Peer Review File

Article Information: http://dx.doi.org/10.21037/apm-20-265

Reviewer A

The authors performed a retrospective study evaluating the association between six-minute walking test and cardiopulmonary exercise test in patients with chronic heart failure and have done some fantastic work with this study. However, in the present manuscript, some questions need to be further answered and some improvements need to be done.

I do have some concerns with the study and have highlighted them.

1. Short title: The short title is vague. Since a short title should reflect the feature or contents of a study, it needs to accurately capture what was achieved, and was different from other studies. If the word limit of the short title was not over, please reconsider it

Reply 1: It has been revised as follow.

Changes in the text: line 13: Exercise intensity of AT and 6MWD in CHF.

2. Abstract, Background: "The study aims to investigate the relationship between six-minute walking distance (6MWD) and anaerobic threshold (AT) in chronic heart failure (CHF) individuals."

"To investigate the relationship between 6MWD and AT" would not become a purpose, but it is merely a method to prove this work. Why did the author do this study?

Reply 2: Proved to be beneficial to chronic heart failure patients, aerobic exercise can improve their exercise endurance and quality of life. Since the suitable intensity of aerobic exercise is crucial for effective therapy, the intensity is a key element. Present, CPET is the gold standard for noninvasive detection of exercise endurance of CHF patients. And our team's research shows that exercise intensity, based on AT detected by CPET, enable CHF patients to carry out safe and effective aerobic exercise. However, the equipment of CPET is expensive, complicated to operate and difficult to interpret, which cannot be popularized in primary hospitals and limits the popularity of exercise rehabilitation for CHF patients in primary hospitals. 6MWT has low requirements, simple operation, low cost and high repeatability, and is suitable for primary hospitals. Therefore, the purpose of this study is to study the correlation between the aerobic exercise intensity determined by six-minute walking distance (6MWD) and its counterpart based on anaerobic threshold (AT) in chronic heart

failure (CHF) individuals for exploring suitable means for CHF exercise rehabilitation.

Changes in the text: It has been revised from line 21 to 24.

3. Introduction, lines 36-37: "It has been proven safe and effective that the aerobic exercise intensity established by the AT." A reference (or references of this statement) has not been shown on this paper. Please add a related previous study (or studies). Reply 3: There has been a reference 13 supporting this opinion. Changes in the text: Reference 13 has been inserted.

4. Introduction, lines 42-46: "6MWT is simple, -----. It objectively evaluates a patient functional capacity. In people with ----." The flow of sentences is difficult to understand because the meaning is somewhat obscured by the disjointed flow of sentences. Please revise it.

Reply 4: It has been revised as follow. Sorry for the mistakes.

Changes in the text: lines 52-59: Six-minute walking test (6MWT), as a kind of submaximal test, which is simple, low-cost and convenient to administer without the need of sophisticated equipment (15,16), objectively evaluates a patient's functional capacity (17). Moreover, 6MWT has been proved to be suitable for prescribing exercise intensity in most people with chronic obstructive pulmonary disease (COPD), and 80% 6MWT average speed is likely to result in training benefits in some cases (18). Since it can assess cardiopulmonary function, prescribe exercise intensity, 6MWT has been used as part of assessment for CHF patients (19).

5. Introduction, lines 42-46: "Because the 6MWT can evaluate cardiopulmonary function, it was developed for use in the CHF." At the beginning of sentences, starting a first clause with "because" would not be used especially for a formal writing. Additionally, with regard to the same sentence, "it was developed for use in the CHF." In patients with CHF, what kind of aspect can 6MWT be used for? Please consider and clarify these points. URLs below might be helpful to re-check grammatical rule of scientific papers.

https://writing.msu.edu/starting-a-sentence-with-because/

https://dictionary.cambridge.org/ja/grammar/british-grammar/as-because-or-since https://www.elsevier.com/connect/writing-a-science-paper-some-dos-and-donts Reply 5: The vital aspect of 6MWT is assessment.

Changes in the text: lines 57-59: Since it can assess cardiopulmonary function, prescribe exercise intensity, 6MWT has been used as part of assessment for CHF patients (19).

