Normative Cardiopulmonary Exercise Test Responses at the Ventilatory Threshold in Canadian Adults 40 to 80 Years of Age

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BACKGROUND: Physiologic and symptom responses at the ventilatory threshold (Tvent) during incremental cardiopulmonary exercise testing (CPET) can provide important prognostic information.

RESEARCH QUESTION: This study aimed to develop an updated normative reference set for physiologic and symptom responses at Tvent during cycle CPET (primary aim) and to evaluate previously recommended reference equations from a 1985 study for predicting Tvent responses (secondary aim).

STUDY DESIGN AND METHODS: Participants were adults 40 to 80 years of age who were free of clinically relevant disease from the Canadian Cohort Obstructive Lung Disease. Rate of oxygen consumption ($\dot{V}O_2$) at Tvent was identified by two independent raters; physiologic and symptom responses corresponding to $\dot{V}O_2$ at Tvent were identified by linear interpolation. Reference ranges (5th-95th percentiles) for responses at Tvent were calculated according to participant sex and age for 29 and eight variables, respectively. Prediction models were developed for nine variables (oxygen pulse, $\dot{V}O_2$, rate of CO_2 production, minute ventilation, tidal volume, inspiratory capacity, end-inspiratory lung volume [in liters and as percentage of total lung capacity], and end-expiratory lung volume) using quantile regression, estimating the 5th (lower limit of normal), 50th (normal), and 95th (upper limit of normal) percentiles based on readily available participant characteristics. The two one-sided test of equivalence for paired samples evaluated the measured and 1985-predicted $\dot{V}O_2$ at Tvent for equivalence.

RESULTS: Reference ranges and equations were developed based on 96 participants (49% men) with a mean $\pm$ SD age of 63 $\pm$ 9 years. Mean $\dot{V}O_2$ at Tvent was 50% of measured $\dot{V}O_2$ peak; the normal range was 33% to 66%. The 1985 reference equations overpredicted $\dot{V}O_2$ at Tvent: mean difference in men, −0.17 L/min (95% CI, −0.25 to −0.09 L/min); mean difference in women, −0.19 L/min (95% CI, −0.27 to −0.12 L/min).

INTERPRETATION: A contemporary reference set of CPET responses at Tvent from Canadian adults 40 to 80 years of age is presented that differs from the previously recommended and often used reference set from 1985.

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KEY WORDS: anaerobic threshold; cardiopulmonary exercise testing; CPET; exercise responses; normal values; reference set; ventilatory threshold

ABBREVIATIONS: CanCOLD = Canadian Cohort Obstructive Lung Disease; CPET = cardiopulmonary exercise testing; FRIEND = Fitness Registry and the Importance of Exercise; IC = inspiratory capacity; LLN = lower limit of normal; SHIP = Study of Health in Pomerania; Tvent = ventilatory threshold; ULN = upper limit of normal; $\dot{V}CO_2$ = rate of carbon dioxide production; $\dot{V}O_2$ = rate of oxygen consumption; V_T = tidal volume

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Cardiopulmonary exercise testing (CPET) is unique in its ability to identify pathophysiologic mechanisms underlying exercise intolerance and exertional symptoms noninvasively.[1] Importantly, CPET permits evaluation of both submaximal and maximal physiologic and symptom responses to exercise, both relevant in diagnostic and prognostic evaluation.[1,2] Compared with peak CPET responses (eg, peak rate of oxygen consumption [$\dot{V}O_2$]), submaximal physiologic and symptom responses are not dependent on participant effort or motivation, nor are they susceptible to underestimation because of premature termination of exercise by the supervisor (eg, because of cardiac-related events). Therefore, evaluation of submaximal physiologic and symptom responses to CPET become particularly important in the individual who is unable or unwilling to provide maximal effort and to achieve a peak CPET response.

The ventilatory threshold (Tvent) is a submaximal metabolic inflection point during exercise that has shown particular importance for clinical decision-making and health-related outcomes.[1,2] For example, a low $\dot{V}O_2$ at Tvent is a strong independent predictor of mortality in people with chronic heart failure,[3,4] after surgery,[5,6] and after organ transplantation.[7,8] A low Tvent has been defined as a $\dot{V}O_2$ of less than a critical threshold (eg, < 11 mL/kg/min),[3] less than a certain percentage of the predicted normal $\dot{V}O_2$ peak (eg, < 40%), or both.[1,9] Although absolute thresholds are important in specific contexts, such as surgery recovery, clinical CPET guidelines define a normal Tvent to be a $\dot{V}O_2$ that is 50% to 60% of the predicted normal $\dot{V}O_2$ peak, with a value of < 40% indicating potential underlying pathophysiologic features.[1] However, these normative reference ranges were based on studies from more than three decades ago.[9,10] We recently demonstrated that these historical reference sets by Hansen et al[9] in 1984 and Jones et al[10] in 1985 overpredicted peak cardiac CPET responses (oxygen pulse, heart rate) in a contemporary population-based sample of Canadian adults[11] and likely are no longer applicable to today's population, who generally are less fit and active than adults from the 1980s.[12,13]

The primary aim of this study was to develop a contemporary normative reference set (including normative reference ranges [5th-95th percentiles] and prediction models based on readily available participant characteristics) for physiologic and symptom responses at Tvent during incremental cycle CPET in Canadian adults 40 to 80 years of age. In addition to providing a reference set for $\dot{V}O_2$ at Tvent, we aimed to provide a comprehensive reference set for cardiac, ventilatory, operating lung volume, gas exchange, and symptom responses at Tvent, where several of these parameters also have demonstrated importance for predicting health outcomes.[6] Our secondary aim was to compare the $\dot{V}O_2$ at Tvent measured in contemporary Canadian adults with the $\dot{V}O_2$ at Tvent predicted using reference equations published by Jones et al[10] more than 30 years ago.

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Methods

This study was a secondary analysis of data from the Canadian Cohort Obstructive Lung Disease (CanCOLD) study, a prospective, random-sampled, population-based study conducted across nine sites in

Canada (ClinicalTrials.gov Identifier: NCT00920348).[14] Participants were noninstitutionalized male and female adults 40 years of age or older identified with random telephone digit dialing. All participants provided written informed consent before completing study assessments. The research ethics board for each participating institution approved the study protocol.

Participants

For the current study, 1,367 participants who completed a CPET with a Vmax (SensorMedics) CPET system at the initial CanCOLD cross-sectional assessment phase (visit 1) were considered for inclusion. Breath-by-breath (raw) CPET data collected at visit 1 using other CPET systems in Montréal (Ergocard, Medisoft [n = 26]), Toronto (Ergocard, Medisoft [n = 5]), and Calgary (TrueOne, Parvo Medics [n = 15]) were inaccessible and unavailable for analyses; therefore, these participants (n = 46) were excluded from the current study (e-Table 1 presents participant characteristics and peak $\dot{V}O_2$ responses compared with the final sample). Specific details on further participant eligibility criteria are outlined in e-Appendix 1. Briefly, participants were excluded if they: (1) had a cigarette smoking history of > 5 pack-years; (2) self-reported cardiovascular, pulmonary, or metabolic disease; (3) showed abnormal pulmonary function at rest[15-17]; (4) did not achieve a symptom or physiologic limitation to CPET; or (5) showed an abnormal CPET response determined by the supervising physician. Participants older than 80 years were also excluded because few (n = 4) participants older than 80 years met the abovementioned eligibility criteria.

