Author's response to reviews

Title: Does Left Atrial Volume Affect Exercise Capacity of Heart Transplant Recipients?

Authors:

Mohammad Abdul-Waheed (abdulwm@uc.edu)
Mian Yousuf (yousuma@uc.edu)
Stephanie J Kelly (kellysj@healthall.com)
Ross Arena (raarena@vcu.edu)
Jun Ying (yingj@uc.edu)
Tehmina Naz (natz@uc.edu)
Stephanie H Dunlap (dunlapse@uc.edu)
Yukitaka Shizukuda (shizukya@uc.edu)

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Author's response to reviews: see over
October 24, 2010

Dr. Vipin Zamvar
Royal Infirmary of Edinburgh
Dr. David Taggart
Oxford Health Center, John Radcliffe Hospital
United Kingdom

RE: revised manuscript#1002137730429207

Dear Drs. Zamvar and Taggart:

Please find the revised manuscript “Does Left Atrial Volume Affect Exercise Capacity of Heart Transplant Recipients?” enclosed. Since valuable and thoughtful suggestions from the reviewers, our manuscript has been revised accordingly and significantly strengthened. Particularly, we appreciate that two reviewers have strongly expressed a merit in publishing our manuscript for who are interested in heart transplant surgery. All changes made have been highlighted yellow. Specific response to each reviewer has been attached in separate sheets.

We appreciate your consideration of our article for publication in Journal of Cardiothoracic Surgery.

Sincerely,

Yukitaka Shizukuda, MD, PhD
Division of Cardiovascular Diseases, Department of Medicine
University Hospital, University of Cincinnati
231 Albert Sabin Way, ML 0542
Cincinnati, OH 45267-0542
Response to the reviewers

We have appreciated valuable and thoughtful suggestions from the reviewers. We revised our manuscript accordingly. All changes that we made have highlighted yellow.

Reviewer 1:

We sincerely appreciate strong comments on clinical benefit of our manuscript made by this reviewer.

This study raises interesting questions regarding the reasons for increasing LAV in HT patients over time – whether LV diastolic function or atria mechanical dysfunction. If the authors can add an estimate of LA ejection fraction from LAV in end-systole and end-diastole this will be helpful in providing further clarification to their results. I hope that authors expand on their results in future studies to include LA function and exercise diastolic function assessment.

In response: We plan to analyze echocardiographic parameters of LA function including LA ejection fraction as a future extension of this study.

Reviewer 2:

We appreciate many scientific suggestions, particularly methodological and statistical aspects by this reviewer. We have agreed that our study is a pilot study to raise a significant association of LAV with exercise function in HT patients and warrant future studies to evaluate whether LA volume itself affects exercise capacity or may be a surrogate for factors that affect exercise capacity rather than a primary determinant. Due to the retrospective nature of our study, several concerns of this reviewer will be answered form the future prospective studies and we believe that it will be beyond the scope of our study.

General comments:
1. Thus, the paper would be paradoxically stronger if the authors avoided the term “prediction” for the most accurate terms of association or correlation.

In response: We have agreed to the suggestion. The phrase “associated with” has been used in lines 5,18 of the Abstract on page 2 and in the Discussion, “association” and “a surrogate” have been used in lines 5,6, second paragraph on page 9

a. The study is a retrospective one and therefore only hypothesis generating.

In response: We have agreed and this point has been commented in lines 5, last paragraph on page 11 and line 1, first paragraph on page 12.

b. Statistical correlation is by definition associative not mechanistic.

In response: We have agreed on this point as we revised in line 18 of our abstract and in line 5-7, second paragraph on page 9 in the discussion.

c. The paper would be stronger if the authors adopted a prospective design, controlled for temporal effects, and performed a CPX at the time of each echocardiogram.
In response: We agree to the reviewer’s view. However, we believe that it is beyond the scope of our initial study and it has been commented in lines 1-2, first paragraph on page 12.

Major compulsory Revisions:

2. Introduction: \(\triangledown\) add the potential effect of the anastomosis on LA performance.

In response: It has been commented in lines 7-8, last paragraph on page 3.

3. Methods section:
   a. The authors cannot determine time dependent changes for ventilatory measurement from one exercise test.

In response: We appreciate the comment and it has been commented in lines 2-4, first paragraph on page 5.

b. HT in the abstract and CPX in text body need to be defined.

