Physiological and Perceptual Responses to Incremental Exercise Testing in Healthy Men: Effect of Exercise Test Modality

By

Kristina Marie Muscat

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ABSTRACT

Background: The two most commonly used modes of exercise in both clinical and research settings are the treadmill and cycle ergometer. Whilst the influence of modality on physiological responses at maximal exercise are well established (e.g., $\dot{V}O_{2max}$ is unequivocally higher during treadmill vs. cycle testing), no previous study in healthy adults has compared detailed physiological and perceptual responses at equivalent submaximal work rates during incremental treadmill and cycle exercise testing.

Objective: The primary objective of this study was to compare, for the first time in healthy adults, detailed physiological and perceptual responses during symptom-limited treadmill and cycle exercise test protocols carefully matched for increments in work rate, which is the proximate source of increased skeletal (locomotor) muscle metabolic and contractile demands during exercise.

Methods: In a randomized, cross-over study of 15 healthy, young (20-30 years), non-obese men, we compared detailed assessments of cardio-metabolic function, gas exchange, ventilation, breathing pattern, dynamic operating lung volumes, inspiratory and expiratory muscle pressure development, neural respiratory drive, dyspnea and leg discomfort during symptom-limited cycle and treadmill exercise test protocols matched for increments in work rate (25 watt increments in work rate every 2-min, starting at 25 watts). The treadmill protocol was individualized for each participant based on their body mass using the formula: Work rate (watts) = 0.1634 x treadmill speed (meters/min) x treadmill grade (%) x body mass (kg). The grade started at 5% and was increased by

1% every 2-min, with the increments in treadmill speed required to achieve the 25-watt/2-min increase in work rate determined using the formula.

Results: Exercise endurance time and the work rate achieved at the symptom-limited peak of cycle vs. treadmill testing were similar (both $p>0.05$). At peak exercise during treadmill vs. cycle testing, $\dot{V}O_2$, the rate of CO_2 production ($\dot{V}CO_2$), heart rate (HR), the O_2 pulse and the end-tidal PCO_2 ($P_{ET}CO_2$) were higher, whereas the respiratory exchange ratio (RER), the ventilatory equivalent for O_2 ($\dot{V}_E/\dot{V}O_2$) and end-tidal PO_2 ($P_{ET}O_2$) were lower (all $p\leq0.05$). Despite significant differences in $\dot{V}O_2$ and $\dot{V}CO_2$, ventilation ($\dot{V}_E$), tidal volume (V_T), breathing frequency (f_R), inspiratory capacity (IC), inspiratory reserve volume (IRV), tidal esophageal pressure swings (Pes,tidal), tidal transdiaphragmatic pressure swings (Pdi,tidal), peak expiratory gastric pressures (Pga,peak), and Borg 0-10 scale intensity and unpleasantness ratings of dyspnea were not significantly different between modalities at the symptom-limited peak of exercise (all $p>0.05$). Borg 0-10 scale intensity ratings of leg discomfort were higher at the peak of cycle vs. treadmill exercise testing ($p\leq0.05$), even though peak $\dot{V}O_2$ was lower in the former. A higher percentage (60% vs. 27%) of our participants identified intolerable leg discomfort as the primary reason for stopping cycle vs. treadmill exercise. Similarly, the relative contribution of intolerable leg discomfort to exercise cessation was higher at the end of cycle vs. treadmill testing: 68% vs. 43% ($p\leq0.05$).

Mean values for $\dot{V}O_2$, $\dot{V}CO_2$, HR, the O_2 pulse, $\dot{V}_E$, f_R, Pes,tidal, Pdi,tidal and Pga,peak were higher, while the RER was lower at most submaximal work rates (including the ventilatory threshold (T_{vent})) during treadmill vs. cycle exercise testing (all

$p \leq 0.05$). By contrast, $\dot{V}_E/\dot{V}O_2$, the ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}CO_2$), $P_{ET}O_2$, $P_{ET}CO_2$, V_T, IC, IRV, the root mean square of the crural diaphragm electromyogram (EMGdi,rms) expressed as a percentage of maximal voluntary EMGdi,rms (EMGdi,rms%max), and Borg 0-10 ratings of dyspnea and leg discomfort were similar at most submaximal work rates (including T_{vent}) between modalities (all $p>0.05$).

Summary & implications: In conclusion: 1) cardiometabolic and ventilatory responses were consistently higher at standardized submaximal work rates during incremental treadmill vs. cycle exercise; 2) with few exceptions, detailed assessments of ventilatory efficiency, operating lung volumes, neural respiratory drive, dyspnea and leg discomfort were similar at equivalent submaximal work rates during treadmill vs. cycle ergometry; and 3) dynamic mechanical constraints on ventilation were evident at the limits of tolerance, particularly during treadmill exercise.

Our findings suggest that physiological parameters relevant to the prescription of exercise, specifically peak $\dot{V}O_2$, peak HR and $\dot{V}O_2$ at T_{vent}, should be assessed in each exercise mode for optimal (i.e., mode-specific) training intensity determination. Alternatively, the lack of effect of exercise mode on peak work rate in our study, advocates for the use of this readily available parameter to determine optimal training intensity, regardless of whether exercise training is performed on a cycle ergometer or treadmill.

RÉSUMÉ

Contexte: Les deux modes d'exercice le plus couramment utilisés dans les contextes cliniques et de recherche sont le tapis roulant et la bicyclette ergométrique. Alors que l'influence de la modalité sur les réponses physiologiques à l'exercice maximal sont bien établies (par exemple, le $\dot{V}O_{2max}$ est sans équivoque plus élevé sur le tapis roulant que sur la bicyclette) aucune étude antérieure chez les adultes en santé n'a comparé en détail les réponses physiologiques et perceptives aux taux d'effort sous-maximaux équivalents lors des tests d'exercice incrémentaux sur le tapis roulant et la bicyclette ergométrique.

Objectif: L'objectif principal de cette étude était de comparer en détail, pour la première fois chez des adultes en santé, les réponses physiologiques et perceptives lors des tests d'exercice limités par des symptômes sur le tapis roulant et la bicyclette en utilisant des protocoles d'exercice choisis pour provoquer des taux d'effort équivalents, pour que ceux-ci correspondent aux demandes métaboliques et musculo-squelettique (locomotrices) plus élevées qui se produisent lors de l'exercice.

Méthodes: Dans une étude randomisée , croisée de 15 jeunes hommes en santé (de 20-30 ans) et non-obèse, nous avons comparé des évaluations détaillées de la fonction cardio-métabolique, l'échange de gaz, la ventilation, le motif respiratoire, les volumes dynamiques de fonction pulmonaire, le développement de pressions musculaires inspiratoires et expiratoires, le contrôle respiratoire neuronal, la dyspnée et l'inconfort des jambes, au cours des test d'efforts de bicyclette et de tapis roulant limités par les

symptômes, qui emploient des incréments du taux de travail équivalents (incréments de 25 watts tous les deux-minutes, en commençant par 25 watts). Le protocole du tapis roulant a été établi pour chaque participant en fonction de sa masse corporelle en utilisant la formule: taux de travail (watts) = vitesse du tapis roulant X 0,1634 x (mètres / min) x inclinaison du tapis roulant (%) x masse corporelle (kg). L'inclinaison était 5% en partant et a été augmenté par 1% toutes les deux minutes, en s'assurant que les incréments de vitesse du tapis étaient suffisants pour obtenir une augmentation 25-watt/2-mins au niveau du taux de travail tel que déterminé en utilisant la formule mentionnée ci-haute.

Résultats: Le temps d'endurance et le taux de travail maximums atteints au seuil des tests d'exercice limités par les symptômes sur la bicyclette et le tapis roulant étaient similaires (les deux $p > 0,05$). Au seuil du test d'exercice sur le tapis roulant vs. sur le test de bicyclette, le $\dot{V}O_2$, le taux de production de CO2 ($\dot{V}CO_2$), la fréquence cardiaque (FC), le pouls d'oxygène, et le PCO_2 de fin-d'expiration ($P_{ET}CO_2$) étaient plus élevés, alors que le rapport de l'échange respiratoire (RER), l'équivalent respiratoire pour l'O_2 ($\dot{V}_E/\dot{V}O_2$) et le PO_2 de fin-d'expiration ($P_{ET}O_2$) étaient plus faibles (tous $p \leq 0,05$). Malgré des différences significatives en termes des $\dot{V}O_2$ et $\dot{V}CO_2$, la ventilation ($\dot{V}_E$), le volume courant (V_T), la fréquence respiratoire (f_R), la capacité inspiratoire (CI), le volume de réserve inspiratoire (VRI), les oscillations de pression dans l'oesophage (P_{es}, oscillation), transdiaphragmatique (P_{di}, oscillation), et les pressions gastriques expiratoires (Pga, sommet) et l'intensité de la dyspnée évaluée selon l'échelle Borg 0-10 ne différaient pas de façon significative entre les modalités au seuil de l'exercice (tous $p>0,05$). Les notes d'intensité de l'inconfort des jambes (Borg 0-10) étaient plus élevées au seuil du test de bicyclette vs. lors du tapis roulant ($p \leq 0{,}05$), même si le $\dot{V}O_2$ était plus faible dans celui-ci. Un pourcentage plus élevé (60% vs. 27%) de nos participants ont identifié l'inconfort intolérable des jambes comme la raison principale pour l'arrêt du test de bicyclette vs. le tapis roulant. Similairement, la contribution relative de l'inconfort intolérable des jambes pour la cessation de d'exercice était plus élevée à la fin du test de bicyclette vs. lors du test sur tapis roulant: 68% vs 43% ($p \leq 0{,}05$).

Les valeurs moyennes des $\dot{V}O_2$, $\dot{V}CO_2$, FC, le pouls de l' O_2, V_E, f_R, P_{es}, P_{di}, et P_{ga} étaient plus élevées durant le test d'effort sur le tapis roulant, tandis que le RER était moins élevé à la majorité des taux de travail sous-maximaux (y compris le seuil ventilatoire, T_{vent}) (tous les $p \leq 0{,}05$). Inversement, $\dot{V}_E/\dot{V}O_2$, l'équivalent respiratoire pour le CO_2 ($\dot{V}_E/\dot{V}CO_2$), $P_{ET}O_2$, $P_{ET}CO_2$, V_T, CI, VRI, la moyenne quadratique de l'électromyogramme de la portion crurale du diaphragme (EMGdi,rms) exprimée en pourcentage du EMGdi maximal volontaire, (EMGdi,rms%max), et les cotes de dyspnée et d'inconfort des jambes étaient similaires aux même taux de travail sous-maximaux (y compris T_{vent}) entre les modalités (tous les $p > 0{,}05$).

Résumé & implications: En conclusion: 1) les réponses cardiométaboliques et ventilatoires étaient constamment plus élevées pendant le test de tapis roulant vs. lors du test de bicyclette, et ceci, à des taux de travail sous-maximaux normalisés lors des deux modalités; 2) à quelques exceptions, les évaluations détaillées de l'efficacité ventilatoire, des volumes opérant pulmonaires, du contrôle respiratoire neuronal, de la dyspnée et de l'inconfort des jambes étaient semblables dans les deux modes d’exercices aux taux de travail sous-maximaux équivalents; et 3) les contraintes mécaniques dynamiques sur la ventilation étaient évidentes à la limite de la tolérance, en particulier pendant l'exercice sur le tapis roulant.

Nos résultats suggèrent que les paramètres physiologiques pertinents à la prescription de l'exercice, en particulier le $\dot{V}O_{2pic,}$ la FC_{pic} et le $\dot{V}O_2$ à T_{vent}, devraient être évalués dans chaque mode d'exercice pour optimiser l'intensité de l’entrainement. Alternativement, l'absence de l’effet du mode d'exercice sur le taux de travail dans notre étude au seuil de l’éxercice, suggère l'utilisation de ce paramètre, facilement disponible pour déterminer l'intensité d'entrainement optimale, indépendamment du fait que l’entrainement soit effectué sur une bicyclette ergométrique ou un tapis roulant.

PREFACE AND AUTHOR CONTRIBUTIONS

Muscat, K.M was the primary author and played the principle role in data collection, data analysis, and thesis/manuscript preparation.

Kotrach, H., Schaeffer, M.R., Mendonca, C.T., and Wilkinson-Maitland, C contributed to the collection and analysis of data.

Jensen, D conceived the study; designed the experiments; and contributed to data interpretation and analysis, and preparing the final draft of the thesis/manuscript

Chapter 1: Review of Literature

1.0 Introduction to Cardiopulmonary Exercise Testing. Cardiopulmonary exercise testing is widely used in both clinical and research settings to evaluate the physiological and perceptual determinants of exercise tolerance, i.e., cardiorespiratory fitness. Most organs (e.g., heart, lungs) have a large physiological reserve and measurements made at rest of individual organ system function (e.g., 12-lead electrocardiogram, spirometry) inadequately reflect the reserve capacity of all component physiological support systems (cardio-circulatory, neuromuscular and respiratory) that contribute to exercise tolerance [1]. Furthermore, limitation of exercise, in both health and disease, is multifactorial and never due to one mechanism acting alone. Thus, exercise testing uses the increased metabolic demands of external muscular work to impose a controlled physiological stress on the cardio-circulatory, neuromuscular and respiratory support systems and, by doing so, establishes their capacity to respond.

Exercise tolerance depends on the whole organism. As such, exercise testing must examine all component systems and the integration and interaction between them. Accomplishing this requires an exercise testing protocol that, first, uses incremental increases in external work rate (the proximate cause of increased skeletal muscle metabolic and contractile demands) up to the subject's tolerable maximum and, second, includes simultaneous and quantitative measurement of ventilation, breathing pattern, pulmonary gas exchange, cardio-circulatory and neuromuscular function, metabolism, and symptom intensity.

1.1 Indications for Cardiopulmonary Exercise Testing. By objectively assessing the integrative response of all component systems under stress, exercise testing permits detailed and objective evaluation of exercise tolerance [1-3], which has the potential to reduce the time and costs associated with identifying the nature and source(s) of an individual's functional impairment, disability and/or handicap through a battery of clinical tests made at rest. The maximal rate of oxygen uptake ($\dot{V}O_{2max}$) and the maximal work rate (*W*max) achieved during exercise testing both reflect the integrated response of the cardio-circulatory, neuromuscular and respiratory support systems involved in exercise [1]. As such, they are the most widely used parameter estimates of cardiorespiratory fitness and exercise tolerance in health and disease. For example, a $\dot{V}O_{2max}$ that is >80% of the normal age, sex and height predicted value most often suggests that there is no serious impairment in the integrated function of cardio-circulatory, neuromuscular and respiratory support systems.

Because exercise capacity ($\dot{V}O_{2max}$ and *W*max) depends on the integrated function between many physiological mechanisms, its measurement has been used as an indication of the body's overall capacity to respond to stress, such as a major surgery. Indeed, cardiopulmonary exercise testing is often used to evaluate pre-operative risk for major cardiothoracic surgeries (e.g., lung cancer resection surgery [4], surgical repair of abdominal aortic aneurysm [5]) with measurements of $\dot{V}O_{2max}$ independently predicting post-surgical morbidity and mortality; that is, as pre-surgical $\dot{V}O_{2max}$ decreases, the relative risk of post-surgical morbidity and mortality increases.

