Author's response to reviews

Title: Reduced fractional shortening of right ventricular outflow tract is associated with adverse outcomes in patients with left ventricular dysfunction

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Author's response to reviews: see over
May 31, 2013
Eugenio Picano, MD, PhD
CNR Institute of Clinical Physiology
Rosa Sicari, CNR Institute of Clinical Physiology
Editor-in-Chief, Cardiovascular Ultrasound

Dear Professor Picano:

Enclosed is our revised manuscript entitled “Reduced fractional shortening of right ventricular outflow tract is associated with adverse outcomes in patients with left ventricular dysfunction (MS: 1897751260954373)”, which would be re-considered for publication as an Original Article to *Cardiovascular Ultrasound*.

We are greatly thankful for the reviewer’s for their excellent and insightful comments. Our responses to the reviewer’s are appended, and each revision is highlighted as red in the revised manuscript.

By having addressed the stated concerns with the addition of new analyses, we believe that the manuscript has resulted in an enhanced priority for *Cardiovascular Ultrasound*. All authors have read and approved submission of the manuscript, and the manuscript has not been published and is not being considered for publication elsewhere in whole or in part in any language. There are no financial or other relations that could lead to a conflict of interest.

Thank you very much for your attention to this manuscript.

Sincerely,

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Response to the Reviewer #1.
We appreciate very much for this reviewer’s excellent and insightful suggestions. According to the reviewer’s comments, we revised the manuscript extensively by adding the new analyses.

Major comments
1. Although the Authors excluded patients with some pathologies (such as acute myocarditis or end stage renal disease, etc.) the patient population is still heterogeneous. This should be acknowledged in the limitation section. We agree to this reviewer’s comment. We added the phrase “This is a retrospective observation study with a small number of heterogeneous pathologies in patients with LVSD.” in the section of study limitation in the revised manuscript (p.13, ll.13-14).

2. My major concern is the selection of variables for univariate and multivariate analysis. There are couple of variables which are not tightly linked to left ventricular systolic dysfunction (such as LVD or IVSD, etc) therefore I don’t understand the inclusion of these parameters into the analysis. Although, some of these variables correlated with the RVOT-FS this correlation is not explained in the discussion. This reviewer asked us to explain the reason why several parameters, which were not tightly associated with “right” ventricular systolic dysfunction, were included as variables. We appreciate very much this comment. There are few reports to show the characteristics of RVOT-FS with clinical and echocardiographic variables. Original study by Lindqvist et al. (Ref. 8, Eur J Echocardiogr. 2003;4:29) showed that RVOT-FS correlated with other RV functional parameters. RVOT-FS connects the both-side ventricles through lungs, and our hypothesis was RVOT-FS reflects not only RV function but also LV structure and function, as well as overall hemodynamics. Our analysis underlined the unique characteristics of RVOT-FS measurement, and this would be highlight in this manuscript. We commented it in
the text of revised manuscript (p.11, ll.18-20). There were close relationships between [LVDd and LVDs (r=0.886, p<0.0001)] and [IVSTd and LVPWTd (r=0.650, p<0.0001)], and we removed LVDs and LVPWTd as variables in the univariate and multivariate analyses. We mentioned it in the Method section of the revised manuscript (p.7, l.21; p.8, ll.1-3).

3. In the univariate regression analysis IVSTd and LPWTd emerged as predictors of follow-up events. Please, give an explanation.

We appreciate very much for this reviewer’s valuable comment. LV overload is initially compensated by the adequate increase of wall thickness and preserves cardiac output. Dini FL, et al. (ref. #26, Am Heart J. 2011;161:1088) reported that the increased LV mass index accompanied by the decreased wall thickness was associated with poor outcome. Our data suggest that reduced LV wall thickness appears to be a consequence of maladaptive LV remodeling resulting from myocyte cell loss. We commented it in the Discussion section of revised manuscript (p.12, ll.19-22). As mentioned above in the response to the concern No.2, we removed LVDs and LVPWTd as covariates, and reanalyzed them in the Cox regression analysis.

4. It has been reported, that 17 patients were in NYHA class II and IV. How many patients were in NYHA class I and II? It would be very interesting to see the correlation of NYHA classes, BNP and RVOT-FS.

In the original manuscript, we have shown that 17 patients were categorized in NYHA III-IV (Table 1). According to this reviewer’s suggestion, we presented the absolute number of patients categorized into NYHA functional class (I 31; II 33; III 15; IV 2) in Table 1 of the revised manuscript. In addition, we presented the graphs, showing the correlation of NYHA functional class with BNP (Figure 2A) and RVOT-FS (Figure 2B), and stated the results in text of the revised manuscript (p.9, ll. 8-9).
5. The majority of the correlations are statistically significant but only moderate and the specificity of the chosen cut-off value is disappointingly low. Please, comment!

We are thankful for this reviewer’s important comment. This reviewer concerns the low specificity of RVOT-FS on predicting the future event. To respond this reviewer’s comment, we showed the receiver operating characteristics curve to choose such a value in Figure 4A of the revised manuscript. As shown in Figure 2B, RVOT-FS value was widely distributed in patients with NYHA class I or II. We speculate that it might have led to such a low specificity. We commented it in the Discussion section of the revised manuscript (p.12, l.24; p.13, ll.1-2).

6. The discussion section is in some parts speculative, should be rewritten and expanded. Please, focus on the explanation of the pathophysiological and clinical relevance of the investigated parameters.

