Cardiology in the Young

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A systematic review of clinical study evidence for pulmonary vasodilator therapy following surgery with cardiopulmonary bypass in children with CHD

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Review

Cite this article: Foote HP, Hornik CP, Hill KD, Rotta AT, Kumar KR, and Thompson EJ (2022) A systematic review of clinical study evidence for pulmonary vasodilator therapy following surgery with cardiopulmonary bypass in children with CHD. *Cardiology in the Young* **32**: 1373–1390. doi: 10.1017/S1047951122002293

Received: 11 February 2022
Revised: 29 June 2022
Accepted: 30 June 2022
First published online: 20 July 2022

Keywords:
Pulmonary hypertension; post-operative morbidity and mortality; pulmonary vasodilator therapy

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Abstract

Objectives: Complications from pulmonary hypertension are one of the leading contributors to morbidity and mortality post-cardiopulmonary bypass surgery in children with CHD. Pulmonary vasodilator therapies are commonly used post-operatively, but the optimal target patient population, therapy choice, timing of therapy initiation, and duration of therapy are not well defined. *Methods:* We used PubMed and EMBASE to identify studies from 2000 to 2020 investigating the use of pulmonary vasodilator therapy post-cardiopulmonary bypass in children aged 0–18 years. To ensure eligibility criteria, studies were systematically reviewed by two independent reviewers. *Results:* We identified 26 studies of 42,971 children across four medication classes; 23 were single centre, 14 were prospective, and 11 involved randomisation (four of which employed a placebo-control arm). A disproportionate number of children were from a single retrospective study of 41,872 patients. Definitions varied, but change in pulmonary haemodynamics was the most common primary outcome, used in 14 studies. Six studies had clinical endpoints, with mortality the primary endpoint for two studies. Treatment with inhaled nitric oxide, iloprost, and sildenafil all resulted in improved haemodynamics in specific cohorts of children with post-operative pulmonary hypertension, although improved outcomes were not consistently demonstrated across all treated children. Iloprost may be a cheaper alternative to inhaled nitric oxide with similar haemodynamic response. *Conclusion:* Studies were predominantly single-centre, a control arm was rarely used in randomised studies, and haemodynamic endpoints varied significantly. Further research is needed to reduce post-operative morbidity and mortality from pulmonary hypertension in children with CHD.

Children with CHD are at risk for increased pulmonary vascular resistance following cardiac surgery with cardiopulmonary bypass[1]; 2–16% of these children will experience post-operative pulmonary hypertension, which can produce severe haemodynamic consequences.[1–3] Complications from pulmonary hypertension are one of the leading causes of post-operative mortality.[4]

Cardiopulmonary bypass and intra-operative circulatory arrest contribute to post-operative pulmonary hypertension though complement activation, excess thromboxane and endothelin production, microthrombi development, and inhibition of endogenous nitric oxide release, which together result in endothelial cell dysfunction, increased pulmonary vascular reactivity, vasoconstriction, and increased pulmonary vascular resistance.[5–8] Furthermore, volume and pressure loading of the pulmonary arteries from left-right shunt lesions, vascular congestion from systemic ventricular dysfunction or anatomic strictures, or underlying pulmonary vascular disease can lead to pre-operative pulmonary hypertension, which places children at additional risk for haemodynamically significant post-operative pulmonary hypertension.[3,4,9,10] Haemodynamically significant pulmonary hypertension can lead to pulmonary hypertensive crises, consisting of acute elevations in pulmonary artery resistance leading to right ventricular failure, hypoxia, and systemic hypotension, which can be especially detrimental in the post-operative period.[3,4]

Reducing the incidence and mortality of post-operative pulmonary hypertension is critical and requires early recognition and intervention through careful treatment of hypoxia and acidosis, as well as management of analgesia and sedation.[5,6] To optimise haemodynamics, pulmonary vasodilator therapies are often used in the post-operative setting.[11] These inhaled or systemic medications aim to vasodilate the pulmonary vasculature to improve pulmonary blood flow, reduce right ventricular afterload, and maintain left ventricular cardiac output. No drugs are currently labelled by the Food and Drug Administration for treatment of post-operative pulmonary hypertension or acute pulmonary hypertensive crises.[12–16] This review aims to assess

the current literature of pulmonary vasodilator medications in the post-operative setting, specifically to understand optimal treatment, dose, timing, and patient population, in order to define areas for further research and improve post-operative outcomes in children with CHD.

Materials and methods

Search strategy

Similar to previously described, PubMed and EMBASE were searched to identify studies investigating the use of pulmonary vasodilator medications in children following cardiac surgery with cardiopulmonary bypass.[17–19] Studies from 2000 through 2020 were included to assess medication use in current clinical practice. Children were defined as from birth to age 18 years. The search terms "postoperative care," "heart surgery," "cardiopulmonary bypass," "pediatric," "pulmonary vasodilator," "vasodilator," "vasorelaxant," "vasoactive antagonist," "vasodilatant," "vasodilating," and "vasodilative" were used to generate an initial group of studies. The last search was performed on 5 May, 2021. Animal studies, studies in languages other than English, and studies focused on pre- or intra-operative medication use were excluded. Case reports, letters, editorials, and comments were also excluded. Search strategies are shown in the Appendix. A total of 271 studies were initially identified.

Study selection

Identified studies were imported into EndNote (Version X9, Clarivate Analytics, Philadelphia, PA, USA). Two reviewers independently screened and reviewed study abstracts and titles. Studies were eligible for inclusion if the primary focus was pulmonary vasodilator administration in the postoperative period for children following cardiac surgery with cardiopulmonary bypass. The full article was then reviewed to ensure appropriateness prior to data extraction.

Data extraction and synthesis

A standardised data collection form was used to extract the relevant data from each eligible study. The following data were collected: study characteristics (including study design and years of study), study population characteristics (including age and cardiac defects), intervention (including medication administered and the presence and type of control used), study endpoints, and results. For each medication, the dose, route and timing of administration, primary outcome, and secondary outcomes were compiled and analysed. Search strategies, study inclusion and exclusion criteria, and the standardised data collection form were all prespecified prior to data analysis. We did not assess for risk of bias. Given the heterogeneity of study outcomes, we compared studies qualitatively without performing a quantitative meta-analysis of outcomes or bias across studies. This review followed the guidelines for reporting systematic reviews as outlined by Liberati et al.[20]

Results

A total of 26 studies in 42,971 children across four medication classes met inclusion criteria as shown in Figure 1. Study characteristics are summarised in Table 1. Three studies were multi-centre and 23 were single centre. The majority of patients (41,872) came from one multi-centre registry study.[25] Twelve studies were retrospective and 14 were prospective. Eleven of the prospective studies involved randomisation: four studies had a randomised control arm and seven studies were randomised between therapies.[21–23,31–34,36–38,41,43,44,46] In terms of primary outcomes, 14 studies assessed change in pulmonary pressures[21,23,28–32,34–36,38,40,42,44]; four assessed the incidence of pulmonary hypertensive crises, although definitions varied[22,33,37,40]; three evaluated the requirement for additional therapy for pulmonary hypertension[26,39,41]; and five used clinical endpoints including duration of pleural drainage (n = 3) or mechanical ventilation (n = 2), and mortality (n = 2).[24,25,27,43,45] One included study evaluated the pharmacokinetics of the investigated drug, and three evaluated a dose–response curve.[21,23,36,46] Haemodynamic data included pulmonary arterial pressures as measured by direct pulmonary artery catheter in 13 studies, central venous pressures as measured by direct central venous catheter in six studies, atrial pressures as measured by direct atrial catheter in five studies, and right ventricular pressures as estimated from doppler of tricuspid regurgitation in two studies.[21–23,28–38,40–42,44] Medications studied included inhaled nitric oxide [14/26]; the prostacyclin analogue, iloprost [5/26]; phosphodiesterase inhibitors (sildenafil [9/26] and milrinone [2/26]); and endothelin receptor antagonists (ambrisentan [1/26]). Inhaled nitric oxide was used as routine care or open-label rescue therapy in seven of the 12 studies in which it was not a primary intervention.

