Impact of diabetes, chronic heart failure, congenital heart disease and chronic obstructive pulmonary disease on acute and chronic exercise responses

Patrice Brassard PhD, Annie Ferland RD PhD, Karine Marquis MSc, François Maltais MD, Jean Jobin PhD FACSM FAACVPR, Paul Poirier MD PhD FRCPC FACC FAHA

P Brassard, A Ferland, K Marquis, F Maltais, J Jobin, P Poirier. Impact of diabetes, chronic heart failure, congenital heart disease and chronic obstructive pulmonary disease on acute and chronic exercise responses. Can J Cardiol 2007;23(Suppl B):89B-96B.

Several chronic diseases are known to negatively affect the ability of an individual to perform exercise. However, the altered exercise capacity observed in these patients is not solely associated with the heart and lungs dysfunction. Exercise has also been shown to play an important role in the management of several pathologies encountered in the fields of cardiology and pneumology. Studies conducted in our institution regarding the influence of diabetes, chronic heart failure, congenital heart disease and chronic pulmonary obstructive disease on the acute and chronic exercise responses, along with the beneficial effects of exercise training in these populations, are reviewed.

Key Words: *Chronic heart failure; Chronic obstructive pulmonary disease; Congenital heart disease; Exercise response; Exercise training; Type 2 diabetes mellitus*

L'impacte du diabète, de l'insuffisance cardiaque, de la cardiomyopathie congénitale et de la maladie pulmonaire obstructive chronique sur les réponses physiologiques à un exercice aigu et chronique

Plusieurs maladies chroniques nuisent à la capacité à l'exercice. Cependant, cette diminution de la capacité à l'exercice n'est pas seulement associée à une altération de la fonction cardiaque et pulmonaire. De plus, les effets bénéfiques de l'exercice comme approche thérapeutique pour plusieurs pathologies reliées au domaine de la cardiologie et de la pneumologie sont bien connus. Cette revue résume les résultats provenant d'études effectuées dans notre Institution concernant l'impact du diabète, de l'insuffisance cardiaque, de la cardiomyopathie congénitale et de la maladie pulmonaire obstructive chronique sur les réponses physiologiques à un exercice aigu et chronique ainsi que les effets bénéfiques de l'entraînement à l'exercice chez ces populations.

Cardiac, pulmonary and metabolic disorders are known to negatively impact the capacity to perform exercise. Also, exercise has been shown to play an important role in the management of several pathologies encountered in the fields of cardiology and pneumology. A better understanding of the expected beneficial impact of exercise on several parameters associated with diseases is of clinical importance. The present article describes research that has been conducted in the Institut universitaire de cardiologie et de pneumologie, Université Laval, Quebec, for the past 10 years regarding the influence of diabetes, chronic heart failure (CHF), congenital heart disease and chronic obstructive pulmonary disease (COPD) on acute and chronic exercise responses, along with the beneficial effect of exercise training in patients with such diseases.

EXERCISE AND DIABETES: NUTRITION AND METABOLISM MODULATION

Regular physical activity and healthy food choices are recommended in individuals with type 2 diabetes to achieve a better glycemic control, reduce the need for hypoglycemic drugs and control body weight (1).

Many health care professionals wrongly believe that an aerobic exercise session performed by patients with diabetes in the fasting state may have a deleterious impact on blood glucose levels and lead to an increased risk of hypoglycemia during exercise. However, the blood glucose-lowering influence of an acute exercise session is modest or even nonexistent when exercise is performed in the fasting state (2,3). Indeed, Poirier et al (3) demonstrated that 1 h of exercise at 60% of peak oxygen uptake ($\dot{V}O_2$) performed 2 h after a breakfast enhanced the glucose-lowering effect of exercise (approximately 40%), whereas plasma glucose decline was rather small (approximately 4%) when subjects exercised while fasting. These observations were related to higher insulin levels during exercise in the postprandial state, which is likely to have blunted hepatic glucose production, resulting in a glucose utilization/production imbalance and a greater decrease in blood glucose levels (3-5). A decrease in blood glucose following exercise is largely dependent on both pre-exercise plasma glucose levels and the nutritional status. Indeed, exercise performed in the postprandial state may be associated with a significant decrease in blood glucose levels, ranging from 18% to 50% depending on pre-exercise blood glucose levels, the time between meals and the onset of exercise (Figure 1) (6). The expected decline in blood glucose following exercise is clinically important considering the fact that hypoglycemia may precipitate myocardial ischemia in high-risk patients (7).

One can see that nutritional status is important when considering exercise, because the vast majority of exercise performed by subjects with type 2 diabetes is during the postprandial state. The latter is mainly characterized by hyperglycemia and hyperinsulinemia, promoting a greater peripheral

Centre de recherche de l'Hôpital Laval, Institut universitaire de cardiologie et de pneumologie, Université Laval, Québec
Correspondence: Dr Paul Poirier, Institut universitaire de cardiologie et de pneumologie, Centre de recherche clinique/Hôpital Laval, 2725 Chemin Sainte-Foy, Sainte-Foy, Québec G1V 4G5. Telephone 418-656-4767, fax 418-656-4562, e-mail paul.poirier@crhl.ulaval.ca
Received for publication March 26, 2007. Accepted June 9, 2007

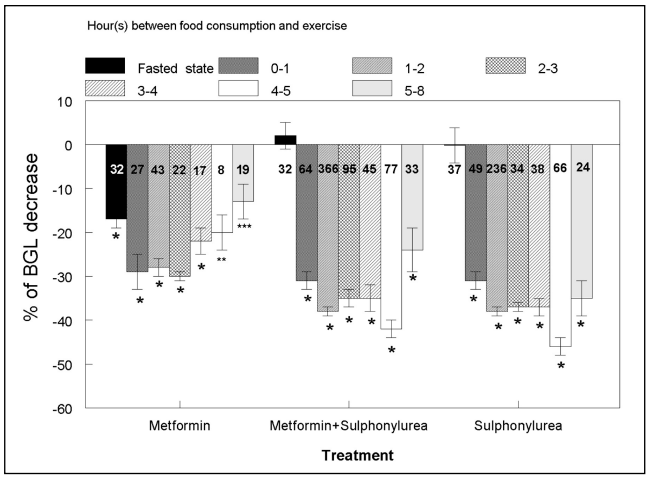

Figure 1) *The effect of different time intervals following food consumption and the onset of exercise on blood glucose levels after 60 min of aerobic exercise in patients with type 2 diabetes depending on the treatment regimen. Data are mean ± SE. Numbers on the bars are the number of exercise sessions. *P<0.001 versus pre blood glucose levels (BGL); **P=0.01 versus pre BGL. From Gaudet-Savard et al (6) with permission*

use of glucose during exercise and inducing a dramatic reduction in plasma glucose levels compared with pre-exercise (6). This reliance on glucose is further enhanced by hyperinsulinemia, which inhibits lipolysis during exercise (3). In the fasting state or during prolonged exercise, which involves an increased demand for ATP, the decrement in plasma insulin stimulates lipolysis. These conditions allow plasma free fatty acids to provide the major substrate for energy (8).

