Using the 6-min Walk Test to Monitor Peak Oxygen Uptake Response to Cardiac Rehabilitation in Patients With Heart Failure

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Purpose: We examined the agreement between peak oxygen uptake ($\dot{V}O_{2peak}$), estimated using prediction equations from the 6-min Walk Test (6MWT), and $\dot{V}O_{2peak}$ measured using a cardiopulmonary exercise test (CPX) to estimate change in $\dot{V}O_{2peak}$ in patients with heart failure (HF) enrolled in cardiac rehabilitation (CR).

Methods: This was secondary analysis of 54 (including 9 women) patients with HF who completed a clinical CR program. Four previously published equations using 6MWT distance were used to estimate $\dot{V}O_{2peak}$ and were compared with a CPX at baseline, follow-up, and change using the standard and modified Bland-Altman method. Analyses were repeated for quartiles of cardiorespiratory fitness (CRF) based on measured $\dot{V}O_{2peak}$ from the CPX.

Results: Bland-Altman plots revealed proportional bias between all prediction equations and the measured $\dot{V}O_{2peak}$. The difference between methods varied by the level of CRF, with overestimation of prediction equations at greater levels of CRF and underestimation at lower levels of CRF. This poor agreement remained when comparisons were made between the estimated and measured $\dot{V}O_{2peak}$ values at quartiles of CRF, indicating prediction equations have limited ability to predict $\dot{V}O_{2peak}$ at any level of CRF.

Conclusion: Estimated $\dot{V}O_{2peak}$ using 6MWT distance demonstrated poor agreement with measured $\dot{V}O_{2peak}$ from a CPX. While distance ambulated on the 6MWT remains an important measure of physical performance in patients with HF, prediction equations using 6MWT distance are not appropriate to monitor changes in $\dot{V}O_{2peak}$ following CR in patients with HF.

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Exercise-based cardiac rehabilitation (CR) increases cardiorespiratory fitness (CRF) in patients with heart failure (HF), as measured by peak oxygen uptake ($\dot{V}O_{2peak}$) using a symptom-limited cardiopulmonary exercise test (CPX), which translates into reduced long-term risk of mortality and enhanced quality of life.[1] Even a modest (i.e. 1.75 mL/kg/min) increase in $\dot{V}O_{2peak}$ following CR is clinically important, as this is strongly associated with lower morbidity and mortality.[2] One quality indicator for CR is an increase in CRF by ≥0.5 metabolic equivalents.[3] In many instances, a CPX is not feasible for clinical CR programs and a 6-min Walk Test (6MWT) is recommended instead.[4] Distance walked during a 6MWT is a practical, noninvasive, and cost-effective method of assessing functional capacity that predicts short-term morbidity and mortality in patients with HF.[5,6] There is a known positive correlation between 6MWT distance and $\dot{V}O_{2peak}$,which has led to the creation of several prediction equations to estimate CRF using the 6MWT distance.[7-10] While evidence suggests that the 6MWT and prediction equations using the 6MWT are not valid measures for predicting $\dot{V}O_{2peak}$ in the HF population,[11] no study has examined this relationship following CR participation. Therefore, the primary purpose of this report was to assess the agreement between $\dot{V}O_{2peak}$ predicted by equations using 6MWT distance and $\dot{V}O_{2peak}$ measured by CPX to estimate change in $\dot{V}O_{2peak}$ in patients with HF enrolled in CR.

METHODS

PARTICIPANTS

This was a secondary analysis of 54 patients with HF who completed baseline and follow-up measures in a previously published study.[12] That study was conducted at the University of Ottawa Heart Institute (UOHI), a tertiary care cardiovascular institute, and received ethics approval from the UOHI Human Research Ethics Board (protocol #2011139-01H) and Ottawa Health Sciences Network Research Ethics Board (protocol #20130774-01H). All participants provided written informed consent before participating. Information on demographic, anthropometric, and CRF measures, as well as a detailed description of the CR program, can be found elsewhere.[12]

CARDIORESPIRATORY FITNESS

Peak oxygen uptake was measured using a symptom-limited CPX on a treadmill at the beginning and end of CR.[13] Gas exchange was monitored continuously using a metabolic cart (Sensormedics). A 12-lead electrocardiogram, blood pressure and heart rate measurements, and Borg ratings of perceived exertion were obtained throughout the CPX.

