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

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Abstract

Background: Right ventricular dilatation in the setting of acute pulmonary embolism is associated with an adverse prognosis. Treatment with a pulmonary vasodilator has never been studied systematically. We evaluated the effect of epoprostenol on right ventricular diameter and function in patients with acute pulmonary embolism and right ventricular dilatation.

Methods: In a randomized, single-blind study, 14 patients with acute pulmonary embolism received epoprostenol or placebo infusion for 24 hours on top of conventional treatment. Effects on right ventricular end-diastolic diameter, systolic pulmonary artery pressure, right ventricle fractional area change and tricuspid annular plane systolic excursion were assessed by serial echocardiography. Furthermore Troponin T and NT-proBNP were measured serially.

Results: Compared to placebo, epoprostenol was associated with a relative change from baseline in right ventricular end-diastolic diameter of +2% after 2.5 hours and -8% after 24 hours. Epoprostenol did not have a significant effect on systolic pulmonary artery pressure, right ventricular fractional area change and tricuspid annular plane systolic excursion, nor on biochemical parameters.

Conclusion: In patients with acute pulmonary embolism and right ventricular overload, treatment with epoprostenol did not improve right ventricular dilatation or any other measured variables of right ventricular overload.

Trial Registration: Registration: URL: NCT01014156

Medical ethical committee: Medisch-ethische toetsingscommissie (METc) from the VUmc (free university medical centre)

Background

Pulmonary embolism is a frequent and potentially fatal disorder. Despite immediate treatment with anticoagulants, morbidity and mortality are still high when hemodynamically stable patients with pulmonary embolism have echocardiographic signs of acute right ventricular overload [1-3].

An acute increase in right ventricular afterload is the hallmark of severe pulmonary embolism, and is responsible for many of its clinical manifestations and complications. The traditional view is that mechanical obstruction by thrombus mass causes pulmonary hypertension. Therefore, treatment focusses on relieving mechanical obstruction, either by anticoagulation if patients are stable, or by thrombolytic therapy in case of hemodynamic instability [4]. The optimal treatment for haemodynamically stable patients with signs of right ventricular overload is unclear. Despite one clinical trial showing some benefit of thrombolysis in normotensive patients with pulmonary embolism and echocardiographic signs of right ventricular dysfunction [5], thrombolytic therapy continues to be highly controversial in this patient category [6-8].

Apart from mechanical obstruction, vasoconstriction of the pulmonary vasculature plays a pivotal role in the
acute rise in pulmonary artery pressure in patients with pulmonary embolism [9]. This is supported by the marked discrepancy between hemodynamic manifestations of acute pulmonary embolism and the degree of mechanical obstruction [10]. Furthermore, bringing about a strictly mechanical obstruction in a pulmonary artery causes only a modest rise in pulmonary artery pressure (PAP), rarely resulting in right-sided heart failure, whereas pulmonary embolism with obstruction of only 25% of the pulmonary vascular tree can cause marked acute pulmonary hypertension [11]. Finally, studies in experimental animal models support a crucial role for pulmonary vasoconstriction in acute pulmonary embolism [12,13].

Given the role of pulmonary vasoconstriction in the pathogenesis of pulmonary embolism-associated pulmonary hypertension, the potential benefit of pulmonary vasodilators is important. There is experimental evidence suggesting that antagonising pulmonary vasoconstriction by administration of selective vasodilators is beneficial. In animal models of acute pulmonary embolism prostacyclin, a relatively selective pulmonary vasodilator, prevented or partially reversed the rise in pulmonary vascular resistance and pressure [14,15]. Pretreatment with a prostacyclin analogue protected mice from pulmonary embolism-related death in a dose-dependent manner [16]. In humans, a case report suggested that inhaled prostacyclin may also be beneficial for acute pulmonary hypertension associated with pulmonary embolism [17]. However, the potentially beneficial role of pulmonary vasodilatory therapy in acute pulmonary embolism has never been studied in a systematic way.

In this randomized, controlled trial, we evaluated the effects of epoprostenol, the pharmacological form of prostacyclin, on echocardiographic abnormalities, cardiac biomarkers and on hemodynamic and respiratory symptoms in patients with pulmonary embolism with echocardiographic signs of right ventricular overload.