Accordingly, the function of carnitine in energy metabolism becomes increasingly important in diabetes. This metabolic disorder is associated with an increase in lipolysis and enhanced mobilization of free fatty acids as the main source of energy. Carnitine is an essential cofactor for the transport of long chain fatty acids across the inner mitochondrial compartment to provide energy (ATP). This occurs via beta-oxidation, after activation from acyl-coenzyme A to acylcarnitine (9). Under normal conditions, the plasma carnitine response to exercise in the noninsulin-resistant state is associated with an elevation in total carnitine, and an increase in plasma acylcarnitine due to a reduction in the free carnitine form (10,11). Thus, when patients with diabetes exercise in the fasting state, the plasma concentration of free carnitine decreases while the acylcarnitine fraction increases, resulting in an increase in the total plasma carnitine pool. In the postprandial state, although the level of plasma free carnitine has been shown to decrease throughout exercise, the acylcarnitine fraction remains unchanged, resulting in no change in the total carnitine content. The metabolic state of patients with diabetes is thus associated with different plasma carnitine availability and may reflect differences in energy metabolism associated with fasting and postprandial hyperglycemia (12).

Numerous factors may exert differential impacts on insulin release and glucose metabolism in patients with type 2 diabetes. Examples are the amount of carbohydrates, the type of sugar (glucose, fructose, sucrose, lactose) and the other food components (fat and protein ratio) (13). Considering the differential impact of various forms of carbohydrate, several guidelines suggest that low-calorie sweetening agents such as aspartame should be an alternative for individuals with diabetes to help control carbohydrate intake and blood glucose (14-17). Pre-exercise plasma glucose and insulin levels have been reported to be similar among sweetened conditions, such as sucrose-, fructose- or aspartame-sweetened meals. With exercise, the anticipated beneficial effect of substituting sucrose for aspartame, which reduces total calories and carbohydrate content of a meal, may not be observed (18). Thus, aspartame may enhance the insulin secretion similar to a sucrose meal, and the importance of glucose and insulin decrement observed after an aspartame meal is similar to that observed after other sweetened meals (18). This phenomenon may influence postabsorptive and exercise glucose modulation, inducing relative hyperinsulinemia, and potentiate the decrease in plasma glucose levels during an aerobic exercise session compared with the fasting state. Notwithstanding the risk of exercise induced-hypoglycemia in patients with diabetes and the safety of aerobic exercise, the authors have reported severe symptoms of hypoglycemia on four occasions following the sucrose- and/or the aspartame-sweetened meals (19).

The regulation of the metabolic response to exercise is also closely regulated via circulating levels of a number of counter-regulatory hormones, such as catecholamines, glucagon and cortisol in response to variations in plasma glucose and insulin levels. These hormones antagonize the hypoglycemic action of insulin by either restraining peripheral glucose utilization or enhancing hepatic glycogenolysis, or both, for the blood glucose concentration to remain stable (20). The adrenaline response after different sweetened meals (sucrose-, fructose- and aspartame-sweetened meals) has been reported to increase similarly during exercise, which has been associated with a similar fall in blood glucose levels (21). Even if the glycemic index and the decrease in glucose levels of the fat meal were similar to the aspartame meal, a significant increment in the adrenaline response was observed only after the aspartame meal. Of note, noradrenaline and dopamine responses were comparable among all groups.

Because cardiovascular disease underlies the majority of deaths due to diabetes, the well-established role of exercise in preventing cardiovascular risk by inducing beneficial changes in insulin sensitivity and lipid metabolism is likely to have long-term effects on cardiovascular complications. Beta-blocker treatment may have some negative metabolic impact in individuals with type 2 diabetes; these include increased plasma glucose and triglyceride levels as well as body weight, increased insulin resistance, decreased high-density lipoprotein-cholesterol levels and hypoglycemia symptoms. Nevertheless, the efficacy of this class of drugs on cardiovascular events and mortality post myocardial infarction is undeniable (22-25). We have evaluated the acute impact of a beta-blocker treatment on glucose and insulin responses in well-controlled sedentary patients with type 2 diabetes, free of cardiovascular complications. Four 60 min exercise sessions were randomly performed in the fasted or the postprandial state, with and without five days of a beta-blocker treatment previous (atenolol 100 mg). Preliminary data show a significant reduction in blood glucose levels by 41% and 37%, with and without the use of beta-blockers, respectively, during the exercise sessions performed in the postprandial state. Of note, the use of a beta-blocker had a minimal impact on blood glucose levels when exercise was performed in the fasting state. Thus, an acute beta-blocker

treatment did not increase plasma glucose and insulin levels, suggesting that the nutritional status has a greater impact on glucose modulation than a beta-blocker per se.

EXERCISE AND DIABETES: INTEGRATIVE EXERCISE PHYSIOLOGY AND EXERCISE CAPACITY

Individuals with type 2 diabetes have a reduced exercise capacity, characterized by a diminished ventilatory threshold, slower $\dot{V}O_2$ kinetics and a lowered $\dot{V}O_2$ peak compared with individuals without diabetes (26-28). Abnormalities related to cardiac function, arteriovenous oxygen difference and skeletal muscle metabolism have been associated with these altered exercise responses in patients with diabetes (29,30). However, the principal underlying pathophysiological process responsible for these limitations is unknown. Furthermore, the importance of diabetes per se as a potential contributor to this reduced exercise capacity compared with the impact of diabetes complications is not well understood. Accordingly, an important area of research in our laboratory over the years has been the impact of type 2 diabetes and its complications on different human body systems during exercise, as well as its influence on exercise capacity.

It is clear that type 2 diabetes has a negative impact on peak $\dot{V}O_2$. However, the early impact of this metabolic disorder per se is not well described. Systemic oxygen transport to tissue is a likely contributor to this altered exercise performance. Indeed, the alteration of beta-adrenergic-related hemodynamic and ventilatory responses to peak exercise limits peak $\dot{V}O_2$ in well-controlled, uncomplicated subjects with type 2 diabetes (31). Specific parameters related to cardiac function may be responsible for this diminished peak $\dot{V}O_2$. Among them, the presence of an early and prevalent clinical evidence of diabetic cardiomyopathy, namely left ventricular diastolic dysfunction (LVDD) (32), has been negatively related to exercise capacity in these patients (33). In this context, we were interested in evaluating the impact of well-controlled, uncomplicated type 2 diabetes on human body systems during exercise compared with a control group without diabetes matched for age and body mass index. Surprisingly, diabetes did not add any burden on exercise capacity; no significant difference in peak $\dot{V}O_2$ was observed between the two groups. Interestingly, we found that LVDD has a negative impact on exercise capacity independent of the presence of diabetes (personal observation). These results suggest that the presence of LVDD, in well-controlled, uncomplicated type 2 diabetics and subjects without diabetes, alters exercise performance. This has previously been shown in a cohort constituted solely of patients with type 2 diabetes (33). Together, these results suggest that it is probably not diabetes per se but the presence of LVDD that could initially alter exercise capacity in well-controlled, uncomplicated patients with type 2 diabetes.