Measures

Body mass and height were measured and postbronchodilator spirometry, diffusing capacity of the lungs for carbon monoxide, and body plethysmography were performed according to current standards.[18] Sociodemographic and health characteristic information (eg, smoking history, self-reported health conditions) were obtained during a structured interview with a trained researcher. Self-reported physical activity levels were obtained via questionnaire.[19]

CPET

CPET was performed in accordance with recommended guidelines[1,20] on an electronically braked cycle ergometer using a computerized CPET system (Vmax, SensorMedics). The CPET protocol was standardized across sites, consisting of a steady-state rest period of 3 to 10 min, 1 min of unloaded pedaling, and then stepwise increases in power output of 10 W/min, starting at 10 W, until symptom limitation.

Gas exchange and breathing pattern responses were collected breath-by-breath while participants breathed through a mouthpiece with a low-resistance flow transducer wearing a nose clip. Heart rate was assessed with a 12-lead ECG and peripheral oxygen saturation via a pulse oximeter. During the steady-state rest period, every 2 min throughout exercise, and at end exercise, maximal inspiratory capacity (IC) maneuvers were performed, BP was assessed, and participants rated the intensity of their breathing discomfort (breathlessness) and leg discomfort using the 0-10 modified Borg scale.[21] Physiologic variables were averaged in 30-s epochs and linked with contemporaneous symptom intensity ratings and IC-derived variables (e-Appendix 1).

Tvent Identification and Analysis of Exercise Responses

The $\dot{V}O_2$ at Tvent was identified by two independent raters (O. E., F. N.) using the V-Slope[22-26] and Dual Criterion[27] methods, as recommended by CPET guidelines[1] and described in detail in e-Appendix 1. Interrater acceptability criteria were defined a priori as ≤ 10% or a ≤ 0.15-L/min difference between the two $\dot{V}O_2$ values at Tvent. If interrater criteria were met, the average of the two $\dot{V}O_2$ values was taken as the final $\dot{V}O_2$ at Tvent. If interrater criteria were not met, a third blinded rater (D. J.) evaluated Tvent, and the two closest $\dot{V}O_2$ values meeting interrater criteria were averaged and taken as the final $\dot{V}O_2$ at Tvent. In the case where the interrater criteria were still not met after evaluation by the third reviewer, the Tvent was considered indeterminant. When the final $\dot{V}O_2$ at Tvent was identified, other physiologic and symptom responses corresponding to this level of $\dot{V}O_2$ were estimated via linear interpolation using the closest available data points (ie, the 30-s averaged $\dot{V}O_2$ values recorded immediately before and after the newly identified Tvent and the physiologic and symptom variables recorded at these same time points).

Statistical Analysis

Participant baseline demographic and health characteristics were summarized. The absolute (L/min) and relative (percentage) difference between $\dot{V}O_2$ at Tvent identified by the two raters was evaluated for each participant, with mean ± SD and range of differences reported. To assess the level of agreement between the two raters for $\dot{V}O_2$ (L/min) at Tvent, the intraclass correlation coefficient and 95% CI were calculated based on a mean-rating (raters, $k = 2$), absolute-agreement, 2-way mixed-effects model.[28] The two-way mixed-effects model was used because each participant's Tvent was assessed by the same set of raters (two-way), with these raters being the only raters of interest (mixed-effects). To define normative reference ranges for physiologic and symptom responses at Tvent, the mean ± SD and 5th (lower limit of normal [LLN]) and 95th percentiles (upper limit of normal [ULN]) were estimated overall and by participant sex. For CPET variables demonstrating significant ($P < .05$) bivariate associations with age, the 5th to 95th percentiles also were estimated in age groups of 40 to 55 years, 56 to 69 years, and 70 to 80 years, providing additional aged-based normative reference ranges. To develop prediction models, correlation matrices and scatterplots were generated to assess strength and shape of crude associations between readily available participant characteristics of sex, age, height, and body mass and CPET responses at Tvent (e-Fig 1); generalized linear models estimated crude bivariate relationships. Explanatory variables were included in the prediction model if (1) crude bivariate associations were significant ($P < .05$) or, (2) if not significant, inclusion in the model improved model fit indicated by an increase in the adjusted R^2 value. Interactions between explanatory variables also were explored using product terms and were included in the final models when significant ($P < .05$). Prediction models were presented for a given CPET variable based on the overall adjusted R^2 value (≥ 0.30), the authors' consideration of the residual SE clinical significance, or both. The final multivariate prediction models were developed using quantile regression. Quantile regression enables prediction of the median response (50th percentile) in addition to other specific quantiles (percentiles), of which we predicted the 5th percentile (LLN) and the 95th percentile (ULN).

The two one-sided test of equivalence for paired-samples evaluated statistical equivalence between the $\dot{V}O_2$ measured at Tvent in the CanCOLD study participants and the $\dot{V}O_2$ predicted at Tvent using reference equations from Jones et al.[10] Upper and lower equivalence bounds were set as raw scores for $\dot{V}O_2$, predefined as ± 0.674 SD. A Z score of ± 0.674 represents a change in $\dot{V}O_2$ from the 50th to the 25th (−0.674 SD) or 75th (+0.674 SD) percentile in a normal distribution. Data are reported as mean ± SD unless otherwise indicated. Significance was considered at $\alpha < 0.05$. Analyses were performed in R version 3.6.0 software (R Foundation for Statistical Computing).

Results

Of the 1,367 participants who completed CPET as part of the initial cross-sectional assessment phase of CanCOLD study, 109 were eligible for inclusion in the current study. Thirteen participants were excluded because the $\dot{V}O_2$ at Tvent was indeterminate (Fig 1). Therefore, the final sample included 96 participants, 47 (49%) men and 49 (51%) women, with a mean age of 63 ± 9 years (Table 1). Most participants were between 60 and 70 years of age (men, n = 19 [40%]; women, n = 22 [45%]) (e-Fig 2).

Participants included in the current study were comparable with Canadian adults 40 years of age or older (2017 and 2018 Statistics Canada data) for standing height (mean CanCOLD: 174.2 cm [men], 161.8 cm [women]; mean Canadian population: 174.4 cm [men], 161.2 cm [women][29]) and physical activity levels (mean CanCOLD: 3.1 h/wk [men], 2.3 h/wk [women]; mean Canadian population: 2.7 h/wk [men], 2.5 h/wk [women][30]), but had a slightly lower body mass (mean CanCOLD: 83.5 kg [men], 69.3 kg [women]; mean Canadian population: 86.5 kg [men], 73.7 kg [women][29]).

The mean ± SD and range of $\dot{V}O_2$ values at Tvent identified by the two raters, as well as the mean absolute and relative differences between rater 1 and rater 2, is presented in e-Table 2. High agreement was found between the two raters (intraclass correlation coefficient, 0.99; 95% CI, 0.98-0.99; $P < .001$).

