Author's response to reviews

Title: Left Ventricular Outflow Tract Velocity Time Integral Outperforms Ejection Fraction and Doppler-derived Cardiac Output for Predicting Outcomes in a Select Advanced Heart Failure Cohort

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Author’s response to reviews:

Dear Editor,

Thank you for your thoughtful consideration of the manuscript. The reviewers comments are appreciated. We have addressed the comments below and in the revised paper attached. All authors have reviewed and finalized the revised draft. Kindly see the responses to individual comments below.

Reviewer #1:

1. The title of the figure 1 should be removed from Methods section (Author reply: The title has been removed in the revised draft.)

2. All tables should be placed at the end of the manuscript (according to instructions for authors) (Author reply: This has been addressed in the revised draft).

3. The authors should add in the table 3 also the multivariate analysis results (Author reply: The results were previously listed but Table 3 has now been updated for enhanced clarity.)
4. The authors should report in the table 1 the cause of dilated cardiomyopathy (ischemic and noninchemic, valvular etc…) 

Author reply: More than 60% of the study population had ischemic cardiomyopathy as the cause of their heart failure, 18% had dilated, non-ischemic cardiomyopathy, and the remaining 20% had tachycardia-induced cardiomyopathy (10%), viral myocarditis (5%), drugs/toxins (4%) and postpartum cardiomyopathy (1%). This has been included in Results, paragraph 1, line 7.

5. Are there difference in the follow-up events between ischemic and noninchemic dilated cardiomyopathy?

Author reply: It would be interested to see if there was a difference between these two subgroups, however given the relatively small size of the study, further subdivision of the study group may not have adequate statistical power and is therefore of unclear benefit.

6. Into the figure 2 the authors should add the X2 (Author reply: The authors believe that figure 2 is best presented in its current form.)

7. The authors should report the inter- and intra- observer variability in the evaluation of LVOT VTI. (Author reply: LVOT VTI inter and intra observer variability testing in our lab demonstrates intra-class coefficient 0.989-0.997 on a sample of 64 pair wise comparisons among physician readers and sonographers).

Reviewer #2: Interesting paper of potential clinical and practical impact on patient management. An "old" method of non-invasive hemodynamic assessment is revisited and demonstrate prognostic significance in a few patients with severe heart failure and low output.

1 - Methods:

- why patients with tachycardia were excluded from the study?

Author reply: Only patients with significant tachycardia defined by heart rate greater than 120 beats per minute were excluded (see methods, para 5, line 4) – this was determined by the authors to be an appropriate exclusion criteria due to the fact that stroke volume and LVOT VTI are affected by severe tachycardia and may be artificially low during uncontrolled arrhythmias, while under normal conditions when the heart rate is controlled, stroke volume and LVOT VTI may be restored to normal ranges. Because of the temporary nature of this finding, patients with their echocardiograms performed during severe tachycardia were excluded.

- No echo-Doppler data on diastole were assessed. Why?

Our study focuses on systolic measures of LV function, including ejection fraction, cardiac output as well as previously proven echo measurements related to HF outcomes such as pulmonary artery pressure. Diastolic parameters would be interesting but less relevant to the research subject.
- Cause of death was not analyzed? How were managed patients who died of non cardiac causes?

Author reply: Given the available sources utilized (social security death index), causes of death were not available and thus not determined in this case.

- Reproducibility of echo-Doppler parameters? See point 7 above.

2 - Statistical analysis: Univariate cox regression analysis... set of predefined variables... In results also other variables were considered. Please clarify

Author reply: The reviewers’ comments are duly noted and the authors agree that there is discrepancy between the methods section and the results section regarding the set of predefined variables, namely, several variables were prespecified but inadvertently left out under the methods section. These include the following: gender, NYHA class, hemoglobin and pulmonary artery systolic pressure. This is amended in the current draft. In addition, LV size has been removed from the results section for clarification purposes.

3 - Discussion

- the hemodynamic difference between ejection fraction (ratio of LV total stroke volume and end-diastolic volume) vs LVOT VTI (index of antegrade LV stroke volume) could be helpful to discuss, thus explaining the superiority of the second on predicting adverse prognosis in HF

Author reply: This is an interesting point and an additional point in the discussion has been made (see Discussion, paragraph 3, line 2) regarding the prognostic use of LVOT VTI over ejection fraction alone. The hemodynamic significance of LVOT VTI is discussed in detail in the remainder of the discussion.

- a potential limitation of the study is in my opinion the fact that no data about evolution of echo-Doppler parameters during follow-up and their potential pergnostic significance were available?

Author reply: At the current time, a one-time measure of LVOT VTI is shown to be of significant prognostic value in patients with heart failure, however certainly the trajectory of LVOT VTI during compensated and decompensated episodes may provide even more prognostic evaluation. We suggest that this be an interested question which may be evaluated in future studies.

4 - Table 1: if all study patients were in advanced HF, why there were some in NYHA class I-II? presence of aortic regurgitation was an exclusion criteria. So how do you explain that AR was present in 16% of patients??

Reply: The methods state that severe aortic regurgitation was excluded (methods paragraph 5, line 3), thus the 16% of patients with AR represent mild and moderate AR only. All subjects had a diagnosis of heart failure as documented by a physician, however in a small minority of patients, heart failure related symptoms described were consistent with minimal to no limitation. Thus, a small percentage of patients NYHA class of I or II is not unusual nor unexpected.