Inhaled nitric oxide

Nitric oxide is produced endogenously by endothelial cells leading to the relaxation of smooth muscles via the conversion of guanosine triphosphate to cyclic guanosine monophosphate.[47,48] When administered as an inhaled gas (inhaled nitric oxide), nitric oxide leads to pulmonary vasodilation in ventilated areas of the lung.[49] Haemoglobin rapidly binds and inactivates nitric oxide, minimising its systemic vasodilator effects.[47] Haemoglobin bound to nitric oxide is oxidised to methaemoglobin, which is then metabolised to nitrate.[49] Methaemoglobinaemia is frequently monitored during inhaled nitric oxide administration, but rarely rises to clinically significant levels.[50] Withdrawal of inhaled nitric oxide is associated with decreased partial pressure of oxygen and rebound pulmonary hypertension within minutes of discontinuation, likely due to downregulation of endogenous nitric oxide production and decreased cyclic guanosine monophosphate.[51] A gradual stepwise wean is recommended to limit this phenomenon.[48,52] Additionally, inhaled nitric oxide is one of the most expensive medications routinely given to critically ill children, suggesting the need for judicious usage.[53]

Inhaled nitric oxide has been used in infants and children with hypoxic respiratory failure for more than two decades. Inhaled nitric oxide increases extracorporeal membrane oxygenation-free survival in children with paediatric acute respiratory distress syndrome and decreases need for extracorporeal membrane oxygenation without a demonstrated mortality benefit in term and near-term neonates with hypoxic respiratory failure and persistent pulmonary hypertension.[54–56] Inhaled nitric oxide is Food and Drug Administration-labelled for neonates with pulmonary hypertension-related hypoxic respiratory failure, but its use in other clinical scenarios, including the post-operative setting, remains off-label.[12] Fourteen studies of inhaled nitric oxide met our inclusion criteria.

Three single centre prospective studies of 148 total children evaluated the haemodynamic effects of inhaled nitric oxide in children with post-operative pulmonary hypertension.[21–23] At initial

https://doi.org/10.1017/S1047951122002293 Published online by Cambridge University Press

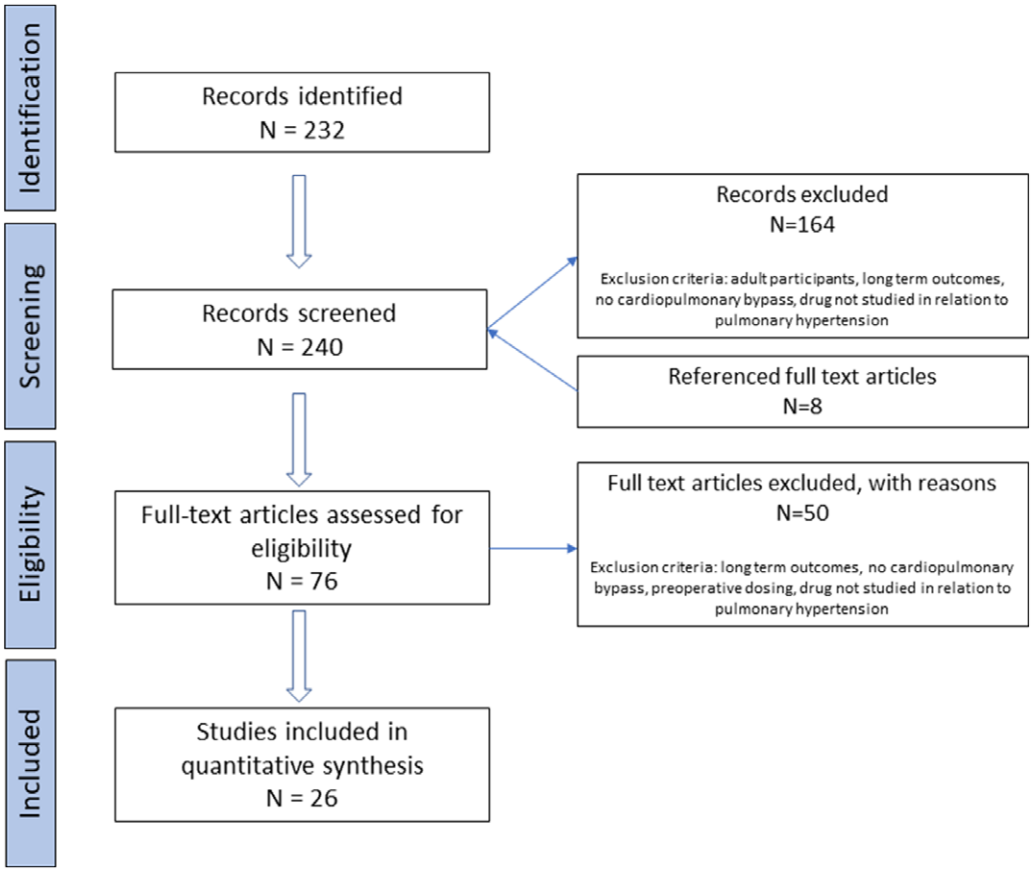

Figure 1. Flow diagram of study selection.

doses ranging from 3 ppm to 10 ppm, inhaled nitric oxide was associated with significantly decreased mean pulmonary artery pressure and pulmonary vascular resistance, as measured by pulmonary artery catheter, and rate of pulmonary hypertensive crises (defined as a ratio of pulmonary to systemic artery pressure greater than 0.75). No dose–response relationship was seen with increasing doses of inhaled nitric oxide from 3 ppm to 80 ppm, and no difference in response was seen between therapy at 5 ppm and 40 ppm.[21,23]

Five single centre retrospective studies of 179 total children investigated the impact of inhaled nitric oxide (starting dose ranging from 10 to 25 ppm) in children following specific surgical repairs.[24,27–30] Combining inhaled nitric oxide with high-flow nasal cannula therapy for children following Fontan operation significantly reduced duration of mechanical ventilation, pleural drainage time, and total hospital stay, regardless of preoperative haemodynamics.[24] In children with elevated cavopulmonary pressures following bidirectional Glenn or Fontan operation, inhaled nitric oxide therapy resulted in significantly decreased cavopulmonary and transpulmonary pressure gradients.[28–30] Of note, each study varied in the definition of elevated pressures using both transpulmonary pressure gradient (>8 mmHg) and elevated cavopulmonary pressure (with threshold ranging from >15 to >20 mmHg). However, children with haemodynamically significant anatomic lesions requiring surgical reintervention (e.g., pulmonary artery thrombus or Glenn shunt stenosis) or those without baseline elevated pressures did not have a significant improvement, suggesting a therapeutic benefit only for children meeting certain haemodynamic criteria. Similarly, for children following surgical atrioventricular canal repair, therapy with inhaled nitric oxide was associated with improved mortality only for the sub-cohort of those who experienced pulmonary hypertensive crises (defined as pulmonary artery pressure >70% systemic arterial pressure with associated decreased venous or arterial oxygen saturation, as measured by either pulmonary arterial catheter or echocardiography.[46]

Two multicentre retrospective studies of 42,088 total children compared outcomes between children who did and did not receive inhaled nitric oxide therapy.[25,26] Inhaled nitric oxide usage was associated with increased intubation time, longer hospitalisation, increased cost of stay, and increased rate of mortality for children both with and without pulmonary hypertension, defined based on diagnosis codes. The strength of these studies is their multi-centre design allowing for analysis across a large cohort of children, but they are limited by an inability to assess indication for usage. They do not incorporate individual haemodynamics, ventilator settings, or inotrope requirements that may have confounded inhaled nitric oxide usage and outcomes.

Phosphodiesterase inhibitors

Phosphodiesterase-5 inhibitors

Intracellular phosphodiesterase degrades cyclic guanosine monophosphate, extinguishing its downstream vasodilator effects.[57] Sildenafil is a phosphodiesterase-5 selective inhibitor that prevents cyclic guanosine monophosphate breakdown and leads to pulmonary vasodilation.[58] Sildenafil is available in both oral and intravenous forms. Short-term oral therapy may reduce the risk for rebound pulmonary hypertension following inhaled nitric oxide wean in infants, and long-term treatment in children with World Health Organization Group I pulmonary hypertension

https://doi.org/10.1017/S1047951122002293 Published online by Cambridge University Press

Table 1. Characteristics of included studies and study populations.

