Author's response to reviews

Title: Impairment of pulmonary vascular reserve and right ventricular systolic reserve in pulmonary arterial hypertension.

Authors:

Enric Domingo (edrcg@hotmail.com)
Juan C Grignola (jgrig@fmed.edu.uy)
Rio Aguilar (rioaguilartorres@gmail.com)
Christian Arredondo (christianharredondo@hotmail.com)
Nadia Bouteldja (ndbo2004@yahoo.com)
Manuel López Messeguer (manuelop@vhebron.net)
Antonio Roman (aroman@vhebron.net)

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Author's response to reviews: see over
Reviewer's report

Title: Impairment of pulmonary vascular reserve and right ventricular systolic reserve in pulmonary arterial hypertension.

Reviewer 1: Sanjay Mehta

Reviewer's report:

Domingo et al study PAH patients and relate previously documented exercise limitation and cardiovascular limitation to the response to DST - dobutamine/Trendelenburg volume loading stress, with assessment of cardiac and vascular reserve responses via echo and PA IVUS. In 18 PAH patients, DST was associated with an impaired hemodynamic response, characterized by a blunted CO, but greater rise in PAP vs 10 controls. PAH group I patients with a greater rise in DST PAP also had evidence of limited pulmonary vascular capacitance reserve (higher deltaEM, dmPAP/dCO, lower deltaSV), and limited RV/cardiac reserve (IVA, deltaTAPSE). Although potential clinical relevance with regards to worse prognosis over 2yrs was hypothesized, this was not observed. This is a novel and physiologically rigorous study, very interesting to clinicians and physiologists, and the paper is well-written with clear data, and largely appropriate conclusions.

Major compulsory revisions:

1. Conclusions: The expectation of worse clinical outcome was not observed, but is consistently stated, in the final sentence of the ABSTRACT, and repeatedly in the DISCUSSION (pg 12, para 1; pg 16, para 2): This is inappropriate and needs to be revised to be at most speculative.

As the reviewer correctly suggests, we have attenuated the final sentence of the Abstract and Discussion.

Abstract: "Pulmonary vascular reserve and RV systolic reserve are significantly impaired in patients with PAH. The lower recruitable cardiovascular reserve is significantly related to a worse hemodynamic response to DST and it could be associated with a poor clinical outcome". We removed: ".....and it is associated with a low pulmonary vascular reserve and RV systolic reserve."

Discussion: pg12, para 1: The lower cardiovascular reserve is significantly related to a worse hemodynamic adaptation to DST and it could be associated with a poor clinical outcome. We also added "Although the two years follow-up showed a non significant worse outcome of PAH group 1, the significant abnormal pressure/flow relationship secondary to a pathological increase in mPAP and a blunted increase in CO, allows to speculate with it [11].” at the end of discussion, before Study limitations. This is in accordance to Blumberg et al that showed the ability to increase cardiac index on exercise is linked to survival. Besides, CI during exercise is dependent on the pressure/flow relationship (ΔmPAP/ΔCO) and the capacity of the right ventricle to adjust to it [11].

2. Discussion/implications: there is no discussion of the potential causes and
outcomes of the differences in PAH groups 1 and 2 (based on DST hemodynamic responses): does this relate to gender, age, etiology of PAH, severity of PAH, Rx type, etc. This would appear to be a major finding of the study, but apart from potential differences in clinical outcomes (which are not demonstrated), other potential implications are not addressed.

We appreciate this observation. We added ref 26 and in pg 14, para 1: "We cannot discard the presence of alterations in the control of pulmonary vascular tone during DST, resulting in blunted pulmonary vasodilation. Since both PAH groups have neither demographic (age, gender or body surface area) nor clinical differences (functional class, 6 minutes walking distance, etiology of PAH), we can speculate that PAH group 1 could have higher endothelial dysfunction with higher imbalance between vasodilators and vasoconstrictors than group 2, explaining the significant higher ΔmPAP/ΔCO ratio [26]."

At the conclusion in the last paragraph we added: "Further study is needed to elucidate whether cardiovascular reserve dysfunction adds independent prognostic information in a multivariate analysis. In addition, further studies needs to assess whether improvement of cardiovascular reserve could be a therapeutic target in patients with established pulmonary hypertension".

Minor essential revisions:

1. ABSTRACT: the 1st 2 sentences of the conclusion seem to be repetitious and need to be revised.

We have revised as it was mentioned before.

2. Awkward statements to revise: RESULTS (p 9, para 3): “…None dobutamine infusion…”; RESULTS (p 10, para 1): “…nine were changed mPAP <5mmHg …”; RESULTS (p 10, para 1): “…none of hemodynamic and IVUS data showed differences …”; DISC (pg 16, para 2) “…Recognition the presence of …”;

We have revised and corrected all the statements.

