Current Cardiology Reviews, 2022, *18*, e090522204486

META-ANALYSIS ARTICLE

Reversed Potts Shunt Outcome in Suprasystemic Pulmonary Arterial Hypertension: A Systematic Review and Meta-Analysis

Brian Mendel[1,*], Christianto Christianto[2], Phoniex Angellia[2], Indra Holiyono[2], Radityo Prakoso[1] and Sisca Natalia Siagian[1]

[1]*Pediatric Cardiology and Congenital Heart Defect Division, Department of Cardiology and Vascular Medicine, National Cardiovascular Center Harapan Kita, Universitas Indonesia, Jakarta, Indonesia;* [2]*Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia*

ARTICLE HISTORY

Received: January 21, 2022
Revised: February 14, 2022
Accepted: March 15, 2022

DOI:
10.2174/1573403X18666220509203335

Abstract: ***Background*:** Reversed Potts shunt has been a prospective approach to treat suprasystemic pulmonary hypertension, particularly when medication treatment fails to reduce right ventricular afterload.

***Objective*:** This meta-analysis aims to review the clinical, laboratory, and hemodynamic parameters after a reversed Potts shunt in suprasystemic pulmonary hypertension patients.

***Methods*:** Six electronic databases were searched from the date of inception to August 2021, where the obtained studies were evaluated according to the PRISMA statement. The effects of shunt creation were evaluated by comparing preprocedural to postprocedural or follow-up parameters, expressed as a mean difference of 99% confidence interval. Quality assessment was conducted using the STROBE statement.

***Results*:** Seven studies suited the inclusion criteria which were included in this article. A reduction in upper and lower limb oxygen saturation [Upper limb: St. Mean difference -0.55, 99% CI -1.25 to 0.15; P=0.04; I^2=6%. Lower limb: St. Mean difference –4.45, 99% CI –7.37 to –1.52; P<0.00001; I^2=65%]. Reversed Potts shunt was shown to improve WHO functional class, 6-minute walk distance, NTpro-BNP level, and hemodynamic parameters including tricuspid annular plane systolic excursion, interventricular septal curvature, and end-diastolic right ventricle/left ventricle ratio.

***Conclusion*:** Reversed Potts shunt cannot be said to be relatively safe, although it allows improvement in the clinical and functional status in patients with suprasystemic PAH. Reversed Potts shunt procedure may be the last resort for drug-resistant pulmonary hypertension as it is considered a high-risk procedure performed on patients with extremely poor conditions.

This meta-analysis is registered in PROSPERO with the registration number 279757.

Keywords: Outcome, pulmonary arterial hypertension, reversed Potts shunt, suprasystemic, PRISMA, pulmonary vascular resistance, pulmonary artery coupling.

1. INTRODUCTION

Pediatric pulmonary arterial hypertension (PAH) is a progressive disease with a poor prognosis. Current treatment strategies intend to decrease the pulmonary vascular resistance and load to preserve RV function. Nevertheless, neither a persistent reversal of pulmonary vascular changes nor reduction of pulmonary arterial pressure could be achieved by currently available vasodilators [1]. To convert PAH with suprasystemic pulmonary arterial pressure into patent ductus arteriosus-Eisenmenger physiology, a novel side-to-side Potts shunt anastomosis was devised, and pilot studies have reported this procedure to be safe [2, 3]. However, since the physiology of Potts shunt creation on RV function, RV-pulmonary artery coupling has not been well studied; a systematic review and meta-analysis was created to study those effects in pediatric PAH.

2. MATERIALS AND METHODS

2.1. Search Strategy

This systematic review and meta-analysis was conducted according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement [4]. We did a

*Address correspondence to this author at the Faculty of Medicine, Universitas Indonesia, P.O. Box: 1358, Jakarta, Indonesia; Tel/Fax: +62-131-930-373, +021-390-1814; E-mails: brianmendel17@gmail.com

1875-6557 /22 $65.00+.00

systematic search in PubMed, ProQuest, ScienceDirect, Lancet, Plos One, and Google Scholar databases using the combination of keywords: (reversed Potts shunt) AND (pulmonary hypertension). The database search was conducted independently in August 2021 by four reviewers (BM, C, PA, IH) with equal contributions. Additionally, hand searching was conducted independently by the same reviewers (Fig. **1**).