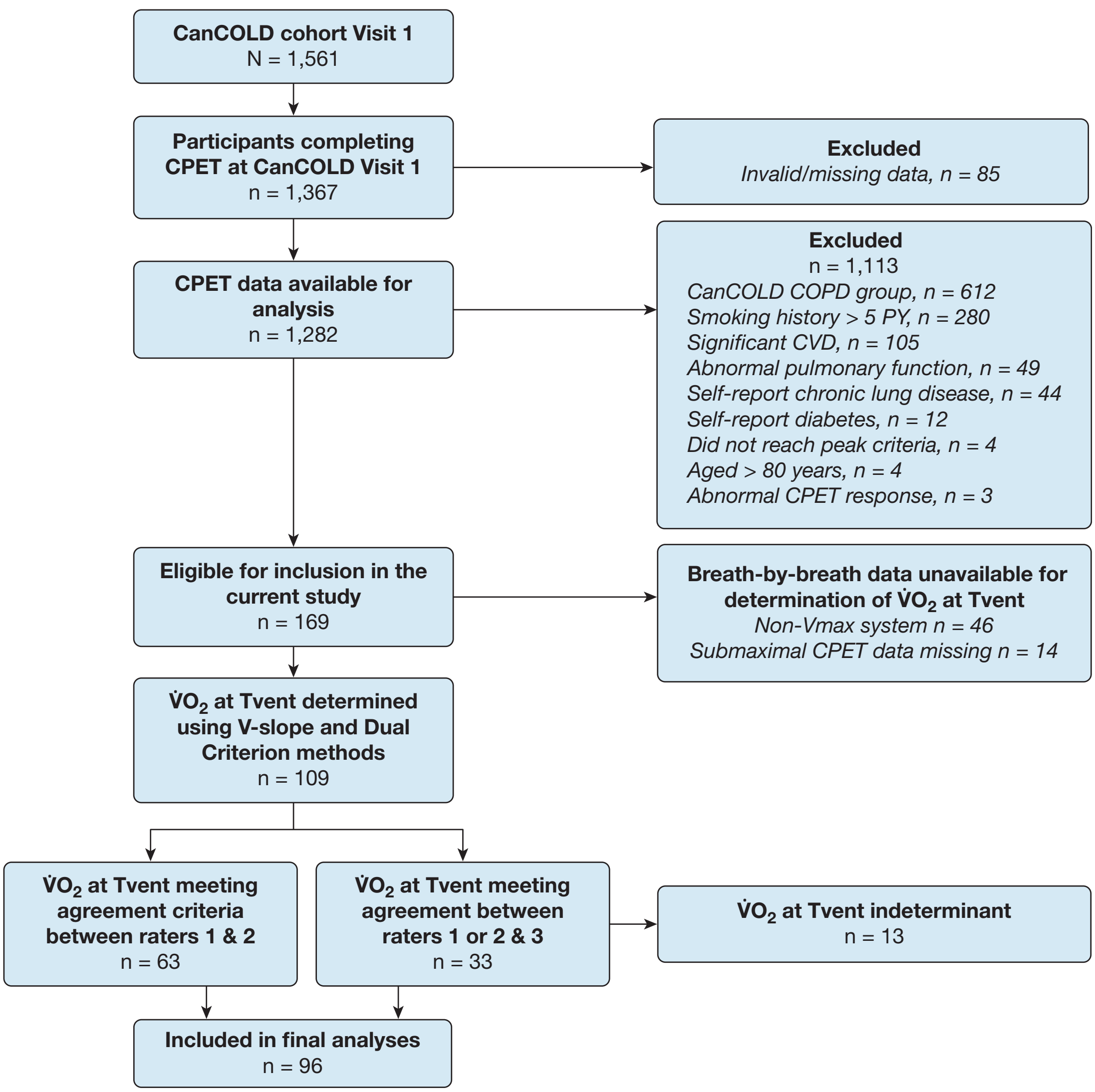

Figure 1 – *Participant flow diagram. CanCOLD = Canadian Cohort Obstructive Lung Disease study; CPET = cardiopulmonary exercise test; CVD = cardiovascular disease; PY = pack-years; Tvent = ventilatory threshold;* $\dot{V}O_2$ *= rate of oxygen consumption.*

TABLE 1] Participant Sociodemographic and Health Characteristics

Participant Characteristic	Total Sample (N = 96)	Men (n = 47)	Women (n = 49)
Age, y	63 ± 9	63 ± 9	63 ± 9
Range	42-79	47-79	42-78
Height, cm	167.9 ± 9.0	174.2 ± 7.5	161.8 ± 5.4
Body mass, kg	76.3 ± 14.1	83.5 ± 12.5	69.3 ± 11.9
BMI, kg/m^2	27.0 ± 4.2	27.5 ± 3.8	26.5 ± 4.5
FEV_1, L	2.95 ± 0.71	3.39 ± 0.64	2.54 ± 0.44
FEV_1, % predicted	104 ± 14	102 ± 14	106 ± 14
FVC, L	3.80 ± 0.91	4.37 ± 0.84	3.26 ± 0.59
FVC, % predicted	104 ± 14	101 ± 13	107 ± 15
TLC, % predicted	102 ± 12	101 ± 12	102 ± 13
DLCO, % predicted	98 ± 18	99 ± 24	97 ± 12
Cigarette smoking, pack-y	0.6 ± 1.4	0.8 ± 1.7	0.5 ± 1.0
Cigarette smoking status			
Never	71 (74)	35 (74)	36 (73)
Former	25 (26)	12 (26)	13 (27)
MVPA, h/wk	2.7 ± 2.5	3.1 ± 2.8	2.3 ± 2.1

Data are presented as No. (%) or mean ± SD, unless otherwise indicated. DLCO = diffusing capacity of the lungs for carbon monoxide; MVPA = moderate to vigorous intensity physical activity assessed by self-report with the Community Healthy Activities Models Program for Seniors questionnaire[20]; TLC = total lung capacity.

The $\dot{V}O_2$ at Tvent was, on average, 48 ± 11% (LLN, 33%; ULN, 66%) of the measured $\dot{V}O_2$ peak and 51 ± 14% (LLN, 33%; ULN, 75%) of the predicted[11] normal $\dot{V}O_2$ peak. The complete set of normative reference ranges (mean ± SD and 5th and 95th percentiles) for cardiac, ventilatory, operating lung volume, gas exchange, and symptom variables at Tvent are presented in Table 2 by participant sex. For eight CPET variables demonstrating significant associations with age, normative reference ranges also are presented in the age groups of 40 to 55 years (men, n = 10; women, n = 9), 56 to 69 years (men, n = 25; women, n = 30), and 70 to 80 years (men, n = 12; women, n = 10) (Table 3). Prediction models to estimate the average (50th percentile), lower (5th percentile), and upper (95th percentile) limits of normal for nine CPET variables at Tvent : rate of carbon dioxide production ($\dot{V}CO_2$), oxygen pulse, minute ventilation ($\dot{V}_E$), tidal volume (V_T), IC, end-expiratory lung volume (in liters and as percentage of total lung capacity), and end-inspiratory lung volume (in liters)—based on participant sex, age, height, and body mass are presented in Table 4.