FUNCTIONAL CAPACITY

Functional capacity was measured using the 6MWT on a measured indoor track at the beginning and end of CR.[14] Participants were instructed to walk as far as possible in 6 min without running or jogging. At 2, 3, and 4 min of the 6MWT, participants were provided with standardized verbal encouragement and informed of the time remaining. Total 6MWT distance was measured in meters.

PEAK OXYGEN UPTAKE PREDICTION EQUATIONS

We used 4 previously published equations to predict $\dot{V}O_{2peak}$ from 6MWT distance in patients with heart disease at baseline, follow-up, and change from baseline to follow-up.[7-10] Our approach was similar to that of a recently published study.[11] Prediction equations were as follows:

- Cahalin et al[8] = 0.03 × 6MWT (m) + 3.98
- Ross et al[9] = 4.9848 + 0.023 × 6MWT (m)
- Adedoyin et al[10] = 0.0105 × 6MWT (m) + 0.0238 × age (yr) – 0.03085 × body mass (kg) + 5.598
- Mandic et al[7] = 0.025 × 6MWT (m) − 2.324 (if female) − 0.281 × BMI + 15.377

STATISTICAL ANALYSIS

Descriptive data are reported as means ± SD for continuous variables and as proportions for categorical variables. Pearson correlation analyses were used to examine the associations between measured and predicted $\dot{V}O_{2peak}$ values at baseline, follow-up, and change over time. Paired *t* tests were performed to compare continuous variables between baseline and follow-up. Paired *t* tests were also performed to examine whether systematic error existed between $\dot{V}O_{2peak}$ from CPX and predictive equations at baseline, follow-up, and changes over time. Linear regression analysis was used to examine whether proportional bias existed between the measured and predicted $\dot{V}O_{2peak}$ values. Standard and modified Bland-Altman plots were used for visual presentation of the agreement between the measured and predicted $\dot{V}O_{2peak}$ values.[15] The statistical level of significance was set at $P < .05$. To adjust for multiple comparisons, significance was set to $P < .004$ for paired *t* tests. All data were analyzed using SPSS for Windows version 24 (IBM Corp).

RESULTS

Participant characteristics are presented in Supplemental Digital Content (SDC) 1 (available at: http://links.lww.com/JCRP/A178). Most were male (83%), had a previous myocardial infarction (55%), had undergone a revascularization procedure (70%), and were prescribed β-blocker medications (98%).

BASELINE ANALYSIS

Mean values and correlations between $\dot{V}O_{2peak}$ measured by CPX and $\dot{V}O_{2peak}$ estimated by the prediction equations at baseline, follow-up, and their change are presented in the Table. Paired *t*-test analyses demonstrated that estimated $\dot{V}O_{2peak}$ values from the Cahalin et al[8] (t_{53}= 1.125, $P = .266$) and Mandic et al[7] (t_{53}= 0.809, $P = .422$) equations were not different from the measured $\dot{V}O_{2peak}$ values, but the estimates calculated using the Ross et al[9] (t_{53}= 4.390, $P < .001$) and Adedoyin et al[10] (t_{53}= 12.110, $P < .001$) equations were significantly different from the measured $\dot{V}O_{2peak}$ results. Bland-Altman plots are illustrated in the Figure and SDC 2 (available at: http://links.lww.com/JCRP/A179), SDC 3 (available at: http://links.lww.com/JCRP/A180), and SDC 4 (available at: http://links.lww.com/JCRP/A181). Results of the linear regression analyses revealed significant proportional bias between the measured and estimated $\dot{V}O_{2peak}$ values, indicating the differences between measured and predicted $\dot{V}O_{2peak}$ values were dependent on their average values.