6. Introduction, lines 47-48: "Because CPET has much limits in primary hospitals, while 6MWT is appropriate for primary hospitals." This is the same as comment 4 above.

Reply 6: It has been revised as follow.

Changes in the text: line 60: Due to great limitations of CPET, 6MWT is suitable for basic hospitals.

- 7. Methods, Study population, line 58: "aged 18-75 years with CHF." Was there age criterion in this research? As the author referred in Introduction section (lines 30-31), the prevalence of heart failure increases with age. Additionally, the severity of patients' conditions, which include exercise capacity, deteriorate with age regardless age criterion and how that influences the results of this study? Reply 7: Age, one of the inclusion criteria, is the age range set according to ethical standards. The purpose of this study is to explore the correlation between patients' 6MWD and AT. And age didn't have been found to affect this study. Changes in the text: lines 69-78: The study originated from a retrospective chart analysis of CHF and non-CHF people, who had completed CPET and 6MWT performed at the Cardiac Rehabilitation Center of Tongji Hospital in Shanghai, from June 2016 to December 2018. CHF patients meet the criteria as follows: aging from 18 to 75 years old, having heart failure symptoms and signs remaining stable for more than two weeks, B-type natriuretic peptide (BNP) > 35 pg/mL or N-terminal pro-BNP (NT-pro BNP) > 125 pg/mL, and having left ventricular systolic or diastolic dysfunction (6). Inclusion criteria of non-CHF people are as follows: aging from 18 to 75 years old, CPET and 6MWT were completed in the Heart Rehabilitation Center of Shanghai Tongji hospital, no symptoms and signs of heart failure and no abnormalities in left ventricular systolic or diastolic function.
- 8. Methods, Study population, line 60: "for more than two weeks" Please add evidence or a reference to support diagnostic criteria for CHF in this research. Reply 8: It has been revised and added as follow.

Changes in the text: lines 71-75: CHF patients meet the criteria as follows: aging from 18 to 75 years old, having heart failure symptoms and signs remaining stable for more than two weeks, B-type natriuretic peptide (BNP) > 35 pg/mL or N-terminal pro-BNP (NT-pro BNP) > 125 pg/mL, and having left ventricular systolic or diastolic dysfunction (6).

- Ref: 6. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891-975.
- 9. Methods, Study population, line 61-65: As for exclusion criteria, please add references. In addition to that, who examined symptoms and diagnosed the patients' medical conditions and how many medical doctors (or other medical experts) were involved in the diagnosis of CHF? It would become a bias.

Reply 9: The reference has been added in the manuscript. A steady staff team consisting of a well-informed sole-duty cardiologist and two experienced physiotherapists was needed in the process, where the cardiologist was responsible for diagnosis and work with physiotherapists to conduct 6MWT and CPET safely. Changes in the text: line 78-85: Patients with pulmonary disease, early acute coronary syndrome (within 2 days), unstable angina, uncontrolled hypertension, high atrioventricular block, acute myocarditis and pericarditis, or symptoms of aortic stenosis severe hypertrophic obstructive cardiomyopathy, acute systemic disease, intracardiac thrombosis were excluded (20). A steady staff team consisting of a well-informed sole-duty cardiologist and two experienced physiotherapists was needed in the process, where the cardiologist was responsible for diagnosis and work with physiotherapists to conduct 6MWT and CPET safely.

Ref: 20. Medicine ACoS. American College of Sports Medicine's guidelines for exercise testing and prescription. Tenth ed. Phliadephia: Wolters Kluwer Health; 2018.

10. Methods, Study population, lines 69-70 and Figure 1: "711 patients who completed the 6MWT within one week before and after the examination". In this sentence, dose "the examination" mean CPET? If so, what are reasoning the author set one week periods between 6MWT and CPET, and within both before and after? During this one week duration, patients' physical condition might be changeable due to various reasons such as daily physical activities and medical events. Reply 10: Sorry for the clerical error, and the period between 6MWT and CPET is one day before and after the examination actually.

Changes in the text: lines 89-90 and Figure 1: -----711 patients who completed the 6MWT within one day before and after the examination.

11. Methods, Study population, lines 70-71 and Figure 1: "Among them, 320 patients had echocardiographic data within 1 week before the examination." As well as comment 8 and 9 above, please clarify the reasons why the author set one week term, and who performed echocardiography of those patients.