Methods

Subjects

A total 82 patients with acute pulmonary embolism, as diagnosed by spiral CT, were screened for eligibility. Patients were potentially eligible if they had a recent (<24 hours) onset or progression of symptoms, and if the clinical probability of finding right ventricular overload by echocardiography was high, as indicated by one of the following symptoms or signs: (near) collapse, systolic blood pressure <100 mmHg, diastolic blood pressure <60 mmHg, pulse rate >100 beats/min, elevated jugular venous pressure, electrocardiographic abnormalities (pulmonary P-waves, S1Q3-complex, right bundle branch block, T-wave inversions in precordial leads), tachypnea (breathing frequency >20/min), PaO2 <80 mmHg (with oxygen supplementation of 2 liters), peripheral oxygen saturation (SaO2) <95% or dyspnea [2,3].

After informed consent was obtained, patients were screened by transthoracic echocardiography for signs of pulmonary hypertension. If acute right ventricle dilatation was present (right ventricular end-diastolic diameter (RVED) >30 mm [2,18] in the absence of substantial right ventricular hypertrophy (free wall thickness <7 mm)) or if systolic pulmonary hypertension (systolic PAP >40 mmHg) was present, patients were included in the study. During echocardiography all patients received 2 liters of oxygen supplementation. Patients were excluded if they refused or were unable to give informed consent, or if one of the following was present: age <18 years, pregnancy, body mass index >35 kg/m2, circulatory shock (blood pressure <80/45 mmHg), mechanical ventilation, treatment with thrombolytic therapy, placement of a vena cava filter, atrial fibrillation or severe pre-existent cardiopulmonary disease (heart failure, obstructive pulmonary disease, emphysema).

The study protocol was approved by the local ethics committee (METc), and written informed consent was obtained from each patient prior to study entry.

Study design

Patients were randomized to receive intravenous epoprostenol sodium (Flolan®; GSK; Zeist, the Netherlands) or saline placebo infusion. Infusion of epoprostenol was started in a dose of 1 ng/kg/min. Every 10 minutes the dose was increased with 1 ng/kg/min to a maximum dose of 4 ng/kg/min. Patients not randomised to epoprostenol received a similar syringe pump containing isotonic saline. During titration of epoprostenol infusion, blood pressure, pulse rate and peripheral oxygen saturation were measured at 5 minute intervals. If, during titration, mean blood pressure dropped by >10 mmHg, the dose of epoprostenol was not further increased and 0.5 liter of extra sodium chloride was administrated in 30 minutes. If blood pressure dropped by >15 mmHg or if oxygen saturation dropped by >7% (or absolute <85%) epoprostenol infusion was decreased to the previous titrated dose. If blood pressure and/or oxygen saturation were not restored by down-titration, epoprostenol infusion was stopped. After inclusion of the first 8 subjects, no side effects of epoprostenol treatment at a dose of 4 ng/kg/min were observed. Because our study is a proof-of-principle study we decided to increase epoprostenol infusion rate every 10 minutes with 1 ng/kg/min to the maximum dose of 8 ng/kg/min, which is substantially higher than maximum initial doses used in epoprostenol intervention trials in patients with chronic pulmonary hypertension [19]. After reaching the
maximum dose, blood pressure, pulse rate and SaO₂ were assessed hourly for the entire duration of epoprostenol or placebo infusion. Epoprostenol infusion was continued for 20 hours, then tapered gradually during 4 hours and stopped. Hence, total treatment with epoprostenol or placebo encompassed a period of 24 hours.

The patient, the technician performing the echocardiographic examinations, as well as the cardiologist assessing the echocardiographic recordings were blinded for treatment allocation. The physician providing clinical care and monitoring vital parameters was not blinded in order to be able to respond appropriately if the patient showed signs of hemodynamic or respiratory deterioration.

All patients were treated with low-molecular-weight heparin adjusted for body weight, acenocoumarol, supplemental oxygen (2 l/min) and a isotonic saline infusion (80 ml/hr).

Study Evaluations
At baseline, after 2.5, 24 and 72 hours echocardiographic parameters were obtained. At baseline, after 4, 24 and 72 hours serum creatine kinase, cardiac troponin T and NT-proBNP were measured. At baseline, after 4 and 24 hours, arterial blood gas analysis was performed to detect hypoxemia or a rise in PaCO₂ as a sign of intrapulmonary shunting due to epoprostenol infusion. The primary end point was the change in RVED between baseline measurement and during treatment (i.e. measurements 2 and 3). Secondary end points were right ventricular diameter 48 hours after treatment was stopped (i.e. measurement 4), systolic PAP, tricuspid annular plane systolic excursion (TAPSE), right ventricular fractional area change (RVFAC), serum cardiac troponin T and NT-proBNP.

