End-Diastolic Forward Flow and Restrictive Physiology in Repaired Tetralogy of Fallot: A Systematic Review and Meta-Analysis

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BACKGROUND: Pulmonary arterial end-diastolic forward flow (EDFF) following repaired tetralogy of Fallot has been thought to represent right ventricular (RV) restrictive physiology, but is not fully understood. This systematic review and meta-analysis sought to clarify its physiological and clinical correlates, and to define a framework for understanding EDFF and RV restrictive physiology.

METHODS AND RESULTS: PubMed/MEDLINE, Embase, Scopus, and reference lists of relevant articles were searched for observational studies published before March 2021. Random-effects meta-analysis was performed to identify factors associated with EDFF. Forty-two individual studies published between 1995 and 2021, including a total of 2651 participants (1132 with EDFF; 1519 with no EDFF), met eligibility criteria. The pooled estimated prevalence of EDFF among patients with repaired tetralogy of Fallot was 46.5% (95% CI, 41.6%–51.3%). Among patients with EDFF, the use of a transannular patch was significantly more common, and their stay in the intensive care unit was longer. EDFF was associated with greater RV indexed volumes and mass, as well as smaller E-wave velocity at the tricuspid valve. Finally, pulmonary regurgitation fraction was greater in patients with EDFF, and moderate to severe pulmonary regurgitation was more common in this population.

CONCLUSIONS: EDFF is associated with dilated, hypertrophied RVs and longstanding pulmonary regurgitation. Although several studies have defined RV restrictive physiology as the presence of EDFF, our study found no clear indicators of poor RV compliance in patients with EDFF, suggesting that EDFF may have multiple causes and might not be the precise equivalent of RV restrictive physiology.

Key Words: antegrade diastolic flow ■ end-diastolic forward flow ■ meta-analysis ■ restrictive physiology ■ tetralogy of Fallot

Tetralogy of Fallot (ToF) is the most common type of cyanotic congenital heart disease. Although great strides have been made in the initial management of this condition, patients with repaired ToF (rToF) carry significant residual hemodynamic burden. Long-term functional deterioration and adverse outcomes, such as arrhythmias, ventricular dysfunction, and mortality, have been related to longstanding pulmonary regurgitation (PR) and right ventricular (RV) volume overload. The concept of RV restrictive physiology (RVRP) has been introduced to refer to abnormalities in RV diastolic function, which have been observed both transiently at the time of initial repair and chronically at late follow-up. Initial reports have linked RVRP to the presence of end-diastolic forward flow (EDFF) into the pulmonary artery (ie, “antegrade diastolic pulmonary flow,” “antegrade diastolic pulmonary artery flow,” and “antegrade diastolic flow”). This phenomenon was thought to result from an RV so “stiff” as to be unfillable late in diastole, as a passive conduit between right atrium (RA) and pulmonary artery during atrial systole.
RVRP has been identified on the basis of the presence of EDFF on Doppler echocardiography or cardiac magnetic resonance (CMR), but studies of its physiological and clinical correlates have yielded divergent results. Some authors have suggested that RVRP is beneficial because it decreases PR, RV dilatation, and QRS duration, resulting in improved exercise capacity and lower risk of ventricular arrhythmias.6–8 Others, in contrast, have found more severe PR, larger RV volumes, and worse exercise capacity in patients with EDFF.5,11–15 On the basis of simultaneous catheter pressure monitoring, EDFF can occur whenever RV diastolic pressure equals or exceeds pulmonary artery pressure.16 An insight emerges that EDFF might not always carry the same implications as true RVRP. The current understanding of the relationship among the various factors leading to EDFF and RVRP remains incomplete. The purpose of this meta-analysis is to clarify the physiological and clinical correlates of EDFF, and to establish a framework to guide current thinking about EDFF and RVRP.

### CLINICAL PERSPECTIVE

**What Is New?**
- In this systematic review and meta-analysis of 2651 patients with repaired tetralogy of Fallot from 42 individual studies, end-diastolic forward flow (EDFF) occurred in 46.5%.
- EDFF was associated with transannular patch repair, greater right ventricular indexed volumes and mass, smaller E-wave velocity at the tricuspid valve, increased rates of moderate to severe pulmonary regurgitation, and longer stay in the intensive care unit.