Type 2 diabetes is also known to be related to arterial stiffness, which, in turn, is associated with increased afterload (34), leading to an elevated systolic blood pressure (SBP) (35). An exaggerated SBP response to exercise is associated with a lower cardiorespiratory fitness level in women (36). In comparison, athletes are known to develop an elevated blood pressure (BP) response in association with a higher exercise capacity compared to nonathletes (37). In fact, a positive relationship between the exercise BP response and left ventricular mass has been documented in this population (37). However,

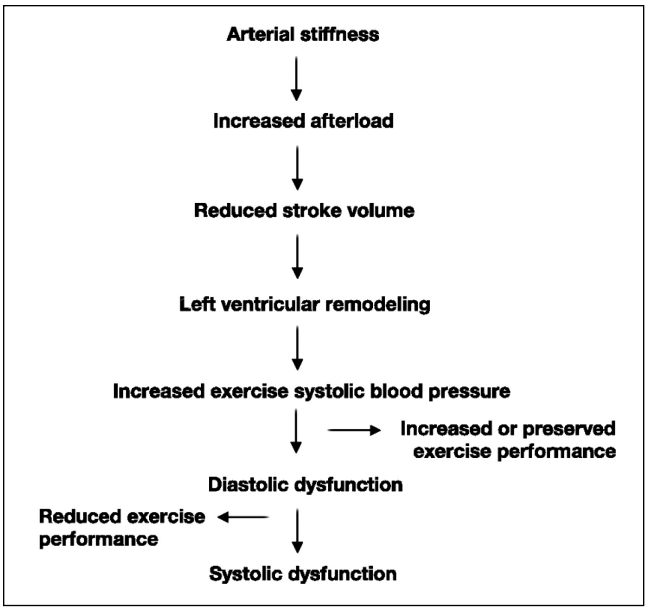

Figure 2) *Schematic representation of the parameters influencing exercise capacity in patients with higher peak exercise systolic blood pressure. From Brassard et al (38) with permission*

the influence of early hemodynamic changes induced by diabetes, such as the presence of an elevated exercise SBP response on exercise performance in subjects with type 2 diabetes without coronary disease, is unknown. Accordingly, we evaluated the impact of an elevated SBP in response to peak exercise on different parameters related to exercise capacity in sedentary subjects with type 2 diabetes free of coronary disease. Contrary to our hypothesis, an elevated exercise SBP was not associated with a reduced exercise capacity (38). Furthermore, SBP modulation during exercise was not related to glycemic control. We suggested that in subjects with type 2 diabetes free of coronary disease with elevated peak SBP, the increased exercise tolerance observed may have been related to an adaptive left ventricular remodelling, inducing a higher cardiac output compared with subjects with low peak SBP. However, this positive influence on exercise capacity may be lost with the appearance of LVDD (38) (Figure 2).

Adequate control of glycemia is an important goal in the management of type 2 diabetes. However, results of studies evaluating whether glycemic control affects exercise tolerance in patients with type 2 diabetes are conflicting (27,28,39-42). Hyperglycemia appears to have a negative influence on parameters associated with the regulation of oxygen transport and utilization (43-48). Thus, we were interested in evaluating the influence of less-than-optimal glycemic control on systemic oxygen transport, the modulation of submaximal $\dot{V}O_2$, pulmonary ventilation ($\dot{V}_E$) and heart rate (HR) during exercise in patients with type 2 diabetes.

Fasting blood glucose (FBG) and glycated hemoglobin (HbA_{1c}) levels and exercise tolerance were evaluated in sedentary men with type 2 diabetes treated with oral hypoglycemic agents and/or diet. We observed that relatively small abnormalities in short- and long-term glycemic control (FBG and HbA_{1c}, respectively) did not affect peak $\dot{V}O_2$ (49). However, higher HbA_{1c} levels were associated with altered pulmonary function, characterized by a lowered $\dot{V}_E$ response during submaximal exercise, and higher FBG concentrations

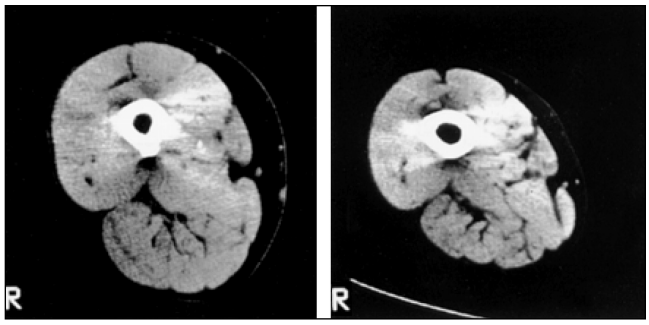

Figure 3) *Computed tomography of a healthy subject* (**left panel**) *and a patient with chronic obstructive pulmonary disease* (**right panel**). *The mid-thigh muscle cross-sectional area was considerably reduced in the patient with chronic obstructive pulmonary disease compared with that of the healthy subject, amounting to 80 cm^2 and 119 cm^2, respectively. From Bernard et al (71) with permission*

were associated with a negative impact on the HR increment in response to increasing exercise loads. Thus, acute hyperglycemia may have had some repercussions on baroreceptor sensitivity and/or autonomic nervous system altering the HR response to exercise. Also, chronic hyperglycemia may lead to alterations in lung structure affecting pulmonary $\dot{V}_E$ in response to exercise. This altered response may have been influenced by an abnormal chemoreflex and/or ergoreflex (49).

EXERCISE, PERIPHERAL MUSCLES, CHF AND CONGENITAL HEART DISEASES

Another area of interest in our Institution over the years has been the relation between exercise and cardiovascular diseases and more specifically the impact of cardiac dysfunctions on the periphery. For instance, skeletal muscle function at rest and during exercise in patients with CHF and congenital heart disease has been investigated. Many studies have demonstrated the existence of a poor relationship between central hemodynamic parameters and exercise tolerance in CHF (50-53), and the contribution of impaired skeletal muscle function to exercise intolerance in these patients has been recognized (54-58). However, in the absence of an objective confirmation of muscle fatigue, the validation of any endurance test based on the motivation of the individual to perform the required task or the attitude of the investigator can be questioned (59). Accordingly, we investigated patients with CHF whether the time to fatigue during isometric contraction, if corroborated by electromyographic signals (60), could be an objective and useful tool to measure muscle isometric endurance. More specifically, we wanted to know if skeletal muscle endurance of the vastus lateralis was reduced in patients with CHF compared with healthy subjects and if this reduction was related to the muscle oxidative metabolism. As expected, this study demonstrated that the endurance of the vastus lateralis muscle was decreased in patients with CHF compared with healthy subjects and that this decrease was related to muscle oxidative capacity. The electromyographic signal during isometric exercise also suggests that this test can be used to objectively assess muscle fatigability in patients with CHF (61).

