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Brief Report

Comparison of the effect of inhaled anaesthetic with intravenous anaesthetic on pulmonary vascular resistance measurement during cardiac catheterisation

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Abstract *Background*: Children with pulmonary hypertension routinely undergo pulmonary vascular resistance studies to assess the disease severity and vasodilator responsiveness. It is vital that results are accurate and reliable and are not influenced by the choice of anaesthetic agent. However, there are anecdotal data to suggest that propofol and inhalational agents have different effects on pulmonary vascular resistance. *Methods*: A total of 10 children with pulmonary hypertension were selected sequentially to be included in the study. To avoid confounding because of baseline anatomic or demographic details, a crossover protocol was implemented, using propofol or isoflurane, with time for washout in between each agent and blinding of the interventionalist. *Results*: Pulmonary and systemic vascular resistance were not significantly different when using propofol or isoflurane. However, the calculated resistance fraction – ratio of pulmonary resistance to systemic resistance – was significantly lower when using propofol than when using isoflurane. *Conclusions*: Although no difference in pulmonary vascular resistance was demonstrated, this pilot study suggests that the choice of anaesthetic agent may affect the calculation of relative pulmonary and systemic vascular resistance, and provides some preliminary evidence to favour propofol over isoflurane. These findings require replication in a larger study, and thus they should be considered in future calculations to make informed decisions about the management of children with pulmonary hypertension.

Keywords: Propofol; isoflurane; pulmonary hypertension; pulmonary vascular resistance; paediatrics

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PULMONARY HYPERTENSION IS A CHRONIC CONDITION, whether idiopathic or in association with conditions such as congenital heart disease. Children with pulmonary hypertension are usually asymptomatic initially, presenting late with breathlessness, fatigue, and in severe cases cyanosis, as heart failure develops. Recent advances in treatment have resulted in improved survival rates of 71.9% in 5 years.[1] Often children with congenital heart disease are known from an early age, but they may present late and have established pulmonary vascular disease occasionally.

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Pulmonary hypertension is defined as a mean pulmonary artery pressure above 25 mmHg at rest.[2] Although pulmonary pressure can be estimated using echocardiography, gold standard measurement is through "pulmonary vascular resistance studies" involving cardiac catheterisation, under general anaesthesia in children. As these investigations guide clinical management, minimal interference from anaesthetic drugs is essential.

Existing data indicate that, in adults with acute pulmonary hypertension, for example during one-lung ventilation, propofol reduces pulmonary and systemic vascular resistance,[3] whereas isoflurane has no effect on pulmonary vascular resistance but does affect pulmonary perfusion.[4] However, data from children with chronic pulmonary hypertension are lacking.

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There is anecdotal evidence from senior anaesthetists to suggest that pulmonary vascular resistance varies whether propofol or volatile agents are used for anaesthesia. This pilot study aims to compare the effect on pulmonary vascular resistance of these two agents in children undergoing cardiac catheterisation.

Patients and methods

Children with clinical and echocardiographic evidence of pulmonary hypertension and with no history of allergy to propofol or isoflurane were included in the study. Ethical and regulatory approval was granted and the study was registered with the clinical trials database. Statistical analysis was performed using the Wilcoxon signed-rank test. Results are shown as median and range.

Children were selected for pulmonary vascular resistance studies if there was evidence of a raised pulmonary artery pressure – tricuspid regurgitant jet peak velocity of more than 3 m/second when awake and breathing spontaneously – and raised pulmonary vascular resistance. The complete clinical data of these children are shown in Table 1.

The pulmonary vascular resistance studies were carried out using the standard cardiac catheterisation protocols. Each child was randomised to receive maintenance anaesthesia with propofol – end target concentration 3 mcg/ml – followed by isoflurane – age-related dose of 1 minimum alveolar concentration – or the reverse. Induction was performed using the first maintenance agent – sevoflurane was substituted for isoflurane – followed by fentanyl and rocuronium.

The clinician performing cardiac catheterisation was blinded as to which agent was being used, although the anaesthetist was aware. An initial blood gas sample was taken to ensure that the arterial partial pressure of carbon dioxide was in the normal range and that the child was stable before the study ensued. Measurements of pulmonary vascular resistance, haemodynamic parameters, bispectral index monitoring, and lung compliance were taken by the catheterising clinician at baseline – oxygen <35% – and at increasing concentrations of nitric oxide 10 ppm then 20 ppm – and then added oxygen (100%). Bispectral index is an empirically derived parameter based on electroencephalographic activity, which indicates the depth of anaesthesia.

