Risk factors for postoperative pulmonary venous obstruction after surgical repair of total anomalous pulmonary venous connection: a systemic review and meta-analysis

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Abstract

OBJECTIVES: A meta-analysis was performed to investigate the risk factors for postoperative pulmonary venous obstruction (PVO) after surgical repair of total anomalous pulmonary venous connection (TAPVC).

METHODS: Data bases including PubMed, Embase, Web of Science and Cochrane Library were searched systematically. The goal was to discuss the risk factors for postoperative PVO after TAPVC. Publications were screened by 2 authors independently for criteria inclusion, methodological quality assessment and data extraction. The Newcastle-Ottawa Scale and the Agency for Healthcare Research and Quality checklist were obtained to assess the quality of the studies. Data were pooled by the random effect model or the fixed effect model according to the heterogeneity test.

RESULTS: A total of 16 studies (2,385 participants) were included in the meta-analysis. All included studies were retrospective studies. Six potential risk factors were pooled, 5 of which were significantly associated with postoperative PVO. Patients with preoperative PVO were more likely to suffer from postoperative PVO [odds ratio (OR)=5.27, 95% confidence interval (CI) = (2.75, 10.11), P < 0.01]. Compared with a sutureless procedure, the conventional operative procedure was associated with postoperative PVO [OR = 1.80, 95% CI=(1.20, 2.71), P < 0.01]. A mixed type TAPVC plays a critical role in postoperative PVO [OR = 3.78, 95% CI=(1.08, 13.18), P = 0.04]. Inverse variance analysis showed that longer cardiopulmonary bypass time [hazard ratio (HR)=1.01, 95% CI=(1.01, 1.02), P < 0.00001] and aortic cross-clamp time [HR = 1.01, 95% CI=(1.01, 1.02), P < 0.01] were significantly associated with postoperative PVO. Heterotaxy [OR = 1.18, 95% CI = 0.13, 10.45, P = 0.88] was not statistically significant as a risk factor for postoperative PVO.

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CONCLUSIONS: This meta-analysis may provide a perspective on the risk factors for postoperative PVO after TAPVC, thus leading to more studies predicting postoperative PVO after TAPVC with our findings.

Keywords: TAPVC • PVO • postoperative • risk factors

INTRODUCTION

Total anomalous pulmonary venous connection (TAPVC) comprises ~3% of congenital heart disease cases [1]. Postoperative pulmonary vein stenosis (PVS) occurs in 15–20% of the survivors and can result in pulmonary hypertension and subsequent right heart failure, which is associated with high morbidity and mortality [2]. Strategies to relieve such stenosis include reoperation and transcatheter intervention; however, the efficacy of the treatment is limited. Sirolimus has recently been reported to be associated with better survival in paediatric patients with PVS [3]. However, in that study, the small number of cases (only 2 patients) receiving sirolimus therapy for PVS after TAPVC surgery may not reflect a clear effectiveness of sirolimus in this subpopulation. Furthermore, postoperative PVS remains an ongoing challenge for the congenital heart community. Searching for factors associated with postoperative PVS in the setting of TAPVC can provide the potential for developing risk-mitigation care management and better disease counselling for parents.

Previous meta-analyses of TAPVC have focused on a comparison of different techniques, (sutureless technique versus conventional confluence-to-left atrium anastomosis) in the primary repair of TAPVC [4] or the prenatal detection of TAPVC regarding descriptions of sonographic features[5]. To our knowledge, no meta-analysis has been conducted to estimate the risk factors for postoperative PVS in this clinical setting, and all of the published evidence on this issue is derived from retrospective observational studies, most of which were single-institutional studies. Thus, the outcomes may be influenced by potential baseline differences and selection bias. Therefore, there is an unmet need to provide better evidence and a more general estimate of predictors for postoperative PVS in patients with TAPVC.