FOLLOW-UP ANALYSIS

Paired *t* tests (Table) demonstrated that estimated $\dot{V}O_{2peak}$ values from the Cahalin et al[8] (t_{53}= −0.435, $P = .665$) and Mandic et al[7] (t_{52}= −0.041, $P = .967$) equations were not significantly different from the measured $\dot{V}O_{2peak}$, but the Ross et al[9] (t_{53}= 3.507, $P = .001$) and Adedoyin et al[10] (t_{52}= 11.061, $P < .001$) equations were significantly different from the measured $\dot{V}O_{2peak}$. Bland-Altman plots are illustrated in the Figure and SDC 2 (available at: http://links.lww.com/JCRP/A179), SDC 3 (available at: http://links.lww.com/JCRP/A180), and SDC 4 (available at: http://links.lww.com/JCRP/A181). Results of the linear regression analyses revealed significant proportional bias between the measured and estimated $\dot{V}O_{2peak}$ values; the difference between measured and predicted $\dot{V}O_{2peak}$ values was dependent on their average values.

CHANGE BETWEEN BASELINE AND FOLLOW-UP ANALYSIS

Paired *t* tests (Table) demonstrated that the estimated $\dot{V}O_{2peak}$ value did not differ from the measured $\dot{V}O_{2peak}$ value for the Cahalin et al[8] (t_{53}= −2.047, $P = .046$), Ross et al[9] (t_{53}= −0.924, $P = .360$), Adedoyin et al[10] (t_{52}= 1.373, $P = .176$), and Mandic et al[7] (t_{52}= −1.133, $P = .262$) equations. Bland-Altman plots are illustrated in the Figure and SDC 2 (available at: http://links.lww.com/JCRP/A179), SDC 3 (available at: http://links.lww.com/JCRP/A180), and

Table

Measured and Predicted $\dot{V}O_{2peak}$ at Baseline and Follow-up[a]

	Baseline	Correlation With CPX	Follow-up	Correlation With CPX	Change	Correlation With CPX
CPX, mL/kg/min	18.7 ± 6.3	…	20.2 ± 7.8	…	1.4 ± 3.6	…
Cahalin et al,[8] mL/kg/min	18.0 ± 2.9	0.696, <.001	20.4 ± 4.1	0.841, <.001	2.4 ± 2.2	0.277, .043
Ross et al,[9] mL/kg/min	15.7 ± 2.2[b]	0.696, <.001	17.6 ± 3.2[c]	0.841, <.001	1.9 ± 1.7	0.277, .043
Adedoyin et al,[10] mL/kg/min	9.2 ± 1.2[b]	0.530, <.001	10.1 ± 1.6[c]	0.773, <.001	0.9 ± 0.8	0.306, .026
Mandic et al,[7] mL/kg/min	18.1 ± 3.8	0.637, <.001	20.2 ± 4.8	0.796, <.001	2.0 ± 1.9	0.307, .025

Abbreviations: CPX, cardiopulmonary exercise test; $\dot{V}O_{2peak}$, peak oxygen uptake.

[a]Data are expressed as mean ± SD (baseline, follow-up, and change) and *r*, *P* value (correlations). n = 53 for Eq. 3 and Eq. 4 for follow-up and change.

[b]Paired *t* test $P < .001$ compared with CPX at baseline.

[c]Paired *t* test $P \leq .001$ compared with CPX at follow-up.