Reply 11: Sorry for the same error as comment 10.

Changes in the text: lines 90-91 and Figure 1: Among them, 320 patients had echocardiographic data within one day before the examination.

12. Results, Demographic and clinical Characteristics, lines 127-128: "Patients were on optimal pharmacological therapy". Is this statement necessary? then, who and how objectively defined "optimal" for each patient? Also, when the author mention "optimal pharmacological therapy", the author needs to describe how much (or dose) did patients take each medicine because it would reflect patients' severity. Reply 12: This statement is unnecessary. When testing exercise endurance of a same group of patients using two different methods, as long as the biases in the detection

process is corrected, there is no other significant differences. Changes in the text: This statement has been deleted and the table 1 has been revised.

13. Results, lines 134-138, 156-161, Table 2 and 6: In this study, CHF group was composed of subgroups; HFrEF, HFmEF, and HFpEF group, which means the data and results of subgroups were common and repetitive with those of CHF group in the first place. From statistics aspect, is it available and what was the purpose of setting CHF group?

Reply 13: The purpose of setting up subgroups in this study is to analyze the influence of subgroups on the results on the basis of the original research further. Changes in the text: There is no change.

14. Results, lines 136-138 and Discussion, lines 168-171: "there were no significant differences in 6MWD, VE/VCO2 slope, \triangle VO2/ \triangle WR, Peak VO2 /HR in sub-groups" in Results section, and "However, there was no statistical difference in VE/VCO2 slope among sub-groups. That means there was no significant difference in ventilation efficiency between the sub-groups. The single factor linear regression-----" in Discussion section. In discussion section, the sentences that the author wrote were unclear. What have the statement "there was no significant difference in ventilation efficiency between the sub-groups." impacted on? Please clarify it and discuss it including the other data too; \triangle VO2/ \triangle WR, Peak VO2 /HR.

Reply 14: This table shows that on the basis of single factor linear regression, the basic data of CPET among subgroups were compared additionally, showing no significant difference. Thus, our study also obtained the result that there was no significant difference in ventilation efficiency, peak oxygen pulse rate and oxygen power between different types of heart failure, classified according to ejection fraction. After discussion by our team, we agreed that this result is not relevant to the main research results of this manuscript, except for VE/VCO2 slope, so we should delete it and keep the core part.

Changes in the text: See Table 2.

15. Results, line 148: "EIAT and EI6MWD". Could you explain what does "EI" mean? and the importance of EIAT and EI6MWD is unclear.

Reply 15: EI means exercise intensity. EI_{AT} and EI_{6MWD} represent exercise intensity based on AT and 6MWD respectively, and the main purpose of this study is to study the correlation between them. The main type of exercise for heart failure is aerobic exercise, and suitable intensity of aerobic exercise is crucial for the effective therapy. Thus, its exercise intensity is the key element.

Changes in the text:

Lines 43-45: The main type of exercise for heart failure is aerobic exercise, and suitable intensity of aerobic exercise is crucial for the effective therapy. Thus, its exercise intensity is the key element.

lines 112-114: The EI_{6MWD} , exercise intensity based on 6MWD, is equal to $6MWD \times 10/1000 (km/h)$. For example, the 6MWD result of patient is 350m, then the exercise intensity is 3.5km/h.

Lines 127-130: The aerobic exercise intensity determined by AT was EI_{AT}, and according to the results, the metabolic equivalent value was obtained by converting the oxygen consumption amount of one metabolic equivalent (1 MET = 3.5ml/kg/min), EI_{AT} = (METs@AT-1)×3.5 x 60/100(km/h) (22).

16. Results, line 159 and Table 6: "non-heart failure groups". The author needs to mention a recruitment method and characteristics of non-heart failure group as well as CHF group and CHF subgroups. It may impact on the results. Moreover, it should be singular (please remove "s").

Reply 16: The study is retrospective. Inclusion criteria of non-heart failure groups are as follows: at the age of 18-75 years old, CPET and 6MWT were completed in Shanghai Tongji hospital Heart Rehabilitation Center, no symptoms and signs of heart failure and no abnormalities in cardiac systolic or diastolic function. Inclusion criteria of heart failure group has been described before. The heart failure group was divided into three heart failure subgroups according to left ventricular ejection fraction. Changes in the text: Remove "s". And study population of methods has been revised.