METHOD

Data searches

Electronic database searches were conducted systematically on PubMed, EMBase, Web of Science and the Cochrane Library. The search terms used were (“total anomalous pulmonary venous return” [Mesh] OR “pulmonary venous return anomaly” [Mesh] OR “TAPVR” [Mesh] OR “TAPVR1” [Mesh] OR “total anomalous pulmonary venous return 1” [Mesh] OR “anomalous pulmonary venous return” [Mesh]) for both title and abstract, before 20 September 2021. References from the retrieved articles were also reviewed manually for eligible studies.

Study selection and inclusion

Inclusion criteria were as follows: (i) Patients were diagnosed as having TAPVC; (ii) the risk factors for postoperative pulmonary venous obstruction (PVO) were reported; and (iii) the postoperative PVO definition was clear. Random controlled trials, cohort studies, case control studies and retrospective studies were included. Case reports, studies irrelevant to the analytic goal and conference abstracts were excluded.

Data extraction and quality assessment

Studies were screened independently and extracted according to the inclusion criteria and the exclusion criteria by 2 researchers (H. Zhang and G. Shi). A third researcher (H. Chen) resolved any discrepancies. Types of studies, patient demographic characteristics, surgical approaches, complications, follow-up data, risk factors for postoperative PVO and end points (the occurrence of postoperative PVO) were collected. The studies included were categorized into groups according to each risk factor studied. Quality assessment was performed by 2 researchers independently utilizing the Newcastle-Ottawa Scale [6].

Statistical analysis

RevMan software (version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark) was used to analyse all the included data. P < 0.05 was considered statistically significant. The Mantel-Haenszel (M-H) and inverse variance methods were used to pool the data. A random effects model was adopted when heterogeneity was high, as evaluated by the Cochrane Q test. Dichotomous and continuous variables were evaluated by odds ratios (OR). Studies focusing on cardiopulmonary bypass (CPB) and aortic cross-clamp (ACC) times were conducted using univariable Cox regression analysis; thus the hazard ratio (HR) was used to evaluate these 2 factors. Publication bias and sensitivity analyses were evaluated using Stata 16.0 (College Station, TX, USA). Funnel plots were used to compare the sutureless technique with the conventional technique using RevMan. Sensitivity analyses were used to compare intrinsic PVO and the conventional technique versus the sutureless technique using Stata software.

RESULTS

We identified a total of 2,169 studies initially. Sixteen studies met the inclusion criteria after screening for duplication and were eligible for inclusion in the meta-analysis [7–22]. All studies were retrospective non-randomized controlled trials. Two reviewers independently double-checked the selected articles. The flow chart of the search strategy is shown in Fig. 1.

Characteristics of the included studies

Sixteen articles met the inclusion criteria for this meta-analysis; all were observational studies. Overall, these studies involved 2,385 patients. Of these, the risk factors for postoperative PVO included heterotaxy [8–10], intrinsic or preoperative PVO [7, 10–13], conventional operative procedures compared to the sutureless technique [10, 14–21], mixed type of TAPVC [7, 9–11, 17], CPB time [10, 14, 21, 22] and ACC time [10, 14, 21, 22]. The Newcastle-Ottawa Scale score assessment showed that all included data were
greater than 6. The basic characteristics of all studies included are shown in Table 1.

### Heterotaxy

The meta-analysis included a total of 3 studies that investigated heterotaxy as a risk factor for postoperative PVO [8–10]. Because the heterogeneity test showed $\chi^2 = 15.97, P = 0.0003, I^2 = 87\%$, we chose a random effect model to pool the data. A meta-analysis showed that complicating with heterotaxy was not significantly associated with postoperative PVO [OR = 1.18, 95% CI = 0.13, 10.45, $P = 0.88$] (Fig. 2). There was no publication bias (Egger’s test $P = 0.491$).