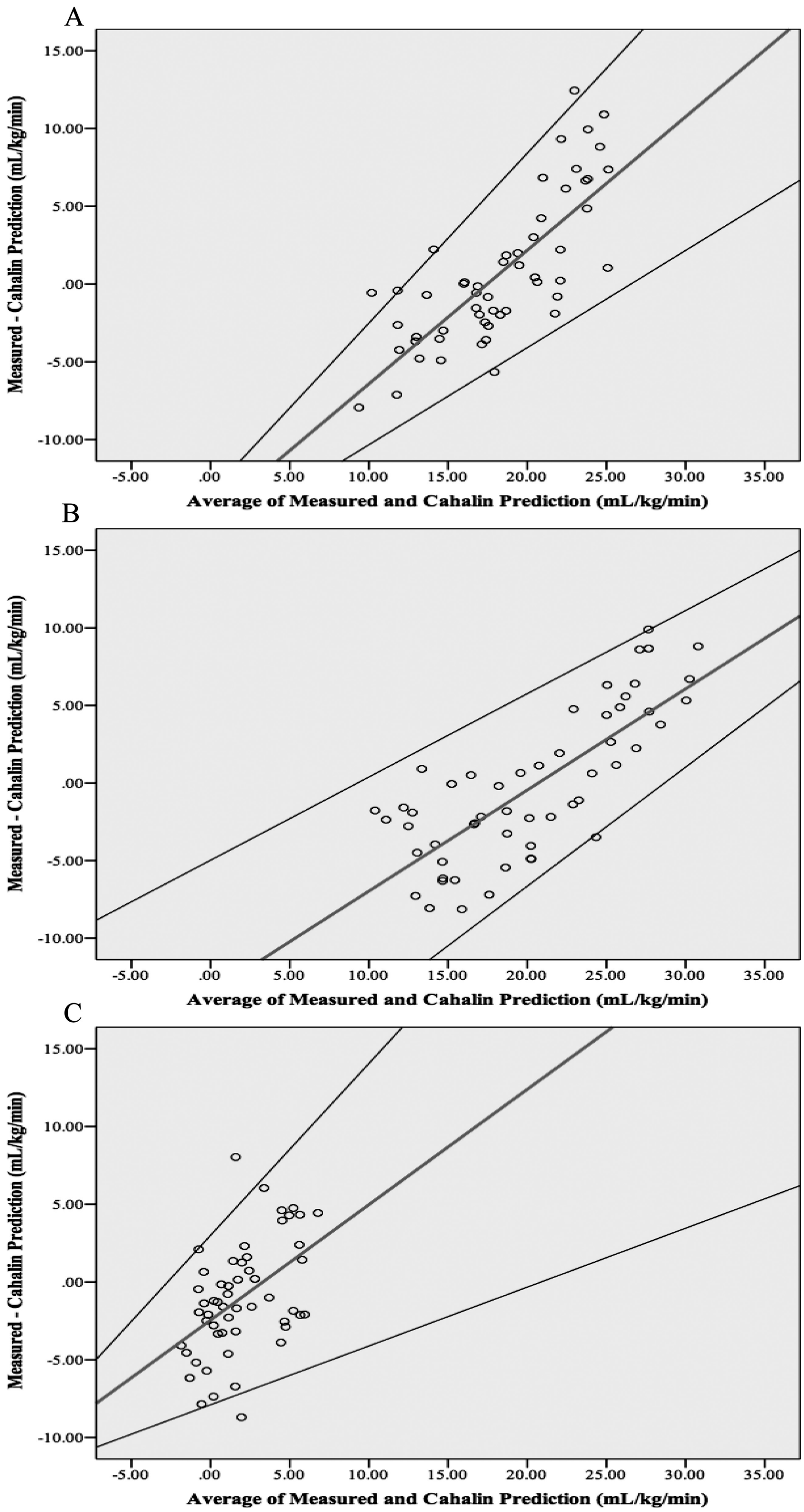

Figure. Bland-Altman plots for (A) baseline, (B) follow-up, and (C) change peak oxygen uptake between values measured using the cardiopulmonary exercise test and those estimated using the Cahalin et al[8] equation.

SDC 4 (available at: http://links.lww.com/JCRP/A181). Results of the linear regression analyses revealed significant proportional bias between the measured and estimated $\dot{V}O_{2peak}$ values; the difference between measured and predicted $\dot{V}O_{2peak}$ values was dependent on their average values.

DISCUSSION

This was the first study to examine the agreement between measured and estimated $\dot{V}O_{2peak}$ values in response to CR. The major novel findings were that mean $\dot{V}O_{2peak}$ values estimated from the Cahalin et al[8] and Mandic et al[7] equations were similar to measured $\dot{V}O_{2peak}$ values from the CPX at baseline and following CR; however, proportional bias existed in both equations—the difference increased with average $\dot{V}O_{2peak}$ values. Therefore, the ability of the prediction equations to accurately estimate $\dot{V}O_{2peak}$ varies with CRF level and may be amplified by the improvements in CRF following CR. This was supported by the weak correlation and lack of agreement between predicated and actual $\dot{V}O_{2peak}$ change values. Comparisons between measured and estimated $\dot{V}O_{2peak}$ values were also made between quartiles of measured $\dot{V}O_{2peak}$ but did not change the results (data not shown). This suggests that prediction equations do not lose their ability to predict $\dot{V}O_{2peak}$ at a given level of CRF; rather, they have a limited ability to predict $\dot{V}O_{2peak}$. These data suggest that the 6MWT is not appropriate to predict $\dot{V}O_{2peak}$ in patients with HF participating in CR.