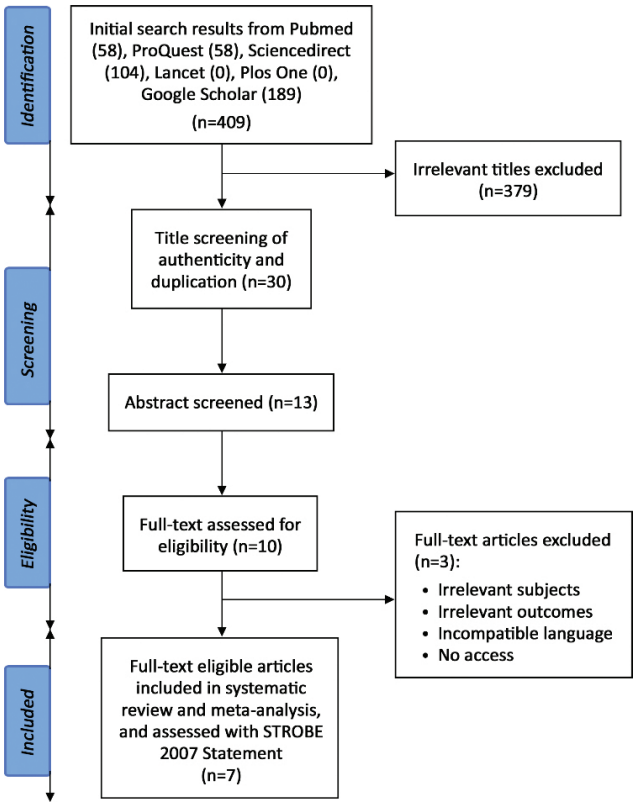

Fig. (1). PRISMA flow of the systematic review and meta-analysis [4].

2.2. Study Criteria

The included studies complied with all eligibility criteria. The inclusion criteria were patients with evidence of suprasystemic pulmonary arterial hypertension, the intervention of either surgical or transcatheter reversed Potts shunt creation, and follow-up assessment of clinical, laboratory, or hemodynamic parameters, including echocardiographic or catheterization outcome. The exclusion criteria were studies using unidirectional valved Potts shunt or modified reversed Potts shunt, studies in the form of editorial, case report, case series, review, or meta-analysis, and studies with the irretrievable full-text articles.

2.3. Data Extraction and Quality Assessment

The screening and reviewing, continued by data extraction of the included studies was completed by four reviewers (BM, C, PA, IH). The data extracted from the included studies were study and patient characteristics (first author, year of publication, study design, setting, duration of follow-up, number of patients, age, weight, procedure either surgical or transcatheter), as well as preprocedural, postprocedural, and follow-up assessment of clinical parameter (WHO functional class, 6-minute walking test, adverse event), laboratory parameter (NTpro-BNP), hemodynamic parameter (upper limb SaO_2, lower limb SaO_2, SaO_2 upper/lower limb gradient, mean pulmonary arterial pressure/MPAP, systolic right ventricular/RV pressure, tricuspid annular plane systolic excursion/TAPSE, interventricular septal curvature, end-diastolic RV/LV diameter ratio). Quality assessment of the included studies was conducted by four reviewers (BM, C, PA, IH) using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [5]. Any disagreement in the data extraction and the quality assessment was resolved by discussion between the four reviewers to reach a consensus (Fig. **2**).

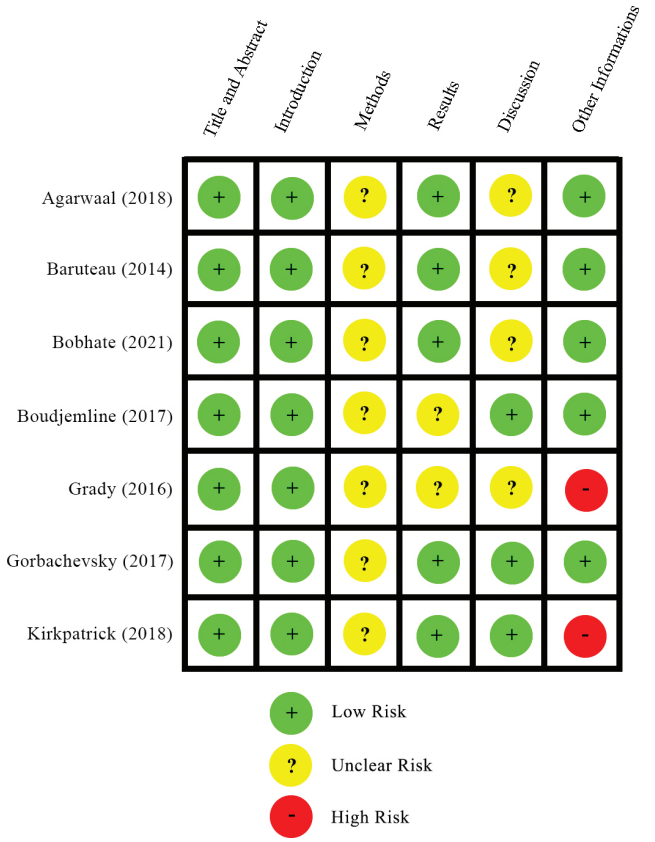

Fig. (2). Summary of quality appraisal using STROBE statement [5]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2.4. Statistical Analysis

