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Systematic Review/Meta-analysis

Pulmonary Valve Replacement for Pulmonary Regurgitation in Adults With Tetralogy of Fallot: A Meta-analysis—A Report for the Writing Committee of the 2019 Update of the Canadian Cardiovascular Society Guidelines for the Management of Adults With Congenital Heart Disease

François-Pierre Mongeon, MD, SM,[a] Walid Ben Ali, MD, MSc,[b] Paul Khairy, MD, PhD,[a] Ismail Bouhout, MD, MSc,[b] Judith Therrien, MD,[c] Rachel M. Wald, MD,[d] Frederic Dallaire, MD, PhD,[e] Pierre-Luc Bernier, MD, CM, MPH,[f] Nancy Poirier, MD,[b,g] Annie Dore, MD,[a] Candice Silversides, MD,[d] and Ariane Marelli, MD, MPH[h]

[a] *Adult Congenital Heart Center, Department of Specialized Medicine, Montreal Heart Institute, Université de Montréal, Montréal, Québec, Canada*

[b] *Department of surgery, Montreal Heart Institute, Université de Montréal, Montréal, Québec, Canada*

[c] *Jewish General Hospital, McGill University, Montréal, Québec, Canada*

[d] *Peter Munk Cardiac Centre, University Health Network, Toronto, Ontario, Canada*

[e] *Division of Pediatric and Fetal Cardiology, Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, Québec, Canada*

[f] *Department of surgery, McGill University Health Center, McGill University, Montréal, Québec, Canada*

[g] *Department of surgery, CHU-Sainte-Justine, Université de Montréal, Montréal, Québec, Canada*

[h] *McGill Adult Unit for Congenital Heart Disease (MAUDE Unit), McGill University, Montréal, Québec, Canada*

See editorial by Vonder Muhll, pages 1620–1622 of this issue.

ABSTRACT

Background: There is no systematic evidence review of the long-term results of surgical pulmonary valve replacement (PVR) dedicated to adults with repaired tetralogy of Fallot (rTOF) and pulmonary regurgitation.

Methods: Our primary objective was to determine whether PVR reduced long-term mortality in adults with rTOF compared with conservative therapy. Secondary objectives were to determine the postoperative incidence rate of death, the changes in functional capacity and in right ventricular (RV) volumes and ejection fraction after PVR, and the postoperative incidence rate of sustained ventricular

RÉSUMÉ

Contexte : Il n'existe aucune revue systématique des résultats à long terme du remplacement valvulaire pulmonaire (RVP) chirurgical chez les adultes ayant une tétralogie de Fallot réparée (TFr) et présentant une régurgitation pulmonaire.

Méthodologie : Notre objectif premier était de déterminer si le RVP réduisait la mortalité à long terme chez les adultes ayant une TFr par rapport à un traitement conservateur. Nos objectifs secondaires étaient de déterminer le taux d'incidence postopératoire de décès, les variations de la capacité fonctionnelle ainsi que des volumes et de la fraction d'éjection ventriculaires droits (VD) après le RVP, et le taux

It is estimated that about 17 per 100,000 adults are currently living with tetralogy of Fallot (TOF).[1] Adults with TOF repaired (rTOF) during childhood who have undergone relief of right ventricular (RV) outflow tract obstruction with the use of a transannular patch or pulmonary valvuloplasty are left with chronic severe (regurgitation fraction $\geq$ 40%) pulmonary valve regurgitation (PR) in at least one-third of cases.[2] Severe chronic PR can result in RV dilation and failure which can be addressed with the use of pulmonary valve replacement (PVR).[3] Adults with rTOF are at risk of exercise

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Corresponding author: Dr François-Pierre Mongeon, Division of Noninvasive Cardiology and Adult Congenital Heart Center, Montreal Heart Institute, 5000 Bélanger Street, Montréal, Québec H1T 1C8, Canada. Tel.: +1-514-376-3330, x2159; fax: +1-514-593-2158.

E-mail: francois-pierre.mongeon@icm-mhi.org

See page 1781 for the list of members of the Writing Committee of the 2019 Update of the Canadian Cardiovascular Society Guidelines for the Management of Adults With Congenital Heart Disease.

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arrhythmias. A systematic search of multiple databases for studies was conducted without limits.

Results: No eligible randomized controlled trial or cohort study compared outcomes of PVR and conservative therapy in adults with rTOF. We selected 10 cohort studies (total 657 patients) reporting secondary outcomes. After PVR, the pooled incidence rate of death was 1% per year (95% confidence interval [CI] 0-1% per year) and the pooled incidence rate of sustained ventricular arrhythmias was 1% per year (95% CI 1%-2% per year). PVR improved symptoms (odds ratio for postoperative New York Heart Association functional class > II 0.08, 95% CI 0.03-0.24). Indexed RV end-diastolic (−61.29 mL/m^2, −43.64 to −78.94 mL/m^2) and end-systolic (−37.20 mL/m^2, −25.58 to −48.82 mL/m^2) volumes decreased after PVR, but RV ejection fraction did not change (0.19%, −2.36% to 2.74%). The effect of PVR on RV volumes remained constant regardless of functional status.

Conclusion: Studies comparing PVR and conservative therapy exclusively in adults with rTOF are lacking. After PVR, the incidence rates of death and ventricular tachycardia are both 1 per 100 patient-years. Pooled analyses demonstrated an improved functional status and a reduction in RV volumes.

d'incidence postopératoire des arythmies ventriculaires soutenues. Nous avons effectué une recherche systématique sans restriction dans plusieurs bases de données afin de trouver des études pertinentes.

Résultats : Aucune étude comparative avec répartition aléatoire ni étude de cohorte admissible comparant les résultats du RVP et ceux du traitement conservateur chez des adultes ayant une TFr n'a été relevée. Nous avons retenu 10 études de cohorte (657 patients au total) les critères d'évaluation secondaires. Après le RVP, le taux d'incidence groupé de décès s'établissait à 1% par année (intervalle de confiance [IC] à 95%: de 0 à 1% par année), et le taux d'incidence groupé des arythmies ventriculaires soutenues s'établissait à 1% par année (IC à 95%: de 1 à 2% par année). Le RVP a atténué les symptômes: le rapport de cotes pour une classe fonctionnelle de la New York Heart Association de II ou plus après l'intervention s'établissant à 0,08 (IC à 95 %: de 0,03 à 0,24). Le volume télédiastolique VD (−61,29 mL/m^2, de −43,64 à −78,94 mL/m^2) et le volume tétlésystolique VD (−37,20 mL/m^2, de −25,58 à −48,82 mL/m^2) ont diminué après le RVP, mais la fraction d'éjection VD n'a pas changé (0,19 %, de −2,36 % à 2,74 %). L'effet du RVP sur les volumes VD est demeuré constant, sans égard à la capacité fonctionnelle.

