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Review Article

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Outcomes of infants and children undergoing surgical repair of ventricular septal defect: a review of the literature and implications for research with an emphasis on pulmonary artery hypertension

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Abstract

Background: Pulmonary vascular disease resulting from CHDs may be the most preventable cause of pulmonary artery hypertension worldwide. Many children in developing countries still do not have access to early closure of clinically significant defects, and the long-term outcomes after corrective surgery remain unclear. Focused on long-term results after isolated ventricular septal defect repair, our review sought to determine the most effective medical therapy for the pre-operative management of elevated left-to-right shunts in patients with an isolated ventricular septal defect. *Methods:* We identified articles specific to the surgical repair of isolated ventricular septal defects. Specific parameters included the pathophysiology and pre-operative medical management of pulmonary over-circulation and outcomes. *Results:* Studies most commonly focused on histologic changes to the pulmonary vasculature and levels of thromboxanes, prostaglandins, nitric oxide, endothelin, and matrix metalloproteinases. Only 2/44 studies mentioned targeted pharmacologic management to any of these systems related to ventricular septal defect repair; no study offered evidence-based guidelines to manage pulmonary over-circulation with ventricular septal defects. Most studies with long-term data indicated a measurable frequency of pulmonary artery hypertension or diminished exercise capacity late after ventricular septal defect repair. *Conclusion:* Long-term pulmonary vascular and respiratory changes can occur in children after ventricular septal defect repair. Research should be directed at providing an evidenced-based approach to the medical management of infants and children with ventricular septal defects (and naturally all CHDs) to minimise consequences of pulmonary artery hypertension, particularly as defect repair may occur late in underprivileged societies.

Nearly a century and a half after the first clinical descriptions of the most commonly recognised coronary heart disease (CHD), the technique of open surgical repair of ventricular septal defects is all but perfected.[1,2] With further refinement over the last three decades, infants and children requiring surgical closure of their ventricular septal defect are now afforded outcomes that, in the proper hands, are excellent.[3] As a consequence, attention can be turned to further improving peri-operative outcomes and to the assessment of long-term quality and quantity of life. More importantly, with the perfection of surgical interventions for CHDs, pulmonary vascular disease from over-circulation may be the most preventable cause of pulmonary artery hypertension worldwide.[4] The immediate priorities for this condition are fourfold: solidify a better understanding of the pathophysiology of pulmonary vascular disease in CHDs; evidence-based guidelines for the management of pulmonary over-circulation in these children with the aim to mitigate pre-operative, peri-operative, and long-term effects; large-scale assessment of the long-term outcomes of infants and children undergoing CHD repair, particularly in less-privileged countries where ventricular septal defect repair may be delayed and peri-operative management is not standardised; and provide a mechanism to offer early repair of CHDs in the developing world. As such, our study is a comprehensive review of outcomes data following open ventricular septal defect repair and is focused on the effects of pulmonary artery hypertension of these infants and children. Specifically, we sought to describe the most effective medical therapy for the pre-operative management of elevated left-to-right shunts in patients with the most common CHD, that being a ventricular septal defect, with the aim of guiding future research.

Materials and methods

Searches were conducted on PubMed and Medline databases to identify English-language articles specific to the surgical repair of ventricular septal defects in infants and children, with

a particular emphasis on pulmonary artery hypertension. Search terms included: "ventricular septal defect," "ventricular septal defect and pulmonary artery hypertension," "ventricular septal defect and pulmonary vascular resistance," and "long-term outcomes of ventricular septal defect repair." Citations of all relevant studies were cross-referenced for completeness of review. Specific parameters addressed included the pathophysiology and medical management of pulmonary over-circulation and pulmonary artery hypertension, as well as general outcomes (both peri-operative and long-term) in those undergoing repair of isolated ventricular septal defects. Animal studies, data specific to individuals not undergoing surgical repair of ventricular septal defects, and surgical repair of CHDs other than ventricular septal defects were excluded from our analysis.