### Intrinsic or preoperative pulmonary venous obstruction

Five studies demonstrated intrinsic or preoperative PVO in patients with TAPVC as a risk factor for postoperative PVO [7, 10–13]. A randomized effect model was obtained for this meta-analysis ($\chi^2 = 9.69, P = 0.05, I^2 = 59\%$). The result indicated that patients with TAPVC with intrinsic or preoperative PVO had a higher incidence

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**Table 1: Basic characteristics of reviewed studies**

| Author       | Country or region | Publication year | Type of study design | Sample size (male) | NOS |
|--------------|-------------------|------------------|----------------------|--------------------|-----|
| Seale [7]    | UK, Sweden        | 2010             | Retrospective        | 422 (266)          | 7   |
| Forster [8]  | USA               | 2008             | Retrospective        | 36 (NA)            | 6   |
| Husain [9]   | USA               | 2012             | Retrospective        | 51 (34)            | 7   |
| White [10]   | USA               | 2019             | Retrospective        | 119 (84)           | 7   |
| Fu [11]      | Taiwan            | 2012             | Retrospective        | 78 (41)            | 7   |
| Hoashi [12]  | Japan             | 2015             | Retrospective        | 46 (24)            | 7   |
| Michielon [13]| Italy             | 2002             | Retrospective        | 89 (NA)            | 6   |
| Shi [14]     | China             | 2017             | Retrospective        | 768 (511)          | 7   |
| Yanagawa [15]| Canada            | 2011             | Retrospective        | 57 (30)            | 7   |
| Kalfa [16]   | Europe            | 2018             | Retrospective        | 75 (42)            | 7   |
| Rito [17]    | Canada            | 2015             | Retrospective        | 195 (118)          | 7   |
| Yamashita [18]| Japan            | 2014             | Retrospective        | 12 (9)             | 6   |
| Zhang [19]   | China             | 2016             | Retrospective        | 179 (130)          | 7   |
| Honjo [20]   | Canada            | 2010             | Retrospective        | 22 (10)            | 7   |
| Qi [21]      | China             | 2021             | Retrospective        | 173 (119)          | 7   |
| Liu [22]     | China             | 2021             | Retrospective        | 63 (NA)            | 6   |

NA: not available; NOS: Newcastle-Ottawa Scale; UK: United Kingdom; USA: United States of America
of postoperative PVO compared to those without intrinsic or preoperative PVO [OR = 5.27, 95% CI (2.75, 10.11), \(P < 0.00001\)] (Fig. 3). A sensitivity test was conducted (Supplementary Fig. 1).

Conventional technique

Nine of the studies focused on a comparison between surgical repair using a conventional and a sutureless technique [10, 14–21]. The sutureless technique has been widely employed as a first-line therapeutic approach in different types of TAPVC [23]. The fixed effect model was utilized to pool the data (\(\chi^2 = 6.97, P = 0.54, I^2 = 0\%\)). Our findings showed that the conventional technique was significantly associated with a higher rate of postoperative PVO [OR = 1.80, 95% CI = (1.20, 2.71), \(P = 0.005\)] (Fig. 4). A funnel plot was conducted to show there was no publication bias (Fig. 5). A sensitivity test was also conducted (Supplementary Fig. 2).

Mixed type total anomalous pulmonary venous connection

Five of the included studies demonstrated that a mixed type TAPVC was a risk factor for postoperative PVO [7, 9–11, 17]. We used a random effect model to pool the data (\(\chi^2 = 14.82, P = 0.005, I^2 = 73\%\)). The meta-analysis indicated a trend toward a higher incidence of postoperative PVO in patients with a mixed type TAPVC [OR = 3.78, 95% CI = (1.08, 13.18), \(P = 0.04\)] (Fig. 6). We performed a publication bias analysis utilizing Egger’s test (\(P = 0.069\)).

Cardiopulmonary bypass time

Prolonged CPB time was measured as a risk factor for postoperative PVO in 4 of the included studies [10, 14, 21, 22]. A random effect model was used to pool the data (\(\chi^2 = 20788.79, P < 0.00001, I^2 = 100\%\)). Because all the studies conducted hazard
models, inverse variance analysis was obtained to reveal that longer CPB time is significantly associated with postoperative PVO [HR = 1.01, 95% CI = (1.01, 1.02), P < 0.00001] (Fig. 7).