Conclusion : Il n'existe aucune étude comparant le RVP et le traitement conservateur exclusivement chez des adultes ayant une TFr. Après le RVP, les taux d'incidence de décès et de tachycardie ventriculaire étaient tous deux de 1 par 100 patients-années. Les résultats des analyses groupées montrent une amélioration de la capacité fonctionnelle et une diminution des volumes VD.

intolerance, congestive heart failure, arrhythmias, and sudden cardiac death.[3,4] Though plausible, it remains uncertain whether timely PVR prevents these outcomes in adults with rTOF. Current indications for PVR in adults with rTOF and PR include the presence of symptoms attributed to PR or the preservation of ventricular size and function in asymptomatic patients with ventricular enlargement or dysfunction.[5] It is widely thought that PVR should be performed before the RV becomes irreversibly dilated.[3] Measurements that do not exceed 150-180 mL/m^2 have been associated with regression of RV size and continue to drive management of PR in patients with rTOF,[6] particularly in asymptomatic patients.

Supportive evidence for performing PVR in adults with rTOF relies largely on surrogate outcomes, such as RV size, owing to the low incidence of death and heart failure after PVR.[3] Yet, the surrogate outcomes that adequately predict heart failure—free survival remain uncertain. No randomized study has ever been completed to compare PVR with conservative therapy in adults with rTOF, especially in asymptomatic patients with enlarged RVs.

Among 48 studies included in a large meta-analysis published in 2013, only 29% reported on an exclusively adult population and 17% included children only.[7] Numerous studies also include a heterogeneous patient population including lesions such as double-outlet RV, pulmonary atresia with a ventricular septal defect, absent pulmonary valve syndrome, and pulmonary stenosis.[7-9] The PVR outcomes in patients with PR after rTOF or relief valvular pulmonary stenosis are likely different.[10]

Thus at the present time, there is no available systematic evidence review of PVR outcomes dedicated exclusively to adults with rTOF. We undertook a systematic review and meta-analysis to review the literature for quantitative evidence that explores the impacts of PVR in adults with rTOF and PR. Our primary research question was whether PVR reduced long-term mortality in adults with rTOF compared with conservative therapy. Our secondary research questions were the postoperative incidence rate of death, the changes in functional capacity and in RV volumes and ejection fraction after PVR, and the postoperative incidence rate of sustained ventricular arrhythmias.

Methods

The systematic review and meta-analyses were performed based on the Meta-analysis of Observational Studies in Epidemiology guidelines.[11] The manuscript was structured using the recommendations of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement.[12] The primary research questions focused on key components of PICOTS:

1) **P**opulation: asymptomatic and symptomatic patients ≥ 18 years of age with rTOF and PR. Studies that reported outcomes of PVR in patients with unoperated TOF, congenital pulmonary stenosis, pulmonary atresia, absent pulmonary valve syndrome, or Fallot-type double-outlet RV were excluded.
2) **I**ntervention: surgical PVR or catheter-based pulmonary valve implantation.
3) **C**omparison: conservative therapy (no intervention for PR).
4) **O**utcomes: the primary outcome was long-term all-cause mortality (> 1 year).

5) **T**iming: from point of intervention (PVR) until > 3 months.
6) **S**etting: hospital and outpatient care.

A consensus was reached among the authors to adapt the research question in case of lack of evidence to answer the primary research question. Specific PICOTS elements related to our secondary research question were as follow:

1) **P**opulation: asymptomatic and symptomatic patients ≥ 18 years of age with rTOF and PR assessed before and after PVR. Studies that reported outcomes of PVR in patients with unoperated TOF, congenital pulmonary stenosis, pulmonary atresia, absent pulmonary valve syndrome, or Fallot-type double-outlet right ventricle were excluded.
2) **I**ntervention: surgical PVR or catheter-based pulmonary valve implantation.
3) **C**omparison: assessment performed before and after PVR.
4) **O**utcomes: the secondary outcomes were long-term postoperative all-cause mortality, PVR improvement in New York Heart Association (NYHA) functional class, improvements in RV volumes and ejection fraction, and sustained ventricular arrhythmias. RV volumes and ejection fraction (RVEF) were measured by means of cardiovascular magnetic resonance (CMR) imaging.
5) **T**iming: from point of intervention (PVR) until > 3 months.
6) **S**etting: hospital and outpatient care.

Eligibility

Studies were included in the systematic review if they met the following eligibility criteria: 1) randomized controlled trial (RCT) or cohort study with ≥ 20 adult participants; 2) patients with rTOF and PR with ≤ 10% of the study cohort with a primary diagnosis of pulmonary stenosis; 3) publication in a peer-reviewed journal; 4) inclusion of only adults (age ≥ 18 years) or separate reporting of outcomes for adult patients; 5) follow-up for ≥ 3 months after PVR with ≥ 90% of the study population with complete follow-up; 6) reporting of ≥ 1 of the primary or secondary outcomes; 7) Newcastle-Ottawa scale ≥ 7[13]; and 8) in case of overlapping cohorts between studies, only the most recent study unless an outcome is reported in an earlier study and not reported in the most recent study. Only studies that reported outcomes of PVR in adults (age ≥ 18 years) with PR since childhood were included because cardiologists caring for adults with congenital heart disease are faced with decision making in this specific clinical situation.

Evidence acquisition

The search strategy was developed with input from the project team, then reviewed by a librarian not otherwise associated with the project. Three databases were searched: Medline, Embase, and Cochrane CENTRAL. No study design, date, or language limits were imposed on the search. The search strategy is provided in Supplemental Table S1. To improve the sensitivity of the literature search, we performed citation chasing in Google Scholar, Scopus, and Web of Science. For the cited reference searches, we used a narrative review published in 2013 by Ferraz Cavalcanti et al.[7] Related journals (*Annals of Thoracic Surgery*, *Journal of Thoracic and Cardiovascular Surgery*, *European Journal of Cardio-Thoracic Surgery*, *Circulation*, and *Journal of the American College Cardiology*) that publish abstracts of major scientific meetings (years 2000-2019) and lists of references of selected articles were also crosschecked for other relevant studies.

Data management

The literature search results were uploaded into EPPI-Reviewer 4 (EPPI-Centre, London, UK), an internet-based software program that facilitates collaboration among reviewers during the study selection process, text mining, citation chasing and duplicate removal. Test screening questions and forms for level 1 and 2 assessments based on the inclusion and exclusion criteria were developed. Before the formal screening process, a calibration exercise was undertaken to refine the screening questions.

Selection process

The study selection was performed by three independent reviewers (W.B.A., I.B., and F.-P.M.) through the following 2 levels of screening: The titles and abstracts of the searched studies were screened at the first level, and then the full texts were reviewed at the second level. The reviewers were not blinded to the journal titles, study authors, or institutions. Reasons for exclusion were recorded. Controversies were discussed and resolved via e-mail discussions.