In response: We appreciate the comment. HT has been added in line 1, first paragraph on page 3. CPX has been defined in line 2, first paragraph on page 4.

c. Define the duration the patient were off beta blocker before the exercise test in half lives.

In response: We appreciate the comment. Since we could not verify how long beta blocker was held in each patient who was on a beta blocker before CPX, we removed 4 patients who were prescribed a beta blocker from our analysis and the use of beta-blocker was listed as an exclusion criteria in lines 9-10, second paragraph on page 4. Because of this, the correlation coefficient between indexed LAV and indexed \(\Delta LAV\) and VE/VCO\(_2\) have slightly increased (r=278 to r=0.300, r=0.457 to r=0.484 respectively).

d. The underlying cause of the patients’ heart failure, e.g. non-sichemic cardiomyopathy, coronary artery disease, should be given.

In response: The information has added provided in lines 4-6, last paragraph on page 7.

e. The time duration from transplant to the echocardiogram and cardiopulmonary stress test (CPX) study should be define more precisely.

In response: We appreciate the comment. The time duration has been defined in lines 4-6, first paragraph on page 5. The CPX has been explained in more detail in lines 1-4, second paragraph on page 6.

f. The authors should have considered measuring the anaerobic threshold as the measurement along with ventilatory efficiency are less effort dependent that maximal oxygen consumption (Gitt AK et al. Circulation 2002; 106:3-3079-3084).

In response: We appreciate the comment. It will be our future plan as an extension of this study.
g. It would have been helpful to the readers if the authors defined worsening ventilatory efficient, i.e. increasing slope.

In response: We appreciate the comment. It has been described in lines 5-6, first paragraph on page 7.

h. The technique employed to calculate LA volume biplane Simpson’s rule, is a good on and does employ fewer geometric assumptions than the area-length method. However, the authors should have defined the inter- and intra-observer variability for their laboratory. I could not find it in the papers referenced. In addition, the comparison to LA volume measured by 3D echocardiography required more than and n=3 to valid.

In response: We appreciate these comments. We have provided the inter- and intra-observer variabilities observed in our preliminary study in lines 13-15, last paragraph on page 5. These findings were typical for 2-dimensional volume measurements by a Simpson rule. In exchange, we have removed the preliminary data comparing 2-dimensional with 3-dimensional LAV measurements since we do not have any more data points at this point.

i. Were the echocardiographic measurements obtained at the time they were performed? If not, were the analyzed in a blinded manner and how many readers were used.

In response: The measurements were done blindly by a single reader. It has been commented in lines 9-10, first paragraph on page 6.

j. The 2 sentences that begin: “Briefly, in all cases…” should be placed near the beginning of the beginning of the echocardiographic methods section but after the description of the machines.

In response: The sentences have been relocated as suggested in lines 4-7, second paragraph on page 5.

k. As there were additional measurements obtained from the echocardiograms, the methods used to obtain those measurements should be defined and/or referenced (see ref 9).

In response: We appreciate the comment. They have been described in lines 4-10, first paragraph on page 6.

l. Why was the Wasserman protocol chosen? I cannot find the protocol described in ref 17. Please define the protocol in the methods sections and explain why it was chosen.

In response: We have described our exercise protocol in more detail in lines 1-4, last paragraph on page 6 to avoid a confusion about our exercise protocol as pointed out by the reviewer. We have added two more references (18 and 19) to support the reason why our exercise protocol has been chosen.

m. Results: ¶1: Did the authors consider temporal effects in the analysis.

In response: It has been concerned for the most of papers published on LAV. Majority of papers documented only single time point measurement of LAV to predict clinical outcomes or clinical symptoms including references 8,9,26 listed.
Line 11: How many had LA enlargement?

In response: it has described in lines 5-6, first paragraph on page 8.

n. \( \frac{2}{2} \), line 4: The lack of time dependence only applies to the group. One would need to perform 2 or more CPX to determine the temporal effects for the individuals.

In response: We have agreed to the point made the reviewer. It has been accommodated in lines 4-6, last paragraph on page 8.

o. The correlations depicted in Figure 2 demonstrate that LA volume index an change in LAV volume index has only a 7.8% and 20.9% effort on VE/CO\(^2\) slope, respectively. Thus as previously been shown by Donal et al. (ref 8) in CHF patients, LA volumes and changes in volume measurements are not robust enough in themselves to predict changes in exercise performance. Their conclusion that may be one significant factor limiting the exercise capacity of HT patients is not justified from the data presented unless the authors excluded the possibility that LA remodeling may be a surrogate for other, more important cardiac factors that influence exercise performance in these patients.