Reference	Medication studied	Study design (study years)	N	Study population	Route, dose, and time to drug initiation	Primary outcome	Findings
Nitric oxide							
Gothberg et al[21]	iNO	Single centre, prospective cohort (study years not specified)	12	Infants with repaired AVSD, VSD, combined ASD and PDA, TAPVR, or combined TGA, ASD, and VSD with post-operative PH (defined as mean PAP >20 mmHg or mean PAP/mean systemic artery pressure >0.25 as measured by pulmonary artery catheter) who remained intubated; Median age 3.8 months (range 1 day to 12.6 months)	Inhaled; Increased stepwise in 10 minutes intervals (0, 5, 10, 20, 40 ppm for six patients and 0, 3, 10, 30, 80 ppm for six patients); Started on median post-operative day 1 (range 0–2)	Systemic and pulmonary blood pressure. Cardiac output. $PaCO_2$, PaO_2, metHb	Mean PA pressure significantly decreased from 33 ± 2 mmHg to 28 ± 2 mmHg ($p < 0.001$) and arterial oxygen tension significantly increased from 13.3 ± 2.3 kPa to 16.7 ± 2.7 kPa ($p < 0.05$) with initiation of iNO at either 3 or 5 ppm; No further significant improvement was seen with up titration of iNO; No significant change in cardiac output seen
Miller et al[22]	iNO	Single centre, prospective randomised double-blind placebo controlled (study years not specified)	124	Infants with VSD, AVSD, truncus arteriosus, or TAPVR and high pulmonary pressure (defined as mean PAP >25 mmHg or PAP/systemic artery pressure >0.5 as measured by pulmonary artery catheter); Median age 3 months [1, 5] for treatment group and 2 months [1, 4] for placebo group	Inhaled; Initiated at 10 ppm after surgery until extubation or for maximum of 7 days if remained intubated for that time	Incidence of PHTC; PHTC defined as pulmonary/systemic arterial pressure >0.75	Incidence of PHTC was significantly decreased (4 [0, 12] v 7 [1, 19], $p < 0.001$) compared to placebo; Time to extubation readiness was significantly decreased (80 hours [38, 121] v 112 hours [63, 164], $p = 0.019$); No difference in time to extubation
Morris et al[23]	iNO	Single centre prospective randomised cross over (study years not specified)	12	Infants following biventricular repair with post-operative PH (defined as mean PAP >25 mmHg at a normal pH as measured by pulmonary artery catheter); Median age 0.6 years (range 0.1–17.7 years)	Inhaled; iNO started at 5 ppm for 15 minutes and increased to 40 ppm for 15 additional minutes; Hyperventilation with goal arterial pH > 7.5; Infants received randomised initial therapy for 30 minutes followed by 30 minutes washout period prior to starting alternate therapy. Followed by additional 30 minutes period with both interventions concurrently; Therapy started at a median 8.5 hours (range 4–40 hours) after ICU admission	Pulmonary arterial pressure, PVR, cardiac index, and systemic vascular resistance	Both hyperventilation and iNO were associated with significantly decreased mean PAP (36.8 ± 9.8 to 28.4 ± 5.3, $p < 0.001$ and 34.5 ± 2.8 v 29.4 ± 2.8, $p < 0.01$ respectively) as well as a significantly decreased PVR index (8.5 ± 4.1 v 6.4 ± 2.4, $p < 0.01$ and 8.1 ± 3.3 v 6.1 ± 2.2, $p < 0.001$ respectively); Hyperventilation was associated with a concomitant significant decrease in cardiac index (3.08 ± 1.11 v 2.76 ± 0.96, $p < 0.05$) and increase in systemic vascular resistance index (19.5 ± 12.7 v 22.7 ± 12.3, $p < 0.01$); No significant change in cardiac index or systemic pressures was seen with iNO

Table 1. (*Continued*)

Tominaga et al[24]	iNO	Single centre retrospective cohort study (2010–2016)	38	Children who required iNO prior to extubation following Fontan operation; Mean age 3.5 ± 1.2 years for Epoch 1 and 2.7 ± 1.0 years for Epoch 2	Inhaled; Epoch 1 (24 children): iNO while intubated only at 20 ppm; Epoch 2 (14 children): iNO while intubated and iNO with HFNC after extubation. iNO concentration 1–5 ppm with HFNC.	Duration of post-operative intubation, pleural drainage time, and post-operative hospitalisation length	Children in Epoch 2 had significantly shorter duration of intubation (3.5 hours [3.0, 4.6] v 7.2 hours [2.7, 49], $p = 0.033$), fewer days with pleural drainage (9.5 days [8.3, 18] v 23 days [13, 34], $p = 0.007$), and shorter total hospital stay (27 days [22, 36] v 36 days [29, 49], $p = 0.017$); Median duration iNO-HFNC therapy was 58 hours [20, 102]; No children in HFNC group required re-intubation compared to two children in earlier Epoch (no significance value given)
Wong et al[25]	iNO	Multicentre retrospective cross-sectional study (2004–2015)	41,872	Children who underwent cardiac surgery who did or did not have PH (as defined by billing codes); Median age 1 year [0, 17] for those without PH and 0 years [0, 17] for those with PH	Inhaled; Exposure to post-operative iNO as assessed by billing code	Hospital length of stay, billed charges, inpatient mortality	Frequency of iNO use increased over time in both children with (3.5% in 2004 to 16.7% in 2015) and without (0.4% in 2004 to 2.7% in 2015) PH; For patients without PH, exposure to iNO was associated with significantly increased length of stay (+10.2 days, $p = 0.01$), cost (+$378,174, $p < 0.01$), and rate of inpatient mortality (OR 2.45 95% CI 1.78–3.37); For patients with PH, exposure to iNO was associated with significantly increased length of stay (+3.4 days, $p = 0.02$) and cost (+$226,721) with no effect on mortality (OR 1.21 95% CI 0.71–2.06)
Riley et al[26]	iNO	Multicentre retrospective cohort study (2009–2016)	216	Infants undergoing definitive repair of truncus arteriosus without aortic arch obstruction; Median age 10 days [7, 23] at first operation	Inhaled; Median duration 4 days (range 1–21 days), median maximal dose 20 ppm (range 10–40 ppm)	Exposure to iNO	102/216 children received post-operative iNO: 69/102 had treatment started in OR and 33/102 had treatment started in ICU; There was significant inter-left variability in proportion of patients receiving iNO ($p < 0.001$) and in location of iNO initiation (OR v ICU, $p < 0.001$): Higher volume lefts (>3 surgeries/year) had significantly less iNO usage ($p < 0.001$); Infants receiving iNO had significantly longer intubation time (193 hours [116, 532] v 108 hours [72, 168], $p < 0.001$) and hospital length of stay (28 days [18, 51] v 20 days [12, 33], $p < 0.001$)

(*Continued*)

Table 1. (*Continued*)

Reference	Medication studied	Study design (study years)	N	Study population	Route, dose, and time to drug initiation	Primary outcome	Findings
Journois et al[27]	iNO	Single centre retrospective cohort study (1984–1994)	64	Children with post-operative PHTC following AVSD repair (defined as PAP >70% systemic arterial pressure with associated decreased venous or arterial oxygen saturation, as measured by either pulmonary arterial catheter or echocardiography); Median age 0.54 years (range 0.2–35 years)	Inhaled; iNO at 25 ± 8.6 ppm for median 5.2 days given to later cohort	Early post-operative mortality (within 30 days or before hospital discharge)	iNO treatment was associated with a significant decrease in early mortality (24%, [95% CI 7–41%] v 56% [95%CI 37–75%], p = 0.02) in children with severe PHTC; When all AVSD patients were included, iNO exposure no longer had a significant effect on mortality (p = 0.81)
Yoshimura et al[28]	iNO	Single centre retrospective study (1996–2002)	47	Children following Fontan operation; Median age 4 years (range 1–16 years)	Inhaled; Median dose 10 ppm (range 5–30 ppm) started in operating room (n = 33) or ICU (n = 14) and continued for median 2 days (range 5 hours to 52 days)	CVP, left atrial pressure, TPP, systemic arterial pressure	For the entire cohort, iNO treatment significantly decreased CVP (16.2 ± 2.2 mmHg v 14.6 ± 2.2 mmHg, p < 0.0001) and TPP gradient (9.9 ± 2.9 mmHg v 8.4 ± 2.7 mmHg, p < 0.001) and increased systemic systolic pressure (71.9 ± 15.2 mmHg v 76.8 ± 14.5 mmHg, p < 0.05) without change in left atrial pressure; No improvement seen in CVP or TPP for children with initial CVP <15 mmHg or TPP <8 mmHg; 17/47 children had an immediate increase in CVP and TPP after iNO cessation that improved with restarting medication
Agarwal et al[29]	iNO	Single centre retrospective study (2000–2003)	16	Infants following bi-directional Glenn with elevated Glenn pressures (defined as ≥20 mmHg); Mean age 7.0 ± 3.1 months	Inhaled; Initial dose 20 ppm with increase to 40 ppm if no response and started within 3 hours post-operatively.	Glenn pressures	After 3 hours of therapy, 11/16 infants had a significant decrease in Glenn pressures (22.7 ± 3.9 mmHg v 17.1 ± 3.4 mmHg, p < 0.001) and a concomitant significant decrease in inotrope score (14.9 ± 8.7 v 11.4 ± 7.4, p < 0.001) and increase in PaO2/FiO2 ratio (49.4 ± 17.3 v 74.3 ± 23.4, p < 0.001); The five non-responding infants were all found to have hemodynamically significant anatomic lesions requiring surgical re-intervention (eg pulmonary thrombus, or Glenn shunt stenosis)