Data extraction

Using standardized forms, 2 reviewers (W.B.A. and F.-P.M.) extracted data independently and in duplicate from each eligible study. To ensure consistency across reviewers, calibration exercises were performed before starting the review. Abstracted data included demographic information, methodology, intervention details, and all reported patient-important outcomes. Disagreements were discussed and resolved via verbal and e-mail discussions, and 1 arbitrator (A.M.) adjudicated unresolved disagreements as necessary. Summary statistics for each outcome were extracted (n, mean ± SD) before and after the intervention. When data were expressed in median (range or interquartile range), the mean and SD were calculated based on equations reported by Luo et al.[14] and Wan et al.[15]

Risk of bias assessment

Risk of bias was assessed with the use of the Newcastle-Ottawa scale[13] (NOS) and the Cochrane Risk of Bias 2.0 tool[16] for cohort studies and randomized studies, respectively, by 2 independent reviewers (W.B.A. and F.-P.M.). The NOS was preferred over the Risk of Bias in Nonrandomized Studies of Interventions tool[17] because it was more suitable for cohort studies. Funnel plots were used to study publication bias.

Statistical analysis

Long-term mortality risk and linearized incidence rates of sustained ventricular arrhythmias were calculated (number of events per number of patient-years or %/y) for each individual

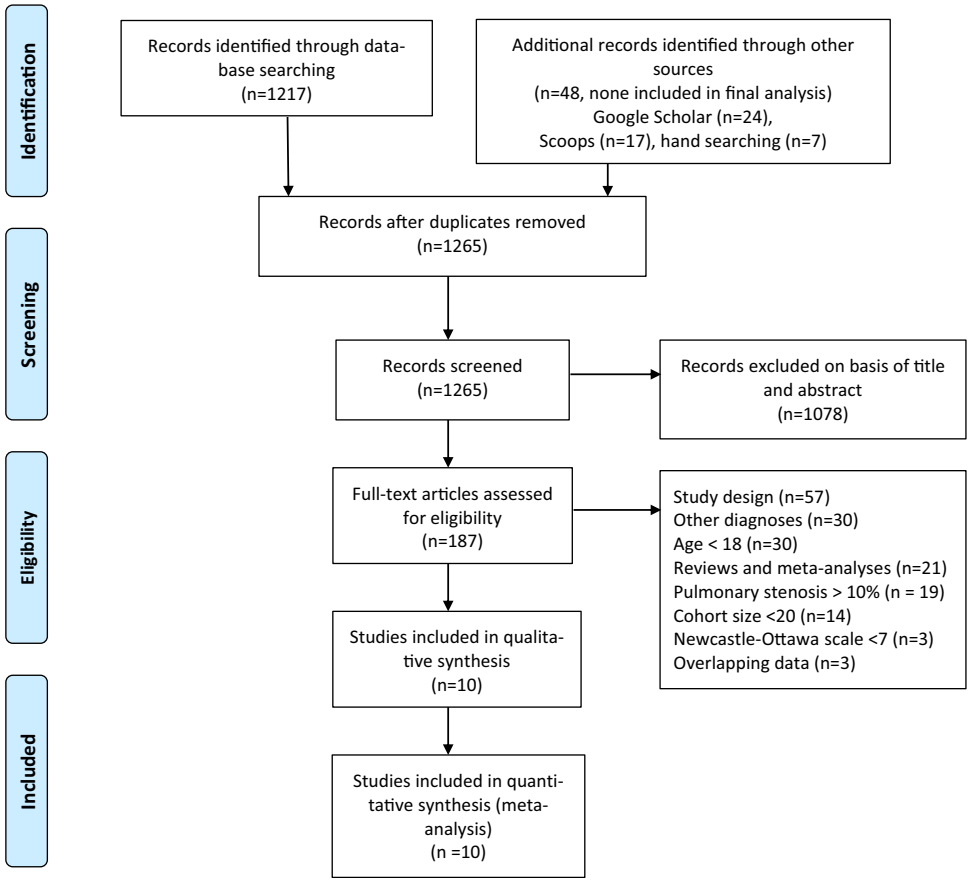

Figure 1. Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) flow diagram. "Other diagnoses" included double-outlet right ventricle Fallot type, pulmonary atresia, and absent pulmonary valve syndrome.

study and pooled on a logarithmic scale with the use of the inverse variance method in a fixed-effects model. The pre- vs postoperative treatment effect of PVR was measured by calculating the odds ratio (OR) with the associated 95% confidence interval (CI) for the functional class outcome and weighted mean difference (WMD) before and after the intervention with the associated 95% CI for the RV volume and RVEF outcomes. DerSimonian-Laird random-effects models were used to calculate OR, WMD, and their 95% CIs. Meta-regression analysis was used to investigate the effects of covariates, especially variations in patient characteristics, on observed PVR effects. Analyses were performed with the use of Stata software (StataCorp, College Station TX).

Results

Literature search results

Primary research question: mortality with PVR compared with conservative therapy in adults with rTOF. After the first- and second-level screening processes, only 3 studies[18-20] were found that reported a direct comparison between a matched cohort of PVR and conservative treatment of rTOF and PR. None of these studies met the eligibility criteria, however. The studies by Harrild et al. and Quail et al. did not report outcomes for adults only.[19,20] The study by Gengsakul et al. included patients with double-outlet RV.[18]

Secondary research question. The search identified 1265 studies. After the first-level screening of article titles and abstracts, 187 articles remained for full-text review. Among those, 10 articles reporting secondary outcomes met full inclusion criteria and were included in the meta-analysis. The flow chart in Figure 1 represents the selection and inclusion of articles in the meta-analysis for the secondary outcomes. Common factors limiting study eligibility were study design, cohort size $<$ 20 patients, inclusion of both children and adults without separate reporting of results for adults, severe risk of bias (NOS $<$ 7) and $>$ 10% of included patients with severe pulmonary stenosis.

Study characteristics

Ten cohort studies[21-30] fulfilled the eligibility criteria for the secondary outcomes, including a total of 657 patients (Table 1). Among the 10 included studies, 6 were published from 2017 to 2018. PR was addressed surgically in all of the series; no study of catheter-based pulmonary valve

Table 1. Characteristics of studies included in the meta-analysis for secondary outcomes