In the CanCOLD study participants, the Jones et al[10] reference equations overpredicted $\dot{V}O_2$ at Tvent, particularly for women (Fig 2, Table 5). Differences between the Jones et al[10] predicted $\dot{V}O_2$ at Tvent and the measured $\dot{V}O_2$ at Tvent both were statistically significant and outside the predefined acceptable equivalence bounds (ie, not statistically equivalent) (Fig 2, Table 5).

Discussion

This study developed a contemporary normative reference set for cardiac, ventilatory, operating lung volume, gas exchange, and symptom responses at Tvent during incremental cycle CPET in Canadian adults 40 to 80 years of age. Although normative reference sets for peak cycle CPET responses are more widely available,[31,32] including a recently published reference set for Canadian adults 40 years of age and older,[11] few normative reference sets have been published for physiologic and symptom responses at Tvent.[31,32]

It could be argued that the normal reference ranges for symptom (breathing and leg discomfort) responses at Tvent seem low (Table 2). However, previous studies in healthy volunteers 40 to 80 years of age have shown that, on average, intensity ratings of breathing discomfort do not increase beyond 1 to 2 on the 0-to-10 Borg scale until a $\dot{V}O_2$ corresponding to > 50% of the achieved $\dot{V}O_2$ peak, or just more than Tvent.[33] Breathing discomfort during exercise has been shown to correlate with inspiratory reserve volume and V_T (%IC), with intensity ratings

TABLE 2] Normative Reference Values and Ranges for Physiologic and Symptom Responses at the Tvent During Symptom-Limited Incremental CPET According to Participant Sex

	Total Sample (N = 96)		Men (n = 47)		Women (n = 49)	
CPET Parameter	Mean ± SD	LLN-ULN	Mean ± SD	LLN-ULN	Mean ± SD	LLN-ULN
$\dot{V}O_2$ at Tvent, L/min	0.95 ± 0.31	0.51-1.56	1.11 ± 0.28	0.75-1.60	0.80 ± 0.25	0.49-1.23
$\dot{V}O_2$ at Tvent, mL/kg/min	12.6 ± 3.9	7.7-18.3	13.7 ± 3.9	8.7-21.2	11.6 ± 3.6	6.6-16.3
$\dot{V}O_2$ at peak, L/min	2.01 ± 0.58	1.20-2.96	2.38 ± 0.51	1.63-3.40	1.66 ± 0.40	1.05-2.23
$\dot{V}O_2$ at peak, mL/kg/min	26.7 ± 7.2	17.0-42.7	28.8 ± 6.7	20.5-43.0	24.5 ± 7.2	16.0-37.5
$\dot{V}O_2$ at Tvent, %$\dot{V}O_2$ peak	48.3 ± 10.6	32.6-65.6	47.6 ± 9.5	31.6-63.0	49.0 ± 11.6	32.8-65.7
$\dot{V}O_2$ at Tvent, % predicted[a] $\dot{V}O_2$ peak	51.2 ± 13.5	32.9-75.4	48.5 ± 11.2	33.5-67.2	53.8 ± 15.1	33.1-82.0
$\dot{V}CO_2$, L/min	0.83 ± 0.31	0.41-1.39	0.98 ± 0.28	0.64-1.45	0.69 ± 0.27	0.35-1.14
RER	0.85 ± 0.10	0.69-1.02	0.86 ± 0.09	0.72-0.99	0.84 ± 0.11	0.68-1.03
Power output, W	51 ± 24	16-94	60 ± 23	29-97	42 ± 20	15-71
HR, beats/min	101 ± 16	77-123	100 ± 19	75-121	102 ± 13	84-123
Oxygen pulse, mL O_2/beat	9.5 ± 3.0	5.5-14.6	11.2 ± 2.9	7.5-14.8	7.8 ± 2.0	5.3-11.1
BP, mm Hg						
Systolic	147 ± 32	112-188	153 ± 32	117-188	142 ± 31	105-187
Diastolic	77 ± 14	62-95	77 ± 14	61-95	76 ± 14	65-93
$\dot{V}_E/\dot{V}CO_2$	30.2 ± 3.8	25.1-37.9	29.2 ± 2.7	25.4-33.9	31.2 ± 4.5	25.2-39.5
$\dot{V}_E/\dot{V}O_2$	25.8 ± 3.3	20.8-32.3	25.5 ± 3.0	21.4-31.6	26.2 ± 3.6	20.7-32.3
$P_{ET}CO_2$, mm Hg	40.6 ± 4.2	34.5-47.1	41.0 ± 4.4	35.1-47.5	40.2 ± 4.1	34.5-46.8
$P_{ET}O_2$, mm Hg	101.6 ± 7.7	90.6-111.4	100.8 ± 9.1	89.3-112.4	102.2 ± 6.0	93.4-111.0
SpO_2, %	97 ± 2	95-99	97 ± 3	94-99	98 ± 1	96-99
$\dot{V}_E$, L/min	24.4 ± 8.0	13.7-38.7	28.2 ± 7.3	18.7-40.7	20.8 ± 6.8	12.1-34.3
$\dot{V}_E$, % MVV	24 ± 8	14-36	25 ± 8	14-36	24 ± 8	14-37
V_T, L	1.22 ± 0.36	0.68-1.88	1.41 ± 0.31	0.98-2.02	1.04 ± 0.31	0.62-1.50
V_T, % IC	41.5 ± 9.7	25.8-61.0	43.0 ± 8.3	29.0-60.7	40.1 ± 11.2	25.0-60.6
Bf, breaths/min	20 ± 4	16-94	20 ± 4	15-27	21 ± 5	13-28
IC, L	2.98 ± 0.67	2.01-4.01	3.34 ± 0.66	2.10-4.17	2.63 ± 0.46	2.01-3.52
IRV, L	1.76 ± 0.56	0.90-2.66	1.93 ± 0.61	0.94-2.84	1.59 ± 0.45	0.89-2.36
EILV, L	4.20 ± 0.97	2.82-5.78	4.77 ± 0.93	3.21-6.53	3.69 ± 0.68	2.68-4.74
EELV, L	2.98 ± 0.80	1.86-4.42	3.35 ± 0.84	2.06-4.57	2.66 ± 0.61	1.78-3.73
EILV, % TLC	70 ± 7	58-82	70 ± 8	58-83	69 ± 6	61-81
EELV, % TLC	49 ± 7	38-62	49 ± 8	36-60	50 ± 6	39-62
Breathlessness, Borg 0-10	1 ± 1	0-3	1 ± 1	0-3	1 ± 1	0-3
Leg discomfort, Borg 0-10	1 ± 1	0-3	2 ± 1	0-4	1 ± 1	0-3