Table 1. (*Continued*)

Georgiev et al[30]	iNO	Single centre retrospective study (study years not specified)	14	Children following cavopulmonary connection with either elevated cavopulmonary pressure (>16 mmHg) or low oxygen saturation (<75% for BDG and <85% for TCPC); Median age 43.8 months (range 4.8–108 months)	Inhaled; Median initial dose 20 ppm (range 10–20 ppm) started at median 5 hours post-operatively (range 1–48 hours) and continued for median 46 hours (range 13–312 hours)	Cavopulmonary pressure, TPP, arterial oxygen saturation	iNO therapy was associated with a significant reduction in cavopulmonary pressures (18.1 ± 2.3 mmHg v 16.6 ± 3.5 mmHg after 12 hours, p = 0.006), decrease in TPP (9.8 ± 3.7 mmHg v 7.0 ± 3.5 mmHg after 12 hours, p = 0.009), and increase in arterial oxygen saturation (78.7 ± 5.9% v 84.5 ± 6.0% at 12 hours, p = 0.001)
Stocker et al[31]	iNO and sildenafil	Single centre, prospective randomised trial (study years not specified)	15	Infants following VSD or AVSD repair; Mean age 139 ± 32 days for iNO then sildenafil group, and mean age 123 ± 26 days for sildenafil then iNO group	Inhaled (nitric oxide); Intravenous (sildenafil); iNO at 20 ppm, sildenafil 0.35 mg/kg; Therapy started between 3.8 and 6.7 hours post-operatively; Received first medicine over 20 minutes followed by addition of second medicine	Vascular pressures, cardiac output, alveolar – arterial oxygen gradient	Both therapies alone were associated with a significant decrease in PVR index with an augmented effect when the second therapy was added (3.45u baseline v 2.95u for iNO alone, p = 0.01, v 2.45 with iNO + sildenafil, p < 0.05; 2.84u baseline v 2.35u for sildenafil alone, p < 0.05, v 2.15u with sildenafil + iNO, p = 0.01); When added either alone or as the second agent, sildenafil was associated with significantly reduced systemic blood pressure (70.6 ± 2.1 mmHg v 58 ± 2.3 mmHg following sildenafil, p < 0.05), systemic vascular resistance (17.4 ± 1.4 v 13.3 ± 0.9 following sildenafil, p < 0.05), and increased alveolar – arterial oxygenation gradient (160 ± 23 mmHg v 190 ± 39 mmHg, p < 0.05); iNO alone significantly decreased the alveolar – arterial oxygenation gradient (145 ± 12 mmHg v 118 ± 9 mmHg following iNO, p < 0.05) and did not affect systemic pressures
Cai et al[32]	iNO and milrinone	Single centre prospective multi-arm randomised trial (study years not specified)	46	Children following Fontan operation with TPP gradient >10 mmHg or CVP >15 mmHg and impaired oxygenation (<85%); Mean age 5.8 ± 2.1 years for milrinone group, 5.5 ± 2.6 years for iNO group, and 5.7 ± 2.8 years for combined group	Inhaled (nitric oxide); Intravenous (milrinone); Milrinone at 0.5 mcg/kg/minute; iNO at initial dose 20 ppm; Combined group with both therapies	TPP gradient, CVP, arterial blood oxygenation	iNO alone and combined with milrinone resulted in a significant decrease in TPP gradient and CVP as well as an increase in arterial oxygen to inspired FiO2 ratio and systemic saturation within 4 hours of therapy (values not given, p < 0.01); Combined therapy was associated with the most significant decrease in TPP gradient after 24 hours (11.26 ± 1.4 mmHg to 7.93 ± 0.9 mmHg for combined

(*Continued*)

Table 1. (*Continued*)

Reference	Medication studied	Study design (study years)	N	Study population	Route, dose, and time to drug initiation	Primary outcome	Findings
							group v 11.1 ± 1.38 mmHg to 9.69 ± 0.86 mmHg for iNO alone, p = 0.048, and v 11.17 ± 1.41 mmHg to 9.72 ± 1.32 mmHg for milrinone alone, p < 0.001), as well as most significant improvement in arterial oxygen to inspired FiO2 ratio (68.88 ± 14.09 to 131.25 ± 15.92 for combined group v 70.07 ± 14.24 to 120.2 ± 15.92 for iNO alone, p = 0.047, and v 72.6 ± 12.92 to 95.2 ± 13.49 for milrinone alone, p < 0.001); Duration of intubation was significantly shorter in combined group (101.7 ± 36.5 hours for combined v 129.2 ± 47.8 hours for iNO alone v 133.6 ± 23.3 hours for milrinone alone, p < 0.043). Total ICU and hospital stay trended shorter for combined group but this was non-significant
Loukanov et al[33]	iNO; Aerosolized iloprost	Single centre prospective, open label randomised trial (2003–2008)	15	Infants with left-to-right shunt (Qp/Qs ≥ 1.5) and PH (mean PAP >25 mmHg) after weaning from CPB; PHTC defined as pulmonary pressure/systemic pressure >0.75 with associated either >20% decrease in systemic pressures or desaturations <90%. Minor events met pulmonary pressure threshold but without decreased systemic pressures or hypoxia. Measured by pulmonary artery catheter; Median age 4.9 months (range 2.6–8.6 months)	Inhaled; iNO at 10 ppm; Aerosolised iloprost at 0.5 mcg/kg every 2 hours; Treatment continued for at least 72 hours	Occurrence of PHTC	No difference between groups was seen in frequency of PHTC (iNO group with 26 minor and 2 major events, iloprost group with 25 minor and 6 major events, p = 1.0), mean PAP, or duration of mechanical ventilation (mean 11.9 ± 4.6 days for iNO and 37 ± 48.4 for iloprost, p = 0.19)
Prostacyclins							
Limsuwan et al[34]	Inhaled iloprost	Single centre prospective open-label single arm (2004–2005)	8	Children with post-operative PHTC not responding to conventional treatment; PHTC defined as systolic pulmonary artery pressure >60% systolic blood pressure with associated hypoxia; Mean age 44 months (range 1 months to 13 years)	Inhaled; 0.5 mcg/kg over 10 minutes; Dose could be increased to maximal dose 2.0 mcg/kg over 10 minutes and repeated every 30 minutes up to five times	Mean PAP, systemic arterial saturation, systemic arterial pressure	Treatment with iloprost was associated with a significant decrease in mean PAP (47.9 ± 14.9 mmHg v 30.2 ± 7.9 mmHg, p = 0.012) and increase in arterial saturation (82.2 ± 16.7% v 93.4 ± 11.5%, p = 0.012); Mean systemic pressure trended higher (59.4 ± 12.1 mmHg v 64 ± 10.3 mmHg, p = 0.16); No significant airway irritation was noted

Table 1. (*Continued*)