**What Are the Clinical Implications?**
- Although often used as a surrogate marker of right ventricular restrictive physiology, EDFF may have multiple alternative causes and might not be the precise equivalent of right ventricular restrictive physiology.
- Our review supports a specific reconciliation of the conflicting EDFF literature, based on the presence of 2 main phenotypes: (1) early-onset, “primary” EDFF and (2) late-onset, “secondary” EDFF; the latter has become more prevalent in contemporary practice, with improved peroperative ventricular diastolic function but progressive dilatation resulting from longstanding pulmonary regurgitation.
- Future studies should refine the diagnostic criteria for right ventricular restrictive physiology and clarify the potential prognostic relevance of EDFF in various settings.

### Eligibility Criteria, Databases, and Search Strategy

We followed 2 internationally recognized protocols: Preferred Reporting Items for Systematic Reviews and Meta-Analyses17 and Meta-Analysis of Observational Studies in Epidemiology.18 Studies were included if (1) the population consisted of patients with ToF, (2) patients had undergone full ToF repair by the time of evaluation, (3) patient characteristics, surgical history, hemodynamic parameters, and/or other measurements were compared between patients with EDFF and those without, and (4) studies were prospective or retrospective observational studies or randomized controlled trials. Exclusion criteria included the following: (1) nonoriginal articles, such as review articles, meta-analyses, guidelines, consensus statements, conference abstract, editorials, letters, and book reviews, (2) in vitro or in vivo preclinical research, or (3) publications did not include data on EDFF status.

Databases were searched for articles meeting our inclusion criteria and published by March 8, 2021: PubMed/MEDLINE, Embase, Scopus, and reference lists of relevant articles. The detailed search terms that were used for this search are given in Data S1. The following steps were taken: (1) identification of titles of records through databases searching, (2) removal of duplicates, (3) screening and selection of abstracts, (4) assessment for eligibility through full-text articles, and (5) final inclusion in the study. Studies were selected by 2 independent reviewers (J.V.D.E. and E.D.). Discrepancies were resolved by consensus.

### Data Items

All variables that were compared between EDFF and no EDFF groups in least 2 studies were included in the
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Meta-analysis. These variables included patient characteristics, surgical history, hemodynamic parameters, and other measurements. For studies reporting interquartile ranges, the mean was estimated according to a well-accepted and commonly used formula. Two reviewers independently extracted the data (J.V.D.E. and E.D.). Discrepancies were resolved by consensus. From each study, we extracted first authors’ name, year of publication, country of origin, study design, years of enrollment, sample size, EDFF prevalence, mean age at initialToF repair, mean interval betweenToF repair and assessment, and mean age at assessment.

Statistical Analysis

Mean differences (MDs) with 95% CI and \( P \) values were calculated for continuous variables. For binary variables, odds ratios (ORs) with 95% CI and \( P \) values were considered. \( P \), describing the percentage of total variation across studies that is attributable to heterogeneity rather than chance, was calculated to assess the degree of statistical heterogeneity, and its accompanying \( P \) value was obtained using the \( \chi^2 \) test of the Cochrane Q heterogeneity statistic. The MD and OR were combined across the studies using a random-effects method (DerSimonian and Laird inverse variance). The choice for random-effects models was made on the basis of the assumption that the effect sizes in the individual studies represented samples from a mixing distribution. In addition, the results were reanalyzed using fixed-effects models to explore whether this yielded differences on the summary inferences. Forest plots were used to visualize the individual study and summary effect estimates. These analyses were conducted using the “metacont” and “metabin” functions of the R package “meta” (version 4.19-0). Funnel plots were produced for visual representation of publication bias, and were analyzed quantitatively by Beggs and Mazumdar’s rank correlation method and Egger’s linear regression method, using the “funnel” and “metabias” functions of the R package “meta” (version 4.19-0). The proportions of patients who had EDFF were pooled into a global estimated prevalence using the same random-effects method (DerSimonian and Laird inverse variance) as described above, via the “metaprop” function of the R package “meta” (version 4.19-0).