Parametric data are expressed as mean ± standard deviation (SD), while nonparametric data are expressed as median (interquartile range). The outcome of the reversed Potts shunt creation on the patients was evaluated by comparing preprocedural with postprocedural or follow-up parameters, expressed as a mean difference of 99% confidence interval (CI). A random-effects model was used to analyze the data with consideration of inconsistency in the baseline characteristics and outcomes of the patients. A p-value <0.05 was considered statistically significant for hypothesis testing. All statistical analyses were done using REVMAN (version 5.4; Cochrane Collaboration, Oxford, UK) [6].

Table 1. Study and patient characteristics of the included studies.

No	Study (Year)	Study Design	Settings	Duration of Follow-up	No. of Patients	Age	Weight (kg)	Procedure	Adverse Events (n)
1	Aggarwal *et al* (2018)	Retrospective cohort	St Louis Children Hospital, Boston	27 (2.9-50.6) months	11	Median: 11.2 years	Median: 32.8	Surgical	Bilateral lung transplant (1), death (2)
2	Baruteau *et al* (2014)	Retrospective multicenter study	Marie Lannelongue Hospital, Necker Hospital, and Bambino Gesu Children Hospital, France	2.1 (3-14.3) years	24	7.7 (1.5-17) years	19.5 (10.2-47)	Surgical (19), Transcatheter (4)	Death (3)
3	Bobhate *et al* (2021)	Prospective single-center study	Children's Heart Center, Kokilaben Dhirubai Ambani Hospital and Research Center, India	17 (1-40) months	16	10.5 (4.3-17.3) years	24.7 (13.2-50.3)	Surgical	Death (4)
4	Boudjemline *et al* (2017)	Prospective single-center study	Necker University Hospital, France	10 ± 2.6 months	6	11.0 ± 4.2 years	37.8 ± 19.1	Transcatheter	Cardiac arrest after anesthetic induction and postprocedural irreversible brain damage death (2)
5	Grady *et al* (2016)	Retrospective study single-center study	Washington University School of Medicine	31.42 ± 18.4 weeks	5	10.32 ± 5.1 years	37.1 ± 24.4	Surgical	-
6	Gorbachevsky *et al* (2017)	Retrospective study	Bakoulev Center for Cardiovascular Surgery, Moscow, Russia	17 (2-32) months	8	13.5 (5-154) months	N/A	Surgical	Pulmonary hypertensive crisis (2), heart failure (1), death (2)
7	Kirkpatrick *et al* (2018)	Retrospective study	Children's Hospital of Wisconsin, United States	351 (244-441) days	3	20.7 ± 5.7 years	N/A	Surgical (1), Transcatheter (2)	Significant hemorrhage, pulmonary contusion, and respiratory failure (1)

N/A, not available.

3. RESULTS

3.1. Search Results

The PRISMA flow diagram of the literature screening and selection for this systematic review and meta-analysis is shown in Fig. (**1**). The initial search generated 409 potential studies from the selected databases. The exclusion of studies with irrelevant titles produced 30 studies for authenticity and duplication review. Eighteen studies were qualified for abstract screening, eliciting 15 studies for full-text screening. Elimination of 6 studies was performed due to irrelevant intervention and no access to full-text papers. Conclusively, nine studies complied with the eligibility criteria and thus were included in this systematic review and meta-analysis.

3.2. Study Characteristics

This systematic review covers nine studies that analyzed various outcomes of reversed Potts shunt in patients with suprasystemic PAH (Table **1**). These studies consisted of three retrospective studies [7-9], one multicenter retrospective study [2], one retrospective single-center study [10], and two prospective single-center studies [3, 11] that were published from 2012 to 2021 in France, the USA, India, and Rusia [2, 3, 7-11]. Each included study had a distinct duration of follow-up with a mean and median of less than one year in two studies [3, 9], mean and median between 1-3 years in five studies [2, 7, 8, 10, 11]. The total number of participants involved in this review is 73 patients with the age of intervention ranging from 13.5 months to 20.7 years old [8, 9]. Weight of the patients varies among studies with the median and mean above 30 kg in three studies [3, 7, 10], a mean and median between 20-30 kg in one studies [11], and median of less than 20 kg in one study [2]. The remaining studies had no information on the participants' weight data. Four studies performed Potts shunt interventional surgery through thoracotomy [7, 8, 10, 11], two studies reviewed both surgical and transcatheter intervention [2,9], and a study by Boudjemline *et al.* (2017) [3] used the transcatheter approach as the interventional method. The adverse events of Potts shunt intervention reported in the included studies were bilateral lung transplantation [7], cardiac arrest after anesthetic induction, irreversible brain damage [3], pulmonary hypertensive crisis, heart failure [8], significant hemorrhage, pulmonary contusion, respiratory failure [9], and death. The total number of deaths of participants included in this systematic review and meta-analysis were 17 participants.