Study	n	Age at TOF repair (y)	Age at PVR (y)	NYHA ≥ II	ASD closure	Residual VSD closure	RVOT plication	TV surgery	VT ablation	Mean follow-up (y)	NOS
Therrien 2000[21]	25	12.1 ± 10.6	33.9 ± 9.2	6 (24%)	4 (16%)	3 (12%)	10 (40%)	5 (20%)	3 (12%)	2.36	8
Oosterhof 2007[22]	71	5 (2.7-7.4)	29 (23-37)	53 (74.6%)	n/a	4 (5.6%)	18 (25.3%)	24 (33.8%)	0	2.6	8
Henkens 2007[23]	27	5.6 ± 2.8	30.8 ± 8.2	n/a	1 (3.7%)	3 (11%)	2 (7.2%)	7 (26%)	n/a	2.96	8
Tobler 2012[24]	39	5	33	21 (53.8%)	n/a	n/a	n/a	n/a	n/a	2.4	8
Dobbels 2017[25]	167	6 (2.8)	26 ± 10	n/a	n/a	n/a	n/a	n/a	n/a	22	8
Heng 2017[26]	57	4 (0.3-36.5)	35.8 ± 10.1	42 (74.7%)	1 (1.8%)	3 (5.2%)	21 (36.8%)	9 (15.8%)	2 (3.6%)	9.5	8
Mitropoulos 2017[27]	99	n/a	38 ± 8	n/a	n/a	n/a	37 (37.3%)	36 (36.4%)	n/a	3.6	7
Egbe 2018[28]	88	3 ± 2	n/a	n/a	n/a	n/a	n/a	31 (35.2)	4	5.4	9
Yamamura 2018[29]	53	4 ± 2.6	38 ± 11	n/a	15 (28.3%)	4 (7.5%)	n/a	8 (15%)	n/a	2	7
Zaidi 2018[30]	31	n/a	27.5 ± 8.6	n/a	n/a	n/a	n/a	n/a	n/a	1.13	8

Data are presented as mean ± SD, median (interquartile range), or n (%).

ASD, atrial septal defect; n/a, not available; NOS, Newcastle-Ottawa scale of bias; NYHA, New York Heart Association functional class; PVR, pulmonary valve replacement; RVOT, right ventricular outflow tract; TOF, tetralogy of Fallot; TV, tricuspid valve; VSD, ventricular septal defect; VT, ventricular tachycardia.

implantation met the inclusion criteria. The mean age ranged from 26 to 38 years, and the mean follow-up duration ranged from 2 to 22 years.

Risk of bias assessment

All studies were assessed with the use of the NOS. NOS item quotations are listed in Supplemental Table S2. Funnel plots were examined and showed almost symmetric distributions and did not raise any major concerns about potential publication bias for NYHA functional class and indexed RV end-diastolic volume (RVEDVi), end-systolic volume (RVESVi), and RVEF (Supplemental Fig. S1). However, the possibility of such bias still exists and should be taken into account when considering the results.

Evidence synthesis

Formal meta-analyses were performed for the secondary outcomes of interest with results from at least 2 separate studies meeting eligibility criteria.

Long-term mortality. Seven studies[21,22,25-29] including 560 patients reported long-term mortality. Pooled long-term mortality risk was 1 per 100 patient-years (95% CI 0-1 per 100 patient-years; Fig. 2). Only 1 study reported no long-term death with a mean follow-up of 2.36 ± 2.24 years. There was no evidence of significant heterogeneity among the studies.

NYHA functional class. Four studies[21,22,26,27] including 252 patients reported NYHA functional class before and after PVR. PVR improved NYHA functional class with a 12.5-fold (1/0.08) odds of being asymptomatic (NYHA functional class I) after vs before PVR (Fig. 3). There was evidence of significant heterogeneity between studies (I^2 statistic 62.8%). No sensitivity study was conducted owing to the small number of series included in this analysis.

RV volumes and function according to CMR. There were significant reductions in RV volumes but no significant improvement in systolic function. RVEDVi was reported in 5 studies[22,24,26,29,30] including 251 patients. There was a significant reduction of 61 mL/m^2 in RVEDVi after PVR (Fig. 4A). The same studies reported RVEF. Meta-analysis of these data did not reveal any significant improvement in RVEF after PVR (Fig. 4C). Four studies[22,24,26,29] including 220 patients reported RVESVi. There was a significant net decrease of 37 mL/m^2 in RVESVi after PVR (Fig. 4B). There was evidence of significant heterogeneity among the studies for all CMR outcomes. A meta-regression was conducted to explore the effect of the interstudy heterogeneity on the observed RV volumes reductions. The interstudy heterogeneity of patient preoperative NYHA functional class had no statistically significant effect on the observed difference in terms of RVEDVi ($P = 0.257$; Fig. 5A) and RVESVi ($P = 0.387$; Fig. 5B).

Long-term sustained ventricular arrhythmia. Six studies[22,25-29] including 535 patients reported long-term sustained ventricular arrhythmia. The pooled linearized incidence rate of sustained ventricular arrhythmia after PVR was 1 per 100 patient-years (95% CI 1-2 per 100 patient-years;