Subgroup analyses were conducted on the basis of study design (retrospective or prospective), by specifying this grouping variable in the “metacont” and “metabin” functions of the R package “meta” (version 4.19-0). Furthermore, meta-regression analyses were performed to determine whether the association of EDFF with the studied variables was modulated by (1) mean year of enrollment, (2) RV end-diastolic volume indexed (RVEDVi), (3) age at evaluation, or (4) interval from initial repair to evaluation. The regression coefficient describes how the association of EDFF with these variables differs with an increase in each of these variables. These analyses were done using the “metareg” function of the R package “meta” (version 4.19-0).

RESULTS

Study Selection and Characteristics

A total of 552 citations were identified, of which 83 publications were potentially relevant and retrieved as full text. Forty-five reports of 42 individual studies fulfilled our eligibility criteria (Figure 1). Characteristics of each study and its participants are shown in Table 1. A total of 2651 participants (EDFF: 1132 participants; no EDFF: 1519 participants) were included from studies published between 1995 and 2021. All studies were nonrandomized observational studies, except for one randomized controlled trial. The pooled mean age of participants was 16.5 years (39 studies, with 2323 participants) at the time of evaluation and 3.37 years (30 studies, with 2175 participants) at initialToF repair. The interval between initial repair and evaluation was 13.0 years (21 studies, with 1421 participants).

Synthesis of Results

Prevalence of EDFF

Overall, the pooled estimated prevalence of EDFF among patients with rToF was 46.5% (95% CI, 41.6%–51.3%; \( P=0.809\)). The reported prevalence in the 10 studies that used CMR to define EDFF (51.9%; 95% CI, 42.4%–61.1%; \( I^2=70.5\%\) ) tended to be marginally higher than that in the 32 studies that defined EDFF based on Doppler echocardiography (45.6%; 95% CI, 40.2%–51.1%; \( P=0.807\%\) ), although this difference did not reach statistical significance (test for subgroup differences: \( P=0.263\) ). Subanalyses according to study design revealed that a higher prevalence was reported in prospective studies (49.3%; 95% CI, 42.9%–55.6%; \( I^2=81.2\%\) ) than in retrospective studies (40.3%; 95% CI, 35.1%–45.6%; \( I^2=72.9\%\) ) (test for subgroup differences: \( P=0.034\) ). Meta-regression analysis revealed that the prevalence of EDFF increased with increasing RVEDVi (regression coefficient, 0.017; 95% CI, 0.001–0.034; \( P=0.049\); 24 studies). Other analyses revealed no significant findings.

Meta-Analysis

The results of the meta-analysis comparing variables between rToF patients with EDFF and those without
are summarized in Table 2. The accompanying forest plots are given in Figures S1 through S14. The use of a transannular patch was significantly more common among patients with EDFF (random-effects model: OR, 1.98; 95% CI, 1.26–3.11; \(P=0.005\)), and intensive care unit length of stay for these patients was longer (random-effects model: MD, 4.34 days; 95% CI, 1.38–7.29 days; \(P=0.019\)) when compared with those having no EDFF.

EDFF was found to be associated with dilated RVs, as reflected by a greater RVEDVi (random-effects model: MD, 14.7 mL/m²; 95% CI, 4.57–24.8 mL/m²; \(P=0.007\)), greater RV end-systolic volume indexed (random-effects model: MD, 16.1 mL/m²; 95% CI, 1.01–31.3 mL/m²; \(P=0.039\)), and greater RV stroke volume indexed (random-effects model: MD, 9.57 mL/m²; 95% CI, 0.67–18.5 mL/m²; \(P=0.040\)). Correspondingly, RV mass indexed was greater in patients with EDFF (random-effects model: MD, 2.87 g/m²; 95% CI, 0.14–5.61 g/m²; \(P=0.042\)).

Furthermore, E-wave velocity at the tricuspid valve was smaller in patients with EDFF (random-effects model: MD, −11.6 cm/s; 95% CI, −20.9 to −2.32 cm/s; \(P=0.019\)). Last, the PR fraction was greater in patients with EDFF (random-effects model: MD, 12.7%; 95% CI, 8.91%–16.4%; \(P<0.001\)), and moderate to severe PR was more common in this population (random-effects model: OR, 1.27; 95% CI, 1.09–1.48; \(P=0.021\)). No other significant associations with EDFF were found (Table 2).

