Reviewer's report

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

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Reviewer: Joel Strom

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The correlation of LA volume and its change over time with exercise capacity in heart transplant recipients is interesting. However, LA volume is only one of a number of LA and LV anatomic and performance parameters that your group and others have reported to correlate with exercise performance. Exercise capacity is multi-factorially dependent. It reflects the complex interactions, not only of the cardiopulmonary systems, but also of the musculoskeletal, neuro-endocrine, and especially vascular system. With regard to the vascular system, endothelial performance has been shown to be an independent determinant of exercise capacity independent of LV performance. Even when the cardiac performance alone is considered, a number of indicators measurements correlate both singly and in multivariate models with exercise capacity (refs 8 and 9). With the in mind, the manuscript by Abdul-Washeed et al., which attempts to address the hypothesis that left atrial (LA) volume and change in volume influences the exercise capacity of heart transplant recipients, overstates the role of LA volume. Dr. Shizukuda reported that left atrial remodeling and LA volume correlated with diminished exercise capacity in patients with nonobstructive hypertrophic cardiomyopathy (refs 9 and 13) and hereditary hemochromatosis (ref 14). In particular, Sachdev et al. (ref 9) reported that LA end-systolic volume significantly correlated with ventilatory efficiency, the LA volume contributed only 20% (r2 = 0.20) to the determination of exercise capacity. Donal et al. (ref 8) reported that while LA volume correlated with diminished exercise capacity in CHF, the correlation in itself was not clinically useful. LA volume may be a surrogate for factors that affect exercise capacity rather than a primary determinant. Thus, the hypothesis has not been proven.

The following edits and revisions would improve the paper:

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.
   a. The study is a retrospective one and therefore only hypothesis generating.
   b. Statistical correlation is by definition associative not mechanistic.
   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.
Major Compulsory Revisions:

1. Introduction: add the potential effects of the anastomosis on LA performance.

2. Methods section:
   a. The authors can not determine time dependent changes for ventilatory measurements from one exercise test.
   b. HT in the abstract and CPX in text body need to be defined.
   c. Define the duration the patients were off beta blockers before the exercise test in half lives.
   d. The underlying cause of the patients’ heart failure, e.g. non-ischemic cardiomyopathy, coronary artery disease, should be given.
   e. The time duration from transplant to the echocardiogram and cardiopulmonary stress test (CPX) study should be defined more precisely.
   f. The authors should have considered measuring the anaerobic threshold as this measurement along with ventilatory efficiency are less effort dependent that maximal oxygen consumption (Gitt AK et al. Circulation 2002;106:3079-3084).
   g. It would have been helpful to the readers if the authors defined worsening ventilatory efficiency, i.e. increasing slope.
   h. The technique employed to calculate LA volume, biplane Simpson’s rule, is a good one 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 volumes measured by 3D echocardiography requires more than an n=3 to be valid.
   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.
   j. The 2 sentences that begin: “Briefly, in all cases...” should be placed near the beginning of the of the echocardiographic methods section but after the description of the machines.
   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).
   l. Why was the Wasserman protocol chosen? I can not find the protocol described in ref 17. Please define the protocol in the methods sections and explain why it was chosen.
   m. Results: Did the authors consider temporal effects in the analysis.
   i. Line 11: How many had LA enlargement?
   n. 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 individuals.
The correlations depicted in Figure 2 demonstrate that LA volume index and change in LA volume index has only a 7.7% and 20.9% effect on VE/CO2 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.

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

Table 2: LV diastolic volume is reported to be 68±19 ml. Is this an indexed value?

Discussion ¶1: The last sentence is a stretch and needs to be revised

Minor Essential Revisions:
1. Abstract:
   a. Line 1: Add (HT) after heart transplant.
   b. Line 15: Use lower case “p” for consistency.
   c. Line 17: The word “expanded: is awkward.
2. Methods:
   a. ¶1, line 6: define CPX
   b. ¶2, line 11: replace “…much less…” by fewer for example.
3. Discussion:
   a. ¶3, line 3: atrial is misspelled.

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests. Dr. Shizukuda was a trainee in cardiology when I was on the facility.