Exercise testing is also an integral component of cardiac and pulmonary rehabilitation programs [1-3, 6]. For example, the results from the initial (baseline) incremental exercise test allow accurate prescription of the intensity of exercise that is both safe and effective for the patient [7]. Furthermore, exercise testing, when repeated on several occasions in a given patient, is useful for the purpose of evaluating the efficacy of a therapy/intervention (e.g., rehabilitation, surgery, pharmacotherapy) on exercise tolerance and its physiological and perceptual determinants [1-3, 6].

The results obtained from an exercise test(s) may also be used to track the progression of disease and attendant functional limitation, disability and/or handicap; to help in the assessment of disability for industrial compensation; to help decide if occupational demands may be safely met, particularly among individuals with physically demanding jobs, e.g., military personnel, police officers and firemen; and to provide reassurance when the possibility of serious disease is excluded by the integrative exercise test results [1-3].

1.2 Approaches to Cardiopulmonary Exercise Testing. Although numerous approaches to cardiopulmonary exercise testing exist, the most widely used in both clinical and research settings consists of a progressive incremental work rate (power) test performed to a symptom-limited maximum with continuous (breath-by-breath) and non-invasive assessments of ventilation, breathing pattern, pulmonary gas exchange, cardio-circulatory function, muscle metabolic and contractile function, and symptom intensity [1-3]. Incremental exercise test protocols permit rapid (e.g., 8-12 min) acquisition of key physiological and diagnostic data, and are most often performed using either an electronically braked cycle ergometer (non-weight bearing) or a motorized treadmill (weight bearing), with each mode of exercise having its own unique physiological and practical advantages and disadvantages over the other.

1.2.1 Treadmill. The motor-driven treadmill imposes progressively increasing exercise stress through a combination of increases in belt speed and grade (inclination). Treadmill exercise testing has several advantages over cycle ergometry. The most notable advantage is that walking/running is a more familiar physical activity than cycling: everyone walks, but most people do not cycle (at least not in North America). As such, treadmill walking/running is widely believed to better mimic the activities of daily life. In fact, 73% of 305 normal males aged 42-70 years indicated a preference for treadmill walking/running over cycle ergometry in the laboratory setting [8]. Other notable advantages of treadmill exercise testing are that it involves the recruitment of a relatively larger muscle mass and that more work is performed against gravity, thus leading to a greater stress on the physiological support systems mediating the exercise response. Indeed, numerous studies have consistently reported that mean values of $\dot{V}O_{2max}$ are significantly higher when incremental exercise testing is performed on a treadmill than on a cycle ergometer (*refer to Section 1.4.1 below*).

These advantages notwithstanding, the main disadvantage of treadmill exercise testing is that it is difficult to accurately quantify (beyond estimation based on belt speed, grade and the subject's body mass [9]) the external work rate being performed by a given subject. As a result, and with the possible exception of physiological and perceptual responses made at the symptom-limited peak of exercise, direct comparisons of the integrated response of cardio-circulatory, neuromuscular and respiratory support systems at equivalent (standardized) submaximal *absolute* external work rates on the treadmill and cycle ergometer is inherently difficult and technically challenging. Furthermore, walking on a moving belt without holding onto the treadmill handrails, which can decrease the metabolic cost of treadmill exercise, may be difficult for some individuals, particularly those with poor co-ordination and limited mobility due neuromuscular and/or musculoskeletal disease(s)/disorder(s) of the lower extremities. Other practical disadvantages associated with treadmill vs. cycle exercise testing include the treadmill's relatively greater size, weight, and cost.

1.2.2 Cycle Ergometry. Through the use of a variable electromagnetic field that imposes a resistance on the flywheel that is largely independent of pedal cadence, electronically braked cycle ergometers permit direct quantification (and computerized control) of the external work rate being performed by a given subject. This represents the most significant advantage of cycle ergometry as an exercise modality. In contrast to the treadmill, an individual's body mass has much less effect on cycle ergometer exercise test performance. In addition, the cycle ergometer is normally much smaller, lighter and less expensive than the treadmill. It is also safer (i.e., lower risk of falls and injury due to loss of balance) and less likely to introduce movement artifacts into the measurement of key physiological parameters (e.g., ECG and blood pressure auscultation are generally easier).

Notable disadvantages of cycle ergometer exercise testing include: its lack of familiarity to most individuals, i.e., limited applicability to activities of daily life; recruitment of a relatively smaller muscle mass; and the increased likelihood that exercise may be stopped prematurely due to intolerable pain/discomfort associated with sitting on the bicycle seat, particularly in obese men and women.

1.3 Effect of Test Modality on Physiological and Perceptual Responses to Exercise. Over the past 40+ years, at least 50 published studies in both health and disease have sought to identify similarities and/or differences in the acute physiological and perceptual response to incremental exercise testing performed on a treadmill and cycle ergometer. As previously discussed, an inherent challenge to drawing direct and meaningful comparisons of the integrated response of cardio-circulatory, neuromuscular and respiratory support systems to incremental treadmill and cycle ergometer exercise is adequately matching (or standardizing) the increments in external work rate up to the subject's tolerable maximum.

In moving forward, I will review and summarize the results from earlier studies on acute physiological and perceptual responses to exercise performed on the treadmill and cycle ergometer, starting first with comparisons made (primarily) at the symptom-limited peak of exercise, followed by comparisons made (primarily) at standardized submaximal exercise intensities.

1.3.1 Peak/Maximal Exercise Responses. The best-known difference between exercise modes is in $\dot{V}O_{2max}$, which is 5-20% higher on the treadmill vs. cycle ergometer in both health and disease [9-39]. The influence of exercise mode on $\dot{V}O_{2max}$ has been attributed to several factors, most notably differences between treadmill and cycle ergometry in cardiovascular hemodynamics; skeletal muscle blood flow and metabolism; and recruitment and activation of skeletal muscles.

According to the Fick equation, $\dot{V}O_2$ is determined by the combination of changes in cardiac output (CO) and the arteriovenous O_2 difference ($AVDO_2$). It follows that differences in maximal CO (and its determinants, heart rate (HR) and stroke volume (SV)) and/or maximal $AVDO_2$ are most likely responsible for the established differences in $\dot{V}O_{2max}$ between exercise modalities. Indeed, studies by Hermansen et al., [21] Faulkner et al., [20] and Miyamura & Honda [26] in health, and by Kim et al. [25] in heart failure, have shown that the higher $\dot{V}O_{2max}$ response to treadmill vs. cycle exercise is due to the combination of a larger maximal CO (secondary to higher maximal SV, with no difference in maximal HR) and relatively greater widening of $AVDO_2$ (secondary to the recruitment of a relatively larger skeletal muscle mass) in the former. In other words, both increased O_2 delivery and utilization are likely responsible for the higher $\dot{V}O_{2max}$ measured during treadmill vs. cycle ergometry. Evidence further suggests that, in healthy adults and in patients with established cardiovascular disease, the higher maximal SV and CO achieved during treadmill vs. cycle ergometry may reflect the physiological benefits of a relatively lower total peripheral resistance (secondary to lesser sympathetic nervous system activation, as suggested by lower circulating catecholamine concentrations) in the former, including relatively lower cardiac afterload and perhaps also a higher venous return, i.e., cardiac preload [21, 25, 40].

It is reasonable to assume that the combination of a higher CO and lower total peripheral resistance help to maintain a higher skeletal muscle blood flow at maximum treadmill compared to cycle exercise, which, in the face of a relatively greater fall in arterial blood O_2 saturation during treadmill exercise [11, 15, 17, 41-48], would help to maximize arterial blood O_2 delivery/transport and contribute to the higher $\dot{V}O_{2max}$. This hypothesis is bolstered by the results of Matsui et al. [35] who found that lower limb (i.e., leg muscle) blood flow was significantly lower (by 16%) immediately after maximal cycle vs. treadmill exercise. Hermansen et al. [21] and Faulkner et al. [20] postulated that leg muscle blood flow might also be more impaired during cycling than running because the contraction phase of the contraction-relaxation cycle is longer during the former. Regardless of the mechanism(s), impaired leg muscle blood flow during cycle vs. treadmill exercise would have the effect of altering rates of substrate utilization and increasing the rate of development and severity of metabolic acidosis.

Studies by Achten et al., [33] and Cheneviere et al. [49] have demonstrated that whole-body fat oxidation rates are lower, while whole-body carbohydrate oxidation rates are higher during cycling than treadmill running at maximum exercise as well as at equivalent submaximal exercise intensities, expressed as $\dot{V}O_2$ in L/min or as a percentage of $\dot{V}O_{2max}$ (Fig. 1.1).

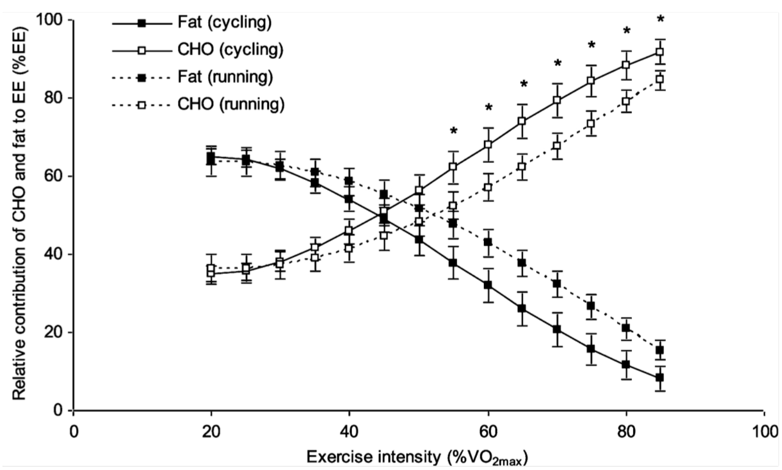

Figure 1.1. Relative contribution of carbohydrate (CHO) and fat to total energy expenditure (EE) during incremental cycling and running tests in 13 healthy and moderately trained men (n=7) and women (n=6). Values are means ± SE. $\dot{V}O_{2max}$, maximal rate of O_2 uptake. *Significant differences in relative contribution of CHO and fat to EE between cycling and running, $p<0.05$. Adapted from Cheneviere et al. [49].

In addition to the aforementioned differences in skeletal muscle blood flow, differences in the rates of substrate utilization may also be due to recruitment of a relatively smaller muscle mass during cycling than running. Under these circumstances, the relatively greater metabolic stress (rate) per unit of contracting muscle mass during cycling would necessitate a relatively greater energy (adenosine triphosphate or ATP) requirement, which can likely only be met by an increased rate of carbohydrate oxidation (*via* anaerobic glycolysis) and by a relatively greater reliance on phosophcreatine (PCr) degradation. This hypothesis is reinforced by the results of:

1. Koyal et al. [50] who found that arterial blood lactate concentrations ([La^-]) were higher, while arterial blood pH and bicarbonate concentrations ([HCO_3^-]) were lower at maximum exercise and at equivalent submaximal exercise intensities (as indicated by $\dot{V}O_2$ expressed in L/min) during cycle vs. treadmill testing (Fig. 1.2);

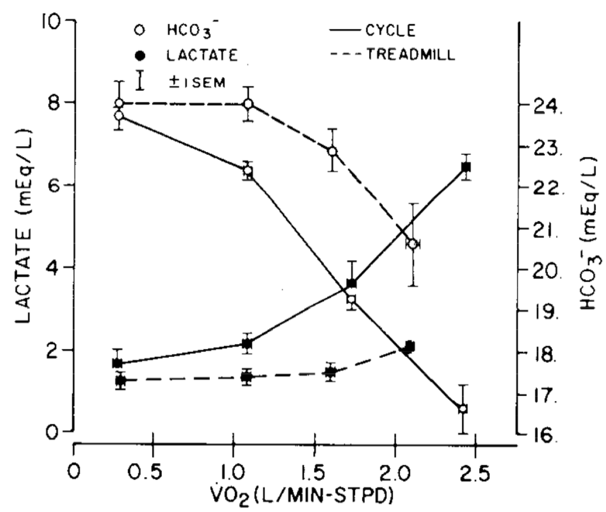

Figure 1.2. Arterial blood lactate and bicarbonate (HCO_3^-) concentrations during incremental cycle and treadmill exercise at several standardized submaximal exercise intensity, expressed in terms of oxygen uptake ($\dot{V}O_2$). Values are means ± SE. Adapted from Koyal et al. [50].

2. Okita et al. [34] who demonstrated, using phosphorus-31 magnetic resonance spectroscopy, that the lower $\dot{V}O_{2max}$ on incremental cycle vs. treadmill exercise was associated with the development of a much greater metabolic stress on the

quadriceps, as indicated by significantly lower intramuscular pH (6.51 ± 0.09 vs. 6.73 ± 0.17) and PCr concentrations (0.10 ± 0.05 vs. 0.33 ± 0.14) at peak exercise.

It is reasonable to predict that the aforementioned differences in lower limb blood flow, substrate utilization, and the severity of both whole-body and intramuscular metabolic acidosis would be associated with relatively greater electrical (neural) activation of the lower limb muscles and, by extension, relatively greater intensity ratings of perceived leg discomfort during incremental cycle vs. treadmill exercise. Indeed, Bijker et al. [51] found that the magnitude of the increase in the electromyogram (EMG) of both the vastus lateralis and biceps femoris (but not the gastrocnemius) needed to support any given increase in external power output was much greater during cycling compared to running in a group of 11 healthy young adults (Fig. 1.3). Unsurprisingly, sensory intensity ratings of perceived leg discomfort are higher at the symptom-limited peak of incremental cycle vs. treadmill exercise, at least in patients with chronic obstructive pulmonary disease (COPD) [15]; and intolerable leg discomfort is more commonly cited as the primary reason for stopping cycle compared to treadmill exercise in both health and disease [23, 36, 52].

Even though $\dot{V}O_{2max}$ is consistently higher when exercise is performed on a treadmill than on a cycle ergometer, it is now well established that the magnitude of the fall in arterial blood O_2 saturation (SaO_2) from rest to the symptom-limited peak of exercise is much greater in the former in both health and disease [11, 15, 17, 41-48]. The mechanisms underlying the effect of test modality on exercise-induced arterial hypoxemia have not yet to been clearly defined, although alveolar hypoventilation as well as relatively greater ventilation-perfusion mismatching and/or O_2 diffusion limitation during treadmill running have been implicated [17, 41-48].