Funnel plot analysis disclosed asymmetry around the axis for transannular patch repair, RA volume indexed, PR duration, and A-wave velocity at the tricuspid valve (Figure S15). Consequently, publication bias related to these outcomes cannot be excluded. No publication biases were found in the other short-term outcomes.
| Study                  | Country of origin        | Study design | Years of enrollment | Sample size, N | Imaging tool used to define EDFF | EDFF prevalence, n/total (%) | Mean age at initialToF repair, y | Mean interval betweenToF repair and assessment, y | Mean age at assessment, y |
|-----------------------|--------------------------|--------------|---------------------|----------------|---------------------------------|------------------------------|---------------------------------|------------------------------------|------------------------|
| Aburawi 201424         | Sweden                   | Prospective  | NR                  | 20             | CMR                             | 9/20 (45.0)                  | NR                              | NR                                 | 10.2                   |
| Ahmad 201225           | Canada                   | Retrospective| 2008–2010           | 112            | Doppler echocardiography        | 58/112 (51.8)                | 0.9                             | NR                                 | 12.9                   |
| Apitz 201026           | Germany                  | Prospective  | NR                  | 25             | CMR                             | 8/25 (32.0)                  | NR                              | 7.1                                 | 17.9                   |
| Babu-Narayan 201226     | United Kingdom           | Prospective  | 2002–2005           | 64             | Doppler echocardiography        | 27/64 (42.2)                 | 6.0                             | 25.1                                | 30.1                   |
| Bonello 201327         | United Kingdom           | Prospective  | 2002–2008           | 148            | Doppler echocardiography        | 38/148 (25.7)                | 4.8                             | NR                                 | 32.1                   |
| Cardoso 200328         | Brazil                   | Prospective  | 2000                | 30             | Doppler echocardiography        | 19/30 (63.3)                 | 3.0                             | 3.2                                 | 8.7                    |
| Chaturvedi 199929      | United Kingdom           | Prospective  | NR                  | 11             | Doppler echocardiography        | 4/11 (36.4)                  | NR                              | NR                                 | 1.7                    |
| Cheng 201929           | United States            | Retrospective| 1999–2014           | 38             | CMR                             | 15/38 (39.5)                 | NR                              | NR                                 | 13.2                   |
| Cheung 200330          | Australia                | Prospective  | 1981–1990           | 45             | Doppler echocardiography        | 24/45 (53.3)                 | 2.1                             | 12.5                                | 15.0                   |
| Choi 200832            | Korea                    | Retrospective| 1997–2000           | 43             | Doppler echocardiography        | 15/43 (34.9)                 | 2.1                             | 5.4                                 | 4.8                    |
| Clark 199533           | United Kingdom           | Prospective  | 1958–1979           | 30             | Doppler echocardiography        | 18/30 (60.0)                 | NR                              | 21.8                                | 27.8                   |
| Cullen 199534          | United Kingdom           | Prospective  | 1992–1993           | 35             | Doppler echocardiography        | 17/35 (48.6)                 | NR                              | NR                                 | 1.9                    |
| Eroglu 199935          | Turkey                   | Prospective  | 1986–1996           | 44             | Doppler echocardiography        | 25/44 (56.8)                 | 4.0                             | NR                                 | 7.7                    |
| Gatzoulis 199536       | United Kingdom           | Prospective  | 1958–1979           | 38             | Doppler echocardiography        | 20/38 (52.6)                 | 5.2                             | NR                                 | 28.8                   |
| Gatzoulis 199837       | United Kingdom           | Retrospective| 1985–1994           | 92             | Doppler echocardiography        | 36/92 (39.1)                 | NR                              | 4.5                                 | 14.7                   |
| Helbing 199638         | The Netherlands          | Prospective  | NR                  | 19             | Doppler echocardiography        | 13/19 (68.4)                 | 1.5                             | 10.0                                | 12.0                   |
| Kordybach-Prokopiuk 201839 | Poland                 | Prospective  | NR                  | 83             | Doppler echocardiography        | 16/83 (19.3)                 | 11.9                            | 21.6                                | 31.5                   |
| Krupickova 201840      | United Kingdom           | Prospective  | 2002–2005           | 64             | Doppler echocardiography        | 26/64 (40.6)                 | 6.1                             | 25.1                                | 31.1                   |
| Kutty 201841           | United States            | Retrospective| 2005–2012           | 399            | Doppler echocardiography        | 122/399 (30.6)               | 1.1                             | 18.5                                | 20.5                   |