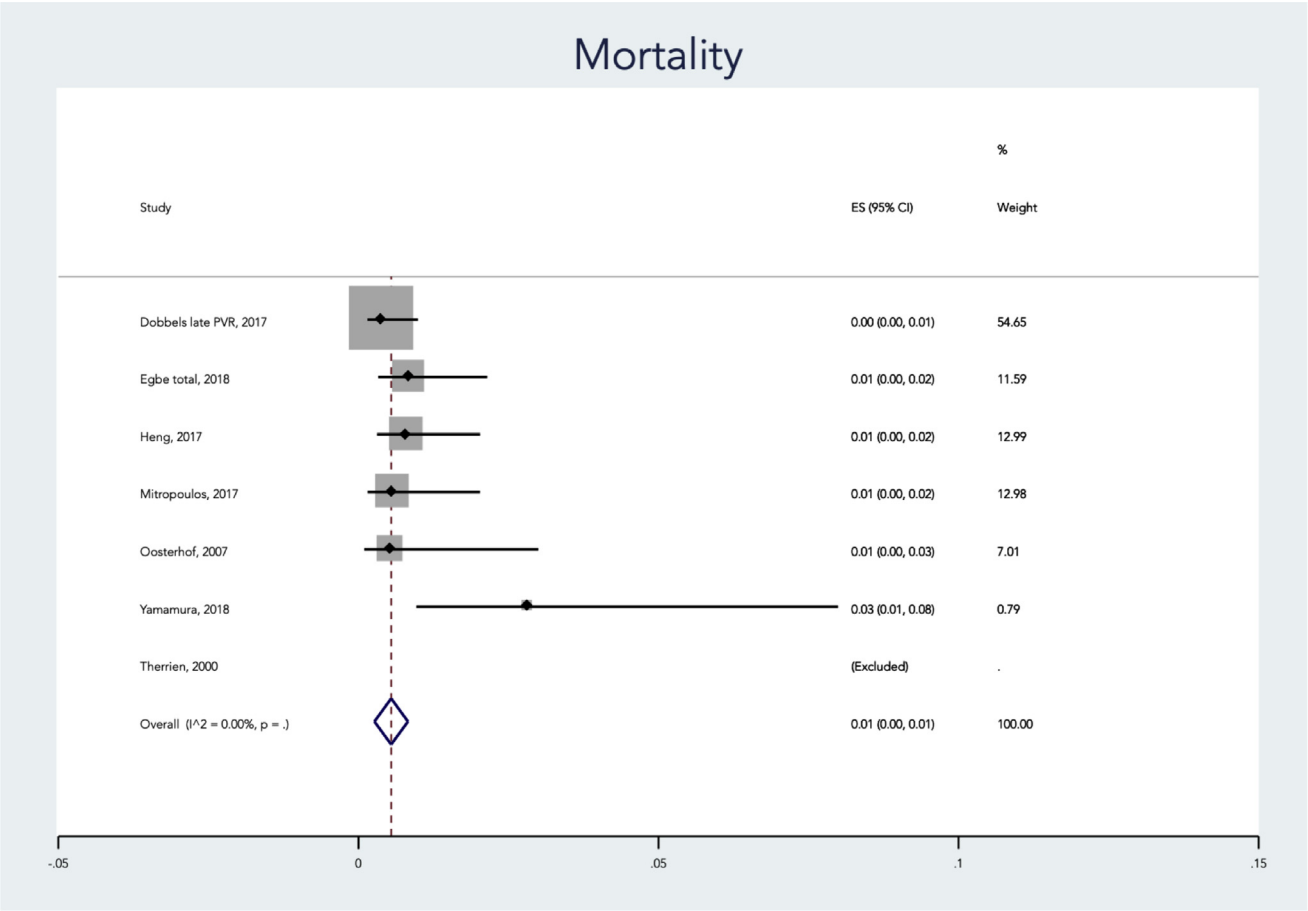

Figure 2. Forest plot of long-term mortality meta-analysis. Effect size (ES) expressed as incidence rates in patient-years.

Fig. 6). There was no evidence of significant heterogeneity among the studies.

Discussion

Summary of results

We report the only systematic review of PVR in adults with rTOF. We found that cohort studies comparing PVR and conservative therapy exclusively in adults with rTOF were lacking. We found that the pooled incidence rate of death after PVR is 1 per 100 patient-years (95% CI 0-1 per 100 patient-years). The benefits of PVR include a substantial improvement in functional class and a reduction in RV volumes. The reduction of RV volumes is observed even if symptoms have developed at the time of PVR. The pooled incidence rate of sustained ventricular arrhythmias after PVR is 1 per 100 patient-years (95% CI 1-2 per 100 patient-years).

Earlier meta-analyses

Previously published meta-analyses of PVR in patients with rTOF included studies of both children and adults. In the meta-analysis by Cheung et al.,[8] adult and pediatric studies were separated based on the mean age at PVR. However, a mean age > 18 years does not guarantee that the cohort falls in the adult or pediatric age group if the confidence interval is wide. Previous meta-analyses included studies with heterogeneous causes of PR, such as repaired double-outlet RV, pulmonary atresia with a ventricular septal defect, and pulmonary stenosis.[7-9] In the meta-analysis by McRae et al.,[9] TOF patients composed the largest proportion of the study groups of the selected studies. However, caution should be exercised in pooling outcomes of patients with various forms of congenital heart disease,[31] even if the underlying pathophysiology is similar, such as PR in rTOF or after relief of congenital pulmonary valvular stenosis.[10] Compared with patients with rTOF, patients with PR after relief of congenital pulmonary stenosis require less RV aneurysm resection and pulmonary artery angioplasty at the time of PVR and show more substantial improvement in RVEF after PVR.[10] Patients with a congenital pulmonary valvular stenosis do not have prior cyanosis, and have a less extensive surgical history, smaller preoperative RV size, and less ventricular dyssynchrony.[10]

Mortality with PVR compared with conservative therapy in adults with rTOF

No cohort study could show a mortality benefit for patients with rTOF undergoing PVR for PR compared with patients with rTOF and PR treated conservatively. The 3

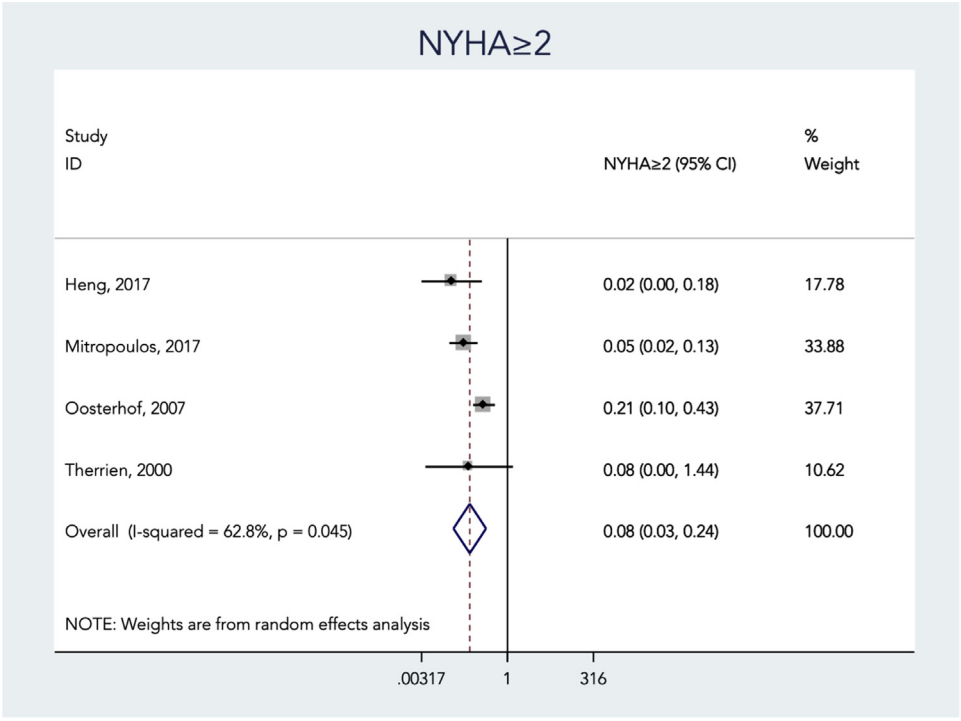

Figure 3. Odds of having impaired functional capacity after pulmonary valve replacement (PVR). Effect expressed as odds ratio of being in New York Heart Association (NYHA) functional class II or greater after PVR compared with before PVR.

available studies did not meet the inclusion criteria for our meta-analysis. In matched cohort studies, Harrild et al. and Gengsakul et al. found that PVR did not reduce the incidence of ventricular tachycardia or death compared with rTOF patients who had not undergone PVR.[18,19] In the cohort reported by Harrild et al., patients undergoing PVR had more RV dilation.[19] In a propensity-matched cohort study, Quail et al. tested the hypothesis that delaying PVR in patients with rTOF would lead to deterioration in biventricular dimensions and function.[20] They did not observe a significant deterioration in biventricular measurements in the matched patients treated conservatively over a median of 1.8 years.[20] No patient died in either patient group.[20] The lack of eligible studies in the present systematic review highlights a substantial gap in evidence for the management of adults with rTOF and PR. Even though existing studies cannot be pooled, the comparison between PVR and conservative treatment does not identify a definite survival advantage with PVR in adults with rTOF, which is especially relevant for decision making in asymptomatic patients.