Results

Pathophysiology

From 1958 to 2011, 13 studies were identified which addressed the pathophysiology of pulmonary vascular disease of infants and children undergoing ventricular septal defect repair (Table 1). The average study size was 32 patients (range from 1 to 85). The focus of these studies was most commonly the histologic changes to the pulmonary vasculature induced by increased pulmonary flow and/or pulmonary artery hypertension as the consequence of the ventricular septal defect. Less commonly, other studies investigated thromboxanes, prostaglandins, nitric oxide, endothelin, and matrix metalloproteinases. No study mentioned pharmacologic therapies targeted to any of these systems prior to, during, or after ventricular septal defect repair.

Table 1. Studies which address the pathophysiology of pulmonary vascular disease in infants and children undergoing repair of ventricular septal defect

Author	Year	Sample size	Effector(s) implicated
Heath et al[5]	1958	32	Histologic changes
Wagenvoort et al[6]	1961	32	Histologic changes
Rabinovitch et al[7]	1978	26	Histologic changes
Rabinovitch et al[8]	1984	81	Histologic changes
Yeager et al[9]	1984	49	Histologic changes
Fleming et al[10]	1986	26	6-keto-prostaglandin F1 alpha, TXB_2
Fried et al[11]	1986	10	Histologic changes
Haworth[12]	1987	85	Histologic changes
Adatia et al[13]	1993	5	2,3-dinor-TXB_2
Adatia et al[14]	1994	14	TXA_2, PGI_2
Takaya et al[15]	1998	29	NO
Maeda et al[16]	2003	1	Histologic changes
Pan et al[17]	2011	24	Histologic changes and NOS, endothelin, and MMP systems

MMP, matrix metalloproteinase; NO, nitric oxide; NOS, nitric oxide synthase; TXA, thromboxane A; PGI, prostaglandin I; TXB, thromboxane B

Pharmacologic management

As shown in Table 2, few studies documenting early or late outcomes after ventricular septal defect repair included details about pre-operative pharmacologic management or optimisation of congestive heart failure or pulmonary artery hypertension. Only two of 44 studies described pre-operative/post-operative pharmacologic management of pulmonary artery hypertension beyond those which discuss intra-operative considerations.[18,19] One of these is the study by Ademir et al in 2013. These authors compared 282 infants (median age 5 months) based on age at the time of surgery: Group 1, age 0–3 months; Group 2, age 3–6 months; and Group 3, age 6–12 months. The authors noted that the ratio of pulmonary-to-systemic blood pressure, the ratio of pulmonary vascular resistance to systemic vascular resistance, and the pulmonary vascular resistance remained higher post-operatively in both Groups 2 and 3 compared to Group 1 ($p < 0.05$ for both comparisons). This indicated a persistence of post-operative pulmonary hypertension in the older age groups. As there was also a greater frequency of mortality in the older age groups compared to Group 1, the authors concluded that early surgical repair of infants with isolated ventricular septal defects and severe pulmonary hypertension should be pursued. In this report, Ademir et al also described their management of severe pulmonary hypertension as using fentanyl (0.5–1 mcg/kg/h), nitroglycerin (0.5 mcg/kg/min), and/or iloprost (0.5–1 mcg/kg/min) and nitric oxide inhalation after 2006 during the peri-operative period. Post-operatively these authors report their use of oral captopril (1 mg/kg/day) before 2006 and oral sildenafil (3 mg/kg twice daily) after 2006. However, Ademir et al did not mention how titration of the dosages was determined or if these therapies were effective.[18] In a later study, Bhasin et al randomised 60 patients to either pre-operative placebo and post-operative sildenafil (Group 1) or pre- and post-operative sildenafil (Group 2). The median age in Group 1 was 15.8 months, and the median age in Group 2 was 14.5 months at the time of ventricular septal defect repair. The authors found that those in Group 2 had lower pre- and post-operative pulmonary artery pressures ($p < 0.05$) as well as a decreased intensive care length of stay (mean 78.5 versus 98.4 hours; $p = 0.001$). They also report that one patient in Group 1 had three episodes of pulmonary hypertensive crisis, and that two patients in Group 2 each had two episodes of pulmonary artery hypertensive crisis. Though the authors do not document the actual number of mortalities (if any), they do indicate that there was no mortality difference between the groups.[19] Unfortunately, there were no pulmonary vascular resistance indices reported, so these cannot be contrasted between groups. Nonetheless, this study demonstrated similar results of sildenafil to those of others with mixed groups of congenital heart lesions, though the long-term effects are unclear for all.[20–25] In total, there remain little data to indicate what effects the applicable pharmacologic therapies have on individual patient outcomes for those with pulmonary artery hypertension related to congenital ventricular septal defects.