(Continued)
### Table 1. Continued

| Study                  | Country of origin | Study design | Years of enrollment | Sample size, N | Imaging tool used to define EDFF | EDFF prevalence, n/total (%) | Mean age at initial ToF repair, y | Mean interval between ToF repair and assessment, y | Mean age at assessment, y |
|------------------------|-------------------|--------------|---------------------|----------------|---------------------------------|-------------------------------|-------------------------------|-------------------------------------|-------------------------|
| Latus 2013 [38]        | Germany           | Retrospective | 2007–2011           | 53             | CMR                             | 15/53 (28.3)                  | 1.3                           | 12.1                                 | 13.3                    |
| Lee 2013 [39]          | Canada            | Retrospective | 2007–2009           | 50             | CMR                             | 33/50 (66.0)                  | 1.3                           | NR                                   | 13.0                    |
| Lu 2010 [32]           | United States     | Prospective  | 2008–2009           | 59             | CMR                             | 40/59 (67.8)                  | 11.0                          | NR                                   | 35.0                    |
| Luijtenburg 2013 [40]  | The Netherlands    | Prospective  | 2007–2010           | 51             | CMR                             | 31/51 (60.8)                  | 2.8                           | NR                                   | 21.0                    |
| Maskatia 2013 [34]     | United States     | Retrospective | 1997–2011           | 178            | CMR                             | 77/178 (43.3)                 | 3.0                           | NR                                   | NR                      |
| Maskatia 2015 [42]     | United States     | Retrospective | NR                 | 99             | Doppler echocardiography        | 43/99 (43.4)                  | NR                            | NR                                   | 14.2                    |
| Mercer-Rosa 2018 [43]  | United States     | Prospective  | NR                 | 88             | Doppler echocardiography        | 77/88 (87.5)                  | 0.4                           | NR                                   | 12.7                    |
| Mori 2017 [36]         | Japan             | Retrospective | 2009–2016           | 62             | Doppler echocardiography        | 23/62 (37.1)                  | 3.1                           | NR                                   | 15.7                    |
| Munkhammar 1998 [37]   | United Kingdom    | Prospective  | 1985–1996           | 47             | Doppler echocardiography        | 13/47 (27.7)                  | 0.7                           | NR                                   | 4.4                     |
| Munkhammar 2013 [35]   | Sweden            | Prospective  | NR                 | 31             | Doppler echocardiography        | 16/31 (51.6)                  | 1.0                           | 9.2                                  | 10.2                    |
| Norgard 1996 [44]      | United Kingdom    | Retrospective | 1985–1994           | 92             | Doppler echocardiography        | 36/92 (39.1)                  | 11.5                          | NR                                   | 14.7                    |
| Norgard 1998 [7]       | United Kingdom    | Retrospective | 1992–1995           | 34             | Doppler echocardiography        | 16/34 (47.1)                  | 5.9                           | 1.8                                  | NR                      |
| Norgard 1998 [7]       | United Kingdom    | Prospective  | 1992–1995           | 32             | Doppler echocardiography        | 10/32 (31.3)                  | 5.6                           | 1.8                                  | NR                      |
| Peng 2012 [45]         | United Kingdom    | Prospective  | NR                 | 18             | Doppler echocardiography        | 4/18 (22.2)                   | 1.6                           | NR                                   | 1.6                     |
| Pijuan-Domenech 2014 [46] | Spain           | Prospective  | 2009–2012           | 20             | Doppler echocardiography        | 16/20 (80.0)                  | 7.7                           | NR                                   | 35.0                    |
| Rathore 2006 [39]      | Australia         | Prospective  | 2001–2003           | 80             | Doppler echocardiography        | 52/80 (65.0)                  | NR                            | NR                                   | 7.9                     |
| Sachdev 2006 [50]      | India             | Prospective  | 2004–2005           | 50             | Doppler echocardiography        | 24/50 (48.0)                  | NR                            | NR                                   | 5.0                     |
| Samyn 2013 [33]        | United States     | Prospective  | 2006–2009           | 29             | Doppler echocardiography        | 12/29 (41.4)                  | 1.4                           | 14.0                                 | 16.3                    |
| Sandeep 2019 [33]      | China             | Prospective  | 2017–2018           | 50             | Doppler echocardiography        | 28/50 (56.0)                  | NR                            | NR                                   | 2.2                     |
| Sani 2020 [42]         | Iran              | Prospective  | 2015–2016           | 30             | CMR                             | 18/30 (60.0)                  | 20.2                          | 26.5                                 |                         |
| Shekerdemian 1999 [53] | United Kingdom    | Prospective  | NR                 | 23             | Doppler echocardiography        | 8/23 (34.8)                   | NR                            | NR                                   | 2.5                     |