Long-term mortality after PVR in adults with rTOF

Previously published meta-analyses reported postoperative mortality rates from 0.87% to 2.1% and long-term mortality rates from 0.5%/y to 2.2%/y after PVR.[7-9] Mortality data were pooled with the use of a variety of methodologic approaches. Ferraz Cavalcanti et al. pooled the total number of deaths divided by the total number of patients with known vital status across studies at 30 days and at 5 years.[7] Cheung et al. used, as we did, incidence rates to account for the variable duration of follow-up across studies.[8] In one cohort study of PVR in rTOF, operative mortality was 1.4%.[32] Predictors of operative mortality included older age at TOF repair, > 3 previous cardiac surgeries, advanced functional class, and large body surface area at the time of PVR.[32] In the same cohort, 15-year survival after PVR was 79.6%.[32] In a cohort of 873 adults with rTOF, the best predictive model for death or sustained ventricular tachycardia was composed of RV mass-to-volume ratio > 0.3 g/mL, LVEF $< 55\%$ in men or $< 54\%$ in women, or RVEF $< 48\%$ in men or $< 50\%$ in women and a history of atrial tachyarrhythmias.[33] RVEDVi was not associated with mortality,[33] although such an association had been previously observed in a smaller cohort.[34] Therefore, if PVR is performed, the postoperative incidence rate of death should be $\sim$1 per 100 patient-years.

Effect of PVR on symptoms and functional class

We observed that PVR improves the NYHA functional class of adult patients with rTOF undergoing PVR. The NYHA functional class is used as an index of symptomatic status that can be pooled across studies. Symptomatic improvement reinforces the indication for PVR in symptomatic adults with rTOF, even if PVR has little impact on measured peak oxygen consumption.[26,35] If adults with rTOF adapt their activity level to PR and exercise intolerance, subjective symptomatic improvement may therefore be more important than measured peak oxygen consumption. However, it is thought that relying on symptoms leads to patients receiving a PVR when their RV has become markedly dilated and dysfunctional.[3] While this is

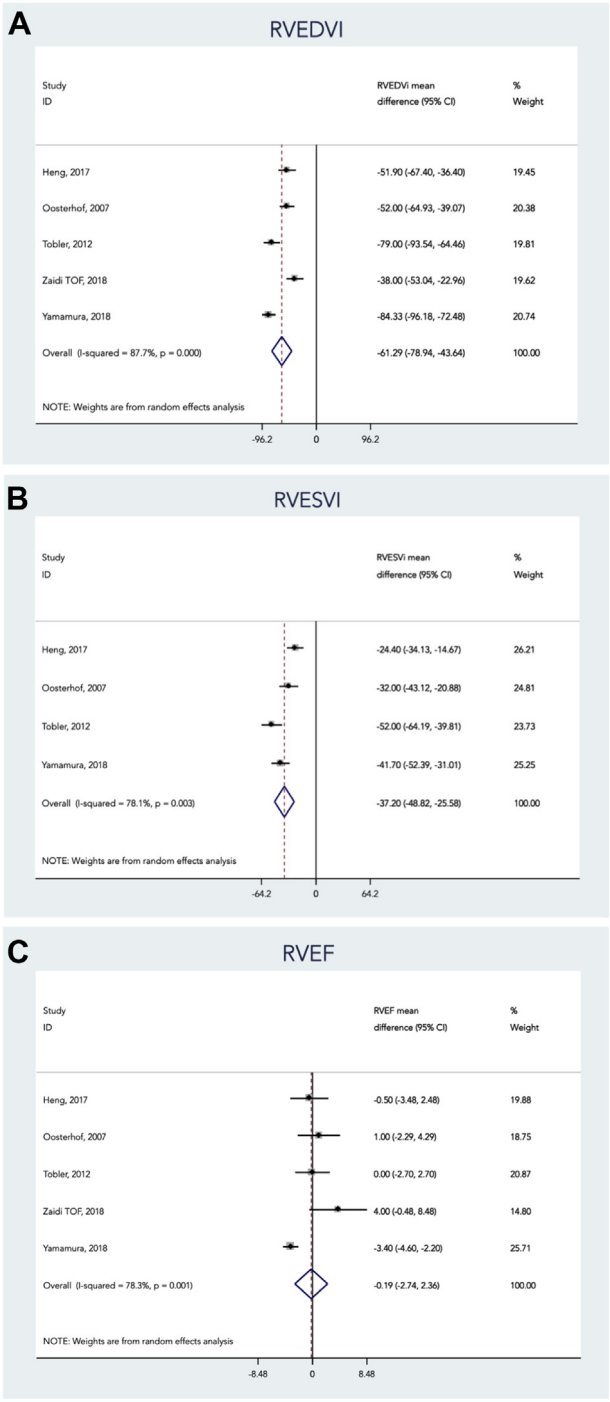

Figure 4. Effect of pulmonary valve replacement on right ventricular size and function. Forest plots of mean differences in (**A**) indexed right ventricular end-diastolic volume (RVEDVi, mL/m^2), (**B**) indexed right ventricular end-systolic volume (RVESVi, mL/m^2), and (**C**) right ventricular ejection fraction (RVEF, %).

a legitimate concern, performing PVR in asymptomatic patients with a dilated or dysfunctional RV must be balanced against operative mortality and the eventual need for repeated PVR. In a mixed cohort of patients who underwent PVR (rTOF, pulmonary atresia with ventricular

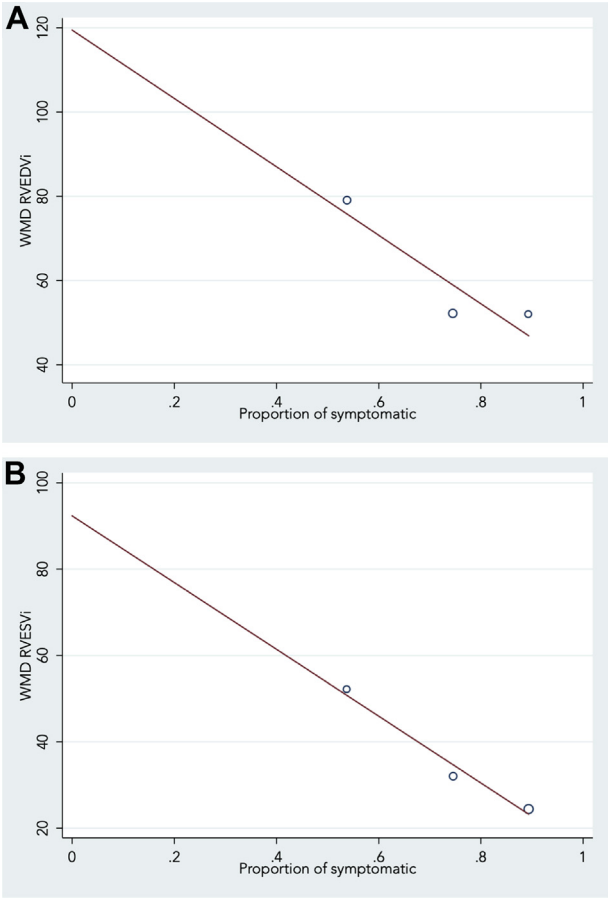

Figure 5. Meta-regression analyses. (**A**) The proportion of symptomatic patients (defined as NYHA class $\geq$ II) had no effect on the observed weighted mean difference (WMD) in RVEDVi ($P = 0.257$). (**B**) The proportion of symptomatic patients (defined as NYHA class $\geq$ 2) had no effect on the observed WMD in RVESVi ($P = 0.387$). Abbreviations as in Figures 3 and 4.