3. Units mPAP/CO don’t seem right: should be mmHg/L/min rather than mmHg/min/L.

Done

4. Figure 2 legend: I think “Fig 2A y B” is Spanish!

We rewrite the legend: "A. Correlation between delta elastic modulus (ΔEM) and delta mean pulmonary artery pressure (ΔmPAP); B. correlation between ΔEM and delta cardiac output (ΔCO); C. correlation between delta myocardial isovolumic acceleration (ΔIVA) and ΔmPAP; D. correlation between ΔIVA and ΔCO in PAH patients. (delta = value during dobutamine stress test and Trendelenburg minus value at rest)."
Reviewer's report

Title: Impairment of pulmonary vascular reserve and right ventricular systolic reserve in pulmonary arterial hypertension.

Reviewer 2: Darcy Marciniuk

Reviewer's report:

Domingo E, et al. Impairment of pulmonary vascular reserve and right ventricular systolic reserve in pulmonary arterial hypertension.

The cardiac and pulmonary vascular responses to dopamine/Trendelenburg volume loading were compared between 18 subjects with pulmonary arterial hypertension (PAH) and 10 control subjects. The PAH subjects were later divided into those with a greater pulmonary arterial pressure (PAP) response to DST compared to those with ≤5 mmHg response. PAH subjects demonstrated a lower heart rate and cardiac output response, associated with significantly greater increases in PAP and derived variables, and less cardiac reserve. The authors conclude the hemodynamic response to DST is impaired in PAH subjects, and is associated with a low pulmonary vascular reserve and RV systolic reserve. They further conclude that these responses would be associated with a poor clinical outcome.

This is an interesting and thoughtful research study that addresses an interesting physiologic issue. The study methods are appropriate and vigorous, and appropriately described. The investigators should be commended for their attention to detail.

Major Comments:

A. While it is stated that 2 years of prospective follow-up were undertaken, the only data presented to validate this statement are the 3 deaths in the 2-year follow-up time period. Additional information should be noted in the manuscript to support the assertion of a poor long-term clinical outcome. Alternatively, the conclusion should be altered and/or tempered.

We chose hard end-points (death/transplantation) to analyze clinical outcome since it is a retrospective study. As the reviewer correctly suggests, we have attenuated the final sentence of the Abstract and Discussion.

Abstract: "Pulmonary vascular reserve and RV systolic reserve are significantly impaired in patients with PAH. The lower recruitable cardiovascular reserve is significantly related to a worse hemodynamic response to DST and it could be associated with a poor clinical outcome".

Discussion: pg12, para 1: The lower cardiovascular reserve is significantly related to a worse hemodynamic adaptation to DST and it could be associated with a poor clinical outcome. We also added "Although the two years follow-up showed a non significant worse outcome of PAH group 1, the significant abnormal pressure/flow relationship secondary to a pathological increase in mPAP and a blunted increase in CO, allows to speculate with it [11]." at the end of discussion, before
Study limitations. This is in accordance to Blumberg et al that showed the ability to increase cardiac index on exercise is linked to survival. Besides, CI during exercise is dependent on the pressure/flow relationship ($\Delta mPAP/\Delta CO$) and the capacity of the right ventricle to adjust to it [11].

B. The stratification and results from the PAH subject groups are interesting. It would be informative if the authors were able to further clinically characterize these groups (beyond the physiologic measurements provided), and offer in the manuscript further discussion/opinion regarding reason(s) for the observed differences.

We appreciate the suggestion of the reviewer.

We added ref 26 and in pg 14, paragraph 1: "We cannot discard the presence of alterations in the control of pulmonary vascular tone during DST, resulting in blunted pulmonary vasodilation. Since both PAH groups have neither demographic (age, gender or body surface area) nor clinical differences (functional class, 6 minutes walking distance, etiology of PAH), we can speculate that PAH group 1 could have higher endothelial dysfunction with higher imbalance between vasodilators and vasoconstrictors than group 2, explaining the significant higher $\Delta mPAP/\Delta CO$ ratio [26]."

At the conclusion in the last paragraph we added: "Further study is needed to elucidate whether cardiovascular reserve dysfunction adds independent prognostic information in a multivariate analysis. In addition, further studies needs to assess whether improvement of cardiovascular reserve could be a therapeutic target in patients with established pulmonary hypertension".

Other Comments:

1. The use of abbreviations and use of symbols requires further attention. For instance, abbreviations should only be used once initially written in full ie. IVUC [Abstract, Results; and others). Moreover, terms such as ‘echo’ [Abstract, Results] should be revised to ‘echocardiogram’ in the manuscript. In addition, there should be consistency in the use of symbols and terms such as ‘delta’ and ‘≤’ in the text, tables and figures [Abstract, Results; and others]

We made the corrections suggested.

2. While much of the manuscript is well-written, there are other parts [aspects of the Results and Discussion] that require more careful editing and attention.

We revised carefully the manuscript and made the appropriate corrections.

3. Baseline demographic and anthropometric data should be presented. The authors should consider the addition of a traditional ‘Table 1’ listing this information. The remaining Tables and Figures are appropriate to include as presented.

We added a Table 1 with demographic and anthropometric data of the patients and corrected the numeration of the other ones.