Peri-operative and long-term outcomes

Also shown in Table 2 are 44 studies containing data on outcomes (peri-operative and long-term) of infants and children undergoing isolated ventricular septal defect repair. These studies are from 1958 to 2019, of which the median study population was 53 patients (range from 4 to 767), with one undetermined. Repeat studies from the same institution were few and were usually published a decade apart. Of the 28 studies containing data on long-term outcomes (≥1 year), 20 had follow-up assessment of the pulmonary vasculature as indicated by objective measurements by catheterisation or

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Table 2. Studies of patients undergoing surgical closure of isolated ventricular septal defects with objective data on pulmonary artery hypertension and its relevant pre-operative pharmacologic management, peri-operative outcomes, and long-term outcomes

Author	Year	Study size	Pharmacologic management	Outcomes	
				Peri-operative	Long-term
Heath et al[5]	1958	32	–	Yes	–
Kirklin and DuShane[25]	1961	65	–	Yes	–
Sigmann et al[26]	1967	45	–	Yes	–
Wada and Iwa[27]	1969	46	–	Yes	–
Hallidie-Smith et al[28]	1969	38	–	Yes	Yes
Park et al[29]	1969	4	–	Yes	–
Gotsman et al[30]	1969	34	–	–	Yes***
Lueker et al[31]	1969	31	–	–	Yes
Maron et al[32]	1973	11	–	–	Yes
Friedli et al[33]	1974	57	––	Yes	Yes
Weidman et al[34]	1977	437*	–	Mixed	Mixed
Sigmann et al[35]	1977	106	–	Yes	Yes
Hallidie-Smith et al[36]	1977	27	–	–	Yes
McNicholas et al[37]	1978	78	–	Yes	–
Richardson et al[38]	1982	32	–	Yes	Yes
McNamara and Latson[39]	1982	Unclear	–	–	Yes**
Blake et al[40]	1982	187	–	–	Yes**
Rabinovitch et al[8]	1984	81*	–	Yes	Yes
Yeager et al[9]	1984	128	–	Yes	Yes**
Fried et al[11]	1986	10	–	Yes	–
Haneda et al[41]	1988	43	–	Yes	–
Moller et al[42]	1991	296*	–	–	Yes
Hardin et al[43]	1992	48	–	Yes	Yes**
Backer et al[44]	1993	141	–	Yes	–
Meijboom et al[45]	1994	176*	–	–	Yes
Haneda et al[46]	1994	58	–	–	Yes
Ikawa et al[47]	1995	32	–	–	Yes
Reddy et al[48]	1999	22	–	Yes	Yes**
Nieminen et al[49]	2001	767	–	Yes	Yes**
Kannan et al[50]	2003	38	–	Yes	Yes
Bol-Raap et al[51]	2003	188*	–	Yes	Yes**
Mavroudis et al[4]	2003	673	–	Yes	Yes**
Roos-Hesselink et al[52]	2004	176*	–	Yes	Yes
Scully et al[53]	2010	215	–	Yes	–
Aydemir et al[18]	2013	282	Yes	Yes	–
Anderson et al[54]	2013	285	–	Yes	–
Yang et al[55]	2014	99	–	Yes	–
Heiberg et al[56]	2015	27	–	–	Yes
Gabriels et al[57]	2016	47	–	–	Yes
Bhasin et al[19]	2017	60	Yes	Yes	–
Gabriels et al[58]	2017	53	–	–	Yes**