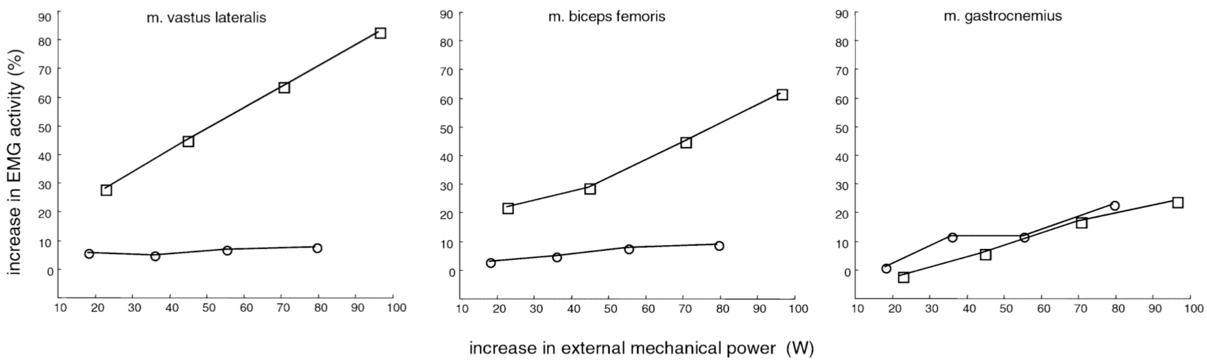

Figure 1.3. Increases in mean electromyogram (EMG) activity of three leg muscles resulting from increases in external mechanical power output during running (circles) and cycling (squares). Values are means. Adapted and modified from Bijker et al. [51].

1.3.2 Submaximal Exercise Responses. Although the influence of test modality on peak (maximal) physiological and perceptual responses to exercise are now well established, relatively few studies have examined the impact of exercise mode on physiological and perceptual responses at standardized (or equivalent) submaximal intensities, most often expressed in terms of $\dot{V}O_2$ (either in L/min, ml/kg/min or as a percentage of $\dot{V}O_{2max}$).

1.3.2.a Cardiovascular Hemodynamic, Metabolic & Gas Exchange Responses. Hermansen and colleagues [21, 22] were among the first to show that 1) heart rate (HR), blood [La^-] and the respiratory exchange ratio (RER) are significantly higher, 2) SV and its surrogate measure, oxygen pulse [53, 54], are significantly lower and 3) total peripheral resistance, mean arterial blood pressure and CO are not significantly different during cycle vs. treadmill ergometry at standardized submaximal levels of $\dot{V}O_2$ ranging from 1.0 to 5.0 L/min. With few exceptions, these findings have been replicated by several investigators, provided measured parameters are compared between modalities at equivalent submaximal levels of $\dot{V}O_2$, expressed either in L/min, ml/kg/min or as a percentage of $\dot{V}O_{2max}$ [26, 38].

The influence of exercise test modality on estimates of ventilatory and gas exchange efficiency is equivocal. Nevertheless, the majority of available evidence indicates that, in both health and disease, the ventilatory equivalent for O_2 ($\dot{V}_E/\dot{V}O_2$) is higher, while the ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}CO_2$) is not different at any standardized submaximal exercise intensity during cycling vs. running [14, 15, 55]. In the setting of a relatively preserved $\dot{V}_E/\dot{V}CO_2$, the higher $\dot{V}_E/\dot{V}O_2$ observed during submaximal cycling vs. running exercise reflects respiratory compensation for the more severe whole-body and intramuscular metabolic acidosis observed at any standardized submaximal $\dot{V}O_2$ during cycling vs. running (*refer to Section 1.4.1 above*). Indeed, both Koyal et al. [50] and Miles et al. [38] found that test modality had no demonstrable effect on the relationship between exercise-induced decreases in plasma [HCO_3^-] and increases in the $\dot{V}_E$ above and beyond that needed to support any given increment in $\dot{V}O_2$ (i.e., “excess ventilation”) during exercise above the AT/T_{vent} (Fig. 1.4).

In contrast to the above, mean values of $\dot{V}_E/\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$ and arterial PO_2 (PaO_2) are significantly lower, while those for arterial PCO_2 ($PaCO_2$) are significantly higher at the symptom-limited peak of treadmill vs. cycle exercise in both health [11, 17, 46, 48, 55] and disease [15, 41, 43]. Whether this apparent 'alveolar hypoventilation' indicates the existence of critical dynamic mechanical constraints on exercise hyperpnea at the limits of tolerance during treadmill vs. cycle ergometry remains unclear and requires further investigation.

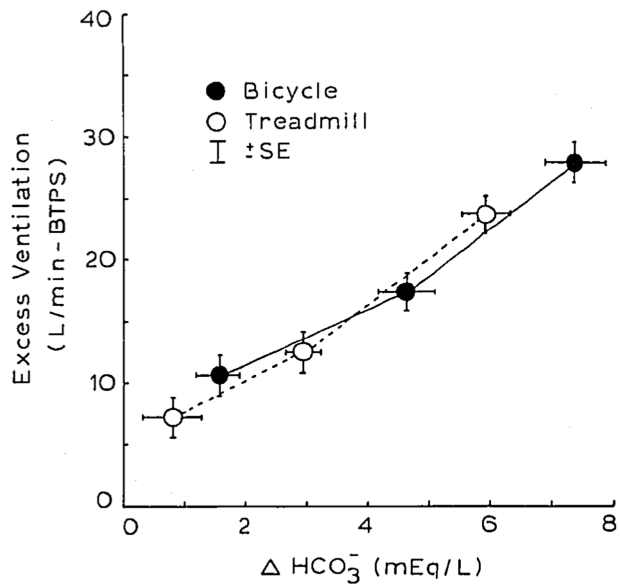

Figure 1.4. Relationship between exercise-induced decreases (Δ) in plasma bicarbonate (HCO_3^-) concentrations and increases in the ventilation above and beyond that needed to support any given increment in oxygen uptake (i.e., excess ventilation) during submaximal and maximal exercise on a cycle ergometer and treadmill. Values are means ± SE. Adapted from Miles et al. [38].

1.3.2.b Ventilatory (Anaerobic) Threshold. Numerous studies in both health and disease have reported that the $\dot{V}O_2$ at the anaerobic (AT) or ventilatory (T_{vent}) threshold is significantly higher when incremental exercise testing is performed on a treadmill than on a cycle ergometer [9, 12, 15, 18, 19, 23, 25, 30, 32, 43]. These differences are believed to reflect recruitment of a relatively smaller muscle mass and, by extension, a more rapid rate of development of intramuscular and whole-body metabolic acidosis during cycling than running. A muscle biopsy study by Jacobs et al. [23] provided evidence to suggest that differences in the $\dot{V}O_2$ at AT/T_{vent} between exercise modalities may also reflect, at least in part, a higher glycolytic (lactate dehydrogenase) relative to oxidative (citrate synthase) enzyme activity in skeletal muscles predominantly involved in cycling (vastus lateralis) vs. those primarily involved in running (gastrocnemius). Under these circumstances, the greater capacity of muscles primarily involved in treadmill running to oxidize pyruvate through oxidative phosphorylation may be responsible for the observation that the RER as well as the circulating concentrations of [La^-] and pyruvate are lower during treadmill vs. cycle exercise at equivalent submaximal exercise intensities [56]. This is substantiated by the results of Carter et al. [57] who found that $\dot{V}O_2$ kinetics are much slower during cycling vs. treadmill running for the same relative exercise intensity (Fig. 1.5), signifying a more sluggish 'turning on' of oxidative phosphorylation and a greater reliance on PCr degradation and anaerobic glycolysis to support the increased ATP demands of muscular work during cycling.

1.3.2.c Ventilation, Breathing Pattern, and Operating Lung Volumes. In keeping with the results of Gavin and Stager [17], Kalsas and Thorsen [37] found that $\dot{V}_E$ was significantly greater (by ~10 L/min or ~10%) at the symptom-limited peak of incremental treadmill (1 km/hr increase in treadmill speed starting at 3 km/hr and with a constant inclination of 1%) vs. cycle exercise testing (15-20 watt/min increases in work rate starting at 15-20 watts), and that this difference could not be explained by greater V_T

expansion. Throughout much of cycle vs. treadmill exercise, however, $\dot{V}_E$ was achieved through the adoption of a relatively deeper and slower breathing pattern; that is, V_T was higher, while f_R was lower at any standardized submaximal $\dot{V}_E$ between 30 and ~90 L/min (Fig. 1.6).

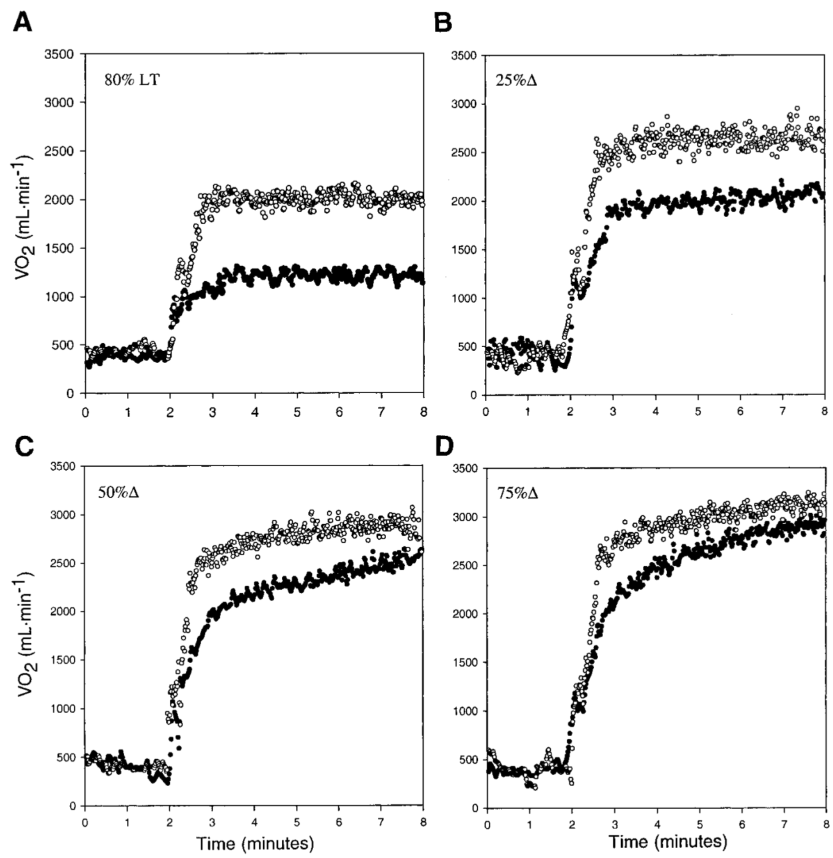

Figure 1.5. Example of oxygen uptake ($\dot{V}O_2$) response in a representative subject to 4 transitions at different exercise intensities [80% lactate threshold (LT; **A**), and 25 (**B**), 50 (**C**), and 75% (**D**) of the difference between LT and maximal $\dot{V}O_2$ during running (open circles) and cycling (closed circles). Adapted from Carter et al. [57].

A similar study by Elliott and Grace [58] characterized the breathing strategies adopted during symptom-limited incremental cycle (25 watt/min increases in work rate starting at 100 watts) and treadmill exercise (1 km/hr increase in treadmill speed starting at 5 km/hr and with a constant inclination of 1%) in healthy adults. In contrast to the results of Gavin and Stager [17] and Kalsas and Thorsen [37], symptom-limited peak $\dot{V}_E$ was significantly higher (by ~31 L/min or ~21% and secondary to increased V_T expansion) when exercise was performed on the cycle ergometer than on the treadmill. In keeping with the results of Kalsas and Thorsen [37], however, V_T expansion was significantly greater, while f_R was consistently lower all standardized submaximal levels of $\dot{V}_E$ during incremental cycle vs. treadmill exercise (Fig. 1.7). Importantly, exercise mode is reported to have no effect on the relationship between increasing mean tidal inspiratory flow rates (V_T/T_I, an index of neural inspiratory drive) and increasing $\dot{V}_E$ (Fig.

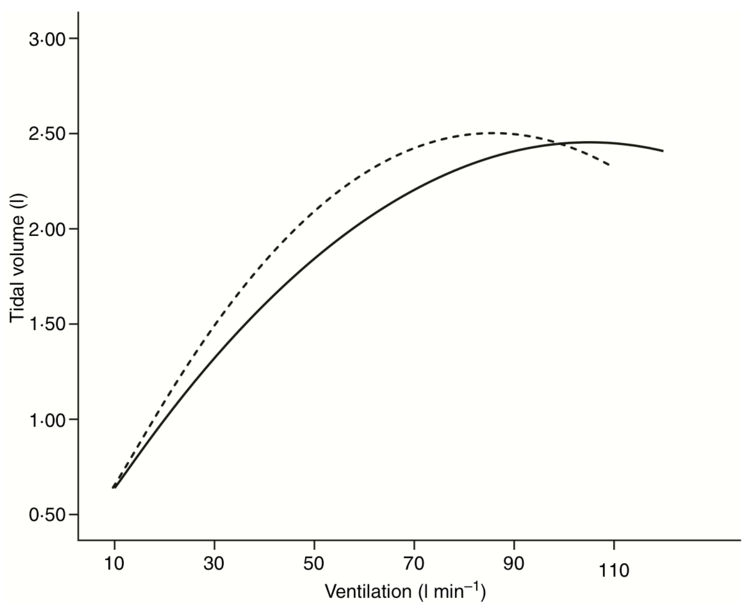

Figure 1.6. Effect of exercise mode on the relationship between increasing minute ventilation and increasing tidal volume expansion during incremental cycle (dashed line) and treadmill exercise (solid line). Adapted from Kalsas and Thorsen [37].

1.7) [58, 59]. The extent to which differences in breathing pattern, which may reflect entrainment of increasing leg movement frequency and f_R during treadmill running [59], are responsible for preservation of the V_T/T_I-$\dot{V}_E$ relationship during incremental cycle vs. treadmill exercise remains unclear.

In contrast to the results of Gavin and Stager [17], Kalsas and Thorsen [37], and Elliott and Grace [58], recent reports by Tanner et al.[11] and Duke et al. [55] showed that $\dot{V}_E$ was not significantly different at the symptom-limited peak of treadmill vs. cycle exercise, even though peak $\dot{V}O_2$ and $\dot{V}CO_2$ were significantly greater in the former. In these studies, end-expiratory lung volume (EELV) and end-inspiratory lung volume (EILV) were significantly greater (for example, by 0.34 L and 0.19 L, respectively [11]) during maximal cycling vs. running. These differences in dynamic operating lung volumes could not be easily explained by differences in the posture adopted during these modes of exercise [55] nor do they likely reflect a respiratory system limitation to cycle exercise tolerance since V_T expansion was also significantly greater during maximal cycling vs. running. Whether the observed differences in EELV and EILV at the end of cycle vs. treadmill exercise are associated with any meaningful sensory consequences (particularly as they may relate to dyspnea) requires further investigation.