Bf = breathing frequency; CPET = cardiopulmonary exercise testing; EELV = end-expiratory lung volume; EILV = end-inspiratory lung volume; HR = heart rate; IC = inspiratory capacity; IRV = inspiratory reserve volume; LLN = lower limit of normal; MVV = maximum voluntary ventilation; $P_{ET}CO_2$ = end-tidal P_{CO_2}; $P_{ET}O_2$ = end-tidal P_{O_2}; RER = respiratory exchange ratio; SpO_2 = peripheral oxygen saturation; TLC = total lung capacity; Tvent = ventilatory threshold; ULN = upper limit of normal; $\dot{V}CO_2$ = rate of CO_2 production; $\dot{V}_E$ = minute ventilation; $\dot{V}_E/\dot{V}CO_2$ = ventilatory equivalent for CO_2; $\dot{V}_E/\dot{V}O_2$ = ventilatory equivalent for oxygen; $\dot{V}O_2$ = rate of oxygen consumption; V_T = tidal volume.
[a]Predicted using reference equations by Lewthwaite et al.[11]

increasing at and beyond previously defined critical thresholds (ie, inspiratory reserve volume ≤ 0.7 L; V_T [%IC] ≥ 73%).[34,35] In the CanCOLD participants, the inspiratory reserve volume and V_T (%IC) had not yet reached these critical thresholds at Tvent (Table 2).

Jones et al[10] and Hansen et al[9] were among the first to provide normative values for $\dot{V}O_2$ at Tvent during cycle CPET, which form the basis of current recommendations by clinical CPET guidelines.[1] In each of these studies, Tvent was identified using just the dual criterion method presumably by a single rater.[9,10]

TABLE 3] Age Based Normative Reference Ranges for Physiologic Responses at the Tvent During Symptom-Limited Incremental CPET in Men and Women

Variable	LLN (5th Percentile)			Average (50th Percentile)			ULN (95th Percentile)		
Age group, y	40-55	56-69	70-80	40-55	56-69	70-80	40-55	56-69	70-80
Men (n = 47)	...	...	...	n = 10	n = 25	n = 12	...	...	...
Power output, W	22	31	37	58	54	57	111	96	85
$\dot{V}_E/\dot{V}O_2$	20.6	21.9	22.6	24.3	25.1	27.6	25.9	29.5	32.8
$\dot{V}_E/\dot{V}CO_2$	25.0	25.4	27.3	28.6	28.9	30.0	32.0	33.2	34.5
$P_{ET}O_2$, mm Hg	88.9	94.0	97.1	99.6	99.0	106.0	104.8	109.2	119.4
$P_{ET}CO_2$, mm Hg	37.0	34.9	35.5	41.8	40.8	40.2	46.7	46.9	46.4
Bf, breaths/min	13	15	18	21	19	22	25	26	27
IC, L	2.84	2.50	2.01	3.80	3.56	2.92	4.15	4.18	3.90
IRV, L	1.35	1.05	0.75	2.48	2.14	1.60	2.86	2.80	2.39
Women (n = 49)	...	...	...	n = 9	n = 30	n = 10	...	...	...
Power output, W	11	16	15	50	42	31	65	75	62
$\dot{V}_E/\dot{V}O_2$	19.9	21.4	23.5	26.5	25.1	28.6	30.1	31.8	33.4
$\dot{V}_E/\dot{V}CO_2$	25.6	25.0	28.6	28.7	30.6	32.7	34.9	38.4	41.5
$P_{ET}O_2$, mm Hg	92.6	93.4	94.3	101.4	102.1	104.2	109.5	111.1	109.8
$P_{ET}CO_2$, mm Hg	37.4	34.9	31.8	41.5	39.8	37.7	47.9	46.6	41.5
Bf, breaths/min	13	12	18	19	20	23	24	29	26
IC, L	2.23	2.14	1.92	2.52	2.59	2.39	3.20	3.59	3.11
IRV, L	0.96	0.93	0.95	1.49	1.55	1.40	2.13	2.33	2.28

Bf = breathing frequency; CPET = cardiopulmonary exercise testing; IC = inspiratory capacity; IRV = inspiratory reserve volume; LLN = lower limit of normal; $P_{ET}CO_2$ = end-tidal P_{CO_2}; $P_{ET}O_2$ = end-tidal P_{O_2}; Tvent = ventilatory threshold; ULN = upper limit of normal; $\dot{V}_E/\dot{V}CO_2$ = ventilatory equivalent for CO_2; $\dot{V}_E/\dot{V}O_2$ = ventilatory equivalent for oxygen.

Normative reference values developed by Jones et al[10] were based on 50 men and 50 women 15 to 71 years of age sampled conveniently from the university and general population in Hamilton, Ontario, a younger age group than in this multicenter CanCOLD study. The average $\dot{V}O_2$ at Tvent for participants in the Jones et al[10] study was 1.64 ± 0.42 L/min (56 ± 12% measured peak $\dot{V}O_2$) in men and 1.23 ± 0.30 L/min (74 ± 14% measured peak $\dot{V}O_2$) in women. Hansen et al[9] included only men (n = 77) who were former shipyard workers 34 to 74 years of age. The $\dot{V}O_2$ at Tvent for participants in the Hansen et al[9] study was similar to male participants in the Jones et al[10] study: 56 ± 8% (range, 40%-78%) measured $\dot{V}O_2$ peak. These values for $\dot{V}O_2$ at Tvent are considerably higher than in the current study (men: 1.11 ± 0.28 L/min, 48 ± 10% measured $\dot{V}O_2$ peak; women: 0.80 ± 0.25 L/min, 49 ± 12% measured $\dot{V}O_2$ peak).

Since these early studies by Jones et al[10] and Hansen et al,[9] a number of publications have provided updated reference sets for normative responses at Tvent during cycle CPET. Perhaps the most comprehensive reference set, not including the current study, is that published in 1994 by Meyer et al.[36] This study provided normative reference ranges by participant age decade as the mean ± SD and 95% CI for power output, $\dot{V}O_2$, $\dot{V}CO_2$, respiratory exchange ratio, HR, oxygen pulse, $\dot{V}_E$, ventilatory equivalent for O_2, ventilatory equivalent for CO_2, end-tidal P_{O_2}, end-tidal P_{CO_2}, and dead space to V_T ratio.[36] However, these normative reference ranges were based on only male participants (n = 69) who were volunteer clinical staff at the testing site in Germany. No prediction models were provided for estimating CPET responses at Tvent based on readily available participant characteristics. Physiologic responses at Tvent reported by Meyer et al[36] were higher than male participants in the current study of comparable age (eg, average $\dot{V}O_2$ of Meyer et al[36] participants 40 to 49 and 50 to 59 years of age: 18.4 and 16.4 mL/kg/min, respectively vs 13.7 mL/kg/min, of male participants in the current study).