(*Continued*)

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Table 2. (*Continued*)

Author	Year	Study size	Pharmacologic management	Outcomes	
				Peri-operative	Long-term
Nederend et al[59]	2018	33	–	–	Yes**
Gabriels et al[60]	2019	27	–	–	Yes
Rex et al[61]	2019	30	–	–	Yes

*Data unavailable on all patients
**Data limited, no mention of pulmonary arterial flow, or pressure measurements
***Follow-up at one year

imaging, or indirect measurement by exercise capacity. The majority of these reports indicated a measureable frequency of pulmonary artery hypertension or diminished exercise capacity late after ventricular septal defect repair, though the studies varied considerably in terms of decade published, age at the time of ventricular septal defect repair, means of pulmonary flow measurements, and time since surgery that follow-up measurements were performed. However, it is important to keep in mind that persistence of pulmonary hypertension is rare in the current era when ventricular septal defects are repaired in early infancy.

In their report from the 1960s, Halladie-Smith et al studied 36 patients with pulmonary vascular disease aged 3–12 years (mean 7.2 years) at the time of ventricular septal defect repair, of which 25 patients were investigated 1–8 years after operation. The authors report an overall mortality of 24% which is considerably greater than the 5% of their own patients with ventricular septal defects not complicated by pulmonary vascular disease. Of the deaths, three patients had pulmonary artery hypertension that did not resolve post-operatively. In this study, the greatest diameter of the ventricular septal defect ranged from 1.0 to 4.0 cm (mean 2.3 cm excluding one patient whose measurement was reported errantly in the report). Though overall "the results showed a fall in pulmonary artery pressure and in pulmonary vascular resistance, [t]he majority had some residual pulmonary vascular disease."[28] Similarly, in their report from 1969, Gotsman et al studied 34 patients (age at ventricular septal defect repair not specified). According to their own classification scheme using defect size and the ratio of pulmonary systolic pressure to systemic systolic pressure, they found that 1-year post-surgery pulmonary artery pressures fell in all patients but that there was little change in pulmonary-to-systemic vascular resistance in patients with Type 1B (small defect, shunt 10–40%), Type 1C ("slightly larger" defect, shunt > 40%), or Type 2 (moderate-sized defect, shunt 40–80%), compared to a variable response in Type 3A patients (large defect, shunt > 40%).[30] Soon thereafter, Maron et al studied 11 patients aged 11–40 years at the time of ventricular septal defect repair. These authors performed exercise studies 3–15 years after ventricular septal defect closure and found that during intense exercise, cardiac output was below normal in five patients and that two patients had an abnormally elevated mean pulmonary artery pressure.[32] In another study, Friedli et al described the results of 57 children who had undergone ventricular septal defect repair at ages 11 months to 17 years (mean 4.8 years), of whom 18 (32%) died at or immediately after operation. Of 32 long-term survivors who underwent cardiac catheterisation 1–11 years after ventricular septal defect closure, five had "evidence of progressive pulmonary vascular disease by both clinical and hemodynamic criteria, and [three] more [had] increased pulmonary vascular disease not suspected clinically."[33] During the latter part of the same decade, Hallidie-Smith et al studied 27 patients 6–16 years after they underwent ventricular septal defect closure at ages 3–12 years. Of these patients, 15 underwent supine exercise recording of their pulmonary artery pressure. These authors found that five had pulmonary artery pressures which closely approximated systemic pressures, and in all except three, the systolic pulmonary artery pressure rose 30 mmHg or more.[36]

