Anaya et al. 1995, Remy-Jardin et al. 1994, Cortet et al. 1997, Perez et al. 1998).

There are numerous studies on lung function in RA, and these have demonstrated a high prevalence of abnormality characteristic of interstitial and both large and small airway disease. A high incidence of small airways defect expressed by a reduction of FEF25–75% is reported in RA patients (Radoux et al. 1987, Vergnenègre et al. 1997, Cortet et al. 1997, Perez et al. 1998, Avnon et al. 2009). The reduced values of MVV, MIP and MEP in pulmonary function tests show that patients with RA have reduced inspiratory and expiratory muscle strength and endurance (Cimen et al. 2001).

Studies on involving individuals with RA have revealed reduced exercise capacity (VO_2) levels (Ekdahl and Broman 1992, Cimen et al. 2001, Häkkinen et al. 2002, van Brussel et al. 2007). It is suggested that this pattern of RA-related poor aerobic fitness stems from the direct

impact of chronic inflammation, and from the secondary effects of a sedentary life style (Del Rincón et al. 2003, Sattar and McInnes 2005, Chang et al. 2009).

CVD morbidity and mortality is increased in patients with RA, and CVD events are strongly associated with signs and markers of systemic inflammation (Turesson and Matteson 2007, Turesson et al. 2008). Structural cardiac lesions, which have been described in association with RA, include pericarditis, nonspecific mitral and aortic valve abnormalities and endocardial rheumatoid nodules (Goodson and Solomon 2006). RA patients seem to have an increased prevalence of conduction disturbance (atrioventricular block) possibly due to disruption of the atrioventricular node by rheumatoid granulomata (Ahern et al. 1983, Goodson and Solomon 2006). Autonomic nervous system disturbance has been observed in RA cohorts which may be a risk factor for silent CVD (Toussirot et al. 1993, Curtis and O'Keefe 2002, Maradit-Kremers 2005). The results showed that RA patients have increased HR at rest, irrespective of the severity of the disease and patients with severe RA have increased systolic and diastolic blood pressures before and after tilting (Toussirot et al. 1993).

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