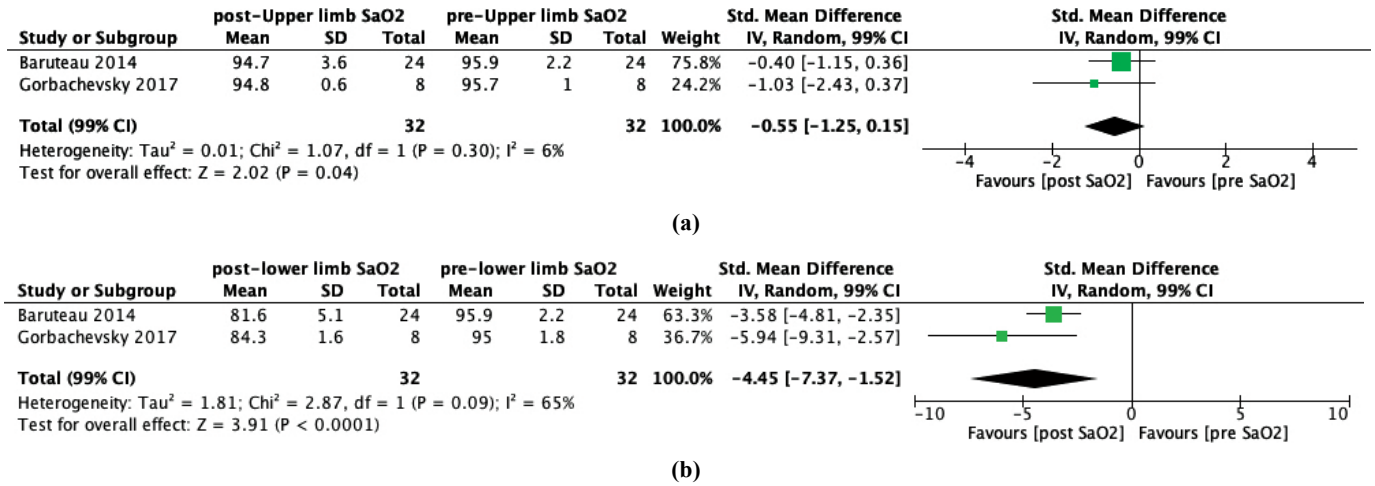

Fig. (3). Forest plot of random-effect model for the preprocedural and postprocedural conditions of (**a**) upper limb oxygen saturation, and (**b**) lower limb oxygen saturation. CI: Confidence Interval.

3.3. Effect of Reversed Potts Shunt on Upper Limb SaO_2

Upper limb SaO2 of most patients with suprasystemic PAH were not significantly influenced by the reversed the Potts shunt procedure [2, 8] (2 studies, Std. mean difference -0.55, 99% CI -1.25 to 0.15; P=0.04; I^2 = 6%); Fig. (**3A**). Studies conducted by Gorbachevsky *et al.* (2017) demonstrated a negligible change of preprocedural upper limb SaO_2 from 95.7 ± 1.0 % to 94.8 ± 0.6 % after Potts shunt procedure. In the follow-up period, the values returned to their initial upper limb SaO_2 of 95.6 ± 1.2 % [8]. Furthermore, the other study by Baruteau *et al* (2014) showed a minimal lowering of preprocedural upper limb SaO_2 from 95.9 ± 2.2 % to postprocedural of upper limb SaO_2 of 94.7 ± 3.6 %, respectively [2].

3.4. Effect of Reversed Potts Shunt on Lower Limb SaO_2

In contrast to upper limb SaO_2, lower limb SaO_2 were remarkably reduced following Potts shunt procedure [2, 8] (2 studies, Std.mean difference -0.55, 99% CI -1.25 to 0.15; P=0.04; I^2 = 6%; Fig. **3a)** (2 studies, Std. mean difference –4.45, 99% CI –7.37 to –1.52; P < 0.0001; I^2 = 65%; Fig. **3b**). The consequence of prominent lower limb arterial oxygen desaturation was portrayed by Baruteau *et al* (2014) from 96.9 ± 2.2% to 81.6 ± 5.1 % [2]. The same result was also presented as a decline of preprocedural lower limb SaO_2 from 95.0 ± 1.8 % to postprocedural lower limb SaO_2 of 84.3 ± 1.6 % in a study conducted by Gorbachevsky *et al* (2017), respectively. Fortunately, these lower limb arterial saturations slightly improved to 85.0 ± 2.9 % during the follow-up time [8].

