

Answers to reviewer's comments	
Reviewer 1	
Comment	The major limitation is that the number of patients in particular in the reversible group is quite small. Is there any "responder" among those 15 subjects not included in the study because of short follow-up and /or no cardiac catheterization? Should it be possible to increase the number of "responder"?
Answer	<p>Thank you for your valuable comment.</p> <p>We agree that the major limitation of the study is the small number of patients. The reasons are</p> <ol style="list-style-type: none"> (1) We included only patients with isolated large VSD to maintain uniformity in the study population. We strictly excluded patients with large VSDs who had other associated shunts (ASD or PDA), valve abnormalities and arterial malalignment (e.g.; DORV with normally related great arteries) (2) It was practically very difficult to get these high risk 'postoperative' patients for follow-up catheterization as majority of them are symptomatic and are not doing well after surgery. <p>Out of 30 patients who were operated, three could not be contacted after the first review. They were very symptomatic and had severe RV dysfunction during the first review itself. Their survival could not be confirmed. Sudden late death of one child who had severe symptoms and RV dysfunction after surgery could be confirmed. Among the remaining 26 patients who could be contacted, all of them had completed at least one year postoperative period but only 14 patients gave consent for follow-up catheterization.</p> <p>During data analysis, when we found only three 'Responders', we looked in to the case details of the remaining 12 patients who could not be catheterized. We analyzed their preoperative' catheterization data, postoperative symptom status & latest echocardiographic data to know whether there are more number of responders. We found that only two out of these twelve patients had the clinical and hemodynamic profile similar to 'Responders'. This suggested that majority of 'borderline operable' patients in our group are not doing well at midterm after high risk VSD closure. Even if these twelve patients are catheterized in future, we are sure that the number of 'responders' may remain very low compared to the non responders.</p> <p>We did not want to include patients who were operated after December 2010 because they may not have completed one year postoperative period. Survival in the long-term is the ideal end point for this study. As this goal is practically difficult, we chose a short-term end point of post operative survival and a PVR <3 Wu.m2 at 1 year after surgery with or without the need for continued PAH therapy. One year postoperative period is a reasonable time when patient would have recovered from the stress of surgery and the hemodynamic data would better reflect their long term status. Also the chances of losing the patients for follow up may be minimal at one year postoperative period.</p>
Changes in the manuscript	We have modified the limitations section of the manuscript. [Ref Discussion - Limitations of the study [Page number 16 ; Highlighted]
Reviewer 2	

Comment	The study has several limitations, some of which are acknowledged by the authors and some are not. The authors should include a separate limitations section and clearly state the shortcomings of the study.
	<ol style="list-style-type: none">1. Very small sample size: There are only 3 “responders”. Most statistical comparisons would have very limited validity because of this.2. Loss to follow up: While only 3 patients were lost to follow up this represents 10% of the original sample and is therefore significant in the context of this study.3. Measurement of oxygen consumption: While the authors have not stated the method used, it is quite likely that oxygen consumption is assumed from table. This is significantly error prone.4. The variable use of pulmonary vasodilators: Sildenafil was used in the latter part of the study. It is quite possible that sildenafil could have influenced baseline calculations.5. Interestingly, only 14 of 26 study patients completed one year follow up. This suggests that most patients were operated in the last few years of the study. Perhaps, the availability and widespread use of sildenafil may have resulted in relatively liberal recommendation for surgery.6. Since this is a retrospective study, the criteria for operation for VSD with PAH may not be uniform for the institution. This may limit the external validity of the results.

<p>Answer</p>	<p>Thank you for the suggestion. We will surely include a separate limitations section and mention all the shortcomings of the study.</p> <ol style="list-style-type: none"> 1. We agree that the sample size is small and makes statistical analysis less valid. There were practical difficulties involved in getting these high risk patients for followup catheterization as majority of them are not doing well after surgery. Also we had included only patients with isolated large VSDs to maintain uniformity in the study population. We had strictly excluded patients with large VSDs who had other associated shunts (ASD or PDA), valve abnormalities and arterial malalignment (e.g.; DORV with normally related great arteries). 2. The three patients lost to follow up representing 10% of the study group are definitely significant in this study. These patients were lost to follow up after the first review at three months after surgery. All were symptomatic with high RV pressure during the first review and one of them had severe RV dysfunction. The survival of these three patients could not be confirmed. 3. We have already mentioned in the limitation section that oxygen consumption is assumed and not measured : “Oxygen consumption was assumed and not measured and this could contribute to errors in flow and resistance calculations.” 4. We would like to highlight a fact that sildenafil was not used preoperatively in only two out of the thirty operated patients. Sildenafil was not included in the latter part of the study. In this study, we could not comment on the influence of sildenafil on the hemodynamic data and the outcome as it needs future prospective case controlled study. We made some observations in this study about the use of sildenafil. Irrespective of the use of optimal dose of sildenafil for a minimum period of 3 months preoperatively, only those who had baseline PVRI < 6 and baseline RR<0.3 became responders. The response to 100% oxygen while on sildenafil therapy did not influence outcome. One child (Non responder patient 1) who received sildenafil for 18 months showed gradual reduction in base line PVRI and RR in three consecutive preoperative catheterization. She was operated based on the third Her PVRI and RR bounced back to high values after surgery despite continued use of Sildenafil. This case revealed the fact that sildenafil may have influence on the preoperative base line hemodynamic data but may not have any influence on the progression of pulmonary vascular obliterative disease with increasing age. This fact needs confirmation with future prospective studies as suggested by Beghetti et al.⁷ 5. We apologize for not making it clear that all the thirty patients included in the study have completed at least one year postoperative period. This is why we had limited the study period till 2010. It is mistaken that most patients were operated in the last few years of the study. Only two out of the thirty patients did not receive sildenafil before surgery. However we fully agree that throughout the study period, the availability and widespread use of sildenafil may have resulted in relatively liberal recommendation for surgery. 6. As there was no standard operability criteria available in the literature, the decisions for operability are often taken arbitrarily by the treating team using an empirical institutional criteria as a guide line. In this retrospective analysis, as the criteria for operation may not be uniform for the institution, the external validity of the study results is also limited. We have added this information in the limitation section.
<p>Changes in the manuscript</p>	<ol style="list-style-type: none"> 1) We have modified the limitations section of the manuscript. [Ref Discussion - Limitations of the study [Page number 16 ; Highlighted] 2) We have included the information about sildenafil therapy in the discussion section [Page number 16 - paragraph before limitations of the study] 3) In page number 3, patient selection section, we have highlighted that all the study patients had completed at least one year of postoperative period.