Aortic cross-clamp time

Four studies were included in this category [10, 14, 21, 22]. The data were pooled via a random effect model ($\chi^2 = 1569.58$, $P < 0.00001$, $I^2 = 100\%$). The meta-analysis confirmed that patients who underwent surgical repair with longer ACC times tended to have a higher incidence of postoperative PVO [HR = 1.01, 95% CI = 1.01, 1.02, $P < 0.0001$] (Fig. 8).

DISCUSSION

This meta-analysis included 2,385 individuals in 16 retrospective studies undergoing surgical repair of TAPVC. As is well known, preoperative PVO is related to postoperative PVO, yet not all the previous studies had consistent conclusions. When faced with a mixed type TAPVC complicated by heterotaxy syndrome, due to the low morbidity, few studies focused on this critical question. It was our main goal to clarify this ongoing issue.

Influence of operative factors on restenosis

Sutureless versus standard technique. The choice of techniques for TAPVC operations remains a topic of debate; final conclusions are still lacking. Results from the present meta-analysis favoured preferentially choosing an atro-atriopericardial anastomosis [also known as a "sutureless technique" (ST)] for the primary repair of TAPVC in an attempt to diminish PPVO; this result was in line with results from several previous studies [4]. One important advantage of the ST is its relatively higher tolerance for surgical imprecision and its shorter learning curve. The ST appears to be superior to the direct atriovenous anastomosis, which is usually technically demanding and requires a comprehensive understanding of the spatial relationship of the anatomical structures involved. Additionally, the rarity and high morphological variations of this lesion can further complicate the anastomosis. Patients are therefore prone to PPVO (anastomotic restriction) when there is an imprecise anastomosis between the confluence and the left atrium (LA). However, given the heterogeneity among the different studies, the final answer in terms of the superiority of ST still remains to be elucidated. Variation in patients undergoing the sutureless repair across studies may affect the observed effects. There was a propensity toward the primary use of ST in infracardiac or mixed TAPVC. Most previously published reports [24] have revealed a distinct advantage of ST over the standard technique in this clinical setting, whereas such an advantage in supracardiac or cardiac variation remains inconclusive. Favoured freedom from PPVO using a direct [14] or a modified atriovenous anastomosis has indeed been reported in several large cohorts. Therefore, comparing outcomes following sutureless versus standard repair in a mixed cohort of patients with all 4 TAPVC subtypes may not be appropriate. In addition, the results of 1 study [15] indicated that isolated peripheral PVO, though more benign than an anastomotic restriction, can still occur following sutureless repair, probably given the acute angulation of the individual PV resulting from a purse-string effect of the suture line. Because constructing an unobstructive PV return while avoiding a geometrical distortion of the individual PVs remains the mainstay of TAPVC repair, more evidence is needed to confirm the clear superiority of the ST. Taken together, perhaps further randomized controlled studies can answer whether ST benefits the whole TAPVC population or merely a TAPVC sub-population who are at higher risk for PPVO.

Cardiopulmonary bypass. Our results revealed that both longer CPB and ACC times were significantly associated with postoperative PVO. Unsurprisingly, this result may reflect the greater complexity of the surgical manoeuvres or the poorer preoperative status in patients who required more time for bypass support, i.e. poor cardiac function, pulmonary hypertension owing to the preoperative pulmonary congestion and/or acidosis [25]. On the other hand, this risk factor can be potentially mitigated by the use of ST because a simpler oval suture line is required in the ST compared with the complex and irregular contour of the incision required in the standard repair. Moreover, the pericardial sac is the component of the neo-LA that is to some extent helpful for lowering the filling pressure in the PVs given the large communication between the PV system and the LA.

Figure 5: Funnel plot of publication bias of studies of conventional technique versus sutureless technique. OR: odds ratio; SE: standard error.