More recently, normative responses at Tvent from large cycle CPET databases have been published, including the Fitness Registry and the Importance of Exercise

TABLE 4] Reference Equations for Estimating the 5th, 50th, and 95th Percentiles for CPET Responses at the Tvent During Symptom-Limited Peak Incremental CPET in Canadian Adults 40 to 80 y of Age

Variable	Percentile	Prediction Model	RSE	Adjusted R^2
Oxygen pulse, mL/beat	5th	(−0.03533121 × A) + (0.09011971 × H) + (0.05225060 × BM) + (0.55640862 × S) − 10.98937749	2.29	
	50th	(0.005140994 × A) + (0.127872626 × H) + (0.067945521 × BM) + (0.971916363 × S) − 18.014483023	2.23	0.44
	95th	(−0.100909091 × A) + (0.072918660 × H) + (0.003899522 × BM) + (4.019066986 × S) + 5.697559809	2.55	
$\dot{V}O_2$, L/min	5th	(0.003400268 × A) + (0.001307452 × H) + (0.002167187 × BM) + (0.217925033 × S) − 0.108384650	0.26	
	50th	(−0.004884696 × A) + (0.005723270 × H) + (0.007316562 × BM) + (0.125324948 × S) − 0.330859539	0.24	0.36
	95th	(−0.016777814 × A) + (0.013341037 × H) + (0.005153516 × BM) + (0.094767250 × S) − 0.211875206	0.27	
$\dot{V}CO_2$, L/min	5th	(0.007850010 × A)—(0.000689250 × H) + (0.004826708 × BM) + (0.188562757 × S) − 0.356657529	0.28	
	50th	(−0.004115224 × A) + (0.004663891 × H) + (0.006672310 × BM) + (0.181162769 × S) − 0.302360774	0.26	0.27
	95th	(−0.014787252 × A) + (0.017253462 × H) + (0.008488236 × BM) + (0.014583681 × S) − 1.294810612	0.30	
$\dot{V}_E$, L/min	5th	(0.2623758 × A) + (0.2588337 × H) + (0.1332613 × BM) + (3.1646220 × S) − 55.8834557	6.7	
	50th	(−0.006474397 × A) + (0.152884049 × H) + (0.090700412 × BM) + (4.063095939 × S) − 10.601589170	6.6	0.30
	95th	(−0.03091813 × A) + (0.59708755 × H) + (0.32857397 × BM) − (1.09069437 × S) − 86.33411472	7.8	
V_T, L	5th	(0.005076481 × A) − (0.001306902 × H) + (0.002103524 × BM) + (0.349656143 × S) + 0.369177068	0.32	
	50th	(−0.006037296 × A) + (0.003076923 × H) + (0.002703963 × BM) + (0.285454545 × S) + 0.725920746	0.30	0.29
	95th	(−0.008875830 × A) + (0.003832397 × H) + (0.003362289 × BM) + (0.421486970 × S) + 1.244828820	0.31	
IC, L	5th	(−0.0228894428 × A) − (0.0006870968 × H) + (0.0022351906 × BM) − (2.0071149560 × S) + (0.0278563050 × BM × S) + 3.4489973607	0.52	
	50th	(−0.01409342 × A) + (0.01630130 × H) + (0.00536711 × BM) − (0.96017019 × S) + (0.01855641 × BM × S) + 0.39616067	0.47	0.49
	95th	(−0.018708633 × A) + (0.021608276 × H) + (0.000502157 × BM) − (0.130127032 × S) + (0.006159484 × BM × S) + 1.037483841	0.48	
EILV, L	5th	(0.006772217 × A) + (0.067003745 × H) − (0.020371127 × BM) + (0.084525026 × S) − 6.942032686	0.67	
	50th	(0.01523658 × A) + (0.09257164 × H) − (0.03361260 × BM) + (0.31317782 × S) − 9.84548408	0.62	0.59
	95th	(−0.001598174 × A) + (0.067899543 × H) − (0.037031963 × BM) + (0.520593607 × S) − 3.462739726	0.64	
EELV, L	5th	(0.005558408 × A) + (0.071604621 × H) − (0.018048780 × BM)—(0.210436457 × S) − 8.836469833	0.57	
	50th	(0.01302074 × A) + (0.07131571 × H) − (0.03290423 × BM) + (0.30861324 × S) − 7.40879795	0.53	0.55
	95th	(0.03236735 × A) + (0.06967347 × H) − (0.03081633 × BM) + (0.45330612 × S) − 7.61955102	0.56	
EELV, % TLC	5th	(0.10161365 × A) + (0.25263672 × H) + (0.03069661 × BM) + (47.47714565 × S) − (0.60105097 × BM × S) − 9.69830357	6.0	

(Continued)

TABLE 4] *(Continued)*

Variable	Percentile	Prediction Model	RSE	Adjusted R^2
	50th	$(0.1196350 \times A) + (0.3994345 \times H) - (0.1885312 \times BM) + (26.7201143 \times S) - (0.3433643 \times BM \times S) - 9.8796655$	5.7	0.39
	95th	$(0.3716889 \times A) + (0.7825651 \times H) - (0.2659657 \times BM) + (29.4583111 \times S) - (0.4273232 \times BM \times S) - 72.8113778$	6.1	

A = age (y); BM = body mass (kg); CPET = cardiopulmonary exercise testing; EELV = end-expiratory lung volume; EILV = end-inspiratory lung volume; H = height (cm); IC = inspiratory capacity; RSE = residual SE in the units of the given variable, where residual SE is the SD of the residuals; S = sex, where male = 1 and female = 0; TLC = total lung capacity; Tvent = ventilatory threshold; $\dot{V}CO_2$ = rate of CO_2 production; $\dot{V}_E$ = minute ventilation; $\dot{V}O_2$ = rate of oxygen consumption; V_T = tidal volume.

(FRIEND) in the United States[37] and the Study of Health in Pomerania (SHIP) in Germany.[38,39] The FRIEND study included 8,155 participants (81% men) 46 ± 12 years of age (range, 20-79 years),[37] whereas the SHIP study included 534 participants (47% men) 25 to 80 years of age, most of whom (88%) were younger than 65 years.[38] In both of these studies, as with the current study, normative reference ranges for $\dot{V}O_2$ at Tvent were presented as 5th to 95th percentiles by participant sex; however, only the SHIP study provided reference equations for estimating $\dot{V}O_2$ at Tvent based on readily available participant characteristics. We evaluated the SHIP reference equations[38,39] for predicting $\dot{V}O_2$ at Tvent in the CanCOLD study cohort (e-Fig 3). The SHIP equations[38,39] slightly overpredicted $\dot{V}O_2$ at Tvent in the CanCOLD study participants (measured − SHIP predicted mean difference, −0.10 L/min [95% CI, −0.65 to 0.44 L/min]). The SHIP study[38] also presented reference equations for estimating end-tidal P_{CO_2} and ventilatory equivalent for CO_2 at Tvent; however, no reference equations were provided for estimating other CPET variables.