Baseline measurements were repeated for the second anaesthetic agent after at least a 15-minute washout. Measures were also taken to ensure that haemodynamic parameters such as heart rate, blood pressure, and oxygen saturations were back to baseline. The total study time was ~2 hours.

Pulmonary vascular resistance was calculated from anonymised data using Darcy's Law.[5] Mixed venous saturations were taken from the superior and inferior vena cava in the standard manner. Oxygen consumption was measured using a mass spectrometer. A decrease in mean pulmonary vascular resistance in response to nitric oxide of more than 20% was considered to indicate reactive pulmonary vasculature amenable to oral vasodilator therapy. As such, a 20% difference in pulmonary vascular resistance between anaesthetic agents was considered clinically significant.

Results

A total of 10 children were randomised. They had a median weight of 9.8 kg (range 5–62 kg) and age of 1.8 years (range 8 months to 14 years). Their underlying conditions included ventricular septal defects,

Table 1. Demographic and anatomic data for each patient

Patient	Diagnosis	Age (years)	Weight (kg)	$PaCO_2$ (mmHg)	pH	Peak tricuspid regurgitation jet velocity (m/second)
1	Pre-term, bronchopulmonary dysplasia, patent ductus arteriosus ligated	1.2	6.0	44.7	7.36	4.1
2	Supravalvar mitral membrane (repaired)	14.3	62.0	44.1	7.36	3.6
3	Atrial septal defect, left ventricular dysfunction	0.8	7.2	43.8	7.33	3.2
4	Trisomy 21, ventricular septal defect (repaired)	2.4	10.8	45.0	7.34	3.3
5	Coarctation (repaired)	3.0	12.8	36.1	7.40	3.2
6	Trisomy 21, atrioventricular septal defect (repaired), tracheobronchomalacia	3.9	11.4	47.9	7.35	3.5
7	Trisomy 21, obstructive sleep apnoea, small ventricular septal defect	1.0	7.6	46.2	7.35	3.2
8	Ventricular and atrial septal defects (repaired)	0.8	5.0	42.0	7.40	3.4
9	Trisomy 21, tracheomalacia	0.8	8.8	45.0	7.36	3.3
10	Coarctation (repaired), bronchomalacia	4.4	16.2	43.7	7.39	4.2

$PaCO_2$ (arterial partial pressure of carbon dioxide) and pH are recorded at the baseline in each patient.

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Table 2. Measured physiological parameters with isoflurane and propofol anaesthesia

Parameter	Isoflurane	Propofol	p-value
Pulmonary vascular resistance (Wood units/m^2)	2.84 (1.48–11.42)	2.66 (0.95–11.55)	0.25
Systemic vascular resistance (Wood units/m^2)	14.68 (8.89–21.15)	16.04 (9.03–25.80)	0.08
Resistance fraction (Rp/Rs)	0.24 (0.13–1.39)	0.18 (0.05–1.29)	0.004*
Bispectral index	48.6 (24.3–62.0)	47.8 (29.9–66.3)	1.00
Lung compliance (ml/cmH_2O)	11.5 (1.9–24.7)	12.0 (1.8–27.3)	0.57

Rp = pulmonary vascular resistance; Rs = systemic vascular resistance.
Median (range).

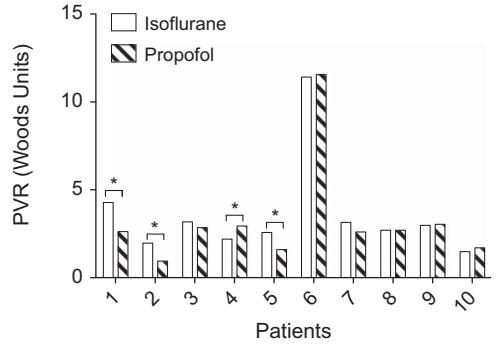

Figure 1.
*Pulmonary vascular resistance (PVR) (Wood units/m^2) measured for each patient with each anaesthetic agent. *Difference >20%.*