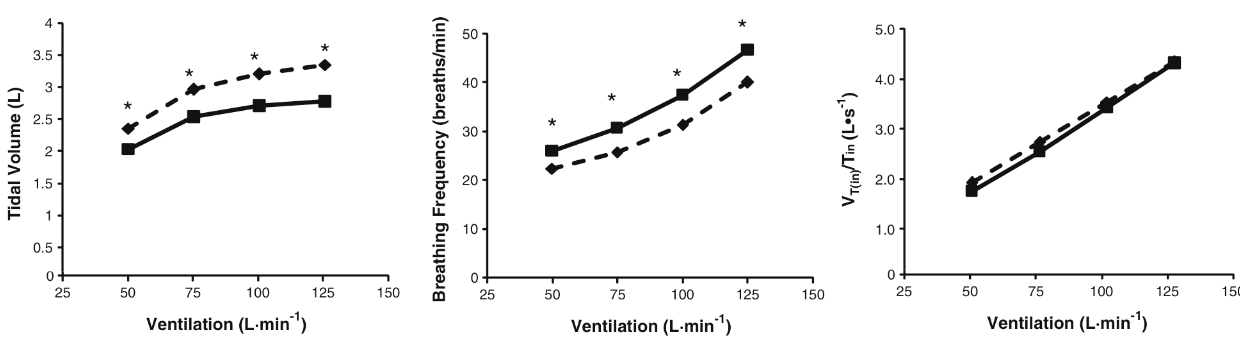

Figure 1.7. Effect of exercise mode on the relationship between increasing minute ventilation and each of tidal volume expansion (left), breathing frequency (middle) and mean tidal inspiratory flow rates ($V_{T(in)}/T_{in}$, an index of neural inspiratory drive) during incremental cycle (dashed line) and treadmill exercise (solid line). Values are means. *Significant difference between exercise modes at equivalent ventilation ($p<0.05$). Adapted and modified from Elliott and Grace [58].

A study of 8 healthy young adults by Wells et al. [60] examined the relative contributions of the rib cage and abdomen-diaphragm to V_T expansion at equivalent submaximal work loads during treadmill and cycle exercise. Despite obvious differences in posture between cycling and treadmill walking, and in keeping with the results of Duke et al. [55], exercise mode had no effect on the relative contributions of the rib cage and abdomen-diaphragm to V_T expansion, even after accounting for differences in $\dot{V}_E$.

1.3.2.d Symptom Responses. To our knowledge, only two studies have examined the effect of exercise mode on intensity ratings of dyspnea and leg fatigue in healthy adults. In 2003, Green et al. [61] reported a tendency for Borg 6-20 scale intensity ratings of perceived leg discomfort to be higher during cycling vs. treadmill exercise at the respiratory compensation point in 34 healthy young men and women: 14.9 ± 2.9 vs. 12.8 ± 2.8 Borg units ($p=0.055$). More recently, Sharma and coworkers [62] tested the hypothesis that bicycle exercise, which involves greater lower limb muscle activity [51], would be associated with greater intensity ratings of leg fatigue and dyspnea compared with treadmill exercise in 20 healthy young adults. In contrast to their *a priori* hypothesis, sensory intensity ratings of leg fatigue and dyspnea were not significantly different at any standardized submaximal $\dot{V}O_2$ ranging from 1.0 to 2.5 L/min during cycle vs. treadmill exercise. Similarly, exercise mode had no demonstrable effect on the relationship between increasing dyspnea intensity ratings and increasing $\dot{V}_E$. Based on these findings, Sharma et al. [62] concluded that sensory intensity ratings of dyspnea and leg fatigue reflect the overall level of cardiopulmonary stress, independent of exercise mode.

1.4 Physiological and Perceptual Responses to Treadmill and Cycle Exercise Testing Protocols Matched for Increments in External Work Rate. In each of the studies cited above, measured parameters were compared between cycle and treadmill exercise test modalities at equivalent submaximal levels of $\dot{V}O_2$, expressed either in L/min, ml/kg/min or as a percentage of $\dot{V}O_{2max}$. However, the true impact of test modality on exercise physiological and perceptual responses is difficult to interpret from these earlier studies because the protocols were not carefully matched for increments in external work rate, which is the proximate source of increased skeletal muscle metabolic and contractile demands. As such, the challenge to appropriately identify similarities/differences in the physiological and perceptual response to cycle vs. treadmill exercise is carefully matching the protocols for increments in external work rate rather than metabolic rate ($\dot{V}O_2$). In other words, the 'independent' effect of modality on exercise physiological and perceptual responses can only be compared when the test protocols are matched for the increments in external work rate – the 'true' exercise stimulus.

To the best of our knowledge, only 1 study in health [9] and 4 studies in COPD [15, 43, 63, 64] have compared physiological and perceptual responses to incremental treadmill and cycle exercise using matched linearized external work rate protocols. Briefly, in each of these studies, the rate of work done against gravity while walking on a treadmill up an incline was estimated according to each individual's body mass, the walking speed and the angle of inclination using the following formula: Work Rate (watts) = Body Mass (kg) x G x V x Sine(α), where G is the gravitational acceleration (9.81 meters/sec^2), V is the treadmill belt speed in meters/sec, and α is the angle of inclination

[9]. Unfortunately, only 3 of these 5 studies, including the 1 in health [9] and 2 of the 4 in COPD [15, 63], made direct comparisons of measured parameters at standardized *absolute* submaximal external work rates.

In 2003, Porszasz and colleagues [9] first described a treadmill protocol that utilizes linear speed changes and nonlinear inclination changes that result in a linear ramp-like change in external work rate. In this study of 22 healthy sedentary adults aged 37.6 ± 12.3 years, symptom-limited peak $\dot{V}O_2$ (2.69 ± 0.74 vs. 2.18 ± 0.60 L/min), $\dot{V}O_2$ at T_{vent} (1.37 ± 0.42 vs. 1.06 ± 0.32 L/min) and the slope of the linear relationship between increasing $\dot{V}O_2$ and increasing external work rate (11.4 ± 2.4 vs. 9.6 ± 2.0 ml O_2/min/watt) were significantly higher during incremental treadmill vs. cycle exercise testing. Unfortunately, Porszasz et al. [9] did not compare cardiovascular, gas exchange, ventilatory, breathing pattern, operating lung volume and perceptual responses at equivalent *absolute* submaximal external work rates during incremental treadmill and cycle exercise testing.

Two recent studies by Ciavaglia et al. [15, 63] compared cardiometabolic, ventilatory, breathing pattern, operating lung volume, neural respiratory drive (diaphragmatic EMG expressed as a percentage of maximum voluntary diaphragmatic EMG; EMGdi%max), respiratory muscle pressure development and symptom (dyspnea & leg discomfort) responses during incremental treadmill and cycle exercise using matched linearized external work rate protocols in 18 elderly and obese patients with COPD. In these studies, $\dot{V}O_2$, $\dot{V}CO_2$ and expiratory muscle activity were significantly higher, while RER, SaO_2 and the $\dot{V}_E/\dot{V}O_2$ ratio were significantly lower at any standardized *absolute* submaximal external work rate during treadmill vs. cycle ergometry (Fig. 1.8). In keeping with the results of a study by Hsia et al. [43] in non-obese COPD, Ciavaglia et al. [15] further showed that the $\dot{V}O_2$ at T_{vent} was 16% higher during treadmill vs. cycle exercise. Despite these differences, HR, $\dot{V}_E/\dot{V}CO_2$, $\dot{V}_E$, V_T, f_R, IC, IRV, EMGdi%max, tidal esophageal and transdiaphragmatic pressure swings, and symptom intensity (dyspnea and leg discomfort) responses were not significantly different at any standardized *absolute* submaximal external work rate during incremental treadmill vs. cycle exercise.

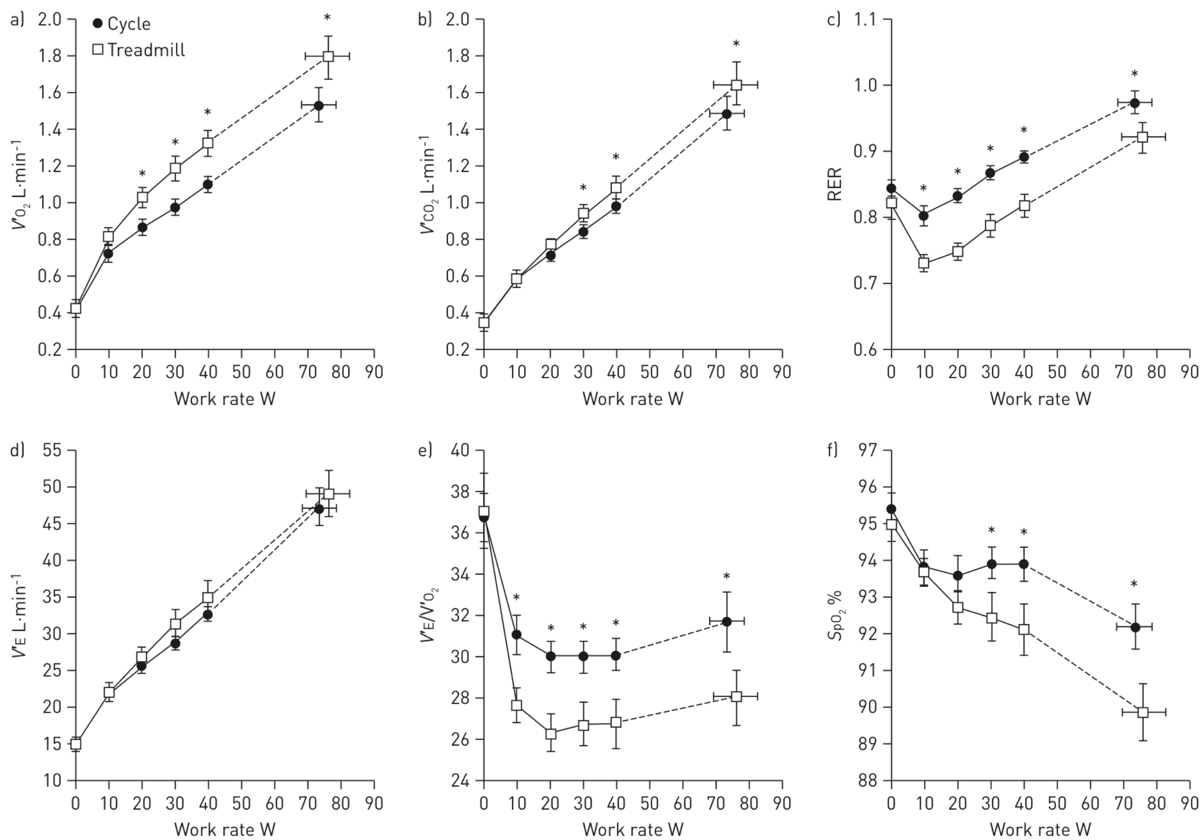

Figure 1.8. Relationship between increasing external work rate and each of a) oxygen uptake (VO_2), b) carbon dioxide production (VCO_2), c) respiratory exchange ratio (RER), d) minute ventilation (V_E), e) ventilatory equivalent for oxygen (V_E/VO_2) and f) arterial blood oxygen saturation (SpO_2) during symptom-limited incremental cycle vs. treadmill ergometry in 18 obese patients with chronic obstructive pulmonary disease. Values are means ± SE. *$p<0.05$ cycle vs. treadmill at equivalent submaximal work rate or at peak exercise. Adapted and modified from Ciavaglia et al. [15].

Notwithstanding these important observations, it is unlikely that the results from Ciavaglia and colleagues' studies in elderly and obese COPD patients [15, 63] can been directly applied, extrapolated and/or generalized to healthy, non-obese and habitually active young adults with normal baseline pulmonary function and cardiorespiratory fitness.

In their respective studies, Porszasz et al. [9] and Ciavaglia et al. [15, 63] postulated that the observed differences in the $\dot{V}O_2$-work rate slope during treadmill vs. cycle exercise testing reflected, at least in part, the increased oxygen cost associated with 1) relatively greater activation of postural (trunk) muscles in the upright posture, 2) swinging of the arms and legs during walking/running and 3) frictional losses as treadmill speed increases. Ciavaglia et al. [15, 63] further proposed that the lack of effect of exercise mode on dyspnea intensity-work rate and dyspnea intensity-$\dot{V}_E$ relationships in obese COPD patients reflected similarities in breathing pattern, the behavior of dynamic operating lung volumes, neural respiratory drive (EMGdi%max) and contractile respiratory muscle pressure (effort) development during treadmill vs. cycle exercise at any standardized *absolute* submaximal external work rate and $\dot{V}_E$. Again, the extent to which these observations in elderly and obese adults with COPD can be applied to healthy, young, non-obese adults remains unclear and requires further investigation.

1.5 Objective. In light of the information cited above, the primary objective of this thesis was to be the first to compare physiological and perceptual responses to matched (linearized) incremental cycle and treadmill ergometer exercise testing in healthy adults. To this end, we compared detailed and integrative assessments of cardio-metabolic function, gas exchange, ventilation, breathing pattern, dynamic operating lung volumes, inspiratory and expiratory muscle pressure development (measured by esophageal and gastric balloons), neural respiratory drive (EMGdi%max, measured by a multipair esophageal electrode catheter), and symptoms of dyspnea and leg discomfort in 15 healthy men aged 20-30 years during symptom-limited cycle and treadmill exercise test protocols carefully matched for increments in external work rate (25 watts/2 min).

Chapter 2: Physiological and Perceptual Responses to Incremental Exercise Testing in Healthy Men: Effect of Exercise Test Modality

2.0 Manuscript

2.1 Abstract

In a randomized cross-over study of 15 healthy men aged 20-30 years, we compared physiological and perceptual responses during treadmill (T) and cycle (C) exercise test protocols matched for increments in external work rate - the source of increased locomotor muscle metabolic and contractile demands. The rate of O_2 consumption ($\dot{V}O_2$) and CO_2 production ($\dot{V}CO_2$) were higher at the peak of T vs. C ($p \leq 0.05$). Nevertheless, work rate, minute ventilation ($\dot{V}_E$), tidal volume (V_T), breathing frequency (f_R), inspiratory capacity (IC), inspiratory reserve volume (IRV), tidal esophageal (Pes,tidal) and transdiaphragmatic pressure swings (Pdi,tidal), peak expiratory gastric pressures (Pga,peak), the root mean square of the diaphragm EMG (EMGdi,rms) expressed as a percentage of maximum EMGdi,rms (EMGdi,rms%max), and dyspnea ratings were similar at the peak of T vs. C ($p > 0.05$). Ratings of leg discomfort were higher at the peak of C vs. T ($p \leq 0.05$), even though peak $\dot{V}O_2$ was lower in C. $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, f_R, Pes,tidal, Pdi,tidal and Pga,peak were higher ($p \leq 0.05$), while V_T, IC, IRV, EMGdi,rms%max, and ratings of dyspnea and leg discomfort were similar ($p > 0.05$) at all or most submaximal work rates between modalities. Our findings highlight important differences (and similarities) in physiological and perceptual responses at maximal and submaximal work rates during incremental T and C exercise testing protocols. The lack of effect of modality on peak work rate, advocates for the use of this readily available parameter to determine optimal training intensity, regardless of exercise training mode.

2.2 Introduction

The two most commonly used modes of exercise in research and clinical settings for the assessment of cardiorespiratory fitness (e.g., maximal rate of O_2 consumption ($\dot{V}O_{2max}$)) are the treadmill and cycle ergometer [65]. Over the past 45 years, numerous studies have sought to identify similarities/differences in the acute physiological response to treadmill and cycle ergometer exercise testing. The best-known difference between these modalities is in $\dot{V}O_{2max}$, which is unequivocally higher (by 5-20%) when exercise testing is performed on a treadmill vs. cycle ergometer in both health and disease [9-11, 15, 17, 20-23, 25, 26, 33-38]. The higher $\dot{V}O_{2max}$ response to treadmill vs. cycle exercise testing has been ascribed to several factors, including: recruitment of a relatively larger muscle mass, with attainment of a higher maximal cardiac output, stroke volume, arteriovenous O_2 difference, lower limb blood flow and total vascular conductance during treadmill running [21, 22, 25, 26, 35, 40]; higher fat and lower carbohydrate oxidation rates during maximal treadmill running vs. cycling [33, 49]; and development of a less severe metabolic acidosis at maximal treadmill vs. cycle exercise [34, 50].

