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Rebuttal Letter „A non-invasive model including right ventricular speckle tracking for the evaluation of pulmonary hypertension“

Reviewer C:

However, there are concerns about this report that the authors are better to take into consideration: the main problem is the low sample size that the authors have mentioned too. This has prevented them from categorizing the patients based on the etiology or predisposing factors for precapillary and/or post capillary PAH. It would be better to add a table to explain type and frequency of different categories of the patients.

We thank the reviewer for this comprehensive comment on our study. Pulmonary arterial hypertension is a rare disease. The reviewer is probably alluding to the clinical classification of pulmonary arterial hypertension according to the ECS-guidelines, but since our approach aimed at a clinically applicable algorithm focusing on the discrimination of pre- and post-capillary pulmonary hypertension, we deliberately kept the categories simple. Given our relatively low sample size we did not expect an additional benefit of further sub-classification.

Specific comments

Moreover, low sample size has led to some ambiguities in statistical analysis. Multivariate analysis is the most unclear part of this study that the authors may need to clarify. In deed it is really difficult to judge how it is possible to do logistic regression on as low number as 15 patients with undeclared number of factors. The other statistic point that may readers need to know is calibration data of logistic regression.

We apologize for this mistake. We agree with the reviewer on this point, that the patient number is far to low for reliably applying a logistic regression analysis. The statement in the statistics method section is from a earlier version of the manuscript and the actual presented results are not derived from any logistic regression. Again: Sorry for this huge mistake!

Although the results show the screening potential for the model, it is still not clear whether or not a model with the specificity of 17% is helpful to discriminate between pre- and postcapillary PAH. A statistician can probably comment on this and possible use of other statistical approaches for rare diseases such as case cohort analysis. With regard to these and the predictable power of the study the authors are recommended to revise their conclusions in the second paragraph of discussion and "clinical impact" at the end of discussion.

Based on this work's results there is no place for pro BNP in diagnosis and differentiation of two types of PAH. Moreover, we probably still need to do RHC to confirm the diagnosis and discriminate between pre- and postcapillary PAH.
We agree with the reviewer's comment on the power of our study and revised the paragraph on the „clinical impact" and conclusion accordingly. However, we do see a place for NT pro-BNP in a possible screening model prior to RHC, hoping that future diagnosis will put non-invasive measures before invasive ones. We described this under „clinical impact" and added a chart accordingly to clarify our suggestion.
Page 18, line 4 to page 19, line 4: "Our study results verified a useful estimation of pulmonary pressure with TTE. Combined with ST analysis of the apical RV, and ECG RV stress signs it seems to be of value to strengthen the suspicion of the rare but malignantly proceeding precapillary form of PH and therefore should be considered as a diagnostic tool in patients with suspected PAH. Taking into consideration all our findings a model for future assessment of suspected PH could provide a incrementally invasive examination beginning with TTE and ECG on the first level, adding NT pro-BNP on a second level and only after evaluating these results, a recommendation for timely RHC could be given. Our study results indicate a necessity for timely RHC assessing PAH if a patient shows RVAS < -6,5%, sPAP > 33 mmHg and electrocardiographic RV stress signs.

In a second step, NT pro-BNP could help to determine the necessity of RHC in patients with RVAS > - 6,5%. Since sPAP < 33 mmHg, no signs of RV stress in ECG and NT pro-BNP < 1000 pg/ml seemed not to correlate with PH, suggestion for RHC should be made reluctantly and other causes of dyspnea should be considered. However, given our small sample size, this model has yet to be tested in a larger patient cohort.

Conclusion

A combination of non-invasive measurements including echocardiography and speckle-tracking analysis allows feasible estimation of PH. With a sensitivity of 82.8% and but only a specificity of 17.2%, ST does not seem to reliably identify PAH at this point and the definite diagnosis has still to be made by invasive RHC. However, since ST has become more applicable in echocardiographic examination, it should be considered as an additional diagnostic tool for patients before invasive RHC."

At the end, as they have not discussed an algorithm, they are better to change the title to "a non-invasive model ..."

Again, we thank the reviewer for his comment and gladly change the title to „A non-invasive model including right ventricular speckle tracking for the evaluation of pulmonary hypertension".