Peripheral abnormalities are likely a contributor to exercise intolerance in patients with congenital heart disease. Patients with a functionally single ventricle without surgical intervention present a reduced exercise capacity compared with healthy subjects (62). The Fontan procedure should enhance functional capacity by eliminating or reducing the right-to-left shunt and eliminating systemic ventricular volume overload. However, despite a 20% enhancement in $\dot{V}O_2$ max after the intervention, a 30% to 40% lower exercise tolerance is observed compared with sex-matched healthy subjects (63,64). Traditionally, the lower exercise performance has been tentatively mainly explained by a reduced cardiorespiratory functional capacity (62). However, because it is known that altered skeletal muscle function is also related to exercise intolerance in patients with CHF (54-58), we investigated whether skeletal muscle function in Fontan patients was altered and if exercise training was feasible and safe in these patients with the aim of improving skeletal muscle function. We reported that these patients had excessive ergo-reflex contribution to BP. Also, Fontan patients had abnormal skeletal muscle function expressed as time to fatigue (65). After an eight-week aerobic and resistance training period, abnormal ergo-reflex activation was diminished (65). These results suggest that exercise training should be an important feature in their rehabilitation and that we should emphasize skeletal muscle training in this growing population in the contemporary adult cardiology practice (66). Noteworthy, we were among the first investigators to stress the importance of skeletal muscle function in regard to exercise tolerance in these patients. These findings can be added to the other abnormalities associated with exercise intolerance in these patients (62).

EXERCISE, PERIPHERAL MUSCLES AND COPD

Exercise intolerance is a common feature of COPD and it has a profound impact on quality of life. Exercise intolerance in patients with COPD results from a complex interplay of central (dyspnea-ventilation) and peripheral (leg fatigue) factors and has been discussed in comprehensive review articles (67,68). Although muscle wasting has long been recognized by clinicians, its relevance to patients' outcome and management has been overlooked. Available information suggests that muscle wasting is present in up to 25% to 50% of patients with COPD (69,70). Importantly, the disproportionately greater reduction in thigh muscle cross-sectional area than in body weight (71) indicates a preferential loss of muscle tissue over other body compartments (Figure 3). Low muscle mass in COPD is associated with weaker peripheral muscles, impaired functional status (71) and poor health-related quality of life (72). We built on this knowledge to show that muscle atrophy also has a strong impact on mortality in patients with severe COPD (73). Probably the most consistent muscle adaptation in COPD is the shift in fibre composition of peripheral muscle with a reduction in the proportion of type I fibres and a reciprocal increase in type IIb fibres (74,75). Although this fibre-type shift may be useful to preserve strength, it could increase susceptibility to fatigue. Capillarization of the vastus lateralis, an important determinant of muscle aerobic capacity, is also reduced when compared with age-matched healthy subjects (74).

The energy metabolism of the peripheral muscles has been studied extensively in COPD. In line with the fibre-type profile described above, low activity of two mitochondrial enzymes, citrate syntase and 3-hydroxyacyl-CoA dehydrogenase, in the vastus lateralis muscle have been reported in COPD (76). These two enzymes, which are respectively involved in the citric acid cycle and beta-oxidation of fatty

acids, are good markers of muscle oxidative capacity. In keeping with these enzymatic changes, the substrate and cofactor levels in the peripheral muscles indicate that the muscle energy metabolism is impaired at rest and during exercise in COPD. These peripheral muscle metabolic abnormalities may be worsened by hypoxemia and can be partially reversed with oxygen supplementation (77) but they are not necessarily related to reduction in peripheral oxygen delivery (78). This last finding suggests that the altered muscle metabolism during exercise in COPD is related, at least in part, to poor muscle oxidative capacity or to abnormal metabolic regulation, and that rephosphorylation of high-energy phosphates is less efficient in these patients during and after exercise. Because the anaerobic energy metabolism yields far less ATP compared with complete oxidative glucose degradation, the lower capacity for muscle aerobic metabolism may influence exercise tolerance in several ways. Premature muscle acidosis, a contributory factor to muscle fatigue and early exercise termination in healthy subjects (79), may be an important mechanism contributing to exercise intolerance in COPD (78). Increased lactic acidosis for a given exercise work rate, which is a common finding in COPD (80), could enhance the ventilatory needs, imposing an additional burden on the respiratory muscles already facing an increased work of breathing. Strength and endurance are two fundamental characteristics of muscle performance. Quadriceps strength is decreased on average by 30% in patients with moderate to severe COPD, but there is considerable interindividual variability. This observation is clinically relevant because peripheral muscle strength is an important determinant of exercise capacity in patients with COPD and correlates with peak $\dot{V}O_2$ and 6 min walking distance (81). The perception of leg fatigue, a common exercise symptom limiting patients with COPD during exercise, is inversely correlated to muscle strength (82). A significant reduction in quadriceps endurance has been reported in patients with COPD (83) and may be another important factor in exercise limitation because it may lead to premature muscle fatigue. The impact of leg fatigue on the exercise response to acute bronchodilation in patients with COPD was also recently evaluated (84). An important contribution of our group was to report that the exercise response to bronchodilation was modulated by the presence of leg fatigue; acute bronchodilation failed to improve exercise tolerance in patients who developed leg fatigue during exercise. This study provides solid evidence of the role of peripheral muscle fatigue on the exercise limitation in COPD.

Regardless of disease severity, patients with COPD show multiple benefits from aerobic training (85-88). Considering the different peripheral muscle abnormalities reported in COPD and the beneficial impact of exercise training on muscle function, this modality would appear as a logical and essential component for the treatment of this disease. Our group has contributed to demonstrate that exercise training is the best available strategy to enhance peripheral muscle function in patients with COPD, providing a strong physiological rationale for its use in the long-term management of these individuals.

At moderate to high training intensity, aerobic training reduces exercise-induced lactic acidosis and improves skeletal muscle aerobic capacity and bioenergetics (89,90). The likelihood of obtaining physiological benefits from an aerobic training program appears more related to the patient's ability to engage in more intense and prolonged exercise than to the disease severity (89,91,92). Compared with aerobic training, strength training has received relatively less attention as a rehabilitative strategy in patients with COPD. In this population, strengthening exercises promote muscle growth and improves strength (93) and are usually well tolerated (94). As it is the case for aerobic training, a greater training intensity will increase the likelihood of obtaining an improvement in muscle function per se. The question of whether further improvement in muscle function and exercise capacity could be obtained by supplementing aerobic training with strength training was addressed (93). Greater improvements in quadriceps and pectoralis major muscle strength and in muscle mass were obtained by combining both training modalities (aerobic training combined with 45 min of strength training performed at 80% of one repetition maximum compared with endurance training alone) (Figure 4). When comparing the efficacy of aerobic and strength training, Spruit and colleagues (95) surprisingly found a similar improvement in peripheral muscle strength, exercise performance and health-related quality of life with both training strategies. Their study suggests that resistance training may be a good alternative in patients having difficulty performing whole body exercise training. Based on our data and those of others, we now routinely combine aerobic and strengthening exercises to treat peripheral muscle dysfunction and improve functional status in patients with COPD.