Whilst the influence of exercise mode on maximal physiological responses is now well established, only a few studies have examined the impact of test modality on physiological and perceptual responses at standardized submaximal exercise intensities. With few exceptions, these studies have found that carbohydrate oxidation rates, blood lactate concentrations ([La^-]), the respiratory exchange ratio (RER) and the ventilatory equivalent for O_2 ($\dot{V}_E/\dot{V}O_2$) are significantly lower, while intensity ratings of breathing (dyspnea) and leg discomfort are no different at equivalent submaximal exercise intensities during treadmill vs. cycle ergometry [21-23, 26, 38, 50, 55, 62]. In each of these studies, however, measured parameters were compared between modalities at ostensibly equivalent submaximal levels of $\dot{V}O_2$, expressed either in L/min, ml/kg/min or as a percentage of $\dot{V}O_{2max}$. As such, the true impact of test modality on exercise physiological and perceptual responses is difficult to interpret from these earlier studies in as much as the protocols were not carefully matched for increments in external work rate, which is the proximate source of increased skeletal muscle metabolic and contractile demands.

In 2003, Porszasz et al. [9] first described an incremental treadmill protocol that utilizes linear increase in speed and nonlinear increase in inclination that result in ramp-like increments in external work rate equivalent to those produced by an electronically-braked cycle ergometer. In this study of 22 healthy sedentary adults, the slope of the linear relationship between increasing $\dot{V}O_2$ and increasing external work rate (15 watts/min) was significantly higher (by 19%) during incremental treadmill vs. cycle exercise. Apart from $\dot{V}O_2$, however, Porszasz et al. [9] did not compare cardiovascular, gas exchange, breathing pattern, operating lung volume, respiratory mechanical/muscular and/or perceptual responses at equivalent submaximal external work rates during incremental treadmill and cycle exercise testing.

Ciavaglia et al. [15, 63] recently compared a constellation of detailed physiological and perceptual responses to symptom-limited incremental treadmill and cycle exercise using matched external work rate protocols (10 watts/2-min) in 18 elderly and obese patients with moderate-to-severe chronic obstructive pulmonary disease (COPD). In these studies, $\dot{V}O_2$, the rate of CO_2 production ($\dot{V}CO_2$) and expiratory muscle activity were significantly higher, while RER, arterial blood O_2 saturation and the $\dot{V}_E/\dot{V}O_2$ ratio were significantly lower at any standardized submaximal external work rate during treadmill vs. cycle ergometry. Despite these differences, mean values for heart rate (HR), the ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}CO_2$), minute ventilation ($\dot{V}_E$), tidal volume (V_T), breathing frequency (f_R), inspiratory capacity (IC), inspiratory reserve volume (IRV), neural respiratory drive (diaphragm EMG), tidal esophageal and transdiaphragmatic pressure swings, and sensory intensity ratings of dyspnea and leg discomfort were not significantly different at any equivalent submaximal external work rate during incremental treadmill vs. cycle exercise. Notwithstanding these novel observations, it is unlikely that the results from elderly and obese COPD patients can be generalized to healthy, young, non-obese adults.

Accordingly, the present study is the first to compare detailed and integrated assessments of cardiovascular and metabolic function, gas exchange, breathing pattern, dynamic operating lung volumes, neural respiratory drive (diaphragm EMG), inspiratory and expiratory muscle function, and dyspnea and leg discomfort in healthy, young, non-obese adults during symptom-limited treadmill and cycle exercise test protocols carefully matched for increments in external work rate.

2.3 Methods

Participants. Participants included healthy, non-smoking, non-obese (body mass index <30 kg/m^2) men aged 20–30 years with normal spirometry [66]. Participants were excluded if they had a known or suspected history of cardiovascular, respiratory, musculoskeletal, endocrine, neuromuscular and/or metabolic disease; were taking doctor prescribed medications; and/or had an allergy to lidocaine. Participants were recruited from the Montréal and surrounding area by word-of-mouth and online postings in the McGill University and Concordia University classifieds.

Study Design. Participants visited the *Clinical Exercise and Respiratory Physiology Laboratory* at McGill University on 3 separate occasions. *Visit 1* included screening for eligibility criteria, spirometry, and a symptom-limited incremental cycle exercise test followed 45-mins thereafter by a symptom-limited incremental treadmill exercise test (both for familiarization purposes). *Visits 2 and 3* included spirometry and a symptom-limited incremental cycle or treadmill exercise test (randomized visit order) with added measurements of the diaphragm electromyogram and of respiratory pressures. Participants were instructed to avoid alcohol, caffeine and strenuous exercise on each test day, which were separated by ≥48-hrs and conducted at the same time of day (±1 hr) for each participant. The study protocol and consent form were approved by the Institutional Review Board of the Faculty of Medicine at McGill University (A00-M74-11B) in accordance with the *Declaration of Helsinki*. All participants provided written informed consent.

Pulmonary function tests. Forced vital capacity (FVC), forced expiratory volume in 1-sec (FEV_1) and the FEV_1/FVC ratio were determined using automated testing equipment (Vmax Encore^{TM}; CareFusion, Yorba Linda, CA, USA). Measurements were obtained with participants seated, utilizing recommended techniques [67] and expressed as a percentage of predicted normal values [68].

Cardiopulmonary exercise testing. Incremental exercise tests were conducted on either an electronically braked cycle ergometer (Ergoline 800s) or a motorized treadmill (Trackmaster Model #TMX425C; Newton, KS, USA) using a Vmax Encore™ cardiopulmonary exercise testing system and consisted of a steady-state resting period of ≥6-mins (while seated on the cycle ergometer and while standing on the treadmill) followed by 25-watt increases in work rate (starting at 25 watts) every 2-min to the point of symptom-limitation. The treadmill protocol was individualized for each participant based on their body mass using the formula [69]: Work rate (watts) = 0.1634 x treadmill speed (m/min) x treadmill grade (%) x body mass (kg). The grade started at 5% and was increased by 1% every 2-min, with the increments in treadmill speed required to achieve the 25-watt/2-min increase in work rate determined using the formula. In this way, incremental cycle and treadmill exercise tests were performed using matched linearized work rate protocols, thus permitting examination of exercise mode on physiological and perceptual responses at standardized submaximal work rates and at peak exercise. Participants remained seated and maintained a pedaling cadence of 50-100 rpm during cycle exercise; and were not allowed to grasp the handrails during treadmill exercise.

Standard respiratory and gas exchange parameters were collected breath-by-breath at rest and during exercise while participants breathed through a mouthpiece and low-resistance flow transducer with nasal passages occluded by a nose clip. Heart rate was monitored continuously using a Polar® heart rate monitor (Lachine, QC, Canada). Inspiratory capacity (IC) maneuvers were performed at rest, within the last 30-sec of every 2-min stage during exercise and at end exercise. Assuming that total lung capacity does not change during exercise [70], changes in IC and inspiratory reserve volume (IRV

= IC – tidal volume (V_T)) reflect changes in dynamic end-expiratory and end-inspiratory lung volume, respectively.

Using Borg's 0-10 category-ratio scale [71], participants provided ratings to the following questions at rest, within the last 30-sec of every 2-min stage during exercise, and at end-exercise: How *intense* is your sensation of breathing overall? How *unpleasant* or *distressed* does your breathing make you feel? How *intense* is your sensation of leg discomfort? Breathing overall (hereafter referred to as dyspnea) was defined as "the global awareness of your breathing," which is consistent with the American Thoracic Society's most recent recommendation that *"…the definition of dyspnea should be neutral with respect to any particular quality"* of breathing [72]. Prior to each exercise test, participants were familiarized with the Borg scale and its endpoints were anchored such that "0" represented "no intensity (unpleasantness) at all" and "10" represented "the most severe intensity (unpleasantness) you have ever experienced or could ever imagine experiencing." At end-exercise, participants verbalized their main reason(s) for stopping exercise (dyspnea, leg discomfort, combination of dyspnea and leg discomfort, other); quantified the percentage contribution of dyspnea and leg discomfort to exercise cessation; and identified qualitative phrases that best described their breathing at end-exercise [73].

Breath-by-breath measures of the root mean square of the crural diaphragm EMG (EMGdi,rms) and of esophageal (Pes), gastric (Pga) and transdiaphragmatic (Pdi = Pga – Pes) pressure were recorded from a gastro-esophageal electrode-balloon catheter (Guangzhou Yinghui Medical Equipment Ltd., Guangzhou, China) and analyzed using published methods [74, 75]. Maximum voluntary EMGdi,rms (EMGdi,max) was identified as the largest of all EMGdi,rms values obtained from IC maneuvers performed either at rest or during exercise. The ratio of EMGdi,rms to EMGdi,max (EMGdi,rms%max) was used as an index of neural respiratory drive. Tidal swings in Pes (Pes,tidal) and Pdi (Pdi,tidal) were calculated as the difference between peak tidal inspiratory and peak tidal expiratory Pes and Pdi. Peak expiratory Pga (Pga,peak) was taken as an index of expiratory muscle activity (effort).

Analysis of exercise end points. Physiological parameters measured breath-by-breath were averaged in 30-sec intervals at rest and during exercise. These parameters, collected over the first 30-sec period of every 2-min stage during exercise, were linked with symptom ratings and IC measurements collected over the latter 30-sec of the same minute to avoid contamination of averaged breath-by-breath data by subject-experimenter interaction and by irregular breaths surrounding IC maneuvers.

Four main time points were used for the evaluation of exercise parameters: (1) *pre-exercise rest*, defined as the average of the last 30-sec of the steady-state period after ≥2-min of quiet breathing on the mouthpiece while seated or standing on the cycle ergometer and treadmill, respectively; (2) *ventilatory threshold* (T_{vent}), which was identified for each participant and test using the V-slope method [76]: physiological parameters and symptom ratings at the $\dot{V}O_2$ corresponding to T_{vent} were calculated by linear interpolation between adjacent measurement points for each participant; (3) *iso-work*, defined as the average of the last 30-sec of the highest equivalent submaximal work rate achieved by a given participant during both cycle and treadmill exercise tests; and (4) *peak exercise*, defined as the average of the last 30-sec of loaded pedalling and treadmill walking/running. Peak work rate was defined as the highest work rate the participant was able to sustain for ≥30-sec, while exercise endurance time (EET) was defined as the duration of loaded pedaling and as the duration of treadmill walking/running.

Statistical Analysis. The effect of exercise modality, measurement time and their interaction on measured parameters was examined using a two-way repeated measures analysis of variance with correction for multiple comparisons using Tukey's honest significant difference test (SigmaStat®; Systat® Software Inc., San Jose, CA, USA). Two-tailed paired *t*-tests (SigmaStat®) were used to examine the effect of exercise mode on (1) measured parameters at T_{vent} and (2) the percentage contribution of dyspnea and leg discomfort to exercise cessation. Reasons for stopping exercise and qualitative descriptors of dyspnea were assessed using frequency statistics. Significance was set at $p \leq 0.05$ and data are presented as mean ± SEM.

2.4 Results

Participant characteristics. Participants included 15 healthy, young (22.5 ± 0.4 years), non-obese (BMI = 23.8 ± 0.5 kg/m^2) men with normal spirometry (FEV_1 = 4.83 ± 0.14 L or 107 ± 3% predicted; FEV_1/FVC = 83 ± 2%) and above normal cardiorespiratory fitness levels: symptom-limited peak $\dot{V}O_2$ on incremental cycle and treadmill exercise testing of 118 ± 5 and 135 ± 4% predicted, respectively.

Responses to cycle and treadmill exercise. There was no significant difference in EET (21.6 ± 0.8 vs. 21.4 ± 0.9 min) or in the work rate (280 ± 10 vs. 279 ± 11 watts) achieved at the symptom-limited peak of incremental cycle vs. treadmill exercise testing.

Cardiometabolic and gas exchange responses. At peak exercise during treadmill vs. cycle testing, $\dot{V}O_2$, $\dot{V}CO_2$, HR, O_2 pulse and $P_{ET}CO_2$ were significantly higher (by 12 ± 2%, 8 ± 2%, 3 ± 1%, 9 ± 2% and 8 ± 2%, respectively), whereas RER, $\dot{V}_E/\dot{V}O_2$ and $P_{ET}O_2$ were significantly lower (by 4 ± 1%, 10 ± 3% and 3 ± 1%, respectively) (Table 2.1, Fig. 2.1).

As illustrated in Fig. 2.1, $\dot{V}O_2$, $\dot{V}CO_2$, HR and O_2 pulse were higher, while RER was lower at most standardized submaximal work rates during treadmill vs. cycle exercise testing (Table 2.1). With the exception of $\dot{V}_E/\dot{V}O_2$ and $P_{ET}O_2$ being higher during cycle vs. treadmill exercise at 25 and 50 watts, mean values of $\dot{V}_E/\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$, $P_{ET}O_2$ and $P_{ET}CO_2$ were not significantly different at any standardized submaximal work rate between modalities (Fig. 2.1, Table 2.1).

Although participants reached their T_{vent} at the same absolute submaximal work rate during treadmill vs. cycle testing, mean values of $\dot{V}O_2$, $\dot{V}CO_2$, HR and the O_2 pulse were significantly higher, while RER was significantly lower at T_{vent} during treadmill exercise (Table 2.1).

Table 2.1. Effect of modality on physiological and perceptual responses at rest and during symptom-limited incremental exercise testing in 15 healthy, young men.