Figure 6: Forest plot of meta-analysis of mixed type of total anomalous pulmonary venous connection. CI: confidence interval; M-H: Mantel-Haenszel.
Preoperative pulmonary venous obstruction. The present study has pooled data from available evidence (228 patients) and performed adjusted risk estimates that strongly indicated that preoperative PVO can independently predict PPVO. However, this finding should be interpreted with caution. First, in general, preoperative PVO can be categorized into 3 subtypes: external expression in an anomalous connector vein, functional obstruction resulting from the restrictive atrial septal defect and hypoplastic PVs or confluence (intrinsic stenosis). From a technical perspective, the course and size of the PVs/confluence are important factors because anastomotic imperfections probably attribute to hypoplastic confluence/peripheral PVs or an unfavorable spatial relationship between confluence and LA [26], whereas relief of the restrictive ASD or external compression is expected to be associated with better outcomes. Thus, it can be argued that using preoperative PVO as a binary variable to estimate the risk of PPVO, as is seen in most studies [27], may not be appropriate. Second, the increasing use of primary ST for the patient subpopulation with obstructed TAPVC in the current era can potentially mitigate the risk of PPVO. Although most studies began to include patients undergoing TAPVC repair from an early era, which may confound the results, this is a possible explanation for the conflicted observed effects [7] of preoperative PVO on PPVO. Finally, the multicollinearity between preoperative PVO and some challenging TAPVC subgroups [24] (e.g. infracardiac or neonatal TAPVC) may also preclude the clear identification of preoperative PVO as a risk factor for PPVO.

Mixed variation and heterotaxy

Mixed TAPVC: Mixed type TAPVC, which is complicated by more than 1 level of PV connection defect, is considered to be the most challenging type of TAPVC and sometimes requires combinations of surgical methods [28]. Few studies have reported clear conclusions as a result of the low morbidity (5–10% of patients with TAPVC), therefore, the reoperation rates of this type of TAPVC have not been clarified by large cohort studies [28]. It is difficult to pool surgical data from the published literature.

Heterotaxy: Individuals with congenital heart defects complicated with the heterotaxy syndrome are frequently combined with complex cardiac structural diseases and often have poor outcomes [8]. When complicated with TAPVC, mortality remains high in the modern era. Recent studies have suggested that lower original pulmonary blood flow, presenting as pulmonary atresia or stenosis in patients with heterotaxy syndrome, may contribute to intrinsic obstruction of TAPVC [29]. We reported that heterotaxy was not strongly associated with the postoperative PVO of TAPVC. The bias remains in several aspects. First, due to the low morbidity, only 3 studies were included in this section of the study, and the heterogeneity of the data was high. Second, high postoperative mortality may influence the follow-up period of postoperative PVO. Thus, the results may indicate that fewer patients had PVO postoperatively. Spigel et al. [30] concluded that the high prevalence of single ventricular physiology in the heterotaxy cohort may contribute to a greater number of PV interventions. Yet, few cohort studies have focused on the relationship between heterotaxy syndrome and postoperative PVO, which may not present much insightful information. Further studies are needed.

Limitations

This study is limited by the categories of articles included, all of which were non-randomized controlled trials, indicating a lower level of evidence. At the same time, we did not exclude the selection bias of the age at surgical approach, because low body weight plays a critical role in many risks of adverse events in all types of cardiac surgery. Further investigation of the relationship between younger age at surgery, low body weight and postoperative PVO is urgently needed.

Additionally, we failed to categorize the patients by severity of intrinsic PVO preoperatively, because the sutureless technique was generally adopted in patients with higher risks. As a result, a selection bias may lie in those included patients when comparing the conventional technique versus the sutureless technique. Last but not the least, we combined the results of the included studies
to confirm the different opinions of the risk factors for postoperative PVO for TAPVC but failed to explore any novel risk factors. A more delicate and detailed subgroup meta-analysis should be conducted.

CONCLUSION

We concluded that intrinsic or preoperative PVO, a conventional technique (versus a sutureless technique), mixed type TAPVC and both longer CPB and ACC times could be strongly associated with postoperative PVO of TAPVC. No significant statistical difference was found in the analysis of whether heterotaxy can be a risk factor for postoperative PVO, maybe because too few criteria were included. Subgroup and regression analyses should be carried out to enhance the level of evidence in risk factors for postoperative PVO of TAPVC.

SUPPLEMENTARY MATERIAL

Supplementary material is available at ICVTS online

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Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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