Absolute values for $\dot{V}O_2$ at Tvent reported by FRIEND were comparable with those of the current study (mean range for participants 40 to 80 years of age: men, 15.3-11.8 mL/kg/min; women, 13.2-10.3 mL/kg/min).[37] However, the $\dot{V}O_2$ at Tvent expressed as a percentage of the measured $\dot{V}O_2$ peak was higher in FRIEND compared with the current study (FRIEND participants 40-80 years of age mean range: men, 57%-61%; women, 61%-67% vs current study mean: men, 48%; women, 49%). This also was true for the SHIP study (SHIP range of LLN [5th percentile] 52%-55% measured $\dot{V}O_2$ peak, with no participant achieving < 41%).[38] It is possible that these higher relative values are the result of FRIEND and SHIP participants achieving a lower measured $\dot{V}O_2$ peak, particularly for FRIEND participants who achieved a similar absolute $\dot{V}O_2$ at Tvent as the current study participants; however, no measured values for $\dot{V}O_2$ peak were reported in either the FRIEND or SHIP studies.[37,38]

Differences between studies for the expected normal physiologic responses at Tvent during incremental cycle

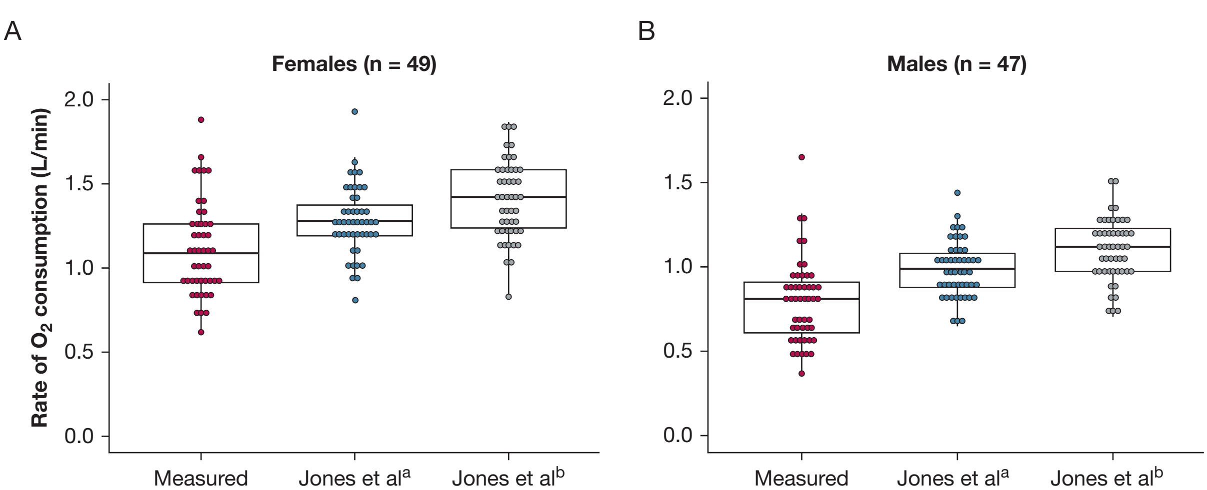

Figure 2 – *Graphs showing the rate of oxygen consumption during symptom-limited incremental cardiopulmonary cycle exercise testing at the ventilatory threshold measured in the Canadian Cohort Obstructive Lung Disease study participants and predicted using reference equations published by Jones et al[10] in 1985. Jones et al[a] reference equations are based on participant height and age, whereas Jones et al[b] reference equations additionally include participant body mass.*

TABLE 5] $\dot{V}O_2$ at the Tvent and at the Symptom-Limited Peak of Incremental CPET Measured in the Canadian Cohort Obstructive Lung Disease Study Participants and Predicted Using the Equations of Jones et al[10] (1985)

Variable	Measured	Jones et al[10] (1985) Mean ± SD	Measured–Jones Mean (95% CI)	Equivalence Margin	TOST-P 90% CI
Men					
$\dot{V}O_2$ at Tvent, L/min	1.11 ± 0.28	1.28 ± 0.20	−0.17 (−0.25 to −0.09)	± 0.19	−0.24 to −0.10
$\dot{V}O_2$ at peak, L/min	2.38 ± 0.51	2.37 ± 0.42	[a]	[a]	[a]
$\dot{V}O_2$ at Tvent, % peak	48 ± 10	54 ± 2	[a]	[a]	[a]
Women					
$\dot{V}O_2$ at Tvent, L/min	0.80 ± 0.25	0.99 ± 0.16	−0.19 (−0.27 to −0.12)	± 0.17	−0.25 to −0.13
$\dot{V}O_2$ at peak, L/min	1.66 ± 0.40	1.20 ± 0.36	[a]	[a]	[a]
$\dot{V}O_2$ at Tvent, % peak	49 ± 12	87 ± 15	[a]	[a]	[a]

CPET = cardiopulmonary exercise testing; TOPT-P = two one-sided test of equivalence for paired samples; Tvent = ventilatory threshold; $\dot{V}O_2$ = rate of oxygen consumption.
[a]No comparisons were made with peak data.

CPET may be the result of differences in sampling methods (convenience based[10,36] vs population based in the current study); participants in previous studies being (1) younger; (2) taller with lower body mass, ie, leaner; (3) more physically active than the contemporary CanCOLD sample, or a combination thereof; For example, participants in the Meyer et al[36] study were 20 to 59 years of age (vs 42-79 years of age in the current study), with an average (range in mean across age groups) standing height of 179 to 181 cm (vs mean ± SD in current study of 167.9 ± 9.0 cm) and a BMI of 23 to 26 kg/m^2 (vs mean ± SD in current study of 27.0 ± 4.2 mg/m^2).

Strengths and Limitations

An important strength of this study is development of prediction models that enable estimation of normative CPET responses at Tvent (beyond just $\dot{V}O_2$) for an individual patient, including individualized estimation of the LLN and ULN. Further, to the best of our knowledge, we provide, for the first time, a comprehensive set of normative reference ranges for multiple cardiac, ventilatory, operating lung volume, gas exchange, and symptom responses at Tvent. The $\dot{V}O_2$ at Tvent was identified by two independent raters using established and recommended methods, with a third independent rater to resolve discrepancies. Strict a priori criteria for interrater reliability also were defined. The CPET protocol was standardized across testing sites and aligned with clinical CPET guidelines.[1,2]

This study is not without its limitations. Although this study was limited by a relatively small sample size (n = 96) of Canadian adults 40 to 80 years of age, this group represents the most commonly tested population within clinical CPET laboratories for identification of exercise intolerance and problematic symptoms. The reference set may not be applicable to adults younger than 40 years or older than 80 years of age. All participant testing for this study was performed using a Vmax SensorMedics CPET system. Because of known differences among metabolic analysis systems, particularly regarding measurement of $\dot{V}O_2$,[40] it is not known whether the current reference set is applicable for use with other CPET systems; previous estimates of differences in $\dot{V}O_2$ at the peak of exercise between CPET systems have ranged from 10% to 17%[41] and at different submaximal time points during exercise from 6% to 22%.[42] The prediction models presented in this study need to be validated externally in a separate population-based random sample of participants with comparable sociodemographic characteristics and using similar CPET methodology.

Conclusions

This study presents an updated comprehensive normative reference set for physiologic and symptom responses at Tvent during incremental cycle CPET in Canadian adults 40 to 80 years of age. This updated reference set facilitates, in the clinical and research settings, comprehensive interpretation of integrative CPET responses at Tvent, particularly useful in people who are unable or unwilling to provide maximal effort and exercise until their symptom-limited peak.