3.5. Effect of Reversed Potts Shunt on SaO_2 Upper/Lower Limb Gradient

Most of the included studies showed a pronounced SaO_2 upper/lower limb gradient because of reversed Potts shunt procedure in patients with suprasystemic PAH (Table **2**). Initially, neither SaO_2 on the upper limb nor lower limb indicated a different value [2, 3, 8]. Nevertheless, the subsequent intervention manifests as SaO2 upper/limb gradient of .2 ± 5.2 % and 10.5 ± 1.8 % according to studies by Baruteau *et al.* (2014) and Gorbachevsky *et al.* (2017) [2, 8]. The SaO_2 differences, as stated by Gorbachevsky *et al* (2017), tended to be slightly increased in the follow-up period to 10.7 ± 2.6 %, respectively [8].On the other hand, other studies observed declining oxygen saturation gradients. Grady *et al* (2016) reported a decrease in postprocedural SaO_2 upper/lower limb gradient from 12.4 ± 5.9 % to 9.8 ± 3.8 % in the follow-up time [10]. The least arterial oxygen saturation difference of the patients in the follow-up period, 7 (0-20) %, was reported by Boudjemline *et al.* (2017) [3]. Unfortunately, there was not enough information presented by Aggarwal *et al.* (2018) for preprocedural and postprocedural SaO_2 upper/lower limb gradient to compare those parameters to a saturation difference of 13 (2-22) % on the follow-up [7].

3.6. Effect of Reversed Potts Shunt on WHO Functional Class

Post-procedural and follow-up WHO Functional Class showed significant improvement from the pre-procedure state in most studies. Studies by Agarwal *et al* (2018) and Baruteau (2014) reported improvement from the pre-procedure functional class of III (II-IV) and IV (II-IV) to post-procedure FC of II (II-IV) and II (I-III) [2, 7]. Recovery of FC on clinical follow-up was also observed by Boudjemline *et al* (2017), Grady *et al* (2016), and Kirkpatrick *et al* (2017) with FC of I (I-II), 2.5 ± 0.9, and 2.5 ± 0.5 compared to the pre-procedural state of III (III-IV), IV, and 3.3 ± 0.6 [3, 9, 10]. Gorbachevsky *et al* (2017) revealed conversion from pre-procedure FC of 3.7 ± 0.5 to 1.4 ± 0.4. Clinical follow-up of the study demonstrated a slight decline of FC outcomes in the post-procedure condition where the FC became 1.6 ± 0.4 [8]. Nevertheless, Bobhate *et al.* (2021) noticed a small FC retrogression on clinical follow-up of 3.88 ± 0.33 in comparison to pre-procedure FC of 3.75 ± 0.43 [11].

3.7. Effect of Reversed Potts Shunt on 6 Minute-Walking Distance Outcome

All included studies revealed an increased 6 MWD in most patients. Baruteau *et al* (2014) reported improvement from pre-procedure 6 MWD of 260.2 ± 85.1 to post-procedure of 522.6 ± 93.2, respectively [2]. Studies by Boudjemline *et al* (2017) and Kirkpatrick *et al.* (2017) observed

Table 2. Clinical and laboratory outcomes of the included studies.

No	Study (Year)	Upper Limb SaO2 (%)			Lower Limb SaO2 (%)			SaO2 Upper/Lower Limb Gradient (%)			WHO Functional Class			6-minute Walking Test (m)			NT-pro BNP (pg/mL)		
		pre	post	follow up	pre	post	follow up	pre	post	follow up	pre	post	follow up	pre	post	follow up	pre	post	follow up
1	Aggarwal *et al* (2018)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	13 (2-22%)	3.33 ± 0.65	2.37 ± 0.74	N/A	N/A	N/A	N/A	N/A	N/A	N/A
2	Baruteau *et al* (2014)	95.9 ± 2.2	94.7 ± 3.6	N/A	95.9 ± 2.2	81.6 ± 5.1	N/A	0	13.2 ± 5.2	N/A	Median: 4 (2-4)	Median: 2 (1-3)	N/A	260.2 ± 85.1	522.6 ± 93.2	N/A	N/A	N/A	N/A
3	Bobhate *et al* (2021)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3.75 ± 0.43	N/A	3.88 ± 0.33	N/A	N/A	N/A	4947 (1143-13204)	N/A	1106 (389-14327)
4	Boudjemline *et al* (2017)	N/A	N/A	N/A	N/A	N/A	N/A	0	N/A	7 (0-20)	3 (3-4)	N/A	1 (1-2)	399 (200-478)	N/A	469 (371-551)	163 (77-4465)	N/A	125 (71-730)
5	Grady *et al* (2016)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	12.4 ± 5.9	9.8 ± 3.8	4	N/A	2.5 ± 0.9	N/A	N/A	N/A	1108.2 ± 818.9	968.2 ± 988.3	237 ± 65.6
6	Gorbachevsky *et al* (2017)	95.7 ± 1.0	94.8 ± 0.6	95.6 ± 1.2	95.0 ± 1.8	84.3 ± 1.6	85.0 ± 2.9	0 (0-4)	10.5 ± 1.8	10.7 ± 2.6	3.7 ± 0.5	1.4 ± 0.4	1.6 ± 0.4	135.3 ± 9.5*	382.7 ±77.5*	360.7 ± 66.3*	N/A	N/A	N/A
7	Kirkpatrick *et al* (2018)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3.3 ± 0.6	N/A	2.5 ± 0.5	385.5 ± 78.5*	N/A	360.7 ± 104.3	74 (BNP), 9000, 3340	N/A	2950 (556-3480)

