Author's response to reviews

Title: No effect of epoprostenol on right ventricular diameter in patients with acute pulmonary embolism: a randomized controlled trial

Authors:

Albertus J Kooter (jkooter@vumc.nl)
Richard G IJzerman (rg.ijzerman@vumc.nl)
Otto Kamp (o.kamp@vumc.nl)
Anco B Boonstra (a.boonstra@vumc.nl)
Yvo M Smulders (y.smulders@vumc.nl)

Version: 2 Date: 12 February 2010

Author's response to reviews: see over
Reviewer 1, dr P Wouters

Thank you for the thoughtfull criticism on our paper.

Major compulsory revision:

1. Our primary aim was to measure and compare RV end diastolic diameter, since this is one of the most commonly used parameters for estimating prognosis and evaluating treatment of PE. This is in line with CT-imaging which shows static parameters like RV dimensions and RV/LV-ratios and, again, shows that such parameters have prognostic significance.

We do, nonetheless, agree with the reviewer that radial function of the right ventricle gives additional information about the pressure-overloaded ventricle. Although we did not measure RV end systolic diameter to assess RV shortening fraction, we have data on RV fractional area change (RVFAC). Change of RVFAC during treatment was not different between treatment groups, and because of large variability between measurements we did not add these results in our original manuscript. We have now added RVFAC in the table and comment on it in the discussion paragraph.

Tricuspid regurgitation was quantified and used for calculation of systolic PAP. Septal motion/position was not quantified.

We agree with the reviewer that cardiac output may affect systolic RV pressure estimation, but this is mostly observed in patients with severe and progressive RV failure. In our patients, cardiac output was not sufficiently hampered to underestimate RV pressures. Furthermore, cardiac output was comparable between treatment groups and did not significantly change during treatment. Nevertheless, we have now added cardiac output to the table.

2. The reviewer is correct by stating that TAPSE is higher than one would expect in a pressure-overloaded ventricle and remains at the lower limit of normality during the study. Massive tricuspid valve regurgitation was not present so could not explain this finding. We have added this apparent discrepant finding to the discussion.

We agree with the reviewer that the relative normal TAPSE could indicate limited RV dysfunction which may have precluded a large effect of a pulmonary vasodilator in acute PE. However, the aforementioned RVFAC suggests more serious RV dysfunction. Although there is a correlation between TAPSE and RVFAC there is a lot of variation in TAPSE measurement, and TAPSE can be normal in patients with low RVFAC (American Journal of Cardiology 2006:98;973-7). We have now discussed this issue in more detail in the text.

In addition, we have added to the discussion that it is possible that the effect of a pulmonary vasodilator may be larger in patients with more seriously hampered right ventricular function.

3. a. We respectfully disagree with the reviewer on the point of multiple comparisons. In our opinion multiple comparisons are appropriate if statistical significant findings are a
result of many comparisons which, if repeated enough, will at the end always deliver 'significant' results. In our study however the results are not significant at a statistical level, so multiple comparisons renders these results even less significant, which adds no further value.

b. The reviewer is correct by stating that several biochemical parameters had no normal distribution. Therefore, analysis (t-test) were performed after logarithmic transformation of these date (method section) after which the data were normally distributed. In the subscript of table 2 we state that biochemical parameters were logtransformed before analysis.

We also performed non-parametric test on all the data, including biochemical parameters, and found the same results. We preferred the t-test since we were interested in confidence intervals which are more difficult to obtain and present with non-parametric tests.

We added the use of nonparametric test in the method section and comment in the same section why we also performed the students-t test.

4. We agree that our inclusion criterium for end diastolic diameter (>30 mm) is arbitrary. No clear consensus exists as to what RV dimensions are to be considered 'dilated'. The same, in our opinion, holds true for these dimensions after indexing for BMI. Our criterium was derived from 2 previous papers (F Mookadam, Cardiology in review 2010;18:29-37 and S Grifoni, Circulation 2000:101:2817-22). References concerning RV end diastolic diameter have been added.

The RV/LV ratio, as suggested by the reviewer, may indeed be more sensitive for RV pressure overload, but since our trial was mainly focussed on change of RV diameter during treatment, our main inclusion criterium was RV end diastolic diameter. RV/LV ratio is shown in table 2.

**Minor**

As requested
- We removed the statement of 'wall stress'
- We changed the sentence as suggested
- We stated clearly about the administration route (inhalation) of prostacyclin
- We have made a clear statement of iv vs inhalation of prostacyclin with respect to pulmonary selectivity and therefore, possibly, a greater effect of inhalation. We also argue that the lack of systemic effects (hypotension) might be caused by low dose and might mirror a possible lack of effect on pulmonary vasculature of iv epoprostenol.
- We decided to include mild RV hypertrophy (5-7 mm) as this was, in our opinion, not likely to influence results to a great magnitude. We considered RV hypertrophy > 7 mm as severe enough to indicate at least partial 'irreversibility' so we excluded these patients. We comment on this in the method section by excluding only 'substantial' RV hypertrophy
- We agree with the reviewer, and we have changed RR to ABP and included diastolic and mean blood pressure to the table
Reviewer 2, dr AR Hemnes

Thank you for the thoughtful criticism on our paper.

Major Compulsory Revisions

1. We agree fully. We changed the sentence to single-blind.

2. There were no effects of epoprostenol infusion on hospital length of stay. None of the patients described were admitted to the ICU.

3. Low partial oxygen pressure may indeed cause hypoxic pulmonary vasoconstriction. This mechanism, however, is unlikely to play a crucial role in our study considering the level of oxygen pressure in the patients. Furthermore pO2 was comparable between treatment groups. We added pO2 to table 1. We did not mention FiO2 in the table since this was the same in all patients. All 14 patients received 2 litres of oxygen, which is comparable to an FiO2 of 24%. This is more clearly stated in the method section.

4. We did not place PA catheters so we do not have these data, although they might have been very informative.

5. We now comment more extensively on RV function and effects of epoprostenol as suggested by the reviewer, although effects of prostacyclin on RV function in acute pulmonary hypertension are hardly investigated. In chronic pulmonary hypertension, animal experiments show conflicting data. In humans epoprostenol has either no or a beneficial effect on RV dimensions or output. We comment on this at the end of the discussion paragraph.

6. It is possible the our inclusion criteria were to broad. However, a systolic PAP > 40 mmHg can be considered (at least moderate) severe pulmonary hypertension in the setting of acute pulmonary embolism.

Parameters of RV dysfunction were measured and discussed, but were no inclusion criterium. RV function as estimated by RV fractional area change was severely hampered, suggesting at least moderately severe pulmonary embolism. Another parameter of RV function, TAPSE, is at the lower level of normality and suggests at most mild dysfunction. We cannot explain the contrast between TAPSE en RVFAC and make a note considering this point in the discussion paragraph. We also state that it is possible that in the presence of more severe PE (for example as indicated by lower TAPSE), a larger beneficial effect of pulmonary vasodilators could be found.

Minor

The 3 suggestions made by the reviewer have been adapted.