Reviewer's report

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

Version: 1 Date: 26 December 2009

Reviewer: Patrick Wouters

Reviewer's report:

The authors evaluate the effects of intravenously administered epoprostenol in the setting of acute pulmonary embolism in a small scale RCT. The rationale for expecting possible benefit from a (pulmonary) vasodilator in treating a mechanical obstruction of the pulmonary vascular system is based on the observation that pulmonary embolism is often accompanied by a reactive pulmonary vasoconstrictive component.

The primary endpoint is right ventricular end-diastolic diameter. Secondary outcome variables, both functional and biochemical, are also soft type endpoints. Patients were included only if they were hemodynamically stable and showed signs of mild RV dilatation.

The authors found no difference in any of the measured variables between patients treated for 24 hrs with low dose intravenous epoprostenol versus control as adjunct therapy for pulmonary embolism - early after onset.

This finding is important and the hypothesis is sound, however, the following remarks could be considered to further improve the manuscript:

Major Compulsory

1. The number of functional determinants provided here is very limited – it is a pity that the authors do not fully exploit the potential of echocardiography being a non-invasive diagnostic technique.

- Only end-diastolic RV diameter is shown but why is end-systolic diameter not included since this would allow calculation of RV shortening fraction. Although TAPSE is provided as a measure of RV performance (long axis function indeed may be equivalent or even more relevant in the normal RV) radial function (i.e. short axis shortening fraction) is particularly important in the pressure-overloaded RV. I can not imagine that such data are not available and would like to have them included in this study.

- Was tricuspid regurgitation not quantified?
- Was septal position and motion not quantified?
- Was no attempt made to measure cardiac output: systolic RV pressure estimates are a very crude measure of RV afterload and are affected significantly by changes in cardiac output. (circulation 2008;117:1717-31)

2. The values for TAPSE are not in line with the expectations for a pressure
overloaded RV – in fact they remain in the normal range throughout the study. How is that possible? Does this suggest that there was very little benefit to be expected from afterload reduction therapy? Or was this related to the presence of tricuspid valve regurgitation? Please comment on the presence of tricuspid regurgitation and— in general— discuss the functional findings to greater detail.

3. Statistics (Students t-test, type not specified) are not appropriate:
   a. There is no correction for multiple comparisons – ANOVA should be used, followed by post-hoc corrections if appropriate, including alpha correction.
   b. Biochemical variables have non-Gaussian distribution and should be analyzed using non-parametric tests

4. Why was the criterion for inclusion set at RVED > 30 mm – is there any reference in the literature to support this? please provide. Why was this value not indexed to BSI? Would it not have been a better idea to use RV/LV size ratio as an inclusion variable since this is more sensitive and more specific for RV pressure overload?

Minor essential
abstract:
-biochemical parameters are not specific for RV wall stress so please remove statement
-conclusion: please change sentence to "any other measured variables of RV overload"

page 3: reference 17 refers to inhaled prostacyclin: please specify this in preceding sentence

page 10: indeed intravenous epoprostenol is NOT selective. Using very low doses with minimal effect on systemic blood pressure perhaps also carries the possibility of having no pulmonary vascular effect either. please discuss In contrast, inhaled administration of prostanoids does provide pulmonary selectivity - please clearly state this to avoid confusion.

table 1: RV free wall measurements suggest RV hypertrophy in some patients (> 5 mm)

table 2: RR is an unconventional reference to systolic blood pressure - change to eg ABPs and provide units. RRd in legend is not provided in table. Please provide systemic blood pressure data fully i.e. systolic, diastolic and mean.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests