Do preoperative haemodynamic data and reactivity test predict the postoperative reversibility of pulmonary arterial hypertension in patients with large ventricular septal defect and borderline operability?

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ABSTRACT

Background Decisions to operate on patients with shunt lesions presenting late with severe pulmonary arterial hypertension (PAH) and borderline operability are often not based on precise cut off values of haemodynamic data owing to paucity of studies.

Objective To assess the reliability of the preoperative haemodynamic data and reactivity test in predicting the postoperative reversibility of PAH in patients with isolated large ventricular septal defects (VSDs) and borderline operability.

Patients and method Between 2004 and 2010, 30 patients underwent VSD closure surgically; no early deaths occurred. Twenty-six patients were followed up regularly (mean 39.6±16 months) and one late postoperative death occurred. Fourteen patients who had been followed up for at least 1 year postoperatively underwent cardiac catheterisation.

Results There were 3 responders (asymptomatic patients with pulmonary vascular resistance (PVR) index <3 WU.m²) and 12 non-responders. The following were lower among responders: mean age at surgery (3.2±0.42 vs 11.55±3.29 years, p=0.027), mean baseline PVR index (3.69±0.8 vs 10.57±9.1, p=0.204), average resistance ratio (RR=0.25±0.01 vs 0.59±0.25, p=0.049) and ratio of pulmonary and systemic mean pressures (PAm:SAm ratio) (0.70±0.009 vs 0.87±0.118, p=0.003).

Conclusions Preoperative ‘base line’ PAm:SAm and RR appear to be better predictors of postoperative outcome than other baseline parameters. Preoperative reactivity test had no significant role in predicting postoperative reversibility of PAH at mid-term.

INTRODUCTION

In patients with a large ventricular septal defect (VSD), surgical closure in the presence of extensive pulmonary vascular obliterator disease (PVOD) may lead to death owing to severe right ventricular (RV) dysfunction. Patients who survive the early postoperative period may also have a worse long-term prognosis owing to persistent postoperative pulmonary arterial hypertension (PAH). Hence knowing the status of the pulmonary vasculature before subjecting these patients to surgery is vital. A wide range in the age of onset and rate of progression of PVOD makes it difficult to determine the extent of the disease before surgery.1–3 In most patients, a combination of clinical assessment and non-invasive investigations can be used to assess operability. A small subset of these patients, however, with high pulmonary vascular resistance (PVR) and ‘borderline operable’ status may not have clear-cut clinical evidence of the extent of PVOD.4 Determining operability in these patients is often difficult because the response of the pulmonary vasculature to high pulmonary blood flow is not uniform and the PVOD does not occur in a predictable manner.5

The empirical operability criteria available in the literature6 vary widely between centres and are based primarily on the experience of the centres managing these patients. Since there are no management guidelines for deciding operability, decisions are usually made arbitrarily on a case-by-case basis.7 Studies testing haemodynamic data against the late outcome after surgery are necessary to develop definitive operability criteria for these high-risk patients. Our study aimed at assessing the reliability of the preoperative haemodynamic data and reactivity test result in predicting the postoperative reversibility of PAH.

PATIENTS AND METHOD

This study was undertaken in a tertiary cardiac care referral hospital in Chennai, India. The institutional ethics committee approved the study. Written informed consent was obtained from all study patients before follow-up cardiac catheterisation, and for patients aged <18 years, consent was obtained from one of their parents.

Patient selection

Between January 2004 and December 2010, 30 patients with isolated large VSD, severe PAH and features of borderline operability underwent high-risk surgical closure in our institution; no early postoperative death occurred. At a mean follow-up period of 39.6±16 months, all 30 patients had completed at least 1 year of postoperative period. Subsequently, one patient died suddenly at home and three patients were completely lost to follow-up. Of the 26 patients available for...
follow-up, 14 gave consent for a prospective study which involved clinical evaluation and follow-up cardiac catheterisation. We retrospectively analysed the preoperative and postoperative clinical, haemodynamic and reactivity test data of 15 patients (14 catheterised and the one patient who died).

The preoperative characteristics of the 15 study patients were as follows:

1. (a) No symptoms suggestive of increased pulmonary blood flow. All except two patients had symptoms of shortness of breath and fatigue. (b) No obvious cyanosis, resting oxygen saturation (SpO2) by pulse oximetry ranged between 90% and 95%. (c) Clinical signs of severe PAH present and no signs of heart failure. (d) Chest x-ray examination showed features of pruning. (e) RV hypertrophy in the electrocardiogram. (f) Echocardiography showed bidirectional but predominantly left to right VSD shunt. Estimated RV systolic pressure and ventricular function by echocardiography suggestive of systemic systolic pulmonary artery pressure and good biventricular function. Right heart enlargement was seen in all patients and one had mild left heart enlargement.

2. All patients had features of borderline operability at the time of presentation, defined as having no obvious cyanosis, no digital clubbing, resting saturation ≥90% by pulse oximetry and bidirectional with predominantly left to right shunt by echocardiography.

3. Except two patients who underwent surgery before we started using sildenafil in our institution, all others received at least 3 months of pulmonary vasodilator treatment before the preoperative cardiac catheterisation. Sildenafil citrate was given orally in a gradually titrated dosage of 2–5 mg/kg/day and as tolerated by the patients.

4. Baseline resistance and reactivity to 100% oxygen were assessed during preoperative catheterisation. All 15 patients were accepted for high-risk VSD repair based on the pulmonary vascular reactivity criteria followed in our institution. Patients were considered operable if all the following criteria were met during reactivity test with 100% oxygen: (a) increase in Qp/Qs to at least twice the baseline value; (b) decrease in PVR index (PVRI) by at least 25% of the baseline value with a final PVRI of <6 WU.m⁻²; (c) decrease in the resistance ratio (RR) by at least 25% of the baseline value with a final RR of <0.3.

5. In line with the strategy followed in the institution, all 15 study patients received a small (3 mm) fenestration in the VSD patch during surgery. Three patients had an additional small muscular VSD and/or a patent foramen ovale left open. To prevent acute RV failure in the immediate postoperative period, measures such as elective ventilation for 24 h, inotropes with pulmonary vasodilatory properties such as vasoressin and milrinone, etc were used. Thirteen patients who were receiving sildenafil treatment preoperatively continued to receive the drug during the postoperative period and at discharge. Patients were followed up postoperatively at 3 months and 12 months after surgery and yearly thereafter.

6. All study patients had been followed up for at least 1 year postoperatively at the time of the cardiac catheterisation. Sildenafil treatment was continued postoperatively if patients were either symptomatic or their follow-up echocardiography showed persistent PAH. Two patients, a 22-year-old man and a 29-year-old woman who were not receiving sildenafil treatment preoperatively, received the drug at 3 years and 6 years postoperatively, respectively, when they presented with symptoms of exertional dyspnoea and fatigue. For two patients, a 3-year-old girl and a 7-year-old boy, the sildenafil treatment was stopped by the treating cardiologist at 3 months and 6 months postoperatively, respectively, as they were asymptomatic and echocardiography was suggestive of normal pulmonary artery pressure.

During patient selection for the follow-up cardiac catheterisation, we excluded patients with the following characteristics: (a) additional anatomical defects, including other shunt lesions, valve lesions and great vessel abnormalities; (b) coexisting major systemic illness; (c) not completed at least 1 year of postoperative period or were not willing to undergo follow-up cardiac catheterisation; (d) persistent postoperative PAH clinically and by echocardiography but drugs discontinued within 6 months before follow-up catheterisation; (e) international patients operated on in our institution but not receiving regular follow-up.

Cardiac catheterisation procedure

During follow-up, all study patients underwent clinical evaluation and non-invasive investigations before undergoing cardiac catheterisation. According to the institution’s protocol all patients were intubated and mechanically ventilated to ensure delivery of 100% oxygen during the reactivity test. Cardiac catheterisation in room air (<30% fractional inspired oxygen) and with administration of 100% oxygen for at least 15 min was carried out to obtain pressure, flow and resistance data. The anaesthetic agents used during the procedure were a combination of intravenous midazolam and fentanyl.

Data analysis

The preoperative and postoperative clinical features analysed were (a) symptoms, (b) cyanosis (SpO₂), (c) presence of signs of heart failure, (d) cardiothoracic ratio and lung vascularity on frontal chest x-ray examination, (e) chamber enlargement or hypertrophy on 12-lead electrocardiogram, (f) estimated RV systolic pressure on echocardiography and (g) duration of preoperative pulmonary vasodilator treatment. Age at surgery was also included in the analysis. For the patient who died, the cause of death was determined.

The haemodynamic data analysed included the preoperative and postoperative baseline and post-oxygen (reactivity test) values of (a) the ratio of pulmonary to systemic mean pressure (PAm:Sam), (b) systemic SpO₂, (c) Qp/Qs, (d) PVRI, (e) systemic vascular resistance index, (f) pulmonary to systemic RR.

The postoperative clinical and haemodynamic data were used to classify the 15 study patients (including one patient who died) into two groups: responders and non-responders. Patients were considered to be responders if they were asymptomatic and their PVRI had fallen to <3 WU.m⁻² at follow-up cardiac catheterisation with or without the need for pulmonary vasodilators. The one patient who died was considered to be a non-responder as the cause of sudden death was determined to be due to severe persisting postoperative PAH. The preoperative clinical and haemodynamic data were analysed to identify the differences between responders and non-responders. The preoperative and postoperative haemodynamic data of all 15 patients are given in table 1.

Statistical analysis

The following parameters were considered for discriminant analysis: age at surgery, preoperative vasodilator treatment, preoperative baseline and post-O₂ PVRI, RR, SpO₂ and PAm:Sam (table 2). An attempt to perform multivariate analysis of the above parameters showed that the discriminant model was not applicable probably owing to the small size of the study group.
<table>
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<th>Age at surgery (years)</th>
<th>Systemic SpO₂ (%)</th>
<th>Qp/Qs</th>
<th>PAm:SAm</th>
<th>PVRI</th>
<th>RR</th>
<th>Systemic SpO₂ (%)</th>
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*A child who underwent three preoperative catheterisation preoperatively.*

PAm:SAm: ratio of pulmonary to systemic mean pressure; PO, pulse oximetry; PVRI, pulmonary vascular resistance index; Qp/Qs, pulmonary to systemic blood flow ratio; RR, resistance ratio.
The above-mentioned variables were used for univariate analysis using an independent t test.

**RESULTS**

Among 15 patients, three were responders and 12 were non-responders. All responders were children (two female, one male) with mean age at surgery of 3.2±0.42 years, mean age at follow-up catheterisation 7.0±0.03 years and mean follow-up period of 38±19.5 months. The 12 non-responders (six male, six female) included four adults. The mean age at surgery was 11.55±3.29 years, the mean age at follow-up cardiac catheterisation was 17.7±3.3 years and the mean follow-up period was 39.6±16 months.

The one patient who died was a child operated on at the age of 2 years and 6 months. Since she had clinical evidence of PAH she was treated with sildenafil for 3 months before cardiac catheterisation. The baseline Qp/Qs was 0.8 and it doubled to 1.96 with oxygen. The baseline PVRI and RR were 9.06 WU.m² and 0.59, respectively, which dropped to 3.145 WU.m² and 0.25, respectively (>50% drop in both values) with oxygen. The PAm:SAm ratio had declined from 0.91 to 0.83. She recovered well after fenestration patch closure. Sildenafil was continued in the postoperative period. At 3 months follow-up, however, she was symptomatic with exertional dyspnoea with SpO₂ of 95%. Her echocardiogram showed bidirectionally shunting fenestration and a tiny residual VSD. The estimated RV systolic pressure (RVSP) was near systemic and there was evidence of RV dysfunction. Sildenafil treatment was continued and a review after 3 months was planned. She suddenly collapsed at home in the late postoperative period.

There was no major difference in the preoperative clinical characteristics of responders and non-responders except for the mean age at surgery (3.2±0.42 years vs 11.5±3.29 years p=0.227). Although the clinical characteristics were similar, differences in preoperative haemodynamic data between responders and non-responders were found. The baseline systemic SpO₂ was >95% in all the responders, whereas it was between 88% and 95% among the non-responders. Five non-responders had baseline systemic saturation <90%.

The average baseline Qp/Qs was higher among responders than non-responders (2.1±0.3 vs 1.2±0.3, p=0.158) and baseline Qp/Qs was <1 in three non-responders. Baseline PVRI was lower among the responders than among the non-responders but this did not reach statistical significance (PVRI=3.69±0.8 vs 10.57±9.1, p=0.204). The average RR (RR=0.25±0.01 vs 0.59±0.25, p=0.049) and the PAm:SAm ratio (0.70±0.009 vs 0.87±0.118, p=0.003) were significantly lower among the responders than among the non-responders. A statistical comparison of the mean values of the haemodynamic data between the responders and the non-responders is given in table 2. The difference in preoperative duration of pulmonary vasodilator treatment did not achieve statistical significance between the two groups.

**DISCUSSION**

Preliminary data have shown worse 10-year postoperative survival for patients with persistent postoperative PAH than for those with Eisenmenger syndrome. This raises the question as to whether high-risk borderline operable patients would be best managed with pharmacological treatment and no operation. It also emphasises the need to establish very strict criteria before subjecting these patients to surgery. However, there is a striking paucity of studies in which haemodynamic data are tested against late outcomes after surgery. A few authors have suggested studies involving follow-up catheterisation at least 1 year after surgery as the ‘gold standard’ method for assessing the reliability of the preoperative haemodynamic data in predicting the late postoperative outcome. Such studies would help to establish definitive operability criteria and a management algorithm for these high-risk patients.

In this study, when preoperative haemodynamic data were analysed against mid-term outcome of borderline operable patients, reactivity test results did not seem to predict the postoperative reversibility of PAH. Among preoperative baseline haemodynamic data, RR and the PAm:SAm ratio were the two parameters which seemed to correlate well with outcome.

There was no difference between responders and non-responders in any of their preoperative clinical features, except age at surgery. All responders were operated on in early childhood, whereas all non-responders had surgery during late childhood (table 1). The child who died in this study group was aged 2.5 years when she was operated on, suggesting a wide range in the age of onset of PVOD. Alt and Shikes have reported five instances of grade IV pulmonary hypertensive arteriopathy in infants with VSD and the youngest was 2.5 months of age, but...
younger patients (<2 years of age) were often considered operable despite advanced changes on lung biopsy.14

In this study, five patients with preoperative baseline systemic SpO2 of <90% and three patients with baseline Qp/Qs of <1 were non-responders. Although these data on baseline systemic SpO2 and baseline Qp/Qs did not have statistical significance in our study, they correlate well with findings of previous studies4 emphasising baseline SpO2 <90% as a strong factor for inoperability.

The two main factors that affect patient outcome after closure of large left to right shunts have been identified by Bando et al15 as age at repair and preoperative PVR. The preoperative baseline PVRI was <6 WU.m² among responders, whereas it was in the inoperable range >9 WU.m² among non-responders (tables 1 and 2). Fried et al14 in the 1950 recognised that higher preoperative pulmonary/systemic arterial pressure (Pp/Ps) and resistance (PVR/SVR) ratios are associated with more advanced stages of pulmonary vascular disease on lung biopsy and a higher incidence of early and late postoperative PAH. Studies based on lung biopsy are limited by the questionable reliability of the test in determining operability in these situations.16 In our study, we matched the preoperative haemodynamic data with the late clinical and haemodynamic outcome of these patients and our results were similar to those of Fried et al.14

Preoperative baseline PAm:SAm and the baseline RR were much lower among the responders and the difference was statistically significant (table 2). The range of RR indicating favourable outcome was 0.231–0.275 and the range associated with unfavourable outcome was 0.46–0.72. This finding strongly supports the conclusions drawn by Lopes and Leary6 on the haemodynamic limits for operability. The range of PAm:SAm associated with favourable outcome was 0.699–0.70 (up to 70%) and the range among the non-responders was 0.81–0.93.

Although we found significant response to 100% oxygen preoperatively in all patients (figure 1), 12 were non-responders at mid-term with symptoms and desaturation. Our experience shows that response to acute vasodilator challenge, as indicated by an increase in SpO2 or Qp/Qs and decrease in resistance, does not predict the postoperative reversibility of PAH. This is similar to the report by Lock et al17 in 25 children with isolated large VSD and raised PVR which showed that preoperative responsiveness of the pulmonary vasculature to oxygen does not predict either operative survival or postoperative PVR.