	Rest		Ventilatory Threshold		Iso-work		Peak	
Parameter	**Cycle**	**Treadmill**	**Cycle**	**Treadmill**	**Cycle**	**Treadmill**	**Cycle**	**Treadmill**
Cardiometabolic and gas exchange parameters								
$\dot{V}O_2$ ($L \cdot min^{-1}$)	0.40 ± 0.03	0.46 ± 0.03	1.68 ± 0.06	2.06 ± 0.08*	3.87 ± 0.15	4.53 ± 0.18*	4.24 ± 0.14	4.74 ± 0.16*
$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	5.1 ± 0.3	5.9 ± 0.3	22.0 ± 1.0	26.9 ± 1.0*	50.1 ± 1.4	58.8 ± 1.8*	55.0 ± 1.3	61.5 ± 1.5*
$\dot{V}CO_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	4.3 ± 0.3	4.5 ± 0.3	18.5 ± 1.1	21.2 ± 1.1*	52.1 ± 1.8	60.1 ± 1.9*	60.4 ± 1.9	64.9 ± 1.8*
RER	0.84 ± 0.03	0.76 ± 0.02*	0.83 ± 0.02	0.78 ± 0.01*	1.04 ± 0.01	1.02 ± 0.02	1.10 ± 0.02	1.06 ± 0.02*
Heart rate ($beats \cdot min^{-1}$)	80.9 ± 2.9	87.8 ± 4.4*	116.1 ± 2.8	122.9 ± 3.8*	178.9 ± 2.7	190.1 ± 2.1*	188.1 ± 2.3	193.8 ± 2.5*
O_2 pulse (ml $O_2 \cdot beat^{-1}$)	5.0 ± 0.3	5.4 ± 0.5	14.6 ± 0.6	16.9 ± 0.7*	21.7 ± 0.8	23.9 ± 1.1*	22.6 ± 0.7	24.5 ± 1.0*
$\dot{V}_E/\dot{V}O_2$	32.8 ± 1.3	29.5 ± 1.3*	21.0 ± 0.5	20.0 ± 0.4	27.4 ± 1.0	27.5 ± 0.4	33.5 ± 1.1	29.9 ± 0.6*
$\dot{V}_E/\dot{V}CO_2$	39.3 ± 1.3	38.9 ± 1.4	25.2 ± 0.5	25.6 ± 0.5	26.3 ± 0.8	27.0 ± 0.4	30.6 ± 0.9	28.4 ± 0.4
$P_{ET}O_2$ (mmHg)	107.0 ± 1.8	103.8 ± 1.4*	98.6 ± 1.1	95.1 ± 1.1	107.3 ± 1.2	107.7 ± 0.6	114.0 ± 0.9	110.4 ± 0.7*
$P_{ET}CO_2$ (mmHg)	34.8 ± 1.0	34.6 ± 0.8	43.1 ± 0.7	42.4 ± 0.8	40.8 ± 1.1	39.8 ± 0.7*	35.5 ± 0.9	37.9 ± 0.4*
Ventilation, breathing pattern and operating lung volume parameters								
$\dot{V}_E$ ($L \cdot min^{-1}$)	12.9 ± 0.9	13.4 ± 0.9	35.2 ± 1.5	41.2 ± 1.9*	107.0 ± 6.9	124.4 ± 4.8*	142.1 ± 6.2	141.0 ± 3.9
V_T (L)	0.99 ± 0.07	0.86 ± 0.06	1.82 ± 0.11	1.82 ± 0.12	3.04 ± 0.14	2.95 ± 0.10	3.08 ± 0.08	2.96 ± 0.10
f_R ($breaths \cdot min^{-1}$)	14.0 ± 0.8	17.2 ± 1.3*	20.7 ± 1.3	24.3 ± 1.4*	35.7 ± 1.9	42.7 ± 1.3*	46.4 ± 1.6	48.1 ± 1.3
IC (L)	3.63 ± 0.13	3.71 ± 0.14	3.94 ± 0.14	3.99 ± 0.13	4.01 ± 0.17	3.96 ± 0.13	3.87 ± 0.14	3.70 ± 0.15
IRV (L)	2.64 ± 0.11	2.84 ± 0.14	2.12 ± 0.16	2.17 ± 0.17	0.97 ± 0.13	1.01 ± 0.11	0.78 ± 0.13	0.74 ± 0.09
Gastro-esophageal electrode-balloon catheter-derived parameters								
EMGdi,rms%max	11.2 ± 2.2	10.5 ± 1.3	20.5 ± 2.6	25.0 ± 2.6	58.0 ± 4.1	63.2 ± 4.6	67.0 ± 4.9	77.2 ± 3.6
Pes,tidal (cmH_2O)	5.2 ± 0.5	5.2 ± 0.5	11.2 ± 0.9	12.6 ± 1.0	28.6 ± 2.0	32.8 ± 1.3*	40.0 ± 2.9	37.6 ± 1.5
Peak inspiratory Pes (cmH_2O)	-11.4 ± 1.0	-10.1 ± 0.9	-14.7 ± 1.2	-13.1 ± 1.4	-25.7 ± 1.8	-23.9 ± 1.3	-29.8 ± 1.8	-24.7 ± 1.3*
Peak expiratory Pes (cmH_2O)	-6.2 ± 0.6	-4.9 ± 0.6	-3.4 ± 0.7	-0.5 ± 1.1*	3.0 ± 1.0	8.9 ± 0.9	10.2 ± 1.8	13.0 ± 1.2
Pdi,tidal (cmH_2O)	10.0 ± 1.0	6.6 ± 0.7*	10.2 ± 2.0	13.0 ± 1.0	22.4 ± 1.3	27.2 ± 1.1*	26.9 ± 1.5	29.4 ± 1.6
Peak inspiratory Pdi (cmH_2O)	23.1 ± 1.2	20.8 ± 2.4	26.6 ± 1.8	24.8 ± 2.6	34.4 ± 1.7	35.1 ± 2.3	38.5 ± 1.9	35.2 ± 2.5
Peak expiratory Pdi (cmH_2O)	13.1 ± 0.8	14.2 ± 2.4	13.1 ± 1.0	11.8 ± 2.3	12.0 ± 0.9	7.9 ± 1.9	11.6 ± 0.9	5.8 ± 1.7*
Peak expiratory Pga (cmH_2O)	12.1 ± 0.8	11.5 ± 2.3	13.7 ± 1.0	14.8 ± 1.8	16.9 ± 1.1	22.5 ± 1.9*	23.1 ± 1.7	23.6 ± 1.9
Symptom parameters								
Dyspnea intensity (Borg scale)	0.1 ± 0.1	0.0 ± 0.0	0.7 ± 0.2	0.5 ± 0.2	5.6 ± 0.7	5.5 ± 0.5	7.8 ± 0.6	7.7 ± 0.5
Dyspnea unpleasantness (Borg scale)	0.1 ± 0.1	0.0 ± 0.0	0.4 ± 0.1	0.1 ± 0.1*	4.4 ± 0.8	4.5 ± 0.6	6.2 ± 0.8	6.7 ± 0.6
Leg Discomfort (Borg Scale)	0.0 ± 0.0	0.0 ± 0.0	0.8 ± 0.2	0.4 ± 0.1*	6.3 ± 0.7	5.5 ± 0.7*	8.6 ± 0.6	7.4 ± 0.7*

Note: Values are means ± SEM. $\dot{V}O_2$ and $\dot{V}CO_2$, rate of O_2 consumption and CO_2 production, respectively; RER, respiratory exchange ratio; $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalents for O_2 and CO_2, respectively; $P_{ET}O_2$ and $P_{ET}CO_2$, end-tidal partial pressure of O_2 and CO_2, respectively; $\dot{V}_E$, minute ventilation; V_T, tidal volume; f_R, breathing frequency; IC, inspiratory capacity; IRV, inspiratory reserve volume; EMGdi,rms%max, root mean square of the crural diaphragm electromyogram (EMGdi,rms) expressed as a percentage of maximal voluntary EMGdi,rms; Pes,tidal and Pdi,tidal, tidal esophageal and transdiaphragmatic pressure swings, respectively; Pga, gastric pressure. *$p \leq 0.05$ vs. cycle at measurement time.

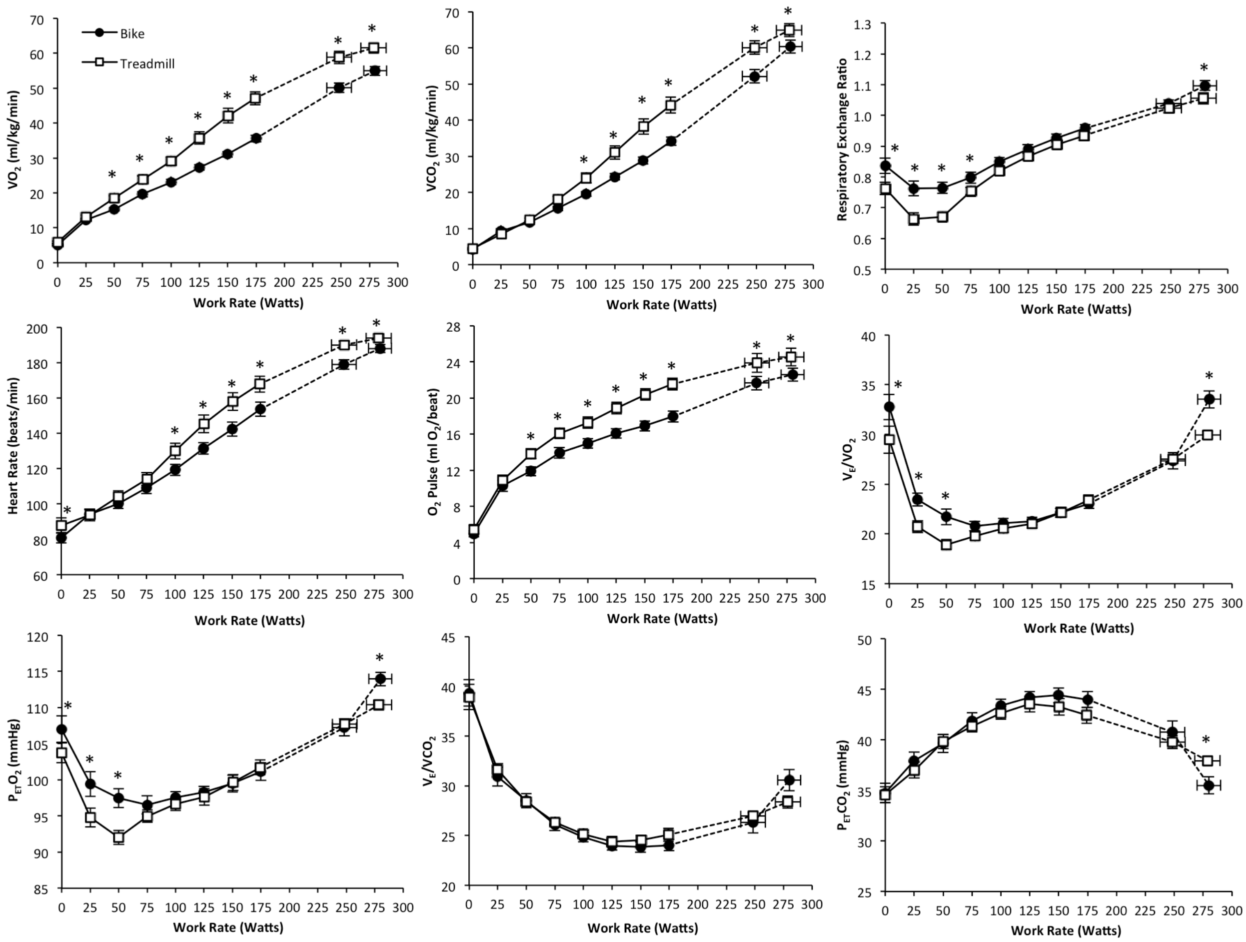

Figure 2.1. Metabolic, cardiovascular and gas exchange responses during symptom-limited treadmill and cycle exercise test protocols matched for increments in work rate. Values are means ± SEM. VO_2 and VCO_2, rate of O_2 consumption and CO_2 production, respectively; RER, respiratory exchange ratio; V_E/VO_2 and V_E/VCO_2, ventilatory equivalents for O_2 and CO_2, respectively; $P_{ET}O_2$ and $P_{ET}CO_2$, end-tidal partial pressure of O_2 and CO_2, respectively. *$p \leq 0.05$ vs. cycle at measurement time.

Ventilatory, breathing pattern and operating lung volume responses. Despite significant differences in $\dot{V}O_2$ and $\dot{V}CO_2$ at the peak of treadmill vs. cycle exercise (Fig. 2.1), $\dot{V}_E$, V_T, f_R, IC and IRV were not significantly between modalities at end-exercise (Fig. 2.2, Table 2.1).

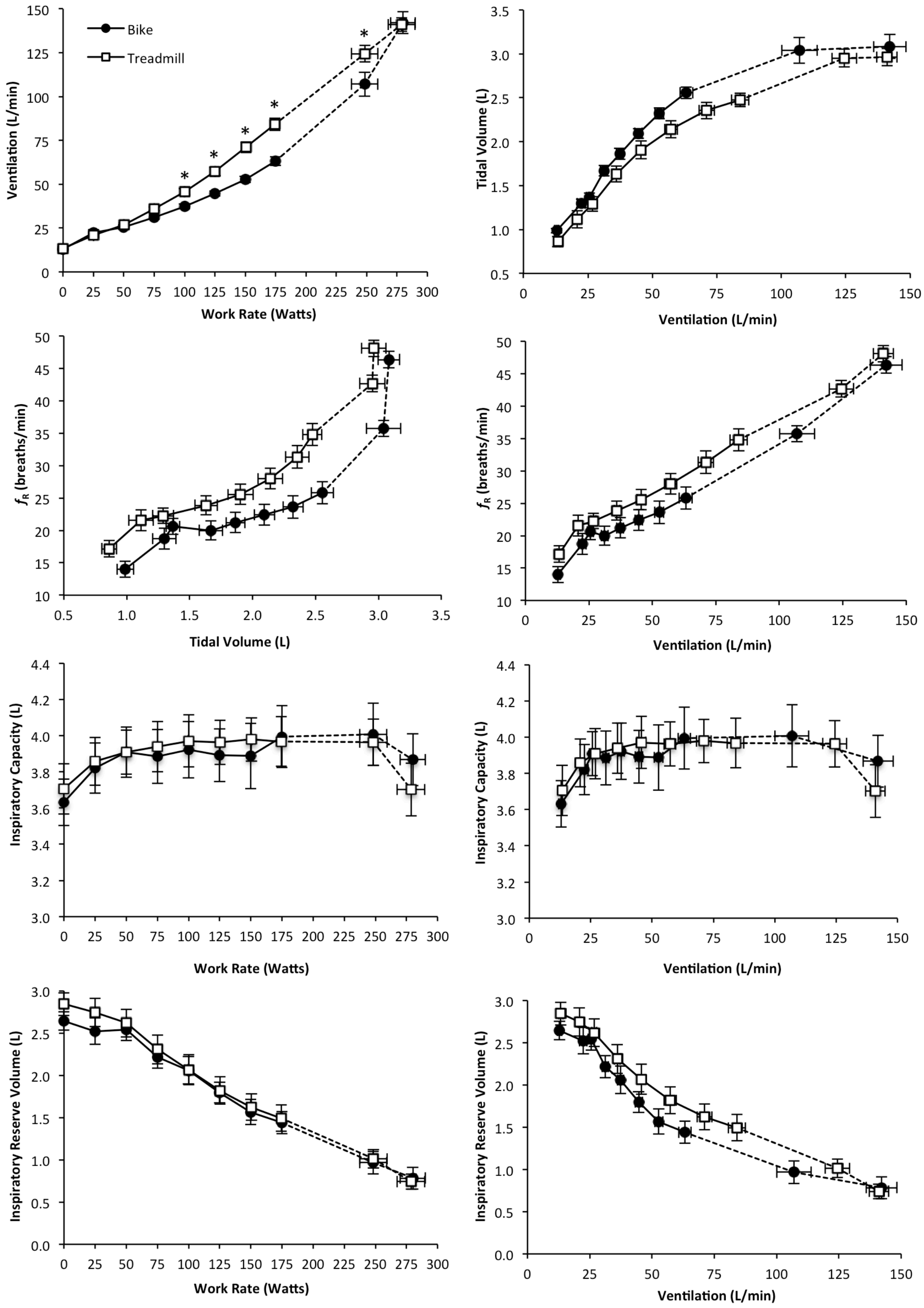

Figure 2.2. Ventilation, breathing pattern and operating lung volume responses during symptom-limited treadmill and cycle exercise test protocols matched for increments in work rate. Values are means ± SEM. f_R, breathing frequency. *$p \leq 0.05$ vs. cycle at measurement time.