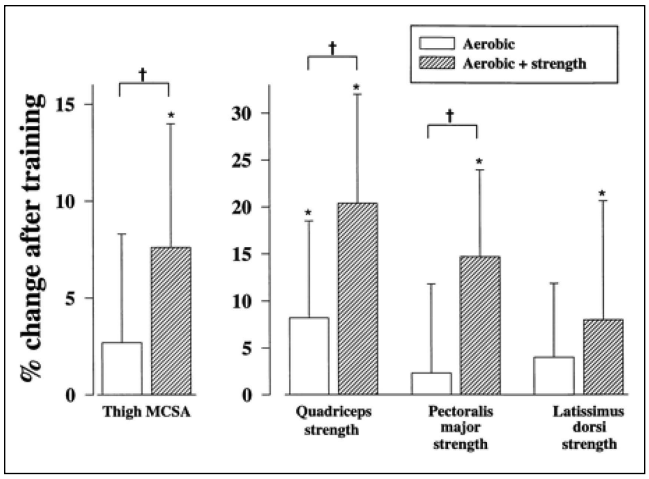

Figure 4) *Mean ± SD percent change in bilateral mid-thigh muscle cross-sectional area (MCSA) and in the strength of the quadriceps, pectoralis major and latissimus dorsi muscles before and after training in the aerobic and aerobic + strength groups. The improvement in bilateral mid-thigh MCSA and in the strength of the three muscle groups was statistically significant in the aerobic + strength group. Quadriceps strength also showed a significant increase in the aerobic group. As can be seen, the magnitude of the changes in mid-thigh MCSA and in the strength of the quadriceps and pectoralis major muscles was significantly greater in the aerobic + strength group than in the aerobic group. *P<0.05 for pre- versus post-training within each study group; †P<0.05 for the aerobic group versus the aerobic + strength group. From Bernard et al (93) with permission*

EXERCISE AND COPD: CARDIOVASCULAR IMPLICATIONS

COPD has been mainly considered as a disease of the lung, characterized by partially reversible limited airflow due to chronic bronchitis and/or emphysema. Furthermore, COPD is

frequently associated with comorbidities. Patients with COPD have a two- to threefold increased risk of ischemic heart disease, stroke and sudden cardiac death independently from other risk factors such as smoking history (96). The mechanisms responsible for this association remain largely speculative (96).

The experience of our cardiopulmonary rehabilitation program suggest that the metabolic syndrome and systemic hypertension are frequently encountered in this population. Thus, in our studies, we evaluated the presence of two major risk factors of cardiovascular morbidity and mortality in COPD patients; the metabolic syndrome and systemic hypertension. The metabolic syndrome is characterized by the presence of abdominal obesity, atherogenic dyslipidemia (elevated triglycerides levels, dense low-density lipoprotein particles, low high-density lipoprotein-cholesterol levels), raised BP, insulin resistance (with and without glucose intolerance), and prothrombotic and inflammatory states. A sedentary lifestyle coupled with a deleterious diet and unknown genetic factors interact to cause the development of the metabolic syndrome (97-99). On this basis, we suspected that patients with COPD would be at risk for the presence of the metabolic syndrome because these patients are limited by respiratory symptoms and therefore adopt a sedentary lifestyle, increasing their risk for weight gain and insulin resistance. Thus, we evaluated the presence of the metabolic syndrome in COPD patients who participated in our cardiopulmonary rehabilitation program and we compared the prevalence of the metabolic syndrome between COPD patients and control subjects matched for age, sex and body mass index. Overall, 61% of men and 27% of women in the COPD presented the features of the metabolic syndrome. In the control group, 20% of men and 21% of women presented three or more risk markers of the metabolic syndrome (100). Because the features of the metabolic syndrome were more frequent in men and women with COPD compared with control subjects, this may provide an explanation for the increased cardiovascular morbidity and mortality in COPD.

Some studies suggest that an abnormal or exaggerated exercise BP is associated with increased cardiovascular morbidity and mortality (101,102) independently of resting BP (103). This phenomenon could also explain, in part, the increased cardiovascular morbidity and mortality in COPD patients. Exercise training reduces BP in individuals with normal BP, as in individuals with hypertension (104). Aerobic exercise training also lowers BP measured at fixed submaximal workload (104). Therefore, we compared the increment in BP during a maximal cycling exercise test between COPD patients and age-matched control subjects and evaluated the impact of aerobic exercise training program on this parameter in patients with COPD. We found that the slopes of the SBP/$\dot{V}O_2$ and diastolic BP/$\dot{V}O_2$ were steeper in COPD patients versus controls at baseline (105). These data suggest that COPD patients may be chronically exposed to high BP at rest and during activities of daily living, and this condition could be associated with an increased risk of cardiovascular morbidity and mortality (106,107). After training, there was no reduction in SBP/$\dot{V}O_2$ and diastolic BP/$\dot{V}O_2$ slopes in COPD patients (105). Consequently, the burden on the cardiopulmonary system may be greater in COPD patients compared with control subjects. Finally, we performed a pilot study to evaluate the efficacy of an aerobic exercise training program alone or combined with an angiotensin II receptor antagonist (irbesartan) on 24 h ambulatory BP and on HR variability in patients with COPD. Resting BP, 24 h BP, daytime BP and maximal exercise BP decreased in the irbesartan group in contrast to the placebo group (108). Night-time BP did not decrease significantly in either group. HR variability did not change following the 12-week aerobic exercise training program in the placebo and in the irbesartan group (109). The association of irbesartan and exercise was better than the association between placebo and exercise to reduce BP. The exercise stimulus alone may not seem sufficient enough to decrease significantly BP in this pilot study (108).

QUÉBEC INTERNATIONAL SYMPOSIUM ON CARDIOPULMONARY PREVENTION/REHABILITATION

These research activities regarding the impact of exercise on cardiovascular and pulmonary diseases rapidly led to the creation of a pivotal activity integrating all aspects (bio-psycho-socio-cultural factors) of cardiovascular and pulmonary rehabilitation. Taking all aspects into consideration is important, because many problems and interventions are very similar in numerous pathologies affecting the person as a whole (110). Furthermore it became evident that primary and secondary prevention should also be included. Therefore, the First Québec international Symposium on Cardiopulmonary Prevention/Rehabilitation was organized in 1999 under the main Theme: "Challenges of the third millennium". It has occurred every two years since then. The attendance at these scientific meetings has evolved from 325 at the initial symposium to 800 participants at the fifth event. Over the years, participants have come from 20 different countries around the world.