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Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

References

1. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. 2003;167(2):211-277.
2. Radtke T, Crook S, Kaltsakas G, et al. ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. *Eur Respir Rev*. 2019;28(154):180101.
3. Gitt AK, Wasserman K, Kilkowski C, et al. Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. *Circulation*. 2002;106(24):3079-3084.
4. Carriere C, Corra U, Piepoli M, et al. Anaerobic threshold and respiratory compensation point identification during cardiopulmonary exercise tests in chronic heart failure. *Chest*. 2019;156(2):338-347.
5. Moran J, Wilson F, Guinan E, McCormick P, Hussey J, Moriarty J. Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. *Br J Anaesth*. 2016;116(2):177-191.
6. Colson M, Baglin J, Bolsin S, Grocott MP. Cardiopulmonary exercise testing predicts 5 yr survival after major surgery. *Br J Anaesth*. 2012;109(5):735-741.
7. Ney M, Haykowsky MJ, Vandermeer B, Shah A, Ow M, Tandon P. Systematic review: pre- and post-operative prognostic value of cardiopulmonary exercise testing in liver transplant candidates. *Aliment Pharmacol Ther*. 2016;44(8):796-806.
8. Epstein SK, Freeman RB, Khayat A, Unterborn JN, Pratt DS, Kaplan MM. Aerobic capacity is associated with 100-day outcome after hepatic transplantation. *Liver Transpl*. 2004;10(3):418-424.
9. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis*. 1984;129(2 Pt 2):S49-S55.
10. Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis*. 1985;131(5):700-708.
11. Lewthwaite H, Benedetti A, Stickland MK, et al. Normative peak cardiopulmonary exercise test responses in Canadian adults aged ≥40 years. *Chest*. 2020;158(6):2532-2545.
12. Colley RC, Garriguet D, Janssen I, Craig CL, Clarke J, Tremblay MS. Physical activity of Canadian adults: accelerometer results from the 2007 to 2009 Canadian Health Measures Survey. *Health Rep*. 2011;22(1):7-14.
13. Hallal PC, Andersen LB, Bull FC, et al. Global physical activity levels: surveillance progress, pitfalls, and prospects. *Lancet*. 2012;380(9838):247-257.
14. Bourbeau J, Benedetti A, Tan WC, et al. Canadian Cohort Obstructive Lung Disease (CanCOLD): fulfilling the need for longitudinal observational studies in COPD. *COPD*. 2014;11(2):125-132.
15. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324-1343.
16. Stanojevic S, Graham BL, Cooper BG, et al. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur Respir J*. 2017;50(3):1700010.
17. Crapo RO, Morris AH, Clayton PD, Nixon CR. Lung volumes in healthy nonsmoking adults. *Bull Eur Physiopathol Respir*. 1982;18(3):419-425.
18. Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. *Eur Respir J*. 2005;26(1):153-161.
19. Stewart AL, Mills KM, King AC, Haskell WL, Gillis D, Ritter PL. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. *Med Sci Sports Exerc*. 2001;33(7):1126-1141.
20. Radtke T, Crook S, Puhan MA, et al. ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. *Eur Respir Rev*. 2019;28(154):180101.
21. Borg GA. Psychophysical bases of perceived exertion. *J Med Sci Sports Exerc*. 1982;14(5):377-381.
22. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol*. 1986;60(6):2020-2027.
23. Balady GJ, Arena R, Sietsema K, et al. Clinician's Guide to Cardiopulmonary Exercise Testing in Adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122(2):191-225.
24. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol*. 2016;121(6):2020-2027.
25. Sue DY, Wasserman K, Moricca RB, Casaburi R. Metabolic acidosis during exercise in patients with chronic obstructive pulmonary disease. *Chest*. 1988;94(5):931-938.
26. Schneider DA, Phillips SE, Stoffolano S. The simplified V-slope method of detecting the gas exchange threshold. *Med Sci Sports Exerc*. 1993;25(10):1180-1184.
27. Caiozzo VJ, Davis JA, Ellis JF, et al. A comparison of gas exchange indices used to detect the anaerobic threshold. *J Appl Physiol Respir Environ Exerc Physiol*. 1982;53(5):1184-1189.
28. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med*. 2016;15(2):155-163.
29. Statistics Canada. Anthropometry measures of the household population. Table 13-10-0319-01. Statistics Canada website. https://doi.org/10.25318/1310031901-eng. Accessed September 24, 2020.

30. Statistics Canada. Physical activity, self reported, adult, by age group. Table 13-10-485 0096-13. Statistics Canada website. https://www150.statcan.gc.ca/t1/tb11/en/tv.action?pid=1310009613. Accessed September 24, 2020.

31. Paap D, Takken T. Reference values for cardiopulmonary exercise testing in healthy adults: a systematic review. *Expert Rev Cardiovasc Ther*. 2014;12(12):1439-1453.

32. Takken T, Mylius CF, Paap D, et al. Reference values for cardiopulmonary exercise testing in healthy subjects—an updated systematic review. *Expert Rev Cardiovasc Ther*. 2019;17(6):413-426.

33. Ofir D, Laveneziana P, Webb KA, Lam YM, O'Donnell DE. Sex differences in the perceived intensity of breathlessness during exercise with advancing age. *J Appl Physiol*. 2008;104(6):1583-1593.

34. O'Donnell DE, Hamilton AL, Webb KA. Sensory-mechanical relationships during high-intensity, constant-work-rate exercise in COPD. *J Appl Physiol*. 2006;101(4):1025-1035.

35. Chin RC, Guenette JA, Cheng S, et al. Does the respiratory system limit exercise in mild chronic obstructive pulmonary disease? *Am J Respir Crit Care Med*. 2013;187(12):1315-1323.

36. Meyer K, Hajric R, Samek L, et al. Cardiopulmonary exercise capacity in healthy normals of different age. *Cardiology*. 1994;85(5):341-351.

37. Vainshelboim B, Arena R, Kaminsky LA, Myers J. Reference standards for ventilatory threshold measured with cardiopulmonary exercise testing: the Fitness Registry and the importance of exercise: a national database. *Chest*. 2020;157(6):1531-1537.

38. Koch B, Schaper C, Ittermann T, et al. Reference values for cardiopulmonary exercise testing in healthy volunteers: the SHIP study. *Eur Respir J*. 2009;33(2):389-397.

39. Glaser S, Ittermann T, Schaper C, et al. [The Study of Health in Pomerania (SHIP) reference values for cardiopulmonary exercise testing]. *Pneumologie*. 2013;67(1):58-63.

40. Hodges LD, Brodie DA, Bromley PD. Validity and reliability of selected commercially available metabolic analyzer systems. *Scand J Med Sci Sports*. 2005;15(5):271-279.

41. Babineau C, Léger L, Long A, Bosquet L. Variability of maximum oxygen consumption measurement in various metabolic systems. *J Strength Cond Res*. 1999;13(4):318-324.

42. Hiilloskorpi H, Manttari A, Pasanen M. The comparison between three different respiratory gas analysers. *Med Sci Sports Exerc*. 2000;31(suppl 5):S354.