Lines 75-78: Inclusion criteria of non-CHF people are as follows: aging from 18 to 75 years old, CPET and 6MWT were completed in the Heart Rehabilitation Center of Shanghai tongji hospital, no symptoms and signs of heart failure and no abnormalities in left ventricular systolic or diastolic function.

Lines 92-96: Among them, 33 patients had EF < 40% for heart failure with reduced ejection fraction (HFrEF) and had HF symptoms and/or signs, 23 patients had 50% > EF \geq 40% for heart failure with intermediate ejection fraction (HFmEF) diagnosis, 51 patients had EF \geq 50% for heart failure with preserved ejection fraction (HFpEF) diagnosis.

17. Discussion, 165-166: "The number of cases, age composition, and sex ratio of each CHF sub-groups was matched." Which results did indicate the contents in this study?

Reply 17: P > 0.05.

Changes in the text: The table 2 has been revised as comment 14.

18. Discussion, lines 170-171 and Results, lines 141-142: "The single factor linear regression analysis of 6MWD for AT showed that there were different degrees of positive correlation between CHF group and each CHF sub-groups." It is hard to

understand this sentence and which result is related to, since the author examined "Correlation between 6MWD and AT" by using single-factor linear correlation analysis in Table 3 and Results of Correlation between 6MWD and AT. Did the author analyze correlation between CHF group and CHF sub-groups by single factor linear regression analysis as well? If so, which results have shown that?

Reply 18: There is a correlation between 6MWD and AT in CHF group, and the same is for each CHF sub-group as well.

Changes in the text: There is no change.

19. Discussion, lines 176-177: "It is feasible to use 6MWD to develop exercise intensity equivalent of AT as the standard for patients with CHF." It is unclear that the relationship between the sentence and previous sentences. Please clarify and add relevant information to connect the results with the discussion.

Reply 19: The previous equation showed that there was a positive correlation between EI_{6MWD} and EI_{AT} , and the linear equation model developed can predict EI_{AT} by EI_{6WMD} , the aerobic exercise intensity based on AT and 6MWD respectively, of CHF patients. In other words, it is feasible to establish the aerobic exercise intensity of patients with chronic heart failure equivalent to anaerobic threshold based on 6MWD, the distance of six-minute walk test.

Changes in the text: It has been revised from line 216-221.

20. Discussion, lines 187-188: "60 stroke patients ——by CPET." Would you refer more highly-related studies, which enrolled patients with heart failure or with other cardiac diseases? Additionally, some of the recent papers in the field are not cited.

Reply 20: At present, there are few literatures about the correlation between 6MWT and CPET, among which the correlation between 6MWT heart rate and CPET is mentioned in the articles. Now it seems that the position of this sentence here is not appropriate, so it should be deleted.

Changes in the text: This statement was deleted.

21. Discussion, lines 189-190: "However, the correlation between aerobic exercise intensity of 6MWT and CPET has not been explored. Our study provides this equation." Over the whole discussion section of the current manuscript needs to be elaborated. Why did you separate the sentence on different lines? and what are the relationship between those two sentences? Furthermore, after "Our study provides this equation.", the author needs to mention potential contributions of this research such as future development in the field.

Reply 21: Adjust paragraph structure and revise the statement. Changes in the text: It has been revised from line 199-221.

22. Discussion, line 200: "6MWT is a sub-maximal exercise test and is easy to perform." What did the sentence work for at the end of paragraph? If the author arrange the sentence to the middle of the paragraph to discuss the usefulness of 6MWT compared to CPET, it would become a better flow.

Reply 22: Thanks for your suggestion, and it has been revised as follow.

Changes in the text: line 231-234: 6MWT is a sub-maximal exercise test and is easy to conduct. The correlation between the exercise intensity of 6MWT and CPET was studied in this study, and a significant conclusion was preliminarily obtained. Thus, it is feasible to use 6MWT to determine the exercise intensity.