Vorhies et al[35]	Inhaled iloprost; iNO	Single centre retrospective review (2010–2011)	7	Infants with post-operative PH (defined as mean PAP >25 mmHg by pulmonary artery catheter) receiving treatment with iNO; Median age 2.8 months (range 0.3–18.4 months)	Inhaled; 1.25–5 mcg/dose every 2 hours. iNO weaned once iloprost at full dose (over median 5 hours, range 1.5–7.5); Started median post-operative day 1 (range 0–3)	Pulmonary and systemic arterial pressures assessed 24 hours after iNO discontinuation	Transition to aerosolised iloprost was not associated with significant change in mean PAP (median 24 mmHg with iNO v 22 mmHg w iloprost, p = 0.27) or systolic PAP (median 45 mmHg v 34 mmHg, p = 0.25). All children had a significant improvement in systolic PAP to systolic arterial pressure ratio (median 0.61 with iNO v 0.49 with iloprost, p = 0.03).
Xu et al[36]	Inhaled iloprost	Single centre prospective randomised, placebo controlled, single blind study (2010)	22	Children with PH (defined as mean PAP >25 mmHg or ratio of systolic pulmonary pressure to systolic arterial pressure >0.5, as measured by echocardiography) following biventricular repair; Median age 7 months (range 0.4–147 months)	Inhaled; Low dose iloprost (30 ng/kg/minute) or high dose iloprost (50 ng/kg/minute) over 10 minutes every 2 hours; Initiated within first 48 hours post-operatively and continued for up to 14 doses (median 12 doses)	Decrease by 20% of systolic PAP to systolic arterial pressure ratio or of pulmonary resistance to systemic resistance ratio without pulmonary hypertensive crisis or death	0/7 placebo group children met primary outcome compared to 6/7 children in low dose group (p = 0.005 compared to placebo) and 4/8 in high dose group (p = 0.077 compared to placebo); Children in placebo group had a significant increase in mean PAP/mean systemic arterial pressure ratio (0.47 v 0.62, p = 0.032), while those in the low dose group had a significant decrease (0.44 v 0.34, p = 0.032) and those in the high dose group trended lower but not significantly
Onan et al[37]	Intravenous iloprost	Single centre prospective randomised controlled study (study years not specified)	27	Children with pre-operative PH (systolic PAP >50 mmHg, mean PAP >25 mmHg) undergoing surgical repair of left-to-right shunt; PHTC defined as PAP >70% of systemic arterial pressure with associated decreased systemic pressures and decreased systemic saturations, as measured by pulmonary artery catheter; Mean age 7.8 ± 5.8 months for treatment group and 5.8 ± 2.3 months for control group	Intravenous; Iloprost infusion at 2.0 ng/kg/minute started immediately after CBP wean and continued for 72 hours	Incidence of post-operative PHTC	PHTC occurred in 2/12 control patients and 4/15 treatment patients (p = 0.53); No significant change in systolic PAP, mean PAP, or PA to systemic pressure ratios was seen during the infusion period with no between group difference (systolic PAP/systemic pressure ratio at 24 hours: 0.37 ± 0.08 in study group v 0.43 ± 0.19 in control group, p = 0.25; at 72 hours: 0.39 ± 0.13 in the study group v 0.4 ± 0.15 in the control group, p = 0.97); Length of ICU or hospital stay were not significantly different between groups (p > 0.05)
PDE inhibitors							
Peiravian et al[38]	Oral sildenafil	Single centre prospective randomised control trial (2002–2004)	42	Children undergoing surgical repair of large septal defects with moderate to severe pre-operative PH (pulmonary artery to systemic pressure ratio >0.7 as measured by pulmonary artery catheter); Mean age 5.25 ± 4.7 years for the	Oral; 0.3 mg/kg every 3 hours for 24–48 hours started at initiation of CPB	Post-operative PAP and pulmonary arterial to systemic pressure ratio	Postoperative PAP and PA to systemic pressure ratio were significantly lower in the treatment group (28.61 ± 7.80 mmHg v 39.40 ± 10.80 mmHg for mean PAP, p = 0.001; 0.28 ± 0.08 v 0.41 ± 0.11 for pressure ratio,

(*Continued*)

Table 1. (*Continued*)

Reference	Medication studied	Study design (study years)	N	Study population	Route, dose, and time to drug initiation	Primary outcome	Findings
				treatment group and 3.97 ± 3.20 years for the control group			p = 0.001); 4/22 control patients and 0/20 treatment patients had PHTC (p = 0.02); Treatment group had significantly shorter duration of intubation (13.75 ± 12.12 hours v 22.60 ± 9.50 hours, p = 0.013) although ICU and hospital length of stay were similar between groups; No significant change in PA pressure was observed following sildenafil discontinuation (26.20 ± 6.6 mmHg v 28.49 ± 10.93 mmHg, p = 0.366); No systemic hypotension was noted in treatment group.
Lee et al[39]	Oral sildenafil	Single centre retrospective study (2003–2004)	7	Children receiving oral sildenafil following failed iNO wean; iNO wean failure defined as significant decrease in cardiac output or increasing frequency of PHTC; Median age 1 month (range 3 day to 21 month)	Oral; Started at 0.3 mg/kg with max dose range 0.22–0.47 mg/kg. Given 4×/day for average 28 days. Children had been receiving iNO for median 10 days (range 5–28 days) prior to sildenafil initiation.	Change in iNO dose	After 24 hours of sildenafil therapy, iNO dose was significantly decreased (29.8 ± 5.9 ppm v 12.2 ± 3.34 ppm, p = 0.024); iNO was discontinued a mean of 4 days after sildenafil initiation (range 1–12 days); Mean pulmonary arterial and systemic arterial pressures after 1 hour of sildenafil therapy did not significantly differ from baseline (27 ± 0.7 mmHg v 29 ± 1 mmHg for mean PAP, p = 0.06; 54 ± 1.2 mmHg v 56 ± 1.2 mmHg for mean arterial pressure, p = 0.202)
Nemoto et al[40]	Oral sildenafil	Single centre retrospective study (2003–2008)	100	Children with post-operative PH who met one of the following criteria 1. Severe PH (PAP >0.5 systemic pressure) despite iNO or IV vasodilator 2. To prevent rebound PH for children stable on iNO 3. First therapy for severe PH rather than iNO 4. For "rebound" severe PH when re-intubation was not performed 5. For cavoplumonary repair with TPP gradient >10 mmHg with hemodynamic instability or desaturations. Age <1 month: 26; 1 month to <6 month: 36; 6 months to <1 year: 19; 1–3 years: 8; 4–9 years: 9; >10 years: 2	Oral; 0.5 mg/kg dose on ICU admission. Dose increased by 0.5 mg/kg every 4–6 hours up to maximum 2 mg/kg and continued for 5–7 days after extubation	Decrease in PA pressure, prevention of severe PHTC (elevation to PA pressure ≥ systemic pressure with hemodynamic instability), prevention of rebound PH after iNO withdrawal, successful weaning of iNO and IV vasodilators	28/34 children with continuous pressure monitoring had a decrease in systolic PA pressure following sildenafil treatment, and the pressure decrease was significant overall (51.8 ± 12.7 mmHg before v 36.1 ± 11.8 mmHg 6 hours after reaching maximal sildenafil dose, p < 0.05); For children following cavopulmonary shunt, the TPP gradient significant decreased after treatment (14.8 ± 4.0 mmHg v 7.2 ± 2.2 mmHg, p < 0.05); No patients developed severe PH or rebound PH following iNO withdrawal; Sildenafil treatment was associated with significant increase in mean systemic pressure (59.6 ± 11.1 v 64.2 ± 12.2, p < 0.05) and no change in heart

Table 1. (*Continued*)

							rate; three patients required additional treatment with bosentan and five developed facial flushing
Fraisse et al[41]	Intravenous sildenafil	Multicentre double-blind, placebo-controlled dose-ranging, parallel group trial (2003–2005)	17	Children with post-operative PH (defined as systolic PAP >50% of systolic arterial pressure as measured by echocardiogram); Median age 5 months (range 3 months–14 years)	Intravenous; Given as bolus over 5 minutes followed by continues infusion for 24–72 hours. Dosing to reach target sildenafil plasma concentrations of 40, 120, and 360 ng/ml in the low, median, and high dose arms, respectively.	Need for additional therapy for PH within 24 hours of treatment initiation	2/5 placebo and 2/12 treatment children required additional therapy for PH ($p = 0.330$); Median duration of intubation (8 v 3 days, $p = 0.023$) and ICU length of stay (15 v 6 days, $p = 0.008$) were decreased in combined treatment group. Length of hospitalisation trended shorter; After 4 hours of therapy, treatment arms had a significantly greater decrease in systolic PAP (− 11 v 0 mmHg, $p = 0.027$). No significant difference in systemic pressures was seen; Study was heavily underpowered for dose comparison. Goal 228 children but study terminated early (17 patients) due to slow patient enrollment precluding comparison between treatment doses.
Giordano et al[42]	Oral sildenafil	Single centre retrospective cohort study (2008–2012)	30	Children following extracardiac Fontan; Mean age 55 ± 12 months for the sildenafil group and 59 ± 14 months for the control group	Oral; Early control cohort: no sildenafil; Late cohort: sildenafil 0.35 mg/kg every 4 hours started at initiation of CPB and continued for 1 week before weaning	Pulmonary pressures at 72 hours post-operatively	Sildenafil cohort had significantly lower mean PAP (12.6 ± 1.1 mmHg v 14.7 ± 1.4 mmHg, $p = 0.0001$), lower mean PAP to mean systemic pressure ratio (0.20 ± 0.02 v 0.23 ± 0.03, $p = 0.0043$), lower inotropic score (18.5 ± 4 v 27 ± 7, $p = 0.0005$), and shorter duration of intubation (15.5 ± 4 hours v 23.3 ± 6 hours, $p = 0.0004$), chest tube drainage (5.9 ± 1.1 days v 7.7 ± 1.3 days, $p = 0.0004$), and ICU stay (86 ± 10 hours v 109 ± 16 hours, $p = 0.0001$) compared to earlier control cohort; No significant difference in 30 day mortality seen (0/13 v 1/17, $p = 0.58$).