septal defect, double-outlet RV, absent pulmonary valve syndrome), freedom from redo PVR at 10 years was 74.7%, and freedom from prosthetic valve failure and dysfunction was 50.3%.[36] Our meta-regression results suggest that the reduction of RVEDVi and RVESVi after PVR persists regardless of symptomatic status. The effect of PVR on RV volumes can be expected even if the patient has changed from asymptomatic to symptomatic. The slopes of the meta-regressions (Fig. 5) raise the possibility of clinically meaningful association between symptomatic status before PVR and RV remodelling after PVR, but that may due to the small number of available studies and should be studied further.

Effect of PVR on RV volumes and function

Our pooled analysis showed that RV volumes consistently decrease while RV function, in terms of RVEF, remains stable after PVR. These results are consistent with previous pooled analyses that found reductions in RVEDVi and RVESVi without improvement in RV function.[7-9] Although 170 mL/m^2 and 85 mL/m^2 have been suggested as preoperative

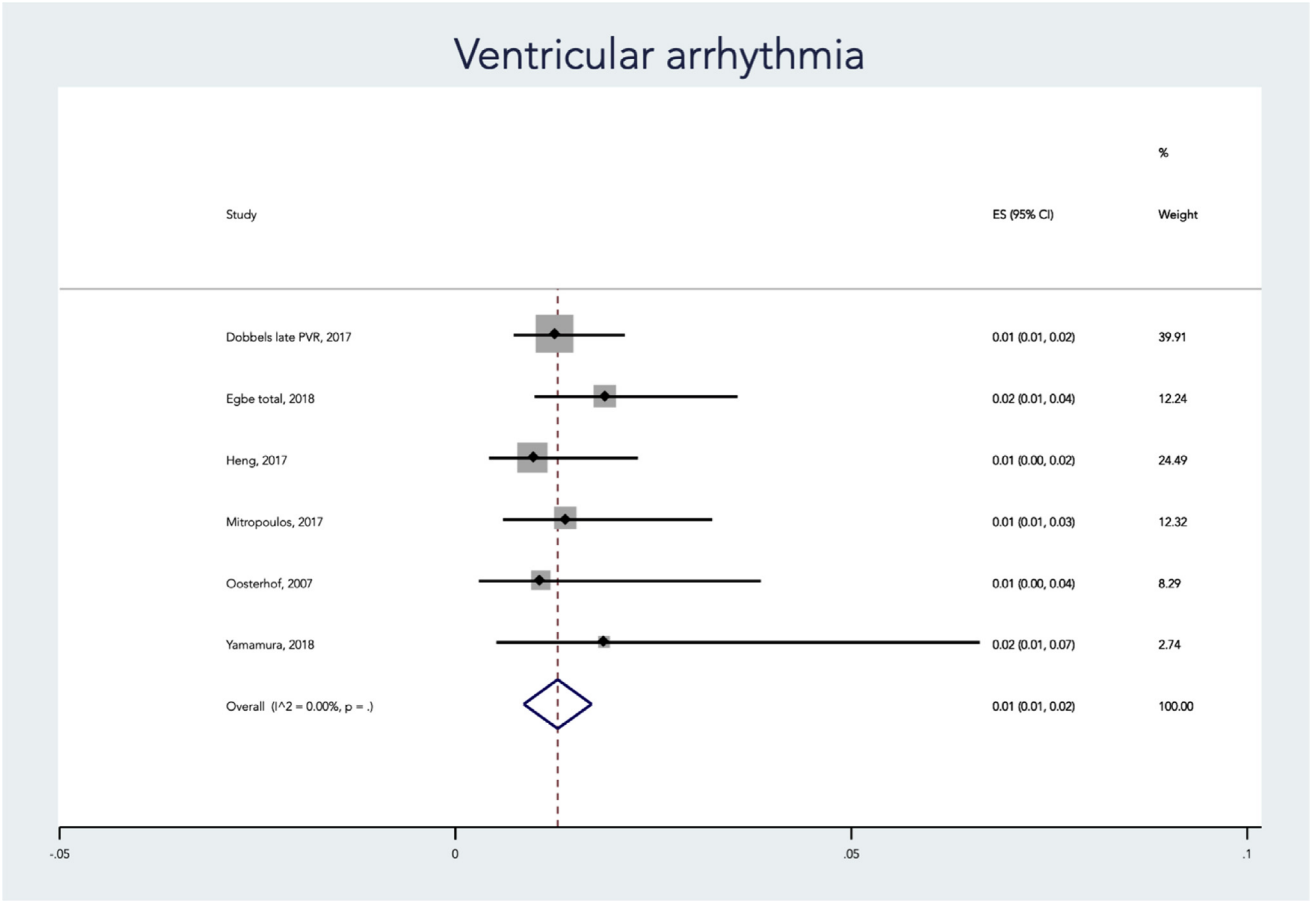

Figure 6. Forest plot of long-term ventricular arrhythmia meta-analysis. Effect size (ES) expressed as incidence rates in patient-years.

thresholds beyond which RVEDVi and RVESVi may not normalize after PVR,[37] a larger study has not identified preoperative upper thresholds for RV volumes to normalize after PVR,[22] suggesting that RV remodelling is the main benefit that can be expected from PVR. The question of whether RV size is an appropriate surrogate outcome to improve survival in adults with rTOF remains unanswered. Burchill et al. noted that given the association between RV dilation, increased QRS duration, ventricular tachycardia, and sudden cardiac death, it is tempting to relate normalization of RV volumes to superior clinical outcomes.[38] However, in a matched study, adolescents and adults with moderate RV dilation and severe PR were at low risk for progression in the absence of PVR.[20] Moreover, in a mixed cohort (75% of patients with rTOF), Hallbergson et al. have shown that RV volumes gradually return toward preoperative values by 7-10 years after PVR and that RVEF and LVEF follow a downward trend over the years which seems to be unaltered by PVR.[39]