N/A, not available; NT-pro BNP; N-terminal-pro brain natriuretic peptide; SaO2, arterial oxygen saturation
*Only included patients with available data

increasing of 6 MWD from 399 (200-478) m and 385.5 ± 78.5 m at pre-procedural state to 469 (371-551) and 393 (244-445) at follow-up time [3, 9]. Gorbachevsky *et al* (2017) showed positive development in 6 MWD of capable patients of 132 (128-146) m, 411 (295-442) m, 335 (311-436) m before the intervention, after intervention, and on clinical follow-up time, respectively. However, the third patient in the study experienced regression from 442 m to 335 m [8].

3.8. Effect of Reversed Potts Shunt on NT-pro BNP Level

Reversed Potts shunt promoted reduced NT-pro BNP level in most studies. Bobhate *et al* (2021) and Boudjemline *et al* (2017) showed improvement in NT-pro BNP levels from 4947 (1143-13204) and 163 (77-4465) preoperatively to 1106 (389-14327) and 125 (71-730) at clinical follow-up time [3, 11]. A study by Kirkpatrick *et al* (2017) reported a decreased NT-pro BNP level in two patients from 9000 and 3340 to 3480 and 2950, respectively [9]. Grady *et al* (2016) observed a reduction of NT-pro BNP from 1108.2 ± 818.9 before the procedure to 968.2 ± 988.3 and 237 ± 65.6 post-procedure and on follow-up, respectively [10].

3.9. Effect of Reversed Potts Shunt on Hemodynamic Parameters

Most studies reported improvement of hemodynamic parameters postprocedural or after follow-up in the patients who had undergone reversed Potts shunt procedures (Table **3**). Aggarwal *et al* (2018) and Bobhate *et al* (2021) reported decreased levels of MPAP, from 85.7 ± 17.2 mmHg to 75 ± 4.5 mmHg and 79.5 (66.8-89.0) mmHg to 75 (44-89) mmHg, respectively [7, 11]. A study by Gorbachevsky *et al* (2017) reported improved systolic RV pressure after the reversed Potts shunt procedures [8]. However, Aggarwal *et al* (2018) reported no improvement in systolic RV pressure in the patients [7]. TAPSE Z score was improved from -3.9 ± 1.3 to -1.3 ± 1.5 and from -2.1 (-2.8-1.1) to 0.3 (-1.5-2.6) in Bobhate *et al* (2021) and Boudjemline *et al* (2017), respectively [3, 11]. Aggarwal *et al* (2018) also reported slight improvement from 11.5 (10.4-12.4) mm to 12.6 (11.7-13.8) mm in post-procedural [7]. There was also an improvement in the interventricular septal curvature from the initial inverted or concave towards the LV to flattening of the septal curvature [8]. Gorbachevsky *et al* (2017) reported decreased end-diastolic RV/LV diameter ratio from 1.5 ± 0.3 to 0.68 ± 0.1 postprocedural and from 1.36 ± 0.14 to 0.99 ± 0.22 postprocedural and 0.90 ± 0.30 on follow-up, respectively [2, 8].

4. DISCUSSION

4.1. Clinical Outcomes of Reversed Potts Shunt

Despite the rapid advancement in the medical treatment of pulmonary hypertension, there are still congenital heart disease patients who progressed to right ventricular failure, recurrent syncope, and even death [12, 13]. Reversed Potts shunt, which connects the aorta with the left pulmonary artery, aims to decompress the right heart while elevating systemic cardiac output [14]. Theoretically, the shunting of desaturated blood from the pulmonary circulation to the systemic circulation could lead to differential cyanosis and induced polycythaemia [15]. It was proven by two included studies that demonstrated a significant decrease in postprocedural lower extremity saturation [2,8]. In our meta-analysis, upper limb oxygen saturation showed no significant reduction(2 studies, Std. mean difference -0.55, 99% CI -

Table 3. The assessment of hemodynamic parameters of the included studies.