(Continued)
Sensitivity Analysis

The results of the fixed-effects models were largely comparable to those from random-effects models, with numerical effect estimates having the same direction and lying close to one another (Figures S1 through S14). However, because of its narrower CIs, the fixed-effects model additionally suggested a significant association with EDFF for the following variables: younger age at repair (fixed-effects model: MD, −0.07 years; 95% CI, −0.11 to −0.02 years; \( P = 0.004 \)), older age at study (fixed-effects model: MD, 0.33 years; 95% CI, 0.04–0.61 years; \( P = 0.024 \)), previous RV–pulmonary artery shunt (fixed-effects model: OR, 0.35; 95% CI, 0.21–0.60; \( P < 0.001 \)), longer aortic cross-clamp time (fixed-effects model: MD, 6.91 minutes; 95% CI, 4.00–9.82 minutes; \( P < 0.001 \)), longer cardiopulmonary bypass time (fixed-effects model: MD, 8.94 minutes; 95% CI, 4.17–13.71 minutes; \( P < 0.001 \)), outflow patch repair (fixed-effects model: OR, 0.31; 95% CI, 0.13–0.72; \( P = 0.006 \)), higher RV ejection fraction (fixed-effects model: MD, 3.91%; 95% CI, 3.65%–4.18%; \( P < 0.001 \)), higher RV end-diasolic pressure (fixed-effects model: MD, 0.97 mm Hg; 95% CI, 0.46–1.47 mm Hg; \( P = 0.006 \)), smaller left ventricular (LV) end-diasolic volume indexed (fixed-effects model: MD, −4.15 mL/m²; 95% CI, −4.86 to −3.44 mL/m²; \( P < 0.001 \)), smaller LV end-systolic volume indexed (fixed-effects model: MD, −2.97 mL/m²; 95% CI, −3.43 to −2.52 mL/m²; \( P < 0.001 \)), smaller LV stroke volume indexed (fixed-effects model: MD, −1.65 mL/m²; 95% CI, −2.05 to −1.24 mL/m²; \( P < 0.001 \)), greater LV ejection fraction (fixed-effects model: MD, 0.64%; 95% CI, 0.23%–0.85%; \( P < 0.001 \)), greater RA area indexed (fixed-effects model: MD, 0.58 cm²/m²; 95% CI, 0.42–0.74 cm²/m²; \( P = 0.028 \)), smaller E-wave deceleration at the tricuspid valve (fixed-effects model: MD, −8.62 cm/s; 95% CI, −11.0 to −6.27 cm/s; \( P < 0.001 \)), greater A-wave velocity at the tricuspid valve (fixed-effects model: MD, 2.92 cm/s; 95% CI, 0.62–5.03 cm/s; \( P = 0.007 \)), smaller E/A (ratio between early (E) and late atrial (A) ventricular filling velocity) at the tricuspid valve (fixed-effects model: MD, −0.09; 95% CI, −0.17 to −0.02; \( P = 0.016 \)), longer PR duration (fixed-effects model: MD, 10.3 ms; 95% CI, 8.68–12.1 ms; \( P < 0.001 \)), shorter QRS duration (fixed-effects model: MD, −2.90 ms; 95% CI, −4.26 to −1.54 ms; \( P < 0.001 \)), higher brain natriuretic peptide levels (fixed-effects model: MD, 11.0 pg/mL; 95% CI, 6.53–15.5 pg/mL; \( P < 0.001 \)), and higher NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels (fixed-effects model: MD, 61.1 pg/mL; 95% CI, 15.2–107 pg/mL; \( P = 0.009 \)). Because these findings were not confirmed by both models, these should be interpreted with caution.