CONCLUSIONS

Our research initiatives over the years have led to numerous publications documenting the deleterious impact of diabetes, CHF, congenital heart disease and chronic obstructive disease on the human body's ability to perform exercise, as well as the beneficial impact of chronic exercise in patients with these diseases. As reported, exercise exerts a positive impact on several aspects of chronic cardiovascular and pulmonary diseases. In fact, exercise rehabilitation offers a unique opportunity to address in a comprehensive manner, several adverse consequences of these diseases. Unfortunately, in contemporary cardiology and pulmonary practices, only minor attention has been dedicated to the study of exercise as an effective tool to slow the progression or reverse pathophysiological processes. Nevertheless, our results have shown that further studies are needed to ensure proper use of exercise as a management tool in several populations encountered in cardiology and pneumology today.

ACKNOWLEDGEMENTS: The work of the authors has been supported by research grants and scholarships from the Canadian Institutes of Health Research (CIHR), the Canadian Diabetes Association, the Fonds de la Recherche en Santé du Québec (FRSQ), the Rx & D Health Research Foundation (HRF), the Foundation of the Québec Heart Institute and by educational grants from Bristol-Myers Squibb and Bayer. François Maltais is a research scholar of the FRSQ. Paul Poirier is a clinician-scientist of the FRSQ. This work is dedicated to the participants of the cardiac and pulmonary rehabilitation programs of our institution who have shown great determination to improve their condition by engaging in regular physical activities.