In response: We appreciate the comment. However, we still consider that LAV may be an independent modulator of exercise capacity in HT patients at the same time being a surrogate for factors influencing exercise capacity in HT patients. Therefore, we urge an extension of our study to evaluate these possibilities in the future. However, we feel that the reviewer’s comment is a scientifically important to be accommodated. It has been accommodated in lines 5-7, second paragraph on page 9 and lines 5, last paragraph on page 11 and line 1, first paragraph on page 12.

p. Did you test for interaction of other measurements of LA and LV performance.

In response: We appreciate the comment. Those were not done at this point. We plan to do these analyses as a future extension of this study.

q. Table2: LV diastolic volume is reported to be 68 ± 19 ml. Is this an indexed value?

In response: We appreciate the comment. It is absolute value. The indexed value of LV diastolic volume has been added in the table 2.

r. Discussion \( \frac{2}{2} \) The last sentence is a stretch and needs to be revised.

In response: We appreciate the comment. The sentence has been revised in lines 1-2, second paragraph on page 12.

Minor essential revisions:

1. Abstract:

   a. Line1: add (HT) after heart transplant.

   In response: We appreciate the comment. It has been added in line 1 of the abstract on page 2.
b. **Line 15: Use lower case “P” for consistency.**

**In response:** We appreciate the comment. It has been changed in 15 of the abstract on page 2.

c. **Line 17: The “expanded : is awkward.**

**In response:** The word has been changed to “enlarged” in line 17 of the abstract on page 2.

2. **Methods:**

a. ¶1, line 6: define CPX

**In response:** It has been defined in line 2, first paragraph on page 4.

b. ¶2, line 11: replace “…much less…” by fewer for example.

**In response:** We appreciate the comment. They have been replaced as suggested in line 13, last paragraph on page 5.

3. **Discussion:**

b. ¶3, line 3: arial is misspelled

**In response:** We appreciate the comment. It has been corrected in line 3, last paragraph on page 10.

Reviewer 3:

We have greatly appreciated the expert suggestions provided this reviewer as well as a positive comment on clinical benefit of our manuscript.

(Discretionary revisions)

However, heart transplant patients are a peculiar type of population. The heart suffers from rejection episodes with corresponding fibrosis, the immunosuppressive drugs (directly or as an agent that favors hypertension and obesity) can impair diastole, and many others causes can contribute for dilatation of left atrium. Other explanation is that the surgical scar of the anastomosis between the primitive and the donor atrium could impair the normal function of the left atrium, impeding the correct pump function and increasing the reservoir capacity. It could be interesting to compare the two types of usual surgical anastomosis: bicaval and pulmonary veins anastomosis versus right and left atria conventional anastomosis.

**In response:** We appreciate the comment. It has been incorporated in lines 7-8 in the last paragraph on page 3 and entire paragraph 2 on page 10.

The population analyzed has normal diastolic and systolic function, with normal ejection fraction and a normal value of E/E' at rest. However 61% of the patients have hypertension. Diastolic dysfunction can occur only with exercise due to abnormalities of left ventricular relaxation.
In response: We appreciate the comment and it has been adopted in lines 8-10, the last paragraph on page 9 and line 1, first paragraph on page 10.

(Major compulsory revisions)
Other aspect is cardiac rhythm of the patient; are all the patients in sinus rhythm? Atrial flutter and fibrillation are frequent in transplant patients and worsen the prognosis.

In response: The reviewer is correct. We excluded the patients with heart rhythm other than sinus rhythm. This has been articulated in lines 8, last paragraph on page 4.

With other type of statistical analysis – univariate or multivariate analysis, this paper could improve and enhance the real importance of left atrial volume in heart transplant patients.

In response: We appreciate the comment. It is true that the additional statistical analyses mentioned by the reviewer could strengthen our observation. However, it requires a larger number of study population than ours to provide reasonable statistical power and we consider these to be a future extension of our study.

(Minor essential revisions)
The last but not the least, “Orthotropic HT means orthotopic HT”? 

In response: The reviewer is correct. The misspelling has been corrected in lines 13 and 14, last paragraph on page 10.