Echocardiographic Studies
Standard two-dimensional and Doppler echocardiography was performed with a commercially available Vivid 7 system (GE medical systems; Horten, Norway) using a 3.0 MHz broadband (M3S) transducer; serial echocardiograms were analysed off-line. All examinations included standard parasternal, apical and subcostal views and were stored digitally for subsequent analysis. Right ventricular function was assessed by TAPSE and RVFAC, right ventricular dimensions by long axis and tricuspid annular size from the apical 4 chamber view. Furthermore, estimation of systolic PAP was obtained by peak tricuspid regurgitant jet with continuous wave Doppler and adding the right atrial pressure derived from the collapse index of the inferior vena cava [20]. Cardiac output (left ventricular outflow traujet) was measured with pulse-doppler. The two-dimensional echocardiograms were interpreted by two experienced echocardiographers.

Laboratory Studies
NT-proBNP concentrations were determined with an immunoradiometric assay kit (Roche diagnostics, module E170; Mannheim, Germany). Normal values are depending on age and gender, but in general a NT-proBNP <200 pg/ml is considered normal. Cardiac troponin T concentrations were determined using a microparticle enzyme immunoassay (Roche Diagnostics, Module E170; Mannheim, Germany). A normal value was considered a troponin T <0.04 ng/ml.

Statistical Analyses
All analyses were performed using the SPSS statistical software package (version 15; SPSS; Chicago, IL). Data are shown as mean ± SD or median (range). Biochemical parameters were log-transformed before analysis. The Student-t test was used to compare RV parameters between treatment arms and to compare relative change of RVED compared to baseline between treatment arms. Students-t test was chosen primarily to calculate confidence intervals which may be appropriate for power analysis for future studies. Moreover, due to small sample sizes and non-normal distributions of biochemical parameters, also a nonparametric test (Mann-Whitney U) was performed.

Differences were considered significant at p < 0.05. This study was intended as a safety and proof-of-concept study. In addition, obtaining point estimates of effect-size of epoprostenol on primary endpoints may be of use for the design of future studies. Hence, the study is designed as a pilot study, and does not include a formal power analysis based on clinically relevant effect sizes.

Results
Subjects
Eighty two patients were screened and 14 patients were randomized to either epoprostenol (n = 7) or placebo (n = 7; Figure 1). The baseline characteristics of the treatment groups were similar, as shown in Table 1. In both groups treatment was started on average 14 hours after the onset or progression of symptoms. All active treatment patients received at least 4 ng/kg/min of epoprostenol. The 3 patients who were treated with increasing dose received 8.0, 8.0 and 5.6 ng/kg/min epoprostenol respectively. The dose in the last patient could not be raised due to facial flushing and headache. In two patients in the placebo group, the measurements at 72 hours, including echocardiography, could not be performed because of logistical reasons.
Effects on Right Ventricle End-Diastolic Diameter

At baseline, the mean RVED was similar in both treatment groups (4.10 ± 0.83 cm in the epoprostenol arm and 4.13 ± 0.84 cm in the placebo arm). Epoprostenol did not have a significant effect on RVED after 2.5 and 24 hours (Figure 2). After 2.5 hours, the relative change in RVED compared to baseline was similar in both treatment groups, +4.2% in the placebo arm and +6.1% in the epoprostenol arm (difference in change compared to baseline +1.9% (95% confidence interval, -5.8 to 9.6, \(P = 0.60\)). After 24 hours, RVED had increased by 2.4% in the placebo arm and had decreased by 5.6% in the epoprostenol arm (difference in change compared to baseline -8.0% (95% confidence interval, -21.2 to 5.2, \(P = 0.21\)). Results were similar for the 3 patients in whom epoprostenol was titrated to a mean dose of 7.2 ng/kg/min (data not shown).