In the early 1980s, Richardson et al reported 32 patients who underwent ventricular septal defect repair at ages 1–24 months. Of these patients, 18 underwent cardiac catheterisation 12–33 months after operation, and only three had a mildly elevated pulmonary vascular resistance (5–7 units/m^2).[38] Later in this decade, Haneda et al described 43 patients who underwent surgical closure of ventricular septal defect in the first year of life.[41] Not surprisingly, these authors found that the peak pulmonary to systemic pressure ratio (Pp/Ps) decreased from pre-operative indices for the majority of the cohort immediately after ventricular septal defect closure [0.79 ± 0.15 to 0.39 ± 0.11 ($p < 0.01$)]; however, there was no long-term follow-up described. Nonetheless, in the 1990s, this same group successfully described the late results after correction of ventricular septal defects with severe pulmonary artery hypertension.[46] In their study of 58 patients with ventricular septal defect repair and severe pulmonary artery hypertension ($Pp/Ps \geq 0.90$), 26 underwent cardiac catheterisation 1 month to 12 years (average 3.0 years) after the operation. Haneda et al found that Pp/Ps and pulmonary to systemic vascular resistance ratio (Rp/Rs) were significantly decreased post-operatively. However, there were significant differences between groups repaired prior to and after age 2, with the delayed repair group having a higher Rp/Rs [0.31 ± 0.19 versus 0.17 ± 0.06 ($p < 0.05$) and Rp [4.55 ± 1.88 versus 2.52 ± 0.65 units $\cdot$ m^2 ($p < 0.05$)]. Moreover, a greater frequency of those with delayed closures had $Pp/Ps \geq 0.40$ (62.5% versus 20 %, $p < 0.05$); $Rp/Rs > 0.30$ (56.3% versus 0, $p < 0.005$); and Rp ≥ 4 units $\cdot$ m^2 (55.6% versus 0, $p < 0.02$). These authors suggested that their results indicated persistence of pulmonary vascular resistance and concluded that ventricular septal defect repair in those with severe pulmonary artery hypertension should occur before age 2.[46]

Also in the 1990s, Ikawa et al assessed pulmonary artery pressure and resistance during exercise late after closure of a large ventricular septal defect with pulmonary hypertension.[47] The authors identified two groups with a pulmonary-to-systemic resistance ratio of 0.15–0.50 (Group 1) and 0.50–0.96 (Group 2). The age at operation was 0.9–13.0 years (mean 4.6 years) in Group 1 and 0.8–15.8 years (mean 4.3 years) in Group 2. These authors found that the mean pulmonary artery pressure increased in both groups during exercise ($p < 0.05$). Pulmonary vascular resistance also increased in both groups during exercise ($p < 0.001$).

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These results were also significantly different from the normal control group's response to the same exercise stimulus. Ikawa et al employed their data to indicate that those with a higher pulmonary-to-systemic resistance ratio should be operated on at a younger age.[47] Furthermore, in their study of 176 patients who underwent isolated ventricular septal defect repair before the age of 15 years, Meijboom et al found in 109 participating patients that exercise capacity at a mean of 14.5 years following ventricular septal defect repair was better ($p = 0.02$) in those with lower pre-operative pulmonary vascular resistance (<400 dynes·s·cm^{-5}). They further stated that elevated pre-operative pulmonary vascular resistance was the only independent predictor for decreased exercise capacity upon linear regression analysis.[45] In addition, Roos-Hesselink et al noted a 4% prevalence of pulmonary artery hypertension in their more recent, longitudinal study of 176 consecutive patients undergoing isolated ventricular septal defect repair at a median age of 4 years (range 0–13 years).[52] Unfortunately, the details of these 4% of the patients were not provided, other than that they did not differ from the rest of the cohort in terms of age at operation. In 2013, Aydemir et al reported their experience of 282 infants undergoing ventricular septal defect repair, with an emphasis on pulmonary hypertension.[18] These authors found that pre-operatively 89.4% had congestive heart failure or failure to thrive and that 87.6% had pulmonary hypertension (43.3% severe). All of the eight patients who died had severe pulmonary hypertension. In this study, there were higher values of post-operative Pp/Ps, pulmonary vascular resistance/systemic vascular resistance, and pulmonary vascular resistance in those repaired at 6–12 months compared to prior to 3 months, indicating persistence of post-operative pulmonary hypertension. The authors conclude that the relatively higher mortality in their study could be due to severe pulmonary hypertension, and "that early repair . . . of isolated ventricular septal defects in patients with severe pulmonary hypertension is strongly advised to achieve favorable results."[18]