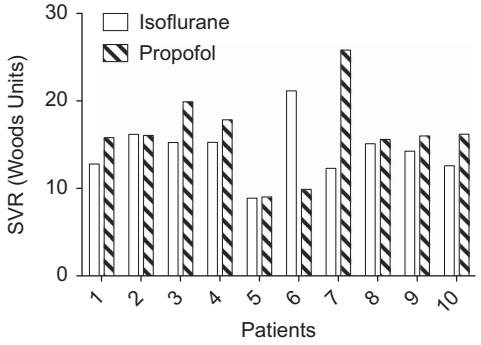

Figure 2.
Systemic vascular resistance (SVR) (Wood units/m^2) measured for each patient with each anaesthetic agent.

coarctation of the aorta, and mixed syndromes (see Table 1).

Baseline measurements of pH and arterial carbon dioxide partial pressure from the beginning in each patient are shown in Table 1. These variables were rechecked before the initiation of the second anaesthetic agent; there were no significant changes.

No significant difference in baseline pulmonary or systemic vascular resistance was seen between propofol and isoflurane (Table 2). In all, four children showed a difference in pulmonary vascular resistance of >20% between the two agents (Figure 1). Systemic vascular resistance and resistance fraction for each child with both anaesthetic agents are shown in Figure 2 and Figure 3. The resistance fraction – ratio of pulmonary to systemic vascular resistance – recorded with propofol was significantly lower than that with isoflurane ($p = 0.004$). Pulmonary vascular responsiveness to nitric oxide, measured for the initial anaesthetic, was not significantly different between the agents ($p = 0.89$). The depth of sedation, as measured using bispectral index, and lung compliance were similar in the two groups.

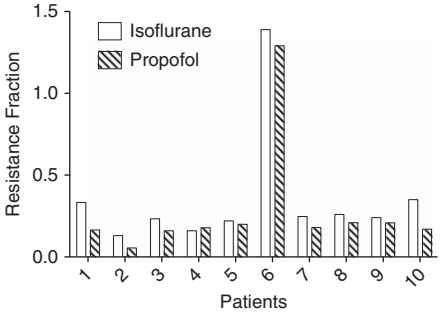

Figure 3.
Resistance fraction – ratio of pulmonary vascular resistance to systemic vascular resistance – measured for each patient with each anaesthetic agent.

Discussion

The effects of anaesthetic agents on the pulmonary vasculature of children with pulmonary hypertension are relatively unknown, and the choice of anaesthetic agent is largely based on individual preference and extrapolation of data from adult studies. However, as the results of pulmonary vascular resistance studies determine both prognosis and treatment, it is vital that the anaesthetic has minimal impact on measurements taken.

Children with pulmonary hypertension represent a significant anaesthetic challenge and it is important that preload, contractility, and systemic vascular resistance are maintained, while avoiding increases in

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pulmonary vascular resistance.[6] Many factors can increase pulmonary vascular resistance, including hypoxaemia, hypercarbia, acidosis, pain, and hypothermia, all of which can be minimised through optimised anaesthesia.[7]

Existing data from adults indicate that volatile anaesthetics lessen hypoxic pulmonary vasoconstriction and impair ventilation–perfusion matching, while also impairing cardiac contractility and reducing systemic vascular resistance.[4,8] Propofol has been shown to significantly reduce pulmonary vascular resistance in adults,[3] whereas in children with congenital heart disease studies have demonstrated that propofol reduces systemic vascular resistance.[9,10]

This study demonstrated no significant difference in pulmonary or systemic vascular resistance between propofol and isoflurane. However, the resistance fraction – ratio of pulmonary to systemic resistance – was significantly higher for isoflurane than propofol. This is partially explained by a tendency towards lower pulmonary vascular resistance with propofol compared with isoflurane, which is in line with existing adult data. However, the data also suggest that isoflurane has a more pronounced effect on lowering systemic vascular resistance compared with propofol. Previous studies show conflicting evidence in this regard,[11,12] and further research directly comparing these two agents is required to substantiate these results.