(*Continued*)

Table 1. (*Continued*)

Reference	Medication studied	Study design (study years)	N	Study population	Route, dose, and time to drug initiation	Primary outcome	Findings
Mendoza et al[43]	Oral sildenafil	Single centre prospective study with historical control (2000–2013)	48	Children following modified Fontan; Mean age 5.4 ± 1.7 years for sildenafil cohort and 5.7 ± 2.7 years for control cohort	Oral; Mean dose 4.6 ± 1.6 mg/kg/day divided three times daily started within first 24 hours post-operatively and continued until hospital discharge	Duration of post-operative pleural effusions, mechanical ventilation, ICU length of stay, length of hospitalisation	There was no significant between group difference in Fontan pressures (14.1 ± 3.3 mmHg for control, 14.7 ± 2.4 mmHg for sildenafil, p = 0.55) or TPP gradient (5.3 ± 2.3 mmHg v 6.1 ± 2 mmHg, p = 0.39); No difference was seen in duration of pleural effusions (18 ± 11.9 days v 14 ± 6.7 days, p = 0.22), intubation (18 hours [7, 36] v 10 hours [8, 23], p = 0.43), ICU stay (5 days [4, 10] v 6 days [5, 8], p = 0.72), or total hospital stay (24 days [15, 29] v 21 days [16, 29], p = 0.80)
Farah et al[44]	Intravenous milrinone; Oral sildenafil	Single centre prospective multi-arm partially randomised trial (2008–2010)	48	Children with pre-operative PH (TR gradient >30 mmHg on echo) from large left-to-right shunts with moderate (defined as pulmonary artery to aortic pressure ratio 0.60–0.84) or severe (defined as ratio ≥0.85) PH as assessed by pulmonary artery catheter inter-operatively; Mean age 17 months (range 3–144 months)	Moderate PH children randomised to either: Intravenous milrinone, 50 mcg/kg bolus at CPB initiation with 0.75 mcg/kg/minute infusion for 36 hours OR oral sildenafil 0.3 mg/kg every 3 hours started before CPB; Severe PH: both therapies without randomization	Pre- and post- operative pulmonary pressures and pulmonary to systemic pressure ratio	Combination group had significantly higher pre-operative pulmonary to aortic pressure ratio (0.94 ± 0.13 compared to 0.78 ± 0.14 in the milrinone group, p = 0.002, and 0.74 ± 0.15 in the sildenafil group, p = 0.001); Post-operatively, compared to the sildenafil group, the milrinone group had significantly lower systolic PAP (24.1 ± 7.6 mmHg v 30.4 ± 5.9 mmHg, p = 0.014) and pulmonary to aortic pressure ratio (0.26 ± 0.6 v 0.33 ± 0.07, p = 0.003); Despite higher pre-operative values, combined group had similar PAP to sildenafil group post-operatively; 0/16 milrinone, 6/16 sildenafil, and 3/16 combination group had PHTC (p = 0.01 comparing the milrinone and sildenafil groups); Mean PAP increased significantly after milrinone discontinuation when given alone (22 mmHg v 27 mmHg, p = 0.001) but no pressure difference was seen after its discontinuation in combined treatment group (34.5 mmHg v 37.3 mmHg, p = 0.6); the Milrinone group had significantly shorter ICU length of stay than the sildenafil group (68 ± 25 hours v 108 ± 65 hours, p = 0.02)

Table 1. (*Continued*)

Koski et al[45]	Oral sildenafil	Single centre retrospective cohort study (2004–2014)	108	Children following TCPC operation; Median age 3.2 years [2.9, 3.8] for sildenafil cohort and 3.0 years [2.7, 3.5] for control cohort	Oral; Mean starting dose 3.4 ± 1.2 mg/kg/day and continued until hospital discharge. Started pre-operatively or within 24 hours of procedure; Control group without exposure	Time to removal of pleural and peritoneal drains	No significant difference between groups in time to remove drains (11 days [8, 19] for sildenafil v 11 days [7, 16] for control, p = 0.532); No difference in duration of intubation (9.6 hours [5.5, 20.4] v 8.1 hours [5.5, 19.3], p = 0.889) or ICU stay (4 days [3, 5] v 4 days [3, 5], p = 0.578) was noted; Sildenafil group had significantly higher fluid balance on day 1 (+47 mL/kg [12, 103] v + 7 mL/kg [−6, 67], p = 0.001) and was significantly more likely to receive iNO (41/48 v 36/60 for control, p = 0.002); first day fluid balance and need for post-operative iNO were both associated with longer need for drains in multiple regression analysis (p = 0.007 and p = 0.042, respectively)
Endothelin receptor antagonists							
Hill et al[46]	Oral ambrisentan	Single centre prospective, randomised, double-blind, placebo-controlled trial (study years not specified)	16	Children following Fontan operation; Mean age 35 ± 7 months for the treatment group and 48 ± 21 months for the placebo group	Oral; 2.5 mg daily started on POD1 for up to three doses	Pharmacokinetics of ambrisentan following Fontan operation	Children had delayed clearance of ambrisentan compared to historical non-post-operative patients (exposure over 24 hours 3504 ng*h/mL/mg [range 2748–5636] v 1000 ng*h/mL/mg [range 490–3080]); Fontan pressure (16.8 ± 2.8 mmHg v 15.6 ± 2.9 mmHg, p = 0.01), PVR index (2.3 ± 0.9 Wood Units*m^2 v 1.8 ± 0.6 Wood Units*m^2, p = 0.01), and BNP (452 ± 479 v 413 ± 462, p = 0.046) all decreased 3 hours following drug exposure. No significant change was seen in the placebo group, but study was underpowered to assess between group differences.

ASD, atrial septal defect; AVSD, atrioventricular septal defect; BDG, bidirectional Glenn; CPB, cardiopulmonary bypass; CVP, central venous pressure; HFNC, high-flow nasal canula; iNO, inhaled nitric oxide; PDE, phosphodiesterase; $PaCO_2$, partial atrial pressure of carbon dioxide; PaO_2, partial atrial pressure of oxygen; PAP, pulmonary artery pressure; PH, pulmonary hypertension; PHTC, pulmonary hypertensive crisis; Ppm, parts per million; PVR, pulmonary vascular resistance; TAPVR, total anomalous pulmonary venous return; TCPC, total cavopulmonary connection; TPP, transpulmonary pressure; TR, tricuspid regurgitation; UOP, urine output.
Data presented as mean ± standard deviation [SD] or median [interquartile range].

(pulmonary arterial hypertension) improved functional class and haemodynamics compared to placebo therapy.[59–61] While commonly used, sildenafil therapy is associated with some controversy, due to the increased mortality risk with high doses seen in the Sildenafil in Treatment-Naive Children, Aged 1–17 Years, With Pulmonary Arterial Hypertension (STARTS) trials.[62] Although there may have been methodological limitations in this observed dose–outcome relationship, both European and Food and Drug Administration guidelines caution against higher doses and chronic use of sildenafil in children.[11,14,63] Side effects of short-term treatment include risk for systemic hypotension, headache, flushing, and gastrointestinal symptoms.[64] Nine studies of sildenafil met our inclusion criteria. Notably, all included studies were performed before the STARTS-2 trial results were made public.

Three studies of 159 total children with post-operative pulmonary hypertension found that treatment with sildenafil (oral starting dose 0.3–0.5 mg/kg with dosing frequency between every 3 and 6 hours; an intravenous continuous dose was selected to reach target plasma concentration of 40–360 ng/mL) was associated with significantly decreased pulmonary artery pressures and transpulmonary pressure gradient (as measured by pulmonary artery catheter or estimated by echocardiography), as well as duration of mechanical ventilation and ICU length of stay.[38,40,41] In two studies of 22 children, the addition of sildenafil (dosed at 0.3 mg/kg orally four times daily or 0.35 mg/kg IV as a single dose) to inhaled nitric oxide therapy at 20 ppm was associated with an additional reduction in pulmonary vascular resistance and a significant decrease in required inhaled nitric oxide dose.[31,39] However, three separate single-centre retrospective studies of 186 total children compared the effect of standardising treatment with sildenafil (starting doses range 2.1–4.6 mg/kg/day) for all children following Fontan operation with diverging results.[42,43,45] One study found sildenafil treatment to be associated with shorter duration of intubation, chest tube drainage, and ICU length of stay, but no difference in outcomes was seen in the other two studies and one suggested a more positive fluid balance on post-operative day one in children receiving sildenafil.