No	Study (Year)	MPAP (mmHg)			Systolic RV Pressure (mmHg)			TAPSE			Interventricular Septal Curvature			End-diastolic RV/LV Diameter Ratio		
		Pre	Post	Follow Up	Pre	Post	Follow Up	Pre	Post	Follow Up	Pre	Post	Follow Up	Pre	Post	Follow Up
1	Aggarwal *et al* (2018)	N/A	N/A	N/A	81(71-98)	81 (77-99)	N/A	11.5 (10.4-12.4)	12.6 (11.7-13.8)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
2	Baruteau *et al* (2014)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Inverted	Flattened	N/A	N/A	N/A	N/A
3	Bobhate *et al* (2021)	79.5 (66.8-89.0)	N/A	75 (44-89)	N/A	N/A	N/A	-3.9 ± 1.3	N/A	-1.3 ± 1.5	N/A	N/A	N/A	N/A	N/A	N/A
4	Boudjemline *et al* (2017)	N/A	N/A	N/A	N/A	N/A	N/A	-2.1 (-2.8 - 1.1)	N/A	0.3 (-1.5 - 2.6)	N/A	N/A	N/A	N/A	N/A	N/A
5	Grady *et al* (2016)	53 (51-87)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
6	Gorbachevsky *et al* (2017)	86.6 ± 11.9	N/A	N/A	109.7 ± 9.4	98.7 ± 9.3	99.5 ± 8.6	N/A	N/A	N/A	N/A	N/A	N/A	1.36 ± 0.14	0.99 ± 0.22	0.90 ± 0.30
7	Kirkpatrick *et al* (2018)	N/A	N/A	N/A	116 ± 21.7	130*	N/A	N/A	N/A	N/A	Flattened	N/A	N/A	N/A	N/A	N/A

LV, left ventricle; MPAP, mean pulmonary arterial pressure; N/A, not available; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.
*Only included patients with available data

1.25 to 0.15; P=0.04; I^2 = 6%), while lower limb oxygen saturation decreased remarkably (2 studies, Std. mean difference -4.45, 99% CI –7.37 to –1.52; P < 0.0001; I^2 = 65%). Oxygen saturation, particularly during the 6-minute walk distance test, is an independent prognostic marker in PAH patients [16].

Unlike atrial septostomy, since the connection of reversed Potts shunt was made on the descending aorta, blood oxygen desaturation should not manifest on the upper extremity (representing coronary and cerebral circulation) [17]. This presumption was convinced by two included studies that showed only a slight decrease in the upper extremity saturation following reversed Potts shunt procedure [2,8]. However, the reversed Potts shunt could still produce both upper and lower limb hypoxemia. The combination of hypoxemia with a recurrent pulmonary hypertensive crisis should be a consideration to narrow the reversed Potts shunt [8,18]. Other consequences of the intervention included a noticeable postprocedural upper/lower limb saturation gradient [2,8]. Boudjemline *et al* (2017) also reported a more pronounced saturation difference between the upper and lower limb at maximal exercise compared to the resting conditions [3].

Patients with suprasystemic pulmonary hypertension (PH) are classified into four functional classes (FC) in the WHO classification based on the impact of the disease on their life [19-21]. The higher the number of WHO FC, the more severe the disease [22]. Improvement of the FC has been observed in PH patients who underwent reversed Potts shunt. Post-procedural and follow-up FC of patients in most reversed Potts studies were significantly recovered compared to pre-operative states [2, 3, 7-10, 23, 24]. This is an expected result of hemodynamic improvement after the reversed Potts shunt procedure. However, Bobhate *et al.* found a small decline in follow-up FC compared to pre-operative conditions [11]. Moreover, follow-up FC is slightly increased in comparison to the post-operative state [8].

A six-minute walk test is commonly used to assess the exercise limitations of PH patients [21, 25, 26]. The output of this test, 6-minute walk distance (6MWD), could predict the prognosis of the PH [27]. A study by Souza *et al* showed a better long-term prognosis in patients with 6MWD of more than 400m. However, changes in 6MWD are not associated with long-term outcomes of PH [28]. The reversed Potts shunt resulted in amelioration of the exercise ability of PH patients. Post-operative 6MWD was significantly improved in comparison to pre-operative states [2, 8]. Clinical follow-up of capable patients also showed improvement of 6MWD compared to the pre-operative condition [3, 8, 9].