23. Discussion, lines 201-201: "The innovation of this research is the research work has initially explored the correlation between 6MWD and AT in CHF." There are some research that already have revealed the correlation between 6MWD and AT in patients with CHF. It is necessary that the author has to mention what is the novelty, and what is the difference between your study and previous research.

Reply 23: Our search base may not be comprehensive, so we can delete this sentence. However, the other conclusion of the study is innovative. And it has been revised as follow.

Changes in the text: It has been revised from line lines 235-241.

- 24. Discussion, lines 202-203: "We innovatively put forward the possibility of using 6MWD to develop the exercise intensity equivalent of the AT." In clinical environment, how can health care providers practically use the theory? Reply 24: The exercise intensity of CHF patients, determined by 6MWD, the distance of 6WMT, is equivalent to AT intensity, which makes it possible for primary hospitals to carry out safe and effective cardiac rehabilitation with 6MWT. Changes in the text: It has been revised from line lines 239-241.
- 25. Study Limitations and Conclusion: "the sample size was small." and "However, these findings are preliminary and must be evaluated in a larger patient population." Statistically, how many number of participants will be required? Reply 25: This is our team's early research, and the purpose of publishing the research result is letting more people pay attention to the relationship and carry out relevant research. Furthermore, our team will carry out further research later. Changes in the text: lines 244-247: On the basis of strict inclusion criteria and exclusion criteria, the sample size was small. However, these findings are preliminary and must be evaluated in a larger patient population. Thus, our team will carry out further research to make the test results more convincing later.
- 26. Study Limitations, lines 208-210: "Therefore, hemoglobin and creatinine should be limited." It is undeniable that low hemoglobin has a negative influence on oxygen capacity; however, what did the sentence mean and what is the relationship with creatinine? Please revise the sentences.

Reply 26: Hb is responsible for the delivery of oxygen. Besides blood pressure, heart rate, the same as 6MWT, the main indicators of CPET include oxygen intake. Some studies have shown that anemia or increased hemoglobin will affect the anaerobic threshold of patients, so HB should be included in the follow-up study as an influencing factor. Similarly, abnormal renal function will affect the blood hydrogen ion and carbon dioxide partial pressure, which will also affect the anaerobic threshold of patients.

Changes in the text: lines 247-251: Furthermore, oxygen uptake of the blood system can be influenced, such as hemoglobin, can lead to a decrease in oxygen uptake (27), and creatinine can affect blood hydrogen ion and carbon dioxide partial pressure (28). Therefore, these two indicators need to be considered in the follow-up study.

27. References: As for reference 16, 22, and 23, these information will be replaced with URLs?

Reply 27: Sorry for the mistakes.

Changes in the text: These references (references 17, 23, 24) have been updated.

25. Overall, the manuscript is not well-organized with lack of essential contents. I recommend that the paper will be proofread in English by native proofreaders. Discussion needs to be revised to clearly emphasize the research.

Reply 25: Thanks for your suggestions, and the manuscript has been revised accordingly.

<Minor edits>

1. Introduction, lines 34-35: "The main form of exercise in heart failure is aerobic exercise, exercise intensity as a key element." What is a relationship of these two sentences? Please add a conjunction.

Reply: It has been revised as follow.

Changes in the text: lines 43-45: The main type of exercise for heart failure is aerobic exercise, and suitable intensity of aerobic exercise is crucial for the effective therapy. Thus, its exercise intensity is the key element.

2. Introduction, line 42: "6MWT" should be spelled out.

Reply: It has been revised as follow.

Changes in the text: line 52: Six-minute walking test (6MWT), as ------

3. Methods, Study population, line 61: "systolic or diastolic dysfunction" Of what systolic and diastolic function that the author mentioned? If left ventricular function, please add the word.

Reply: It has been revised as follow.

Changes in the text: line 74: ----and having left ventricular systolic or diastolic dysfunction----

Line 79-80: ----- no abnormalities in left ventricular systolic or diastolic-----

4. Methods, Study population, line 68: "that Performed CPET between June". Please correct an initial "P" to lower case.

Reply: Sorry for the spelling mistake.

Changes in the text: line 88: ---- that performed CPET between June-----

5. Methods, Six-minute walk test, line 91: "HR" should be spelled out.

Reply: It has been revised as follow.