In this study, we cannot comment on the effect of sildenafil treatment on preoperative haemodynamic data and on mid-term outcome because prospective randomised case-controlled studies are needed to reach such conclusions. However, we can make a few important observations about the use of sildenafil in borderline operable patients. Irrespective of the use of optimal dose of sildenafil preoperatively, only those who had baseline PVRI <6 WU.m² and baseline RR<0.3 became responders. The response to 100% oxygen while receiving sildenafil did not influence the mid-term outcome. One child (non-responder patient 1) while receiving sildenafil treatment for 18 months showed a gradual reduction in baseline PVRI and RR in three consecutive preoperative catheterisation studies. She was operated based on the third haemodynamic study when the PVRI was <6 WU.m² and RR <0.3. Postoperatively, the PVRI

**Figure 1** Graphical representation of the results of a reactivity test performed with 100% oxygen. Solid lines represent non-responders and dashed lines represent responders. PVRI (A) and RR (B) showed a significant fall and SpO2 (D) showed a significant increase with vasodilator challenge. There was no significant change in the mean pressure ratio (C). PVRI, pulmonary vascular resistance index; RR, resistance ratio; SpO2, oxygen saturation.
and RR data of this child bounced back to a high range of values and she was symptomatic despite continued use of silde-
nafil (table 1). This case shows that sildenafil might influence the preoperative baseline haemodynamic data but might have no influence on the progression of PVOD with increasing age. This observation needs confirmation with prospective studies, as suggested by Beghetti et al. 7

Limitations of the study

1. The number of patients is relatively small, limiting the validity of statistical analysis, which is a major limitation. The study group is small due to (a) Only patients with isolated large VSDs were included in the study group to maintain uniformity. Patients with large VSDs associated with other septal defects, aorto-pulmonary shunts, valve abnormalities or arterial malalignment were strictly excluded to minimise fallacies in haemodynamic data. (b) There was practical difficulty in getting consent for follow-up cardiac catheterisation as most patients in this group were symptomatically worse after surgery. When we analysed the preoperative catheterisation data and postoperative follow-up echocardiography of the remaining 12 patients who could not be catheterised, only two patients had a profile similar to the responder group. It is our impression that the number of responders in this study group would remain low even if these 12 patients were catheterised in the future, suggesting that most of these borderline operable patients may not benefit from surgical closure in the mid-term follow-up. This emphasises the need for a consensus statement and strict operability criteria.

2. The three patients lost to follow-up represent 10% of the study group, which is significant. These patients were lost to follow-up after the first review at 3 months after surgery. All were symptomatic with high RV pressure during the first review and one of them had severe RV dysfunction. The survival or otherwise of these three patients could not be confirmed.

3. Although we prospectively enrolled patients for follow-up catheterisation, it was a retrospective study. As there are no standard operability criteria available in the literature, the decision to operate was often taken arbitrarily by the treating team using empirical institutional criteria as a guideline. 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.

4. Oxygen consumption was assumed and not measured. This might have contributed to errors in flow and resistance calculations.

5. Long-term survival is the best end point for this study. In practice this is difficult to measure, and so we chose a short-term end point of postoperative survival and a PVR <3 WU. m² at 1 year after surgery with or without the need for con-
tinued PAH treatment. A 1-year postoperative period is a reasonable time for a patient to have recovered from the stress of surgery and the haemodynamic data at this time would better reflect their long-term status. Additionally, the chances of losing patients for follow-up is minimal at 1 year postoperatively.

We conclude that baseline preoperative haemodynamic data rather than reactivity test results would help in predicting the postoperative reversibility of PAH at mid-term follow-up. A fall in baseline PVR and RR values with 100% oxygen to acceptable levels does not mean a fall in these parameters after surgical VSD closure. To establish the impact of pulmonary vasodilator treatment on the long-term outcome of these patients, further prospective randomised controlled studies are needed.

The literature on assessment of operability in borderline operable patients is inconclusive. Our study results add value to the existing empirical operability criteria. Similar studies from various centres, matching preoperative haemodynamic data against late postoperative outcome would lead to an evidence-based treatment algorithm.

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