**Table 1 Characteristics of Subjects at enrollment**

| Characteristics                  | Placebo (n = 7) | Epoprostenol (n = 7) |
|----------------------------------|----------------|----------------------|
| Male gender                      | 4 (57)         | 4 (57)               |
| Age, yr                          | 54.4 (19.9)    | 55.3 (18.2)          |
| Weight, kg                       | 78.9 (11.2)    | 74.0 (9.7)           |
| RVED, cm                         | 4.1 (0.84)     | 4.1 (0.83)           |
| Systolic PAP, mmHg               | 47 (10.6)      | 57 (13.9)            |
| Right ventricle free wall diameter, mm | 6.1 (0.7)   | 59 (0.9)             |
| NT-proBNP, pg/ml                 | 1467 (39-8549) | 3885 (270-12339)     |
| Troponin T, ng/ml                | 0.01 (0.01-0.13) | 0.03 (0.01-0.12)  |
| PaO₂, mmHg                       | 85 (14)        | 74 (12)              |

Definition of abbreviations: PAP = pulmonary artery pressure; RVED = right ventricular end-diastolic diameter; PaO₂ = partial arterial oxygen pressure

*Data are presented as No. (%), or mean (SD). NT-proBNP and troponin T are presented as median (range).
Other Efficacy End Points

Measurements of systolic PAP, TAPSE, RVFAC, end-diastolic right atrial diameter, end-diastolic right/left ventricular ratio and biochemical parameters of right ventricular overload are presented in Table 2. All echocardiographic parameters of right ventricular function remained stable during follow up. biochemical parameters improved in both groups. At no time point, significant differences of echocardiographic and biochemical parameters between treatment groups were observed ($P > 0.20$). Systolic PAP at baseline and follow up for both treatment groups is presented in Figure 3.

Adverse events

There were no serious adverse events in either treatment arm. Two patients showed facial flushing during infusion with epoprostenol, however, this was transient and did not influence infusion rate. As described above, in one patient administration of epoprostenol could not be increased to a maximum 8 ng/kg/min because of persistent facial flushing and headache. Symptoms disappeared after gradual lowering of the infusion rate. Parameters of pulmonary gas exchange ($\text{PaO}_2$, $\text{PaCO}_2$ or $\text{SaO}_2$) were similar at baseline and did not significantly change during treatment (data not shown). There were no blood pressure changes necessitating fluid resuscitation or lowering of the epoprostenol infusion rate.

Discussion

This is the first study to investigate the effect of a vaso-dilator for treatment of acute pulmonary embolism in a randomized controlled trial. Our study suggests that adding epoprostenol for 24 hours to standard treatment of acute pulmonary embolism in patients with right ventricular dilatation does not result in a significant change in right ventricular overload.

Clearly, the sample size is too small to detect relatively small effects of epoprostenol. However, it should be emphasized that the point estimate of any treatment effect of epoprostenol on right ventricular diameter and function is very small: after 2.5 hours 2% in favour of placebo, after 24 hours 8% in favour of epoprostenol. These small changes are not likely to be clinically relevant. Estimation of relevant degrees of RVED or PAP reduction can possibly be derived indirectly from human thrombolysis studies, since thrombolytic treatment was associated with reduced mortality (4.7% vs 11.1%) in the setting of right ventricular dilatation in acute pulmonary embolism [21]. Three studies reported data on RVED after thrombolytic treatment. These studies demonstrated reductions in right ventricular dimensions ranging from 15% to 49% within 24 hours [22-24]. Combining these results, a decrease in RVED of at least 15% might be the best possible estimation of clinical relevant reduction in RVED. This is twice the maximal observed effect we found in our pilot study. A post-hoc
power analysis of our study data indicated that we had 80% power to detect a difference in RVED between treatment arms as large as 16%. Furthermore, it would require 55 subjects to confirm an 8% difference in treatment effect with a study of sufficient statistical power (80%). In considering such a trial, however, one would need to weigh the objective of demonstrating only a potential modest benefit in mortality reduction against the potential safety concerns and the costs of epoprostenol treatment.

Why doesn’t epoprostenol have a more pronounced effect? In animal models of acute pulmonary embolism, treatment with different vasodilators, including prosta-cyclin, was associated with a more pronounced decrease in mean PAP of 12-33% [14,25-27]. However, the administration of vasodilating agents in these experiments was started immediately after or even before the onset of acute pulmonary embolism. Since pulmonary vasocontraction is an early and partially transient phenomenon in acute pulmonary embolism [14], this might explain why animal models show a larger benefit of vasodilator treatment. In our pilot study, we treated patients with epoprostenol several hours after the onset of symptoms. The absence of a decrease in systolic PAP in either treatment group may indicate that patients were already past the phase of acute pulmonary vasocontriction. Normally, it takes time to get to the hospital, to undergo diagnosis and echocardiography, making earlier treatment difficult to realise in normal practice. This may also be the explanation for the minimal effect of the serotonin receptor blocker ketanserin on PAP and cardiac output in patients with acute pulmonary embolism [28]. For inpatients suffering from acute pulmonary embolism, however, the situation might be different, and pulmonary vasodilatory therapy may still be effective. It might be argued that right ventricular dysfunction was not severe enough to expect a beneficial effect of epoprostenol. Indeed, TAPSE was at the lower limit of normality, suggesting at most mild right ventricular dysfunction. Pseudonormality of TAPSE can be caused