Phosphodiesterase-3 inhibitors

Milrinone is delivered intravenously and inhibits phosphodiesterase-3, which leads to vasodilation and increases inotropy through increased intracellular calcium, cyclic adenosine monophosphate, and cyclic guanosine monophosphate.[65,66] Milrinone is the most used intravenous vasoactive medication for children with pulmonary hypertensive crises and may reduce pulmonary arterial pressures in children with pulmonary hypertension.[17,67] Nevertheless, its use in the paediatric population remains off-label.[15] Additionally, milrinone has a relatively long half-life compared to other inotropes and is primarily renally cleared, so both optimal dosing and timing of therapy in critically ill children at risk for acute kidney injury are important to define.[68,69] Two studies of milrinone met our inclusion criteria. Milrinone has demonstrated it can reduce post-operative low cardiac output syndrome in a multicenter, randomised, double-blind placebo control trial and is routinely used post-operatively to augment cardiac output.[65] While we focused on milrinone's use as a pulmonary vasodilator or in patients with pulmonary hypertension as described in the inclusion criteria, the impact on pulmonary hypertension may be confounded by milrinone's additional lusitropic and systemic vasodilatory effects.

In a single-centre randomised prospective trial, 48 children with both pre-operative pulmonary hypertension (based on echocardiographic tricuspid regurgitation gradient >30 mmHg) and moderate intraoperative pulmonary hypertension (defined as pulmonary artery to aortic pressure ratio 0.60–0.84, as assessed by pulmonary artery catheter) were started on either milrinone or sildenafil at time of cardiopulmonary bypass initiation. Treatment with milrinone dosed with 50 mcg/kg bolus followed by 0.75 mcg/kg/minute infusion compared favourably to oral sildenafil dosed 0.3 mg/kg every 3 hours with significantly lower pulmonary artery pressures and shorter ICU length of stay.[44] In a separate single-centre prospective randomised trial of 46 children with increased pulmonary pressures following Fontan (central venous pressure of >15 mmHg or transpulmonary pressure >10 mmHg), therapy with either inhaled nitric oxide (at 20 ppm) or milrinone (at 0.5 mcg/kg/minute without loading dose) was associated with improved central venous and transpulmonary pressure gradient within 4 hours of therapy.[32] Combined therapy with both agents was associated with the most significant improvement in central venous and transpulmonary pressures, as well as significantly shorter intubation time. Together, these studies demonstrate that milrinone may be a useful therapeutic to augment the effect of other pulmonary vasodilators in children with post-operative pulmonary hypertension. However, a randomised controlled trial comparing milrinone to placebo as standard post-operative therapy for children following Fontan operation found no difference in length of hospital stay or other surrogate markers for efficacy, suggesting further work is needed to define the optimal population for treatment.[70]

Prostacyclin analogues

Prostacyclin is produced by vascular endothelial cells as a metabolite of arachidonic acid and leads to vascular smooth muscle relaxation.[71] Intravenous infusions of prostacyclin rapidly decrease pulmonary vascular resistance, but carry risks for dose-limiting systemic side effects that include systemic hypotension, headache, and vomiting.[72] Iloprost is a synthetic prostacyclin derivative that is available in both intravenous and aerosolised forms and is Food and Drug Administration approved for the long-term treatment of adults with World Health Organization Group I pulmonary hypertension. The use of iloprost in children or in peri-operative settings remains off-label.[13,73–75] Five studies of iloprost met our inclusion criteria.

In a single-centre prospective study of eight children with post-operative pulmonary hypertensive crises (defined as systolic pulmonary artery pressure to systemic arterial pressure >0.6 as measured by pulmonary artery catheter with associated hypoxia), aerosolised iloprost (starting dose 0.5 mcg/kg over 10 minutes) was associated with a significant decrease in mean pulmonary artery pressure as assessed by pulmonary artery catheter and an increase in arterial oxygen saturation.[34] A single-centre retrospective study of seven infants with post-operative pulmonary hypertension found initiation of inhaled iloprost (1.25–5 mcg/dose administered every 2 hours) allowed inhaled nitric oxide therapy to be weaned off over a median of 5 hours without significant change in mean or systolic pulmonary artery pressures as assessed by pulmonary artery catheter.[35] Three single-centre prospective randomised trials with 52 total children evaluated the ability of iloprost to reduce pulmonary hypertensive crises.[33,36,37] The definition of a hypertensive crisis varied across these studies based on the threshold of pulmonary artery to systemic arterial pressure ratio with associated hypotension or desaturation, and one study provided no definition. In infants with pulmonary hypertension, therapy with inhaled nitric oxide (10 ppm) or inhaled iloprost (0.5 mcg/dose) was associated with similar frequencies of pulmonary

https://doi.org/10.1017/S1047951122002293 Published online by Cambridge University Press

hypertensive crises. Compared to placebo, inhaled iloprost (dose 0.3–0.5 mcg/kg) significantly reduced the risk for pulmonary hypertensive crises in children with post-operative pulmonary hypertension. Nonetheless, in children with pre-operative pulmonary hypertension (defined as systolic pulmonary artery pressure >50 mmHg or mean pulmonary artery pressure >25 mmHg), initiation of intravenous iloprost (dosed at 2.0 ng/kg/minute) at time of cardiopulmonary bypass wean had no benefit in pulmonary pressures or in length of stay compared to placebo.[37] These studies suggest that inhaled nitric oxide and iloprost may have similar haemodynamic effects, but further study will be needed to clarify the difference in outcomes between inhaled and intravenous iloprost, which may be related to patient population, route, or dose of drug.

Endothelin receptor antagonists

Endothelin receptor antagonists, including bosentan and ambrisentan, inhibit endothelin-1-mediated vasoconstriction leading to reduced pulmonary vascular resistance and reduced pulmonary artery pressures.[10] Bosentan is Food and Drug Administration-labelled for the treatment of World Health Organization Group I pulmonary hypertension in children.[76] Pre-operative bosentan may improve pulmonary pressures prior to Fontan operation, and bosentan improved exercise capacity and functional status of children with Fontan physiology in a randomised trial[77,78]; however, bosentan is associated with hepatotoxicity, fluid retention, and anaemia that may be especially detrimental in the acute post-operative setting. Unlike bosentan, which is a non-selective endothelin receptor antagonist, ambrisentan selectively binds to endothelin-1 type A receptors and may reduce the risk for hepatotoxicity.[79] Preclinical study of ambrisentan in juvenile rats suggested a potential negative effect on brain weight.[16]

Similar safety concerns in paediatric populations have not yet been demonstrated, but further safety data are needed, especially in younger children.[80] Use of ambrisentan is off-label in the paediatric population, but a single-centre prospective, randomised, placebo-controlled trial of 16 children demonstrated ambrisentan is overall safe in children immediately following Fontan operation.[16,46] The study was primarily designed to assess the pharmacokinetics of ambrisentan in the post-Fontan setting. Three hours following treatment (2.5 mg daily for up to 3 days), children had significantly decreased plasma brain natriuretic peptide levels, Fontan pressures, and indexed pulmonary vascular resistance as assessed by central venous and atrial catheters. No benefit was seen compared to placebo in the clinical endpoints of chest tube output or length of hospitalisation, although the study enrolled only three placebo group patients and was, therefore, underpowered for detecting any difference. Further study will be needed to define the most beneficial timing and target population for endothelin receptor antagonists in the post-operative setting.

Discussion

Overall, we identified 26 studies of 42,971 children following cardiac surgery across four classes of pulmonary vasodilator medications over twenty years. Our review showed promising therapies to reduce postoperative pulmonary hypertensive crises, but more research is needed to identify the optimal dose, timing of initiation, and patient population for these therapies. Only three studies were multicentre, and of these, only one was a prospective trial. Although a relatively large number of studied children were identified across all studies, two retrospective studies of inhaled nitric oxide usage in 42,088 combined children comprised a substantial majority of the included children, and 20 of the 26 studies had fewer than fifty children. These small study sizes provide limited power to detect differences in more clinically significant outcomes such as duration of mechanical ventilation or hospitalisation and mortality. Accordingly, change in pulmonary pressures was the most common primary outcome (used in 14/26 studies), since with small studies it is easier to find significance with a surrogate marker of efficacy.