4.2. Laboratory and Hemodynamic Improvement of Reversed Potts Shunt

NT-proBNP is utilized as a biomarker in assessing RV dysfunction and an outcome predictor of PH [21, 29, 30]. A concentration of NT-proBNP above the 97th percentile revealed PH with 90% sensitivity and 90% specificity [31]. Available data from included studies revealed decreased NT-proBNP levels after reversed Potts shunt procedure [10]. In addition, patients had a lower level of NT-proBNP in follow-up time compared to preoperative and postoperative values [9-11]. This outcome can be explained by the reduced work stress of the heart after the creation of the reversed Potts shunt, thus resulting in a reduction of NT-proBNP secretion.

Hemodynamic parameters assessed with echocardiography or cardiac catheterization (MPAP, systolic RV pressure, TAPSE, interventricular septal curvature, end-diastolic RV/LV diameter ratio) were improved after the

reversed Potts shunt procedure. These hemodynamic parameters have been shown to predict the clinical outcomes in adult and pediatric patients with pulmonary hypertension. Decreased MPAP and systolic RV pressure are associated with increased survival in pulmonary hypertension patients [32]. TAPSE, a parameter of RV function, is correlated strongly with RVEF. Therefore, an increase in the TAPSE shows an improvement in RV function [33]. Interventricular septal curvature is also a useful marker of structural, hemodynamic, and electromechanical as well as ventricular interdependence in patients with right heart diseases including pulmonary hypertension [34]. Decreased RV end-diastolic volume and increased LV end-diastolic volume indicate better survival in these patients [32]. Therefore, these hemodynamic improvements can be correlated with the clinical improvement after the reversed Potts shunt procedure.

4.3. Complication and Mortality of Reversed Potts Shunt

Despite the lower risk of complications compared to the lung transplantation procedure, reversed Potts shunt is an invasive procedure [35]. Its complications ranged from chylothorax, tracheal stenosis, significant upper limb desaturation, bilateral lung transplantation, and death [2,7]. Four deaths occurred in the study by Bobhate *et a.l* because of intolerable pulmonary artery clamping and pulmonary haemorrhage with respiratory failure [11]. Other complications of reversed Potts shunt include cardiac arrest after the anesthetic procedure and irreversible brain damage [3], pulmonary hypertensive crisis, and heart failure [8]. A study by Kirkpatrick reported no complications in the transcatheter procedure, while a patient that underwent the surgical procedure experienced heavy bleeding and respiratory failure [9]. Nevertheless, there is no postoperative complication in the five left thoracotomy Potts shunts conducted by Grady *et al.* [10].

In our included studies, we noted 13 deaths in total from 73 patients who underwent the reversed Potts shunt procedure. Most of the deaths were caused by low cardiac output with two of them developing subsequent cardiac arrest and irreversible brain damage [2, 3]. Heart failure was recorded in 2 patients [7,8], while other deaths were caused by a severe pulmonary hypertensive crisis and adenoviral pneumonia [7,8]. The mortality risk factor was associated with some preoperative data. A high preoperative pulmonary artery to aorta mean pressure ratio was also suggested to have a connection with patient deaths [8]. Furthermore, the operative mortality of the reversed Potts shunt procedure was higher compared to a lung transplant (20% *vs*. 6%), although both did not have significant survival differences [35].

5. LIMITATIONS

The studies included in this systematic review and meta-analysis were mostly retrospective cohort studies which consisted of a small number of subjects and a limited duration of follow-up. The initial baseline characteristics of the patients were different in each study, which reduces the comparability between studies. Furthermore, different primary and secondary outcomes resulted in inadequate data on some of the clinical, laboratory, and hemodynamic parameters, and thus could not be included in the meta-analysis.

CONCLUSION

Reversed Potts shunt cannot be said to be relatively safe, although it allows improvement in the clinical and functional status in patients with suprasystemic PAH. These changes were reflected in the improvement of laboratory and hemodynamic parameters including RV function, which can be markers for better survival. Reversed Potts shunt procedure may be the last resort for drug-resistant pulmonary hypertension as it is considered a high-risk procedure performed on patients with extremely poor conditions. Further studies are necessary to determine the sustainability of these improvements in the long term and to establish a better approach for these procedures.

LIST OF ABBREVIATIONS

PAH	=	Pulmonary Arterial Hypertension
PRISMA	=	Preferred Reporting Items for Systematic Review and Meta-Analysis
CI	=	Confidence Interval
SD	=	Standard Deviation

CONSENT FOR PUBLICATION

Not applicable

STANDARDS OF REPORTING

PRISMA guidelines have been followed for this study.

FUNDING

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors would like to thank all those who have supported them in the making of this systematic review and meta-analysis. The authors are especially grateful to the Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Indonesia, for their guidance in teaching them about research methodology, as well as their assistance in the proofreading of this article.

SUPPLEMENTARY MATERIAL

PRISMA checklist is available as supplementary material on the publisher's website along with the published article.

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