As illustrated in Fig. 2.2, mean values of $\dot{V}_E$ were significantly higher at all standardized submaximal work rates ≥75 watts (as well as at T_{vent}) during treadmill vs. cycle exercise testing; for example, by 17.4 ± 5.6 L/min or 21 ± 7% at iso-work (Fig. 2.2, Table 2.1). The increased $\dot{V}_E$ response to treadmill vs. cycle exercise was associated with the adoption of a more rapid and shallow breathing pattern (Fig. 2.2). Operating lung volumes were not significantly different between modalities at any standardized submaximal work rate and at peak exercise (Fig. 2.2). The relationship between exercise-induced changes in IC and $\dot{V}_E$ was also similar between modalities (Fig. 2.2). In contrast, there was a rightward shift of the IRV- $\dot{V}_E$ relationship during treadmill vs. cycle exercise (Fig. 2.2): mean values of $\dot{V}_E$ were higher at any given IRV during submaximal treadmill vs. cycle exercise; for example, by ~15-20 L/min at IRV's of ~0.5-2.0 L.

Diaphragm EMG and respiratory pressure responses. Mean values of EMGdi,max were not significantly different when evaluated on treadmill vs. cycle exercise test days: 238.2 ± 19.8 vs. 230.0 ± 18.6 μV, respectively (p=0.740). The EMGdi,rms%max was higher at the symptom-limited peak of treadmill vs. cycle exercise (77.2 ± 3.6 vs. 67.0 ± 4.9 %EMGdi,max); however, this difference did not reach statistical significance (p=0.120) (Fig. 2.3, Table 2.1). Neither Pes,tidal, Pdi,tidal nor Pga,peak were significantly different at the symptom-limited peak of treadmill vs. cycle exercise (Fig. 2.3, Table 2.1).

As illustrated in Fig. 2.3, Pes,tidal was significantly higher during treadmill vs. cycle exercise testing at standardized submaximal work rates ≥125 watts (Fig. 2.3).

Similarly, Pdi,tidal was higher at iso-work, while Pga,peak was higher at 175 watts and at iso-work during treadmill vs. cycle testing (Fig. 2.3).

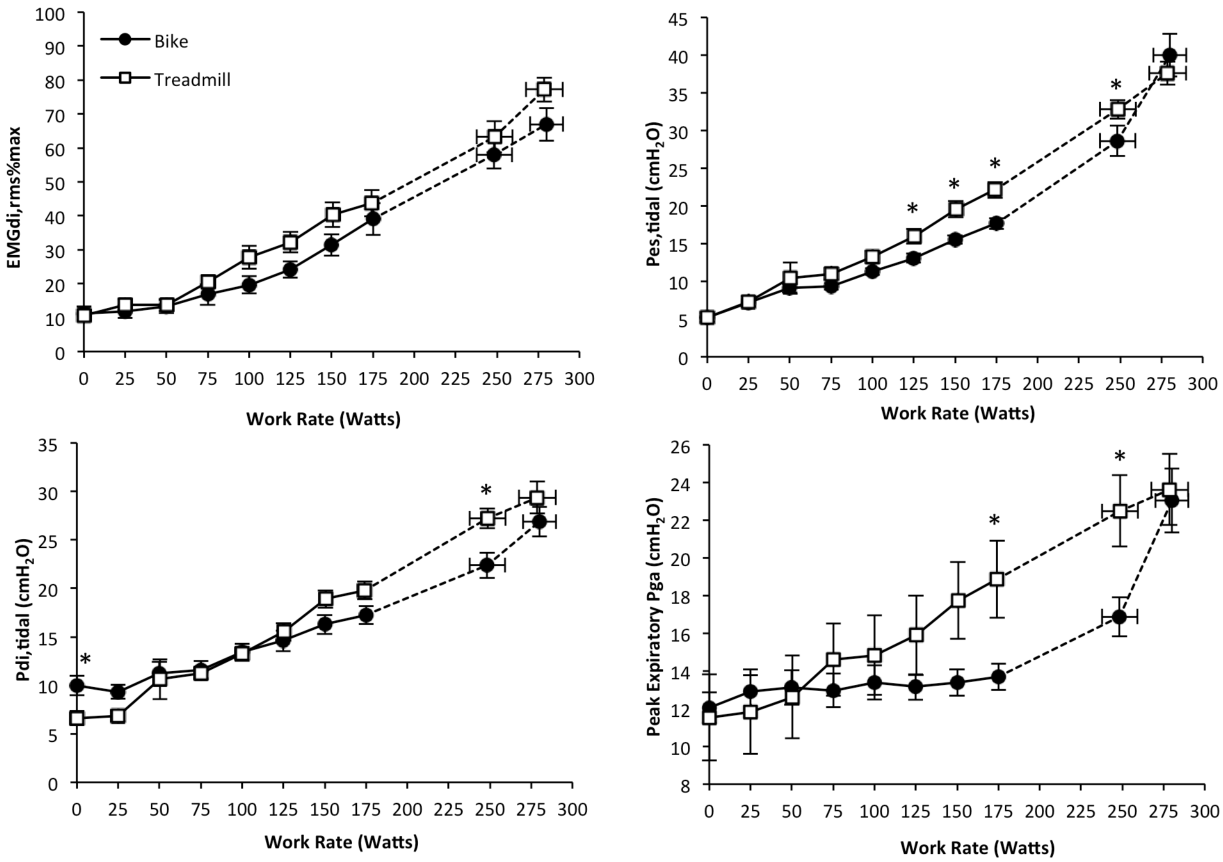

Figure 2.3. Gastro-esophageal electrode-balloon catheter-derived responses during symptom-limited treadmill and cycle exercise test protocols matched for increments in work rate. Values are means ± SEM. EMGdi,rms%max, root mean square of the crural diaphragm electromyogram (EMGdi,rms) expressed as a percentage of maximal voluntary EMGdi,rms; Pes,tidal and Pdi,tidal, tidal esophageal and transdiaphragmatic pressure swings, respectively; Pga, gastric pressure. *p≤0.05 vs. cycle at measurement time.

Symptom responses. A higher percentage (60% vs. 27%) of the participants identified intolerable leg discomfort as the main reason for stopping cycle vs. treadmill exercise. Indeed, the relative contribution of intolerable leg discomfort to exercise cessation was significantly higher at the end of cycle vs. treadmill testing (67.9 ± 6.6%

vs. 43.4 ± 7.7%, $p<0.05$). The majority of participants self-selected descriptor phrases alluding to a heightened sense of 'work/effort of breathing' and of 'rapid breathing' at the symptom-limited peak of both treadmill and cycle testing; for example, *'Breathing in requires effort'* (cycle, 71% vs. treadmill, 64%), *'My breathing is heavy'* (cycle, 79% vs. treadmill, 93%), *'My breathing requires more work'* (cycle, 71% vs. treadmill, 93%) and *'I feel that my breathing is rapid'* (cycle, 85% vs. treadmill, 93%).

Intensity ratings of leg discomfort were significantly higher at iso-work and at peak exercise during cycle vs. treadmill testing (by 0.9 ± 0.5 and 1.2 ± 0.6 Borg 0-10 scale units, respectively) (Fig. 2.4, Table 2.1). As illustrated in Fig. 2.4, the relationship between increasing intensity ratings of leg discomfort and increasing $\dot{V}O_2$ was displaced to the right during treadmill compared with cycle exercise testing.

Borg 0-10 scale intensity and unpleasantness ratings of dyspnea were not significantly different between modalities at any standardized submaximal work rate and at peak exercise (Fig. 2.4, Table 2.1). Compared to cycle testing, treadmill testing was associated with a rightward shift of the dyspnea intensity-$\dot{V}_E$ relationship (Fig. 2.4). By contrast, the relationship between exercise-induced changes in dyspnea intensity ratings and each of EMGdi,rms%max and IRV were relatively superimposed during treadmill and cycle ergometry (Fig. 2.4). A similar influence of exercise mode was observed on the relationship exercise-induced changes in dyspnea unpleasantness ratings and each of $\dot{V}_E$, EMGdi,rms%max, and IRV (data not shown).

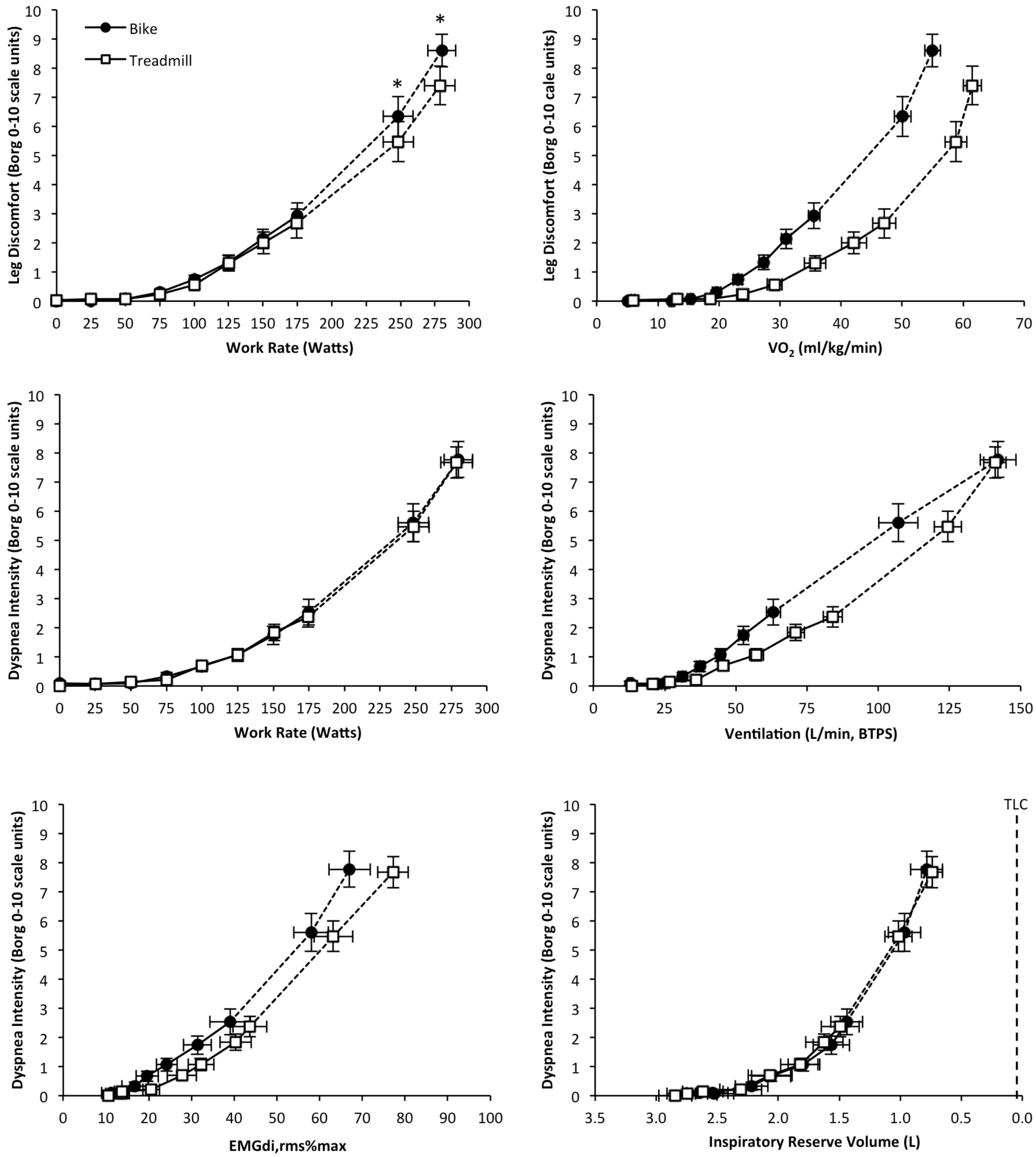

Figure 2.4. Perceptual responses during symptom-limited treadmill and cycle exercise test protocols matched for increments in work rate. Values are means ± SEM. VO_2, rate of O_2 consumption; EMGdi,rms%max, root mean square of the crural diaphragm electromyogram (EMGdi,rms) expressed as a percentage of maximal voluntary EMGdi,rms; TLC, total lung capacity. *p≤0.05 vs. cycle at measurement time.

2.5 Discussion

Consistent with previous reports [9, 11, 20-22, 26, 35, 38, 55], $\dot{V}O_2$ was significantly higher at T_{vent} (by 23%) and at the symptom-limited peak of incremental treadmill vs. cycle exercise testing (by 12%), even though work rate was not significantly different between modalities at either measurement time. These differences likely reflect 1) recruitment of a relatively larger skeletal muscle mass, with attainment of a higher maximal cardiac output, stroke volume, arteriovenous O_2 difference, leg muscle blood flow and total vascular conductance during treadmill running [21, 22, 26, 35, 40]; 2) higher fat and lower carbohydrate oxidation rates during submaximal and maximal treadmill running vs. cycling [33, 49]; 3) higher oxidative relative to glycolytic enzyme activity in skeletal muscles predominantly used in running vs. those predominantly used in cycling [23]; and 4) less rapid rate of development of metabolic acidosis during treadmill vs. cycle ergometry [34, 50]. Indeed, RER was lower, while $\dot{V}CO_{2,}$ HR and the O_2 pulse (a surrogate measure of stroke volume [53, 54]) were higher during treadmill vs. cycle ergometry at T_{vent}, iso-work and at peak exercise.

Muscles of the upper body (e.g., arms, shoulders, chest, back) and/or trunk (e.g., rectus abdominis) are presumably more active during treadmill running than cycling. Although activation of these muscle groups cost metabolic energy, they do not contribute to the production of external mechanical power during treadmill running. It follows that, in our study, the widening disparity between increasing work rate and each of $\dot{V}O_{2,}$ $\dot{V}CO_2$, HR and the O_2 pulse may also reflect, at least in part, progressively greater metabolic activity of the upper body and/or trunk muscles as work rate was increased during treadmill exercise.

Exercise-induced changes in $\dot{V}_E$ are tightly coupled to $\dot{V}CO_2$ [77]. In our study, neither $\dot{V}_E$ nor $\dot{V}CO_2$ was significantly different between modalities at standardized work rates below T_{vent}. By contrast, $\dot{V}_E$ and $\dot{V}CO_2$ were significantly higher during treadmill vs. cycle exercise at T_{vent} and at submaximal work rates above T_{vent}. Under these circumstances, neither $\dot{V}_E/\dot{V}CO_2$ nor $P_{ET}CO_2$ was significantly different at any submaximal work rate across modalities; that is, ventilatory efficiency is similar during treadmill vs. cycle exercise testing when the protocols are carefully matched for increments in work rate.