Single-centre trials of inhaled nitric oxide demonstrated improved pulmonary haemodynamics following drug initiation in some (children with severe pulmonary hypertension following atrioventricular canal repair or elevated pulmonary pressures following cavopulmonary connection), but not all (such as those with residual anatomic lesions or after cavopulmonary connection without significantly elevated pressures) subsets of post-operative children.[21,23,27–30] Of note, only one of these studies had a clinical endpoint for efficacy (mortality), while all others assessed haemodynamic changes.[27] There was variation in studied inhaled nitric oxide dose, with 10 ppm and 20 ppm being the most commonly used starting doses. This variation makes the comparison of outcomes across studies challenging, although two included studies did not find a dose–response relationship with increasing inhaled nitric oxide doses from 3 ppm to 80 ppm, or 5 ppm to 40 ppm.[21,23]

Similarly, oral sildenafil improved post-operative haemodynamics for some cohorts, including those with pre-operative pulmonary hypertension in a single-centre randomised controlled trial.[37] Interestingly, three single-centre retrospective cohort studies found a divergent impact of sildenafil administration following Fontan operation, with only one suggesting improvements in intubation time and ICU length of stay, while two others showed no benefit and worse fluid balance.[42,43,45] These studies highlight the need for multicentre prospective trials to limit the impact of site-specific variation in care or changing protocols over time on study outcomes. Furthermore, there was a wide spectrum of sildenafil doses administered with mean daily dosing ranging from 1.2 mg/kg to 4.6 mg/kg,[39,43] making drawing conclusions across studies more challenging.

Furthermore, there was heterogeneity in the definition of haemodynamic outcomes. Five studies had a primary outcome or enrollment criteria of pulmonary hypertensive crisis, yet each used a different definition, varying in threshold pulmonary artery pressure to systemic arterial pressure ratio from >0.6 to >1.0 and with different requirements for associated hypotension or hypoxaemia.[22,33,37,40] The modality of assessment of pulmonary pressures also varied between pulmonary artery catheter and echocardiogram across studies. Pulmonary artery catheters are considered the gold standard for assessing pulmonary pressures, while echocardiogram is less precise and not recommended to guide therapy alone in the outpatient setting.[11,81] Nevertheless, an echocardiogram may be a reasonable, less invasive technique in the post-operative setting where invasive pulmonary artery catheters are not routinely used. The variation in haemodynamic definitions also reflects the changing thresholds for pulmonary hypertension diagnosis, with recent lowering of threshold mean pulmonary artery pressure from ≥25 mmHg to ≥20 mmHg based on World Symposium of Pulmonary Hypertension 2018 guidelines.[82] Standard and consistent criteria will be necessary to definitively determine which children will most benefit from medical therapy. Additionally, the heterogeneity of outcomes precluded combining the results of studies, performing quantitative meta-

https://doi.org/10.1017/S1047951122002293 Published online by Cambridge University Press

analysis of the included studies, or assessing the risk of bias in individual studies.

Despite the limitations of inhaled nitric oxide described earlier, in a recent survey of North American ICUs, all responding institutions reported inhaled nitric oxide usage for treatment of pulmonary hypertensive crises, although dosing ranges and weaning protocols were non-uniform.[67] Two major drawbacks of inhaled nitric oxide therapy are the risk for rebound pulmonary hypertension, which may prolong weaning of respiratory support, and cost.[52,53] Three studies specifically mentioned the effects of inhaled nitric oxide withdrawal on haemodynamics: two studies of 28 total children found no significant effect, and one study of 47 children noted 17 had significant increases in central venous pressure and transpulmonary pressure gradient that required reinitiating therapy.[23,28,30] Successful earlier weaning from inhaled nitric oxide may be aided by transition to inhaled nitric oxide therapy delivered through high-flow nasal cannula or starting oral sildenafil prior to wean.[24,39] Aerosolized iloprost may have similar efficacy to inhaled nitric oxide at preventing pulmonary hypertensive crises and provide a viable, less expensive option for transitioning off inhaled nitric oxide therapy.[33,35] Milrinone may augment the pulmonary vasodilatory effects of sildenafil and inhaled nitric oxide.[32,44]

Early trials demonstrated the efficacy of inhaled nitric oxide to improve ECMO-free survival in neonates with pulmonary hypertension almost 25 years ago.[55] Multiple therapies for pulmonary hypertension have been developed since that time, and we identified studies across four different classes of medication. These allow for combination therapy either upfront or if initial monotherapy is not effective.[11] None of the included studies investigated combination therapy. Additional medications from the classes we have identified, such the phosphodiesterase 5 inhibitor tadalafil and prostacyclin epoprostenol have shown benefit in children with pulmonary arterial hypertension, but have not been well studied in the post-operative setting.[83,84] Novel medications such as the oral guanylate cyclase stimulant riociguat have shown clinical improvement in adult populations and represent potential options for investigation in children.[85] Further study will be required to optimise these treatment strategies for children following cardiac surgery.

Overall, in single centre studies, children diagnosed with post-operative pulmonary hypertension by pulmonary artery catheter or echocardiogram had improved haemodynamics following initiation of pulmonary vasodilator therapy, yet definitive improvements in clinical endpoints such as intubation time, ICU length of stay, or mortality were not well demonstrated. Additionally, attempts to standardise to therapy for all children following a specific surgical repair, such as after Fontan operation, have largely been unsuccessful. This discrepancy in efficacy was demonstrated in two multicentre retrospective studies that found inhaled nitric oxide exposure overall was associated with increased intubation time, cost of therapy, and length of stay, even among children with a diagnosis of pulmonary hypertension.[25,26] These multicentre analyses are limited by their inability to distinguish the haemodynamics of individual patients and may be selecting for sicker children that require inhaled nitric oxide exposure; however, this variation in outcomes demonstrates the knowledge gap that exists in this population. Additionally, of the included studies, 14 assessed therapies for only children with biventricular repair, nine assessed therapies for only those with single ventricle repair (two in children following Glenn operation, seven in children following Fontan operation), and three included children regardless of heart defect. Children with single ventricle disease represent a distinct cohort with different underlying pathophysiology for pulmonary hypertension. Associated genetic anomalies, as well as altered fetal pulmonary blood flow, may contribute to altered pulmonary vascular development, and passive pulmonary flow following cavopulmonary anastomosis may contribute to underlying endothelial dysfunction in these patients.[86] Further study is required to define optimal timing of therapy initiation and discriminate between those children who would exhibit both haemodynamic and clinical improvement, and those in which therapy may actually increase morbidity and cost without a clinical benefit.

Fraisse et al attempted to compare differing doses of intravenous sildenafil in a multicentre trial, but the trial was prematurely closed, due to slow enrollment.[41] The study planned for 228 children across 27 centres, but enrolled only 17 children across six centres. Their challenge exemplifies many of the difficulties with trials in this complex and high-risk population. Incompletely defined dosing ranges narrow the age of eligible children and infants, and disease heterogeneity limits the available study population. Furthermore, guardians may be hesitant to give consent for a placebo-controlled trial in a vulnerable population.[87,88] Novel trial design may help overcome these barriers. Pragmatic trials that use real-world data and master protocols can support enrollment and reduce the need for trial-specific data collection and analysis.[88,89] Population pharmacokinetic modelling permits the study of drug disposition from sparse sampling methods and can be leveraged to simulate drug exposure from real-world dosing data to inform dosing strategies.[90] Indeed, recent analysis of milrinone highlighted the need for dose reduction in children with renal insufficiency.[69] Children with CHD undergoing surgery with cardiopulmonary bypass, especially those with underlying pulmonary hypertension, remain at high risk for post-operative morbidity and mortality, and further studies leveraging standardised endpoints and novel trial design are required to allow for evidence-based therapies and improved outcomes.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951122002293

Acknowledgements. Erin Campbell, MS, provided editorial review and manuscript submission. Ms. Campbell did not receive compensation for her assistance, apart from her employment at the institution where this research was conducted. The authors would like to thank Duke Pediatric Research Scholars.

Conflicts of interest. Dr Foote reports no relevant disclosures. Dr Hornik reports no relevant disclosures. Dr Hill reports no relevant disclosures. Dr Rotta receives honoraria from BREAS US for participation in a scientific advisory board and royalties from Elsevier for editorial work. He has previously received honoraria from Vapotherm Inc for lecturing and consulting. Dr Kumar reports no relevant disclosures. Dr Thompson reports no relevant disclosures.

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