Among more recent studies, Heiberg et al compared 27 patients approximately 20 years following ventricular septal defect repair versus 30 control patients. Compared to controls, they found that those in the ventricular septal defect group had a significantly lower mean minute ventilation at peak exercise (1.4 ± 0.4 L/kg/min versus 1.8 ± 0.4 L/kg/min, $p < 0.01$) and mean oxygen uptake (38.0 ± 8.2 ml/kg/min versus 47.9 ± 6.5 ml/kg/min, $p < 0.01$).[56] These results were soon thereafter replicated by Nederend et al.[59] Also recently, Gabriels et al reported that 4 of 47 patients approximately 30 years following ventricular septal defect repair had pulmonary hypertension diagnosed by echocardiography.[57] In a later study specifically measuring pulmonary vascular resistance late after ventricular septal defect repair, this same group reported a higher peak total pulmonary vascular resistance compared to controls (2.7 ± 0.8 versus 2.2 ± 0.3 mmHg/L/min, $p = 0.005$), and concluded that life-long follow-up is warranted.[60] Finally, in an age- and gender-matched control study, Rex et al compared 30 patients approximately 23 years after ventricular septal defect repair versus 30 healthy controls. These authors found that those in the ventricular septal defect repair group had lower expiratory volume in 1 second (99 ± 18% versus 118 ± 19%, $p < 0.001$), impaired forced vital capacity (106 ± 12% versus 118 ± 13%, $p < 0.001$), and lower alveolar volume (92 ± 10% versus 101 ± 11%, $p < 0.001$). Rex et al concluded that adults who had undergone ventricular septal defect repair as a child had reduced pulmonary function versus controls.[61]

Discussion

In 1958, Heath and Edwards first proposed a histologic grading system of the effects of pulmonary artery hypertension on the pulmonary vasculature. This work indicated that pulmonary vascular disease progresses from medial hypertrophy, smooth muscle extension to usually non-muscular arteries, and adventitial fibrotic thickening to end-stage lesions consisting of medial thinning and fibrosis, plexiform lesions, and necrotising arteritis.[62] Soon thereafter, Heath and Edwards put into practice their grading system in a population undergoing ventricular septal defect repair and documented that the reversibility of pulmonary artery hypertension was inversely proportional to the graded severity of histologic changes.[5] Since these early studies, others have proposed modified interpretations of lung biopsies taken at the time of ventricular septal defect repair, which focus on distal extension of smooth muscle, medial hypertrophy, and density of small arteries in relation to the number of alveoli.[7,8,12] These studies, in combination with clinical analyses focusing on the reversibility of pulmonary artery hypertension, have established the importance of ventricular septal defect repair within the first 1–2 years of life.[8,9] Fortunately, improvements in cardiopulmonary bypass and surgical techniques have advanced to the point of ensuring excellent outcomes achieved in early ventricular septal defect repair even in very low weight infants.[48]

Though the histopathology of pulmonary artery hypertension in those with ventricular septal defect has been established, the biochemical determinants of disease are not as concretely described. Nonetheless, the combination of animal and human studies indicates a role for growth factors, nitric oxide, prostacyclin, thromboxane, endothelin, matrix metalloproteinases, and vasoactive mediators in the thrombosis, inflammation, vasoconstriction, fibrosis, and apoptosis characteristic of the pathogenesis of pulmonary artery hypertension.[10,13–15,17,62–74]