In keeping with the results of Kalsas and Thorsen [37] and Elliot and Grace [58], the greater $\dot{V}_E$ observed during treadmill vs. cycle exercise at T_{vent} and at submaximal work rates above T_{vent} was the result of a greater f_R at the same V_T. As such, f_R was higher, while V_T was lower at standardized levels of $\dot{V}_E$ throughout much of treadmill vs. cycle exercise. Despite significant differences in the $\dot{V}_E$-work rate relationship during treadmill vs. cycle ergometry, exercise mode had no effect on the relationship between IC and each of work rate and $\dot{V}_E$. Under these circumstances, adoption of a more rapid and shallow breathing pattern during incremental treadmill vs. cycle exercise likely helped to ensure that the IRV-work rate relationship was preserved between modalities.

Our study is the first to examine the effects of exercise mode on detailed assessments of neural respiratory drive and contractile respiratory muscle effort (pressure) requirements in health. The increased demand for $\dot{V}_E$ during treadmill vs. cycle exercise at submaximal work rates above T_{vent} was supported by increased inspiratory and expiratory muscle pressure development. Despite significant differences in $\dot{V}_E$ and respiratory muscle pressures between modalities, mean values of

EMGdi,rms%max were not significantly different at any standardized submaximal work rate during treadmill vs. cycle exercise. By adopting a more rapid and shallow breathing pattern, our participants maintained a larger IRV (by ~200-300 mL) for any given $\dot{V}_E$ throughout the majority of treadmill vs. cycle exercise. We speculate that maintenance of a larger IRV was associated with less elastic loading and functional weakening of the inspiratory pump muscles (e.g., diaphragm) for any given $\dot{V}_E$ during treadmill testing. We further speculate that, for these reasons, exercise mode had no significant effect on EMGdi,rms%max-work rate relationships.

Mean values of $\dot{V}_E$, V_T, f_R, IC, IRV, Pes,tidal, Pdi,tidal and Pga,peak were not significantly different at the symptom-limited peak of incremental treadmill vs. cycle exercise testing, even though $\dot{V}O_2$ (by 12%, $p<0.05$), $\dot{V}CO_2$ (by 8%, $p<0.05$) and EMGdi,rms%max (by 15%, $p=0.120$) were higher in the former. These findings corroborate those of Clark et al. [78], Johnson et al. [79] and McClaren et al. [80] who found that, on average, increased chemostimulation *via* hypercapnia did not elicit further increases in $\dot{V}_E$ and/or peak inspiratory and expiratory esophageal pressures during treadmill and cycle exercise testing near the limits of tolerance in young, endurance trained men with mean maximal $\dot{V}O_2$ values ranging from 63-73 ml/kg/min. Collectively, these findings further support the existence of critical dynamic mechanical constraints on ventilation during treadmill and cycle exercise near the limits of tolerance in healthy, young, fit men with normal baseline pulmonary function.

A study of 20 healthy young adults by Sharma et al. [62] recently reported that 1) intensity ratings of leg fatigue and dyspnea were not significantly different during treadmill vs. cycle exercise at any standardized submaximal $\dot{V}O_2$ ranging from 1.0 to 2.5 L/min; and 2) exercise mode had no effect dyspnea intensity-$\dot{V}_E$ relationships.

In our study, intensity ratings of leg discomfort were similar between modalities up to 175 watts, but became significantly greater at iso-work and at the peak of cycle vs. treadmill exercise. Moreover, the relative contribution of intolerable leg discomfort to exercise cessation was higher at the peak of treadmill vs. cycle testing. It follows that a higher percentage of our participants also stopped cycle compared to treadmill exercise because of intolerable leg discomfort. We speculate that these differences likely reflect the sensory consequences associated with relatively greater electrical (neural) activation of the lower limbs needed to produce equivalent external work rates near the limits of tolerance during cycle vs. treadmill testing. In fact, Bijker et al. [51] found that the magnitude of the increase in the EMG of both the vastus lateralis and biceps femoris needed to support any given increase in external power output was much greater during cycling compared to running in a group of 11 healthy young adults

In contrast to Sharma et al. [62], we observed a marked rightward shift of the leg discomfort-$\dot{V}O_2$ relationship during treadmill vs. cycle ergometry; that is, intensity ratings of perceived leg discomfort were much lower at any standardized $\dot{V}O_2$ during treadmill vs. cycle testing (e.g., by ~3 Borg 0-10 scale units at a $\dot{V}O_2$ of 50 ml/kg/min (Fig. 2.4)). These differences may reflect 1) the development of a more severe metabolic acidosis for any given $\dot{V}O_2$ during cycle ergometry [34, 50] and/or 2) progressively greater activation of the upper body and trunk muscles that do not contribute to the production of external mechanical power (and, by extension, the perception of leg discomfort), but nevertheless cost metabolic energy during treadmill running.

Despite the aforementioned differences in $\dot{V}_E$ and respiratory muscle pressure responses between the two modalities, Borg 0-10 scale intensity (and unpleasantness) ratings of dyspnea were identical at standardized submaximal work rates and at peak exercise during treadmill vs. cycle testing. Consequently, and in contrast to the results of Sharma et al. [62], dyspnea intensity (and unpleasantness)-$\dot{V}_E$ relationships were shifted to the right throughout the majority incremental treadmill vs. cycle exercise testing. Accumulating evidence suggests that neural respiratory drive (and *'central corollary discharge'*) is the proximate source of dyspnea during exercise in health [74, 75, 81] and in patients with COPD [63, 82, 83]. It follows that preservation of the EMGdi,rms%max-work rate relationship during incremental treadmill vs. cycle exercise testing in our study was primarily responsible for preservation of the dyspnea intensity (and unpleasantness)-work rate relationship, despite significant differences in $\dot{V}_E$ and contractile respiratory muscle effort (pressure) requirements. Indeed, exercise mode had no effect on dyspnea intensity (and unpleasantness)-EMGdi,rms%max relationships, except perhaps at the limits of tolerance.

It is possible that the observed rightward shift of the dyspnea intensity (and unpleasantness)-$\dot{V}_E$ relationship during treadmill vs. cycle exercise may also reflect, at least in part, temporal desensitization to the sensory consequences of increased $\dot{V}_E$ and contractile respiratory muscle effort requirements during a form of exercise (walking/running) that was familiar to and/or preferred by our participants. This hypothesis is bolstered by the results of Schneider et al. [84] and Brummer et al. [85] who found that familiar and/or preferred exercise modes (e.g., treadmill running) are associated with decreased neuronal activity (deactivation) in the frontal cortex of healthy recreational runners, where increased neural activation of the prefrontal cortex has been mechanistically linked to the perception of activity-related dyspnea in healthy adults and in patients with COPD [86].

2.5.1 Methodological considerations. Our treadmill protocol employed a linear increase in grade and a curvilinear increase in speed, which is in contrast to previous studies that utilized a linear increase in speed and a curvilinear increase in grade [9, 15, 63]. Despite these differences, all studies reported, first, a linear relationship between increasing $\dot{V}O_2$ and increasing work rate during treadmill testing and, second, that the $\dot{V}O_2$-work rate slope was higher during incremental treadmill vs. cycle exercise.

Our participants were healthy, young, non-obese men with normal-to-above normal levels of cardiorespiratory fitness. As such, our results may not be generalizable to elderly men and women; overweight/obese men and women; physically inactive/deconditioned men and women with abnormally low levels of cardiorespiratory fitness; and/or patients with chronic cardiorespiratory and/or neuromuscular disease.

Training specificity may influence comparisons of the physiological response to treadmill vs. cycle exercise testing [39]. For example, Verstappen et al. [39] found that maximal $\dot{V}O_2$ values were 14% higher during treadmill vs. cycle ergometry in runners, but not significantly different between modalities in cyclists. Although detailed assessments of training history were not recorded in our study, all of our participants were habitually/recreationally active and none were known to be training for participation in any competitive athletic events and/or involved in bicycling as a sport and/or common form of recreation. Indeed, all 15 participants achieved a higher symptom-limited peak

$\dot{V}O_2$ during treadmill vs. cycle testing (Range: 0.07 – 13.43 ml/kg/min). Nevertheless, we cannot rule out the possibility that unmeasured differences in our participants' training histories may have influenced our results.

In our study, stride frequency during treadmill testing and pedal cadence during cycle testing were not matched within- or between-subjects. Thus, we cannot rule out the possibility that maintenance of a relatively higher stride frequency vs. pedal cadence was at least partly responsible for the observed differences in f_R-work rate relationships during incremental treadmill vs. cycle exercise [59].

2.5.2 Summary and implications. In conclusion: 1) cardiometabolic (e.g., $\dot{V}O_2$, $\dot{V}CO_2$, HR, O_2 pulse) and ventilatory (e.g., $\dot{V}_E$, f_R, Pes,tidal, Pdi,tidal, Pga,peak) responses were consistently higher at standardized submaximal work rates during incremental treadmill vs. cycle exercise; 2) with few exceptions, detailed assessments of ventilatory efficiency, operating lung volumes, neural respiratory drive, dyspnea and leg discomfort were not significantly different at any submaximal work rate during treadmill vs. cycle ergometry; and 3) dynamic mechanical constraints on ventilation were evident at the limits of tolerance, particularly during treadmill exercise. In light of our results, physiological parameters relevant to the prescription of exercise, specifically peak $\dot{V}O_2$, peak HR and $\dot{V}O_2$ at T_{vent}, should be assessed in each exercise mode for optimal (i.e., mode-specific) training intensity determination. Alternatively, the lack of effect of exercise mode on peak work rate in our study, advocates for the use of this readily available parameter to determine optimal training intensity, regardless of exercise training mode.

Chapter 3: Concluding Remarks

The general aim of this M.Sc. thesis was to identify, for the first time in healthy adults, fundamental differences and similarities in detailed physiological and perceptual responses at maximal and, most importantly, standardized submaximal work rates during symptom-limited incremental cardiopulmonary exercise testing performed on a treadmill and cycle ergometer. In contrast to earlier studies on the influence of modality on exercise physiological and perceptual responses, our study uniquely employed matched incremental treadmill and cycle exercise testing protocols, which yielded ostensibly identical external work rate profiles.

Our findings confirmed that $\dot{V}O_2$ is significantly higher at T_{vent} and at the symptom-limited peak of treadmill compared to cycle exercise testing, even though work rate was not significantly different at either measurement time. Our study is the first to show that, despite significant differences in $\dot{V}O_2$, $\dot{V}CO_2$, RER, HR, O_2 pulse, $\dot{V}_E$, f_R, Pes,tidal, Pdi,tidal and Pga,peak, detailed assessments of ventilatory efficiency and gas exchange ($\dot{V}_E/\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$, $P_{ET}O_2$, $P_{ET}CO_2$), dynamic operating lung volumes (IC, IRV), neural respiratory drive (EMGdi,rms%max), and exertional symptoms (dyspnea, leg discomfort) were similar at all or most submaximal work rates during incremental treadmill vs. cycle exercise testing. To gain further (mechanistic) insights into the remarkable preservation of ventilatory/gas exchange efficiency, operating lung volumes, EMGdi,rms%max and exertional symptoms, future studies, employing the same matched incremental treadmill and cycle work rate protocols, should incorporate detailed and serial assessments of arterial blood gas and acid-base status; cardiac output, stroke volume and total vascular conductance; leg (e.g., vastus lateralis, biceps femoris, calf, quadriceps) muscle blood flow and vascular conductance; and leg, respiratory (e.g., rectus abdominis, internal/external intercostals, sternocleidomastoid) and upper body/trunk (e.g., deltoid, latissimus dorsi, pectorals major/minor) muscle activity patterns by electromyography.

An interesting and novel observation was that $\dot{V}_E$, V_T, f_R, IC, IRV, Pes,tidal, Pdi,tidal and Pga,peak were not significantly different at the symptom-limited peak of treadmill vs. cycle ergometry, even though $\dot{V}O_2$, $\dot{V}CO_2$ and EMGdi,rms%max were 8-15% higher in the former. Although far from definitive, these findings point to the existence of critical dynamic mechanical constraints on exercise hyperpnea near the limits of tolerance in healthy, young and recreationally active (but not endurance trained) men. Confirmation of this possibility would require that future studies examine the influence of increased chemostimulation *via* hypercapnia (e.g., dead space loading, 3-5% inspired CO_2) on $\dot{V}_E$, breathing pattern, operating lung volumes, respiratory pressures and EMGdi,rms%max. If, under these circumstances, chemostimulation significantly increased EMGdi,rms%max at peak exercise, but nevertheless had no effect on simultaneous measures of $\dot{V}_E$, breathing pattern, operating lung volumes and respiratory pressures, it would have to be concluded that dynamic mechanical constraints on exercise hyperpnea exist at the limits of tolerance, even in healthy, young, recreationally active adults.

We believe that our study, by providing a first description of the influence of exercise modality on physiologically- and clinically-relevant outcome parameters in health, may have important immediate and future implications for the ability of researchers and health care professionals to: 1) better interpret cardiopulmonary exercise test results, particularly as they relate to identifying the nature and source(s) of an individual's functional impairment, disability and/or handicap; 2) make more meaningful exercise prescriptions that are modality-specific and, by extension, most likely to help improve important physiological, clinical and patient-reported outcomes; 3) better interpret and monitor the effects of therapeutic interventions (e.g., pharmacological, surgical, lifestyle) on cardiorespiratory fitness and its physiological and perceptual determinants; 4) more accurately assess/determine whether occupational demands may be safely met; and 5) better evaluate an individual's pre-operative risk for major surgery.

In terms of exercise prescription, our findings suggest that physiological parameters traditionally used to prescribe exercise, namely peak $\dot{V}O_2$, peak HR and $\dot{V}O_2$ at T_{vent}, should be assessed in each exercise mode for optimal (mode-specific) training intensity determination. Alternatively, the lack of effect of exercise mode on peak work rate in our study, advocates for the use of this readily available parameter to determine optimal training intensity, regardless of exercise training mode.

With respect to evaluating an individuals' occupational readiness, our finding of a higher peak $\dot{V}O_2$ on treadmill vs. cycle exercise testing may lead to the identification of occupational tasks with higher metabolic equivalents and that may be unsafe for some adults. By contrast, our finding of a lower peak $\dot{V}O_2$ on cycle vs. treadmill exercise testing may lead to the identification of occupational tasks with metabolic equivalents deemed as "safe" but below the physical requirements of a particular position of employment. These misevaluations may be particularly costly, to both the employee and employer, for occupations with relatively high physical demands, e.g., military personnel, fire fighters, and police officers.

Finally, cardiopulmonary exercise testing-derived measures of peak $\dot{V}O_2$ are widely use to evaluate pre-operative risk for major surgery, with values <14 ml/kg/min being widely considered as indicative of high-risk [65]. In our study, peak $\dot{V}O_2$ was 6.5 ml/kg/min (or 12%) higher when testing was performed on the treadmill vs. cycle ergometer. Furthermore, all 15 of our participants achieved a higher symptom limited peak $\dot{V}O_2$ during treadmill vs. cycle testing (range: 0.07 – 13.43 ml/kg/min). It follows that, in a given surgical candidate, peak $\dot{V}O_2$ measured pre-operatively on a cycle ergometer may indicate "high-risk" (with an attendant delay in or cancellation of surgery), while peak $\dot{V}O_2$ measured pre-operatively on a treadmill may indicate "low/moderate risk" followed by surgical intervention.

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