The 6MWT is a well-established tool to assess functional capacity in patients with HF, which provides an overall assessment of performing everyday activities. A pioneering study by Cahalin et al[8] demonstrated that ambulating a distance below or above 300 m can discriminate between low versus high likelihood of short-term survival, respectively. The 6MWT also demonstrates good reliability (ICC = 0.90), with wide limits of agreement and a learning effect of 31 m in patients with HF.[16] While the most commonly reported minimal clinically important difference on the 6MWT is 54 m,[17] a recent study in patients with chronic HF has reported a minimal clinically important difference of 36 m.[18] The collective findings from the literature to date underscore the important use of the 6MWT as an evaluation of the functional capacity of patients with HF that enables practitioners to determine disease severity and prognosis, with good construct validation.[16]

Several researchers have utilized the 6MWT to develop prediction equations to estimate $\dot{V}O_{2peak}$. The use of an alternative assessment tool to estimate $\dot{V}O_{2peak}$ that is both time- and cost-efficient is desirable and perhaps preferred in a clinical setting where resources are limited. However, a vast majority of studies developing prediction equations to estimate $\dot{V}O_{2peak}$ have examined the association but not the agreement between these measures. In addition, none have evaluated the ability of prediction equations to estimate change in $\dot{V}O_{2peak}$ following CR.

Our findings are supported by a recent study evaluating the agreement of $\dot{V}O_{2peak}$ prediction equations derived from the 6MWT in patients with HF at a single time point.[11] This study found the Cahalin et al[8] equation to be the most accurate at predicting measured $\dot{V}O_{2peak}$, as compared with the Ross et al[9] and Adedoyin et al[10] equations; however, all equations demonstrated proportional bias according to their Bland-Altman plots.[11] We have extended this finding to a larger sample of patients with HF (n = 54) completing a CR program. The proportional bias and lack of agreement limit the use of prediction equations derived from the 6MWT to estimate actual $\dot{V}O_{2peak}$. An important finding from the present study was that the average distance walked on the 6MWT increased by 56 m following CR, meeting the commonly reported clinically important difference of 54 m.[17] This improvement greatly exceeds the recently reported minimal important difference of 36 m that was identified in patients with chronic HF.[18] It is speculated that physiological mechanisms associated with improved CRF may decrease oxygen consumption for a given submaximal workload. In fact, additional analysis demonstrated a significant positive correlation between change in distance walked on the 6MWT and $\dot{V}O_{2peak}$ ($r = 0.277$, $P = .043$).

The 6MWT remains a fundamental measure of functional capacity, which in many settings is the foundation of approaches intended to increase well-being and quality of life. The ability of the 6MWT to predict morbidity and mortality,[8] the ease of its administration, the ability to identify a clinically meaningful result, and the comorbidities present in many with HF are substantial arguments for recognizing the advantages of such functional testing. The 6MWT allows a straightforward assessment of functional capacity while serving to provide self-evident feedback and reinforcement to CR participants. The focus of future research should incorporate clinicians, CR specialists, and researchers and be directed toward determining whether improvements in $\dot{V}O_{2peak}$ or distance ambulated is a more clinically relevant outcome in patients with HF following CR. Future work should also focus on developing appropriate submaximal testing procedures that better predict CRF and changes in CRF in patients with HF.

There are limitations to the current study that are necessary to identify. First, this was secondary analysis of data from a quasi-experimental study, which limits the generalizability. Second, the majority of the study participants were males. This is an important limitation in all studies, as mortality and hospitalization rates due to HF are greater in women.[19] Future work examining sex differences is urgently required. Third, because of the nature of this clinical CR program, we were not able to account for a potential learning effect on the 6MWT, which has been demonstrated.[20] In addition, we did not screen participants for comorbidities, such as chronic obstructive pulmonary disease, which could have influenced their 6MWT and $\dot{V}O_{2peak}$ results.