Changes in the text: line 123: ---- blood pressure, heart rate, pulse oxygen saturation-----

6. Methods, Cardiopulmonary exercise testing, line 96: "In this study we used include the MasterScreen series -----". What does the word "include" mean in this sentence?

Reply: Sorry for the mistake.

Changes in the text: line 117-120: In this study we used the MasterScreen series of the lung function test system produced by CareFusion of Germany, the Cardiosoft motion test system produced by GE Medical of Germany, and the Viasprint 150 electric bicycle produced by ergoline of Germany.

7. Methods, Cardiopulmonary exercise testing, line 101: "J/s". "s" should be spelled out.

Reply: It has been revised as follow.

Changes in the text: line 121-122: ---- and then start from 0 J/second-----

8. Methods, Statistical analysis, line 113: "SPSS". Please give the proper name of the software along with the company name.

https://www.ibm.com/support/pages/how-cite-ibm-spss-statistics-or-earlier-versions-spss

Reply: It has been revised as follow.

Changes in the text: line 134-135: ----- using IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp software.

9. Methods, Statistical analysis, line 119: "t test". What kind of t-test applied to? Reply: The "t test" is independent sample T inspection. Changes in the text: line 142: ------ was analyzed by independent sample T

inspection-----

10. Methods, Statistical analysis, line 121 and others: "p<0.05." It depends on the submission guidelines of the journal, but the author can insert a single space character immediately before and after "<". This way is much legible to readers. Please consider it as well as "<", ">" and "=" in the manuscript.

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Reply: It has been revised as follow.

Changes in the text: All the "<", ">" and "=" have been revised.

11. Results, Demographic and clinical Characteristics, line 127: BMI was written with 2 decimal places (25.71kg/m2), but the other variables (Age, Height, Weight) were without a decimal. To improve the clarity of the document, please be consistent with the writing you use.

Reply: Sorry for the mistakes, and the statements have been revised as follows. Changes in the text: line 151-152: -----62.00 years old, median height of 171.00 cm, median weight 75.00 kg, median BMI of 25.71 kg/m².

12. Discussion, line 187: "CPET peak VO2." "2" should be displayed as a subscript. Reply: Sorry for the mistake.

Changes in the text: line 198: ----- CPET peak VO₂-----

13. Discussion, line 192: "ACC" Please spell out.

Reply: It has been revised as follow.

Changes in the text: line 223: ----- the American College of Cardiology ------

14. Discussion, line 196: "Primary". "P" should be corrected to a lower case.

Reply: It has been revised as follow.

Changes in the text: line 227: ----- to primary-----

Reviewer B

Cardiac rehabilitation is one of the major elements of comprehensive treatment for heart failure, and for the safety and efficacy of training assessing the AT level is important. Therefore the subject of the presented study seems to be interesting and there is a chance of putting the results to everyday clinical practice.

Nevertheless, some issues need to be addressed and the manuscript needs major revision before submitting it to the journal.

Firstly, it requires serious rewriting, since it contains many semantic and grammar errors that make it very difficult to comprehend.

Reply: The English has been revised.

Additionally, I would like to ask whether the equation for the regression analysis should be put in the abstract since its appropriate place is within the Results section. Reply: The equation was deleted.

Also, the p level should be added to the r score whenever it is used in the text, even in the abstract

Reply: Line 30-31: The p levels have been added.

In the Methods section, the EF is presented as decimals, when it should be percentages.

Reply: It has been changed in to percentages.

Statistical analysis requires more consistent and appropriate description (e.g. it is not mentioned what the "M" stands for) and the sentence starting with "Correlation analysis…" is not clear since it uses confusing terms.

Reply: It has been revised.

In the study limitations, there is a sentence: "Therefore, hemoglobin and creatinine should be limited" which is not clear.

Reply: We have revised the sentence.

Changes in the text: lines 250-251: Therefore, these two indicators need to be considered in the follow-up study.

The References section does not have some of the items (e.g. 16, 22, 23). Reply: The references have been updated.

In summary, the aim and results of the study could be useful for the treatment of heart

failure patients referred to cardiac rehabilitation, but current manuscript needs more work, especially in terms of consistency and linguistic clarity.