The limited understanding of these biochemical processes and the inherent difficulties in conducting clinical research in paediatric populations (particularly randomised-controlled trials) restrict the development of evidence-based guidelines for the pharmacologic management of pulmonary over-circulation in infants and children with ventricular septal defect. In a recent and comprehensive analysis, Galie et al observed that " . . . the treatment strategy for patients with pulmonary artery hypertension associated with congenital systemic-to-pulmonary shunts . . . is based mainly on clinical experience rather than being evidence based."[75] This paucity of data is reflected in our having found minimal relevant information in any of 44 studies on the peri-operative and late outcomes of ventricular septal defect repair as related to pulmonary artery hypertension. Accordingly, there is limited evidence-based guidance to the pharmacologic management of pulmonary over-circulation in children with CHDs, nearly half a century since Lillehei first repaired a ventricular septal defect.[76] This point is particularly relevant given the varied nature of those at risk for late complications of pulmonary artery hypertension, as well as infants and children in less-privileged countries who may rely upon control of pulmonary over-circulation to optimise their chances of spontaneous ventricular septal defect closure, or whose repair may be delayed as a consequence of limited resources for open surgical intervention.[4]

Finally, data which address early and late outcomes following ventricular septal defect repair are relatively robust. Recent studies unanimously indicate that excellent outcomes should be expected, particularly as the frequency of the most common causes of

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morbidity (atrioventricular heart block, reoperation, and significant residual ventricular septal defect) is less than 1%.[4] Nonetheless, the majority of studies offering true long-term follow-up data are based on individuals having undergone ventricular septal defect repair in the 1950s–1990s when refinements to surgical technique had not been fully developed. Though the vast majority of individuals lead relatively normal lives decades after ventricular septal defect repair, measurable percentages are found to have persistence of pulmonary artery hypertension and abnormalities in response to exercise, particularly among those reports having patients operated on at older ages.[18,28,32,33,36,38,41,45–47,52,56,57,59–61] As a consequence, investigators such as Meijboom et al have suggested that quality of the pulmonary vascular bed at the time of ventricular septal defect repair may be important for long-term cardiopulmonary performance.[45] These findings reaffirm the importance of medical and pharmacologic optimisation of the child before ventricular septal defect repair as soon as it is feasible.[18,41] This is based on both the relative perfection in surgical technique and the prevalence of CHDs and pulmonary artery hypertension in underprivileged countries where ventricular septal defect repair may be delayed or even impossible.[77–79]

We acknowledge that our manuscript is limited by the vast and complex heterogeneity of the data. Many reports were identified which did contain data on patients undergoing isolated ventricular septal defect repair, but oftentimes outcomes data related to these patients could not be differentiated from those with associated cardiac anomalies; thus, these reports and consequently many patients were excluded to allow for more stricter comparisons. In addition, the data spanned many decades of ventricular septal defect repair, and the outcomes and approach to care were subject to improvements in surgical technique, medical management, and rigor of data interpretation and reporting as well as practice patterns and resources which vary in and among countries throughout the world.

We conclude that long-term analyses following repair of ventricular septal defect should continue to be aggressively pursued. Given the evidence for pulmonary vascular changes and altered exercise performance in some patients late after ventricular septal defect repair, we recommend attention to medical management of pulmonary over-circulation prior to closure, though we cannot provide specific direction on any particular therapeutic regimen other than potentially sildenafil in older patients with elevated pulmonary vascular resistance. Most importantly, the pre-operative management of ventricular septal defects continues to be based on clinical experience rather than on evidence-based guidelines. Novel means (non-invasive or otherwise) at quantifying the degree of pre-operative systemic-pulmonary shunt should be pursued, as should the contraindications for ventricular septal defect repair in the setting of pulmonary artery hypertension given recent improvements in its management. Finally, the void in evidence-based guidance for a scientific approach to pulmonary over-circulation and pulmonary artery hypertension in those with CHDs, and particularly those with ventricular septal defects, remains an area of future research that must be addressed.

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Conflicts of Interest. None.

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