REFERENCES

1. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C. Physical activity/exercise and type 2 diabetes. Diabetes Care 2004;27:2518-39.
2. Kang J, Kelley DE, Robertson RJ, et al. Substrate utilization and glucose turnover during exercise of varying intensities in individuals with NIDDM. Med Sci Sports Exerc 1999;31:82-9.
3. Poirier P, Mawhinney S, Grondin L, et al. Prior meal enhances the plasma glucose lowering effect of exercise in type 2 diabetes. Med Sci Sports Exerc 2001;33:1259-64.
4. Minuk HL, Vranic M, Marliss EB, et al. Glucoregulatory and metabolic response to exercise in obese noninsulin-dependent diabetes. Am J Physiol 1981;240:E458-64.
5. Larsen JJ, Dela F, Kjaer M, Galbo H. The effect of moderate exercise on postprandial glucose homeostasis in NIDDM patients. Diabetologia 1997;40:447-53.
6. Gaudet-Savard T, Ferland A, Broderick TL, et al. Safety and magnitude of changes of blood glucose levels following exercise performed in the fasted and and the postprandial state in type 2 diabetes men. Eur J Cardiovasc Prev Rehabil 2007. (In press)
7. Duh E, Feinglos M. Hypoglycemia-induced angina pectoris in a patient with diabetes mellitus. Ann Intern Med 1994;121:945-6.
8. Zinman B, Murray FT, Vranic M, et al. Glucoregulation during moderate exercise in insulin-treated diabetes. J Clin Endocrinol Metab 1977;45:641-52.
9. Bremer J. Carnitine – metabolism and functions. Physiol Rev 1983;63:1420-80.
10. Lennon DL, Stratman FW, Shrago E, et al. Effects of acute moderate-intensity exercise on carnitine metabolism in men and women. J Appl Physiol 1983;55:489-95.
11. Carlin JI, Reddan WG, Sanjak M, Hodach R. Carnitine metabolism during prolonged exercise and recovery in humans. J Appl Physiol 1986;61:1275-8.
12. Ferland A, Broderick TL, Nadeau A, Simard S, Martin J, Poirier P. Impact of fasting and postprandial state on plasma carnitine concentrations during aerobic exercise in type 2 diabetes. Acta Diabetol 2007;44:114-20.
13. Albright A, Franz M, Hornsby G, et al. American College of Sports Medicine position stand. Exercise and type 2 diabetes. Med Sci Sports Exerc 2000;32:1345-60.
14. American Diabetes Association. Standards of medical care in diabetes – 2006. Diabetes Care 2006;29(Suppl 1):S4-42.
15. Franz MJ, Bantle JP, Beebe CA, et al. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. Diabetes Care 2002;25:148-98.
16. Wolever TMS, Gougeon R, Freeze C, et al. Nutrition therapy. Can J Diabetes Care 2003;15:S27-S31.
17. Gougeon R, Spidel M, Lee K, Field CJ. Canadian Diabetes Association National Nutrition Committee Technical Review: Non-nutritive intense sweeteners in diabetes management. Can J Diabetes 2004;28:385-99.
18. Ferland A, Brassard P, Poirier P. Is aspartame really safer on risk to induce hypoglycemia during exercise in type 2 diabetic patients? Diabetes Care 2007;30:e59.
19. Ferland A, Turbide G, Bogaty P, Jobin J, Larivière MM, Poirier P. Type 2 diabetes and aerobic exercise – Is prior breakfast deleterious? Med Sci Sports Exerc 2004;36(5 Suppl):S216.
20. Turgan N, Coker C, Hamulu F, et al. Glucose metabolism and catecholamine responses during physical exercise in non-insulin-dependent diabetes. Eur J Clin Chem Clin Biochem 1996;34:683-9.
21. Ferland A, Brassard P, Lemieux S, et al. Impact of aspartame and sucrose on adrenergic response to aerobic exercise in type 2 diabetic patients. Med Sci Sports Exerc 2006;38(Suppl 5):1395.
22. Herlitz J, Malmberg K. How to improve the cardiac prognosis for diabetes. Diabetes Care 1999;22(Suppl 2):B89-B96.
23. Vijan S, Hayward RA. Treatment of hypertension in type 2 diabetes mellitus: Blood pressure goals, choice of agents, and setting priorities in diabetes care. Ann Intern Med 2003;138:593-602.
24. McKenney JM, Goodman RP, Wright JT Jr. Use of antihypertensive agents in patients with glucose intolerance. Clin Pharm 1985;4:649-56.
25. Veronee CD, Lewis WR, Takla MW, et al. Protective metabolic effects of propranolol during total myocardial ischemia. J Thorac Cardiovasc Surg 1986;92:425-33.
26. Estacio RO, Regensteiner JG, Wolfel EE, et al. The association between diabetic complications and exercise capacity in NIDDM patients. Diabetes Care 1998;21:291-5.
27. Regensteiner JG, Sippel J, McFarling ET, et al. Effects of non-insulin-dependent diabetes on oxygen consumption during treadmill exercise. Med Sci Sports Exerc 1995;27:875-81.
28. Regensteiner JG, Bauer TA, Reusch JE, et al. Abnormal oxygen uptake kinetic responses in women with type II diabetes mellitus. J Appl Physiol 1998;85:310-7.
29. Roy TM, Peterson HR, Snider HL, et al. Autonomic influence on cardiovascular performance in diabetic subjects. Am J Med 1989;87:382-8.
30. Baldi JC, Aoina JL, Oxenham HC, et al. Reduced exercise arteriovenous O_2 difference in type 2 diabetes. J Appl Physiol 2003;94:1033-8.
31. Brassard P, Ferland A, Croteau S, et al. Impact of beta-blockade on exercise capacity in subjects with type 2 diabetes. Clin Invest Med 2007;In press.
32. Poirier P, Bogaty P, Garneau C, et al. Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: Importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. Diabetes Care 2001;24:5-10.
33. Poirier P, Garneau C, Bogaty P, et al. Impact of left ventricular diastolic dysfunction on maximal treadmill performance in normotensive subjects with well-controlled type 2 diabetes mellitus. Am J Cardiol 2000;85:473-7.
34. Devereux RB, Roman MJ, Paranicas M, et al. Impact of diabetes on cardiac structure and function: The Strong Heart Study. Circulation 2000;101:2271-6.
35. Chen CH, Nakayama M, Nevo E, et al. Coupled systolic-ventricular and vascular stiffening with age: Implications for pressure regulation and cardiac reserve in the elderly. J Am Coll Cardiol 1998;32:1221-7.
36. Kokkinos PF, Andreas PE, Coutoulakis E, et al. Determinants of exercise blood pressure response in normotensive and hypertensive women: Role of cardiorespiratory fitness. J Cardiopulm Rehabil 2002;22:178-83.
37. Karjalainen J, Mantysaari M, Viitasalo M, Kujala U. Left ventricular mass, geometry, and filling in endurance athletes: Association with exercise blood pressure. J Appl Physiol 1997;82:531-7.
38. Brassard P, Ferland A, Gaudreault V, et al. Elevated peak exercise systolic blood pressure is not associated with reduced exercise capacity in subjects with type 2 diabetes. J Appl Physiol 2006;101:893-7.
39. Dwyer GB, Wallace JP, Whaley MH. Influence of metabolic control on the ventilatory threshold in adults with non insulin-dependent diabetes mellitus. Diabetes Res 1994;25:39-46.
40. Demir I, Ermis C, Altunbas H, Balci MK. Serum HbA1c levels and exercise capacity in diabetic patients. Jpn Heart J 2001;42:607-16.
41. Vanninen E, Uusitupa M, Remes J, et al. Relationship between hyperglycaemia and aerobic power in men with newly diagnosed type 2 (non insulin-dependent) diabetes. Clin Physiol 1992;12:667-77.
42. Fang ZY, Sharman J, Prins JB, Marwick TH. Determinants of exercise capacity in patients with type 2 diabetes. Diabetes Care 2005;28:1643-8.
43. Davis WA, Knuiman M, Kendall P, et al. Glycemic exposure is associated with reduced pulmonary function in type 2 diabetes: The Fremantle Diabetes Study. Diabetes Care 2004;27:752-7.
44. Ditzel J. Oxygen transport impairment in diabetes. Diabetes 1976;25:832-8.
45. Kingwell BA, Formosa M, Muhlmann M, et al. Type 2 diabetic individuals have impaired leg blood flow responses to exercise: Role of endothelium-dependent vasodilation. Diabetes Care 2003;26:899-904.
46. Ditzel J. Changes in red cell oxygen release capacity in diabetes mellitus. Fed Proc 1979;38:2484-8.
47. Ditzel J, Standl E. The problem of tissue oxygenation in diabetes mellitus. I. Its relation to the early functional changes in the microcirculation of diabetic subjects. Acta Med Scand Suppl 1975;578:49-58.
48. Ditzel J, Standl E. The problem of tissue oxygenation in diabetes mellitus. Acta Med Scand Suppl 1975;578:59-68.
49. Brassard P, Ferland A, Bogaty P, et al. Influence of glycemic control on pulmonary function and heart rate in response to exercise in subjects with type 2 diabetes mellitus. Metabolism 2006;55:1532-7.
50. Higginbotham MB, Morris KG, Conn EH, et al. Determinants of variable exercise performance among patients with severe left ventricular dysfunction. Am J Cardiol 1983;51:52-60.
51. Franciosa JA, Ziesche S, Wilen M. Functional capacity of patients with chronic left ventricular failure. Relationship of bicycle exercise performance to clinical and hemodynamic characterization. Am J Med 1979;67:460-6.
52. Szlachcic J, Massie BM, Kramer BL, et al. Correlates and prognostic implication of exercise capacity in chronic congestive heart failure. Am J Cardiol 1985;55:1037-42.
53. Franciosa JA, Park M, Levine TB. Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. Am J Cardiol 1981;47:33-9.
54. Jobin J, Doyon JF. Peripheral muscle limitations to exercise in patients with congestive heart failure: Implications for rehabilitation. In: Jobin J, Maltais F, LeBlanc P, Simard C, eds. Advances in Cardiopulmonary Rehabilitation. Champaign: Human Kinetics, 2000:90-104.
55. Harrington D, Anker SD, Chua TP, et al. Skeletal muscle function and its relation to exercise tolerance in chronic heart failure. J Am Coll Cardiol 1997;30:1758-64.
56. Hamilton AL, Killian KJ, Summers E, Jones NL. Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. Am J Respir Crit Care Med 1995;152:2021-31.
57. Drexler H, Riede U, Munzel T, et al. Alterations of skeletal muscle in chronic heart failure. Circulation 1992;85:1751-9.