| Definition of abbreviations: PAP = pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; RVFAC = right ventricular fractional area change; RAD = right atrial end-diastolic diameter; RV/LV = right/left ventricular end-diastolic diameter; ABPs = systolic arterial blood pressure; ABPd = diastolic arterial blood pressure; ABPm = mean arterial blood pressure; RVED = right ventricular end-diastolic diameter; Values are given as the mean ± SD. NT-proBNP and troponin T are given as median (range). |
| At no time point significant differences of these parameters between treatment groups were observed (P > 0.20). Data for NT-proBNP and Troponin T were log-transformed for statistical testing. |

### Table 2 Changes in echocardiographic parameters, blood pressure and biochemical variables associated with acute right ventricular overload

|                      | Baseline     | T = 2.5 hrs | T = 24 hrs | T = 72 hrs |
|----------------------|--------------|-------------|------------|------------|
| RVED (mm)            |              |             |            |            |
| Placebo              | 41 ± 8       | 43 ± 8      | 42 ± 7     | 38 ± 5     |
| Epoprostenol         | 41 ± 8       | 43 ± 7      | 38 ± 6     | 40 ± 9     |
| Systolic PAP (mmHg)  |              |             |            |            |
| Placebo              | 47 ± 11      | 48 ± 17     | 41 ± 7     | 46 ± 9     |
| Epoprostenol         | 57 ± 14      | 50 ± 19     | 55 ± 22    | 50 ± 14    |
| TAPSE (cm)           |              |             |            |            |
| Placebo              | 2.0 ± 0.5    | 2.1 ± 0.6   | 2.3 ± 0.3  | 2.2 ± 0.6  |
| Epoprostenol         | 1.9 ± 0.6    | 1.9 ± 0.5   | 2.0 ± 0.6  | 2.0 ± 0.5  |
| RVFAC (%)            |              |             |            |            |
| Placebo              | 24 ± 18      | 28 ± 21     | 25 ± 17    | 29 ± 16    |
| Epoprostenol         | 34 ± 24      | 34 ± 10     | 35 ± 16    | 33 ± 10    |
| RAD (cm)             |              |             |            |            |
| Placebo              | 4.7 ± 0.7    | 4.4 ± 0.8   | 4.7 ± 1.3  | 4.3 ± 0.9  |
| Epoprostenol         | 4.2 ± 0.9    | 4.6 ± 1.0   | 4.1 ± 1.2  | 4.1 ± 1.0  |
| RV/LV                |              |             |            |            |
| Placebo              | 0.82 ± 0.16  | 0.88 ± 0.10 | 0.89 ± 0.15| 0.69 ± 0.07|
| Epoprostenol         | 0.87 ± 0.24  | 0.97 ± 0.14 | 0.77 ± 0.23| 0.79 ± 0.15|
| ABPs (mmHg)          |              |             |            |            |
| Placebo              | 117 ± 6      | 114 ± 12    | 118 ± 19   | 124 ± 11   |
| Epoprostenol         | 125 ± 27     | 123 ± 26    | 118 ± 18   | 134 ± 29   |
| ABPd (mmHg)          |              |             |            |            |
| Placebo              | 70 ± 10      | 71 ± 6      | 72 ± 12    | 74 ± 11    |
| Epoprostenol         | 66 ± 14      | 70 ± 12     | 71 ± 11    | 72 ± 11    |
| ABPm (mmHg)          |              |             |            |            |
| Placebo              | 86 ± 10      | 86 ± 7      | 87 ± 11    | 91 ± 10    |
| Epoprostenol         | 82 ± 15      | 88 ± 6      | 87 ± 12    | 93 ± 12    |
| CO (l/min)           |              |             |            |            |
| Placebo              | 6.2 ± 1.7    | 6.5 ± 0.6   | 6.7 ± 1.2  | 5.4 ± 1.2  |
| Epoprostenol         | 5.5 ± 1.2    | 6.4 ± 1.1   | 5.9 ± 0.8  | 6.0 ± 0.8  |
| NT-proBNP (pg/ml)    |              |             |            |            |
| Placebo              | 1467 (39-8549) | 925 (33-8322) | 694 (84-6954) | 343 (130-7240) |
| Epoprostenol         | 3885 (270-12339) | 3043 (352-4811) | 3089 (415-4892) | 614 (147-4268) |
| Troponin T (ng/ml)   |              |             |            |            |
| Placebo              | 0.01 (0.01-0.09) | 0.01 (0.01-0.09) | 0.01 (0.01-0.07) | 0.01 (0.01-0.04) |
| Epoprostenol         | 0.03 (0.01-0.13) | 0.02 (0.01-0.12) | 0.01 (0.01-0.07) | 0.01 (0.01-0.08) |
by severe tricuspid valve regurgitation but this was not
the case in our patients. RVFAC, however, another
indicator of right ventricular function, was diminished
suggesting at least moderate dysfunction. It is intri-
guing why TAPSE and RVFAC seem incongruente in
our patients. These parameters usually correlate well,
although TAPSE can be normal in patients with a low
RVFAC [29]. It is, however, possible that a pulmonary
vasodilator would have a more pronounced effect in
patients with more severe right ventricular dysfunction.