Elevations in resistance fraction are associated with worsening right-to-left intracardiac shunting in the presence of a residual shunt and with consequent hypoxaemia. A decrease in systemic vascular resistance also reduces coronary perfusion of the right heart. Therefore, these data provide some initial evidence to suggest that propofol may be a more suitable anaesthetic agent than isoflurane, although further evidence is needed.

This pilot study is limited by patient heterogeneity and a small sample size. However, efforts were made to account for possible confounders, such as hypoxia and hypercarbia, and blinding of the interventionalist to the anaesthetic-minimised measurement bias. The crossover design helps to account for any differences in the way the anaesthetics affected the circulation or in the effect of the anatomic variation of the children. The washout period used was limited for ethical reasons, and although all reasonable efforts were made to ensure complete drug elimination it is conceivable that there may have been some residual drug effect, especially when isoflurane was used first; propofol has a rapid distribution half-life of 2–4 minutes[13] and isoflurane/sevoflurane has an early-phase elimination of around 10 minutes.[14]

Most of the patients included had only moderate elevations in pulmonary vascular resistance, and in some cases pulmonary pressure was normal when the child was intubated. This often indicates that pulmonary hypertension while awake is due to upper airway obstruction. However, these children were still included, as the primary purpose of this study was to assess the impact of anaesthetic agents, irrespective of the initial pulmonary vascular resistance.

In conclusion, this pilot study provides some preliminary evidence to suggest that propofol may be preferable to isoflurane for pulmonary vascular resistance studies, but a larger trial would add statistical weight. Given the multitudinous factors influencing pulmonary vascular resistance, balanced and closely monitored anaesthesia should remain the primary focus, although the anaesthetic agent used must be considered when treatment decisions are made.

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Financial Support

None.

Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the Medicines for Human Use (Clinical Trials) Regulations 2004 and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the Central Bristol Research Ethics Committee.

References

1. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: a national cohort study. Heart 2010; 96: 1401–1406.
2. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. Eur Respir J 2009; 34: 888–894.
3. Hammaren E, Hynynen M. Hemodynamic effects of propofol infusion for sedation after coronary-artery surgery. Br J Anaesth 1995; 75: 47–50.
4. Loeckinger A, Keller C, Lindner KH, Kleinsasser A. Pulmonary gas exchange in coronary artery surgery patients during sevoflurane and isoflurane anesthesia. Anesth Analg 2002; 94: 1107–1112.
5. Freed M. Invasive Diagnostic and Therapeutic Techniques Part 1: Cardiac Catheterisation. Williams and Wilkins, London, 2000.

https://doi.org/10.1017/S1047951114000195 Published online by Cambridge University Press

6. MacKnight B, Martinez EA, Simon BA. Anesthetic management of patients with pulmonary hypertension. Semin Cardiothorac Vasc Anesth 2008; 12: 91–96.
7. Friesen RH, Williams GD. Anesthetic management of children with pulmonary arterial hypertension. Pediatr Anesth 2008; 18: 208–216.
8. Fischer LG, Van Aken H, Burkle H. Management of pulmonary hypertension: physiological and pharmacological considerations for anesthesiologists. Anesth Analg 2003; 96: 1603–1616.
9. Oklu E, Bulutcu FS, Yalcin Y, Ozbek U, Cakali E, Bayindir O. Which anesthetic agent alters the hemodynamic status during pediatric catheterization? Comparison of propofol versus ketamine. J Cardiothorac Vasc Anesth 2003; 17: 686–690.
10. Williams GD, Jones TK, Hanson KA, Morray JP. The hemodynamic effects of propofol in children with congenital heart disease. Anesth Analg 1999; 89: 1411–1416.
11. Mishra L, Pradhan S, Pradhan C. Comparison of propofol based anaesthesia to conventional inhalational general anaesthesia for spine surgery. J Anaesthesiol Clin Pharmacol 2011; 27: 59–61.
12. Keegan RD, Greene SA. Cardiovascular effects of a continuous 2-hour proposal infusion in dogs. Comparison with isoflurane anaesthesia. Vet Surg 1993; 22: 537–543.
13. Kanto J, Gepts E. Pharmacokinetic implications for the clinical use of propofol. Clin Pharmacokinet 1989; 17: 308–326.
14. Behne M, Wilke HJ, Harder S. Clinical pharmacokinetics of sevoflurane. Clin Pharmacokinet 1999; 36: 13–26.

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