CONCLUSION

While the 6MWT is an established tool to assess functional capacity in the form of one's ability to perform daily activities and to identify those at high risk of short-term mortality and hospitalization, it demonstrated less utility in estimating $\dot{V}O_{2peak}$ in patients with HF. Such limitations must be appreciated by clinicians and practitioners when using the 6MWT.

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REFERENCES

1. Sagar VA, Davies EJ, Briscoe S, et al. Exercise-based rehabilitation for heart failure: systematic review and meta-analysis. *Open Heart*. 2015;2(1):e000163.
2. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346(11):793-801.
3. Grace SL, Poirier P, Norris CM, et al. Pan-Canadian development of cardiac rehabilitation and secondary prevention quality indicators. *Can J Cardiol*. 2014;30(8):945-948.
4. Grace SL, Turk-Adawi KI, Contractor A, et al. Cardiac rehabilitation delivery model for low-resource settings: an International Council of Cardiovascular Prevention and Rehabilitation consensus statement. *Prog Cardiovasc Dis*. 2016;59(3):303-322.
5. Peeters P, Mets T. The 6-minute walk as an appropriate exercise test in elderly patients with chronic heart failure. *J Gerontol A Biol Sci Med Sci*. 1996;51(4):M147-M151.

6. Yazdanyar A, Aziz MM, Enright PL, et al. Association Between 6-Minute Walk Test and all-cause mortality, coronary heart disease-specific mortality, and incident coronary heart disease. *J Aging Health*. 2014;26(4):583-599.
7. Mandic S, Walker R, Stevens E, et al. Estimating exercise capacity from walking tests in elderly individuals with stable coronary artery disease. *Disabil Rehabil*. 2013;35(22):1853-1858.
8. Cahalin LP, Mathier MA, Semigran MJ, Dec GW, DiSalvo TG. The Six-Minute Walk Test predicts peak oxygen uptake and survival in patients with advanced heart failure. *Chest*. 1996;110(2):325-332.
9. Ross RM, Murthy JN, Wollak ID, Jackson AS. The Six Minute Walk Test accurately estimates mean peak oxygen uptake. *BMC Pulm Med*. 2010;10:31.
10. Adedoyin RA, Adeyanju SA, Balogun MO, Adebayo RA, Akintomide AO, Akinwusi PO. Prediction of functional capacity during six-minute walk among patients with chronic heart failure. *Niger J Clin Pract*. 2010;13(4):379-381.
11. Ribeiro-Samora GA, Montemezzo D, Pereira DAG, Tagliaferri TL, Vieira OA, Britto RR. Could peak oxygen uptake be estimated from proposed equations based on the Six-Minute Walk Test in chronic heart failure subjects?. *Braz J Phys Ther*. 2017;21(2):100-106.
12. Reed JL, Blais AZ, Keast ML, Pipe AL, Reid RD. Performance of fixed heart rate increment targets of 20 vs 30 beats per minute for exercise rehabilitation prescription in outpatients with heart failure. *Can J Cardiol*. 2017;33(6):777-784.
13. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. 10th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2017.
14. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the Six-Minute Walk Test. *Am J Respir Crit Care Med*. 2002;166(1):111-117.
15. Ludbrook J. Confidence in Altman-Bland plots: a critical review of the method of differences. *Clin Exp Pharmacol Physiol*. 2010;37(2):143-149.
16. Uszko-Lencer N, Mesquita R, Janssen E, et al. Reliability, construct validity and determinants of 6-Minute Walk Test performance in patients with chronic heart failure. *Int J Cardiol*. 2017;240:285-290.
17. Wise RA, Brown CD. Minimal clinically important differences in the Six-Minute Walk Test and the incremental shuttle walking test. *COPD*. 2005;2(1):125-129.
18. Tager T, Hanholz W, Cebola R, et al. Minimal important difference for 6-Minute Walk Test distances among patients with chronic heart failure. *Int J Cardiol*. 2014;176(1):94-98.
19. Sun LY, Tu JV, Coutinho T, et al. Sex differences in outcomes of heart failure in an ambulatory, population-based cohort from 2009 to 2013. *CMAJ*. 2018;190(28):E848-E854.
20. Wu G, Sanderson B, Bittner V. The 6-Minute Walk Test: how important is the learning effect? *Am Heart J*. 2003;146(1):129-133.