This is also an important comment. Although we could not completely elucidate the pathophysiological and clinical relevance of RVOT-FS measurement in this study, we discussed potential mechanism of RVOT-FS, focusing on (1) LV hemodynamics influences the motion of RVOT, (2) RVOT affects the LV output in patients with decompensated heart failure, by citing references including one reference (ref.#21, Pratt RC, et al. Circulation. 1976, 53:947) suggested by the reviewer #2 (p.11, ll.14-24; p.12, ll.1-11). In addition, we described the potential clinical relevance of RVOT-FS measurement on the effect of any specific medical treatment or medical device associated with the morbidity/mortality (p.13, ll.2-11).

7. Results section, first paragraph: don’t repeat the data presented in table

According to this reviewer’s suggestion, we deleted most of the sentences in the first paragraph to avoid the repetition which was presented in the Table 1.

Minor comments
8. Table 2 is useless.
We deleted Table 2 in the revised manuscript.

9. The title of table 3 and table 5 should be rewritten, since the tables contain not only clinical but also echocardiographic variables.
We rewrote the title of Table 3 and 5, as follows; “Correlation of RVOT-FS with clinical and echocardiographic variables” (Table 3 to 2), “Clinical characteristics and echocardiographic variables of patients with or without cardiovascular event” (Table 5 to 4) in the revised manuscript.

10. I would welcome more figures (some figures about the correlations of BNP and RVOT-FS, etc.)
To respond this reviewer’s concern, we added 3 more figures in the revised manuscript [Figure 2, BNP (A) and RVOT-FS (B) according to NYHA functional class; Figure 3, Receiver operating characteristics curve (A) and Kaplan-Meier analysis (B); Figure 4, Bland-Altman plot of RVOT-FS measurement between echocardiography and cine MRI].
Response to the Reviewer #2.
We appreciate very much for this reviewer's excellent and insightful comments. According to the reviewer's suggestion, we revised manuscript by adding the new analyses.

Major issues;
-How were the patients selected? Based on LVEF less than 40% or on clinical symptoms?
Thank you very much for this comment. We selected the patients based on LVEF but not on clinical symptom. According to this reviewer’ suggestion, we added the sentence as follows, “Patients were selected based on the impaired LV systolic function (LV ejection fraction (EF) ≤40%) but not on clinical symptoms” in the Method section of the revised manuscript (p.5, ll.1-2).

-What was the aim for angiography, scintigraphy, PET, MRI and biopsy, which were used in addition to echocardiography?
As stated in the original manuscript (p.5, ll.4-7), we performed several modalities to define the etiology of LV systolic dysfunction. This included ischemic heart disease, hypertensive heart disease, valvular heart disease and secondary cardiomyopathies, such as sarcoidosis or other infiltrative cardiomyopathies. We stated it more detail in the Method section of the revised manuscript (p.5, ll.7-9).

-How did the authors define the diastolic and systolic RVOT dimension? The reference used in the manuscript is based on M-mode measure and ECG.
We appreciate very much for this reviewer's important comment. As stated in the original manuscript (p.6, ll.4-6), we measured systolic and diastolic diameter of RVOT using 2D-mode, but not on M-mode. This study was retrospective and we did not store the M-mode at the short axis view of the level of aortic valve, routinely. We used all echo data stored by 2D-mode at parasternal-short axis view at the
level of the aortic valve. But we agree that original reference used M-mode, and we acknowledged this point to avoid the misinterpretation to the readers in the Method section of revised manuscript (p.6, ll.10-11). In addition, all echocardiographic measurements were defined at diastole and systole on electrocardiogram, and we stated it precisely in the revised manuscript (p.6, l. 9).

-How was the echo data described, as a mean of how many measures, especially in the 23% with atrial fibrillation.
This is also an important comment. We should have measured multiple times to define the RVOT systolic function, but it depended on the sonographers and cardiologists how many cardiac cycles they stored data in the server. Actually, 1 to 3 cycles were stored. This might lead to the over- or under-estimate of the value. We mentioned it in the Method section (p.6, l.9), and acknowledged this point in the section of Study limitation of the revised manuscript (p.13, ll.18-19).

-To compare RVOT-FS using echocardiography and MRI a Bland-Altman plot should be used.
We are thankful for this reviewer’s important suggestion. According to this reviewer’s comment, we presented a Bland-Altman plot. As shown in Figure 4 in the revised manuscript, we found no evidence of substantial fixed or proportional bias in the variability of echocardiography and cine MRI. We described it in the Method section (p.8, ll.12-15) and stated the result in the text of revised manuscript (p.10, ll.12-14).

-Regional RV function (RVOT-FS) is shown to have prognostic value in HF and to be related to LV size and function, how do the authors explain this relationship and what is the likely mechanism behind the relationship between RVOT-FS and LV function? The findings should be discussed in the light of the reference which highlights the role of the aortic root motion in determining the stroke volume R C Pratt, et al. The influence of left

We appreciate very much for this reviewer's insightful comment. According to this reviewer’s suggestion, we revised the Discussion extensively, focusing on (1) LV hemodynamics influences the motion of RVOT, (2) RVOT-FS affects LV output in patients with decompensated heart failure, by citing the reference suggested by this reviewer (ref.#21, p.11, ll.14-24; p.12, ll.1-11).