58. Maltais F, Débigaré R, Saey D, Jobin J. Peripheral muscle dysfunction in chronic obstructive pulmonary disease and chronic heart failure: Two diseases, one common consequence. In: Jobin J, Maltais F, Poirier P, LeBlanc P, Simard C, eds. Advancing the Frontiers of Cardiopulmonary Rehabilitation. Champaign: Human Kinetics, 2002:181-92.
59. De Luca CJ. Myoelectrical manifestations of localized muscular fatigue in humans. Crit Rev Biomed Eng 1984;11:251-79.
60. Buonocore M, Opasich C, Casale R. Early development of EMG localized muscle fatigue in hand muscles of patients with chronic heart failure. Arch Phys Med Rehabil 1998;79:41-5.
61. Brassard P, Maltais F, Noel M, et al. Skeletal muscle endurance and muscle metabolism in patients with chronic heart failure. Can J Cardiol 2006;22:387-92.
62. Brassard P, Bedard E, Jobin J, et al. Exercise capacity and impact of exercise training in patients after a Fontan procedure: A review. Can J Cardiol 2006;22:489-95.
63. Zellers TM, Driscoll DJ, Mottram CD, et al. Exercise tolerance and cardiorespiratory response to exercise before and after the Fontan operation. Mayo Clin Proc 1989;64:1489-97.
64. Driscoll DJ, Danielson GK, Puga FJ, et al. Exercise tolerance and cardiorespiratory response to exercise after the Fontan operation for tricuspid atresia or functional single ventricle. J Am Coll Cardiol 1986;7:1087-94.
65. Brassard P, Poirier P, Martin J, et al. Impact of exercise training on muscle function and ergoreflex in Fontan patients: A pilot study. Int J Cardiol 2006;107:85-94.
66. Webb G. Improving the care of Canadian adults with congenital heart disease. Can J Cardiol 2005;21:833-8.
67. Gosker HR, Wouters EF, van der Vusse GJ, Schols AM. Skeletal muscle dysfunction in chronic obstructive pulmonary disease and chronic heart failure: Underlying mechanisms and therapy perspectives. Am J Clin Nutr 2000;71:1033-47.
68. Mador MJ, Bozkanat E. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. Respir Res 2001;2:216-24.
69. Schols AM, Soeters PB, Dingemans AM, et al. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. Am Rev Respir Dis 1993;147:1151-6.
70. Vestbo J, Prescott E, Almdal T, et al. Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: Findings from the Copenhagen City Heart Study. Am J Respir Crit Care Med 2006;173:79-83.
71. Bernard S, Leblanc P, Whittom F, et al. Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;158:629-34.
72. Mostert R, Goris A, Weling-Scheepers C, et al. Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease. Respir Med 2000;94:859-67.
73. Marquis K, Debigare R, Lacasse Y, et al. Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002;166:809-13.
74. Jobin J, Maltais F, Doyon JF, et al. Chronic obstructive pulmonary disease: Capillarity and fiber-type characteristics of skeletal muscle. J Cardiopulm Rehabil 1998;18:432-7.
75. Whittom F, Jobin J, Simard PM, et al. Histochemical and morphological characteristics of the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. Med Sci Sports Exerc 1998;30:1467-74.
76. Maltais F, Simard AA, Simard C, et al. Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. Am J Respir Crit Care Med 1996;153:288-93.
77. Payen JF, Wuyam B, Levy P, et al. Muscular metabolism during oxygen supplementation in patients with chronic hypoxemia. Am Rev Respir Dis 1993;147:592-8.
78. Maltais F, Jobin J, Sullivan MJ, et al. Metabolic and hemodynamic responses of lower limb during exercise in patients with COPD. J Appl Physiol 1998;84:1573-80.
79. Hultman E, Del Canale S, Sjoholm H. Effect of induced metabolic acidosis on intracellular pH, buffer capacity and contraction force of human skeletal muscle. Clin Sci (Lond) 1985;69:505-10.
80. Maltais F, Bernard S, Jobin J, et al. Lactate kinetics during exercise in chronic obstructive pulmonary disease. Can Respir J 1997;4:251-7.
81. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. Am J Respir Crit Care Med 1996;153:976-80.
82. Hamilton AL, Killian KJ, Summers E, Jones NL. Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. Am J Respir Crit Care Med 1995;152:2021-31.
83. Allaire J, Maltais F, Doyon JF, et al. Peripheral muscle endurance and the oxidative profile of the quadriceps in patients with COPD. Thorax 2004;59:673-8.
84. Saey D, Debigare R, Leblanc P, et al. Contractile leg fatigue after cycle exercise: A factor limiting exercise in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2003;168:425-30.
85. Goldstein RS, Gort EH, Stubbing D, et al. Randomised controlled trial of respiratory rehabilitation. Lancet 1994;344:1394-7.
86. Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2006;CD003793.
87. Griffiths TL, Burr ML, Campbell IA, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: A randomised controlled trial. Lancet 2000;355:362-8.
88. Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. Ann Intern Med 1995;122:823-32.
89. Casaburi R, Patessio A, Ioli F, et al. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. Am Rev Respir Dis 1991;143:9-18.
90. Maltais F, Leblanc P, Simard C, et al. Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1996;154:442-7.
91. Puente-Maestu L, Sanz ML, Sanz P, et al. Effects of two types of training on pulmonary and cardiac responses to moderate exercise in patients with COPD. Eur Respir J 2000;15:1026-32.
92. Maltais F, Leblanc P, Jobin J, et al. Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1997;155:555-61.
93. Bernard S, Whittom F, Leblanc P, et al. Aerobic and strength training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159:896-901.
94. Simpson K, Killian K, McCartney N, et al. Randomised controlled trial of weightlifting exercise in patients with chronic airflow limitation. Thorax 1992;47:70-5.
95. Spruit MA, Gosselink R, Troosters T, et al. Resistance versus endurance training in patients with COPD and peripheral muscle weakness. Eur Respir J 2002;19:1072-8.
96. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation 2003;107:1514-9.
97. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595-607.
98. Bouchard C. Genetics and the metabolic syndrome. Int J Obes Relat Metab Disord 1995;19(Suppl 1):S52-9.
99. Liese AD, Mayer-Davis EJ, Haffner SM. Development of the multiple metabolic syndrome: An epidemiologic perspective. Epidemiol Rev 1998;20:157-72.
100. Marquis K, Maltais F, Duguay V, et al. The metabolic syndrome in patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil 2005;25:226-32.
101. Mundal R, Kjeldsen SE, Sandvik L, et al. Exercise blood pressure predicts cardiovascular mortality in middle-aged men. Hypertension 1994;24:56-62.
102. Mundal R, Kjeldsen SE, Sandvik L, et al. Exercise blood pressure predicts mortality from myocardial infarction. Hypertension 1996;27:324-9.
103. Filipovsky J, Ducimetiere P, Safar ME. Prognostic significance of exercise blood pressure and heart rate in middle-aged men. Hypertension 1992;20:333-9.
104. Pescatello LS, Franklin BA, Fagard R, et al. American College of Sports Medicine position stand. Exercise and hypertension. Med Sci Sports Exerc 2004;36:533-53.
105. Maltais F, Whittom F, Leblanc P, et al. Blood pressure and double product increases during exercise in patients with COPD. Am J Respir Crit Care Med 1998;157:A451. (Abst)
106. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. JAMA 2003;289:2560-72.
107. Lacasse M, Maltais F, Poirier P, et al. Post-exercise heart rate recovery and mortality in chronic obstructive pulmonary disease. Respir Med 2005;99:877-86.
108. Marquis K, Maltais F, Poirier P. L'exercice est-il suffisant pour diminuer la tension artérielle chez les patients atteints d'une MPOC ? Médecine/Sciences 2006;22:S20.
109. Marquis K, Maltais F, Fortin C, Poirier P. Effets de l'entraînement et de l'Irbesartan sur la variabilité cardiaque des patients atteints d'une MPOC. Médecine/Sciences 2006;22:S20.
110. Jobin J, Maltais F, Leblanc P, Simard C. Advances in Cardiopulmonary Rehabilitation, Human Kinetics. Illinois: Human Kinetics, 2000.