Ventricular arrhythmias

In our meta-analysis, the pooled incidence rate of sustained ventricular arrhythmias after PVR in adults with rTOF was 1 per 100 patient-years (95% CI 1-2 per 100 patient-years). Although this rate could not be compared with patients without PVR, it is not lower than rates reported in cohorts of adults with rTOF at large (~0.4 per 100 patient-years[40]). Moreover, matched-cohort studies failed to show that surgical PVR was protective against ventricular arrhythmias.[18,19] Similarly, observational studies of patients undergoing transcatheter PVR have not demonstrated a reduction in ventricular arrhythmias.[41] Consistent with those observations, a study in defibrillator recipients with rTOF after PVR noted a persistently high rate of appropriate shocks.[42] Importantly, published data limited to rates of ventricular arrhythmias after PVR do not allow us to separate the effects of PVR alone from PVR with concomitant surgical ventricular arrhythmia ablation, which likely affects the incidence rate of subsequent ventricular arrhythmias. In one large cohort study (19% of patients with TOF and pulmonary atresia), RVEF $< 40\%$, RV mass-to-volume ratio ≥ 0.45 g/mL, and age at PVR ≥ 28 years were independent and incremental predictors of the occurrence of death or sustained ventricular tachycardia after PVR.[43] That study did not report whether patients had undergone surgical ventricular arrhythmia ablation at the time of PVR. The pooled incidence rates of death and sustained ventricular arrhythmias after PVR in our meta-analysis are similar. This observation may generate the hypothesis that residual mortality after PVR is primarily driven by arrhythmic rather than hemodynamic complications.

Clinical implications

The present study was conducted in the context of the 2019 update of the Canadian Cardiovascular Society Guidelines for the Management of Adults with Congenital Heart

Disease. This meta-analysis highlights that conclusive evidence linking PVR for PR late after TOF repair to improved survival is still lacking. The increasing frequency of PVR[44] based on relatively low-quality evidence is concerning. The findings of our meta-analysis should stimulate further detailed examination of the indications and outcomes of PVR in adults with rTOF. Further evidence should ideally be derived from multicentre cohort studies comparing intervention and nonintervention groups. Presumed causal associations between RV size and function, the development of symptoms, and outcomes should be tested. The current evidence specific to adults with rTOF does not allow balancing the risk of PVR, especially in an asymptomatic patient, with the consequences of decades of iatrogenic severe or free PR. PVR carries a postoperative mortality that is similar to primary TOF repair (0.68% during 1-8.8 years of follow-up)[3] and a risk of reintervention (~25% at 10 years[36]).

Symptomatic patients. According to the present meta-analysis, PVR improves functional class in symptomatic adults with rTOF and PR. Therefore, PVR appears to be justified for the symptomatic patient. The presence of symptoms does not preclude the reduction of RV volumes. No predictor emerges to identify symptomatic patients for whom PVR would be futile. RV dysfunction appears to be irreversible despite PVR. However, an RVEF threshold that would preclude PVR remains to be clearly established.

Asymptomatic patients. To propose PVR to asymptomatic adults with rTOF, the intervention must decrease mortality, prevent fatal arrhythmias, prevent RV dysfunction or clinical heart failure, or improve unrecognized exercise intolerance with low postoperative mortality and morbidity. No data could be pooled to determine if PVR decreased mortality or sustained ventricular arrhythmias. According to our pooled analysis, RVEF does not increase after PVR. However, RVEF may improve along with normalization of RV volumes in 22% of patients after PVR.[10] Corrected RVEF (net pulmonary flow/RVEDV) is also known to improve after PVR, suggesting improved forward cardiac output.[26] PVR is associated with obligatory reinterventions as valve prostheses age. Whether documented early improvement in RV size is sustained has been questioned.[39] Overall, if PVR is proposed to carefully selected adults with rTOF and PR, the current pooled data does not document measurable effects on key outcomes beyond a reduction in RV size. Patient age, comorbidities, level of activity and exercise capacity, longitudinal change in RV size and function, planned pregnancy, and personal choice may be additional factors to consider when determining the ultimate management plan for an individual patient.

Study limitations

This study is a meta-analysis and thus carries the limitations of the individual studies. The number of sufficiently comparable studies to perform a meta-analysis remains small. We excluded several large studies of PVR in rTOF patients because they did not report results separately for adults or they included patients with pulmonary atresia, double-outlet RV, absent pulmonary valve syndrome, or > 10% of patients with predominant pulmonary stenosis instead of PR. This meta-analysis was not designed to study outcomes of PVR performed during childhood or adolescence, and its results apply only to patients with rTOF who have survived until adulthood. We were also unable to pool studies with event rates in comparable groups of adults with rTOF with and without PVR. The impact of PVR on mortality cannot be assessed by a meta-analysis of studies that compare outcomes before and after PVR. Addressing this issue requires comparing PVR with conservative therapy. We explored the possibility of conducting such a meta-analysis but no suitable studies were identified. As such, there are currently no data to support a survival benefit from PVR in adults with rTOF. Comparisons between studies are also limited by the variable duration of follow-up for clinical events and by the variable time interval between PVR and assessment of functional class or RV volumes by means of CMR. To mitigate the effect of variable duration of follow-up, we used incidence rates for pooled analysis of mortality and occurrence of sustained ventricular arrhythmias. For RV volumes and function, we pooled the mean differences in RVEDVi, RVESVi, and RVEF regardless of duration of follow-up, based on the finding that most of the reduction in RVEDVi occurs in the first 14 days after PVR.[26] Individual studies reported means or medians for continuous variables such as RVEDVi, RVESVi, and RVEF. We used robust formulas to transform medians into means.[14,15] We elected not to pool results for repeated PVR, because prosthetic pulmonary valve degeneration depends on the type of prosthesis, which was not consistent within and between studies.

Conclusion

In conclusion, pooled data analysis on the impact of PVR in adults with rTOF was notably limited owing to the lack of not only randomized controlled trials, but also observational studies with data comparing those with PVR and those without. When data were pooled to analyze incidence rates of adverse outcomes, we were able to demonstrate that the incidence rate of death after PVR is performed is 1 per 100 patient-years. The few cohort studies in this population demonstrated improvement in functional status and RV volumes and function as shown by means of CMR. However, our findings suggest that at the time of this publication, insufficient data are available to determine the impact of PVR on mortality rates in adults with rTOF.

Members of the Writing Committee (Primary Panel) of the 2019 Update of the Canadian Cardiovascular Society Guidelines for the Management of Adults With Congenital Heart Disease

- Ariane Marelli, McGill University Health Centre, Montréal, Québec
- Candice Silversides, Toronto General Hospital, Toronto, Ontario
- Luc Beauchesne, University of Ottawa Heart Institute, Ottawa, Ontario
- Judith Therrien, Jewish General Hospital, Montréal, Québec
- Jasmine Grewal, Providence Health, Vancouver, British Columbia

- Isabelle Vonder Muhll, Alberta Health Services, Edmonton, Alberta
- Paul Khairy, Montreal Heart Institute, Montréal, Québec
- Rachel Wald, Toronto General Hospital, Toronto, Ontario
- Michelle Keir, Libin Cardiovascular Institute, Calgary, Alberta
- Robin Ducas, University of Manitoba, Winnipeg, Manitoba
- Erwin Oechslin, Toronto General Hospital, Toronto, Ontario

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Supplementary Material

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