The choice for intravenous epoprostenol as a vasodila-
tor merits discussion. Firstly, it could be argued that
intravenous administration of epoprostenol might cause
nonselective vasodilation which could lead to intrapul-
monary shunting and systemic hypotension. However,
hypotension or a decrease in PO₂ (data not shown) did
not occur in the patients who received epoprostenol
infusion in our study. Inhalation of prostacyclin or nitric
oxide is more selective for pulmonary vasculature and
has shown to decrease pulmonary artery pressure in
case reports of acute pulmonary embolism [30,31].
However, inhalation of prostacyclin might increase dead
space, possibly due to mucosal swelling [32] and inhala-
tion of nitric oxide is difficult to implement in patients
who are not on mechanical ventilation. Secondly, it has
been suggested that intravenous administration of epo-
prostenol in pigs was associated with reduced right
ventricular contractility [33], yet a recent study could
not detect a change in measures of right ventricular
contractility [34]. In humans with chronic pulmonary
hypertension, epoprostenol was associated with
unchanged right ventricular dimensions or even
increased cardiac output [35,36]. The effect of epopros-
tenol on right ventricular function in acute pulmonary
hypertension is not well known. Thirdly, it is possible
that the dose of epoprostenol was not sufficient to
decrease PAP. One might argue that uptitrating iv epo-
prostenol until systemic side effects like arterial hypo-
tension occur, would be more likely to reveal beneficial
effects on right ventricular overload and pulmonary
pressures. However, increasing the dose of epoprostenol
to 7.2 ng/kg/min, which is generally considered as high-
dose, in 3 patients did not result in reduction in RVED.
We did not further increase epoprostenol infusion rate
because higher doses are usually associated with intoler-
able side-effects [37]. Finally, it is also important to
point out that other pulmonary vasodilators have differ-
ent pharmacological properties, and our findings thus
cannot be extrapolated to these alternatives.

Conclusions
This small randomized controlled trial investigated the
effect of epoprostenol in patients with acute pulmonary
embolism and right ventricular dilatation. In contrast to
the results of several case reports and studies in animals, treatment with epoprostenol in humans did not improve right ventricular dilatation or any other measured variables of right ventricular overload.

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Authors’ contributions
AJK was involved with data acquisition, participated in the design of the study, performed the statistical analysis and drafted the manuscript; RGIJ carried out the echocardiographic analysis; ABB participated in the design of the study; YSM supervised the design of the study, participated in the statistical analysis and manuscript drafting. All authors read and approved the final version of the manuscript.

Competing interests
Alberius J Kooter has no conflicts of interest to disclose; Richard G Lizerman has no conflicts of interest to disclose; Otto Kamp has no conflicts of interest to disclose; Anco Boonstra’s employer received in the past 3 years an unrestricted educational grant from GSK and Actelion, and has been reimbursed for doing phase III trials for GSK and Actelion. Anco Boonstra has served as a paid speaker for Actelion; Yvo M Smulders has no conflicts of interest to disclose.

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