Subgroup Analyses and Meta-Regression Analyses

In an attempt to explain sources of heterogeneity and to further investigate the underlying mechanisms of EDFF in rToF, subgroup analyses and meta-regression
Table 2. Meta-Analysis of EDFF in rToF: Summary of Results

| Variable                               | Summary measures | Heterogeneity |
|----------------------------------------|------------------|---------------|
|                                       | OR/MD            | 95% CI        | P value | I², % | χ² P value |
| Patient characteristics                |                  |               |         |       |            |
| Age at repair, y                       | 16               | 0.329         | −0.419 to 1.077 | 0.363 | 96.2 | <0.001 |
| Time of follow-up since repair, y      | 9                | 0.316         | −0.654 to 1.290 | 0.472 | 82.8 | <0.001 |
| Age at study, y                        | 24               | 0.769         | −0.080 to 1.617 | 0.074 | 90.2 | <0.001 |
| Surgical history                       |                  |               |         |       |            |
| Previous RVPA shunt                   | 3                | 0.365         | 0.122 to 1.091 | 0.058 | 0 | 0.423 |
| Previous BT shunt                     | 10               | 0.865         | 0.620 to 1.205 | 0.347 | 0 | 0.960 |
| Aortic cross-clamp time, min          | 7                | 7.786         | −1.053 to 16.624 | 0.075 | 78.7 | <0.001 |
| CPB time, min                         | 7                | 5.962         | −12.243 to 24.166 | 0.454 | 88.0 | <0.001 |
| Transatrial repair                    | 4                | 0.474         | 0.100 to 2.233 | 0.223 | 1.9 | 0.383 |
| Transannular patch repair             | 21               | 1.983         | 1.264 to 3.112 | 0.005* | 55.9 | 0.001 |
| Outflow patch repair                  | 4                | 0.323         | 0.095 to 1.099 | 0.061 | 0 | 0.520 |
| ICU length of stay, d                 | 4                | 4.339         | 1.384 to 7.294 | 0.019* | 75.2 | 0.007 |
| Hemodynamics                           |                  |               |         |       |            |
| RVEDVi, mL/m²                          | 16               | 14.706        | 4.572 to 24.840 | 0.007* | 91.0 | <0.001 |
| RVESVi, mL/m²                          | 11               | 16.146        | 1.012 to 31.280 | 0.039* | 94.9 | <0.001 |
| RVSVi, mL/m²                           | 6                | 9.570         | 0.674 to 18.466 | 0.040* | 98.3 | <0.001 |
| RVMi, g/m²                             | 7                | 2.873         | 0.139 to 5.606 | 0.042* | 93.9 | <0.001 |
| RVEF, %                                | 12               | −0.555        | −2.640 to 1.530 | 0.570 | 95.7 | <0.001 |
| RVEDP, mm Hg                           | 4                | 1.216         | −0.293 to 2.724 | 0.083 | 75.8 | 0.006 |
| RVESP, mm Hg                           | 5                | 0.824         | −5.563 to 7.210 | 0.738 | 69.9 | 0.010 |
| LVEDVi, mL/m²                          | 5                | 0.005         | −6.334 to 6.344 | 0.998 | 87.7 | 0.008 |
| LVESVi, mL/m²                          | 2                | −1.728        | −27.074 to 23.618 | 0.546 | 57.3 | 0.126 |
| LVSVi, mL/m²                           | 2                | −1.179        | −12.443 to 10.088 | 0.411 | 91.9 | <0.001 |
| LVEF, %                                | 9                | −0.196        | −1.256 to 0.866 | 0.682 | 74.3 | <0.001 |
| RAAi, cm²/m²                           | 3                | 1.083         | −0.319 to 2.484 | 0.080 | 92.8 | <0.001 |
| RAVi, mL/m²                            | 3                | 4.863         | −10.111 to 19.836 | 0.297 | 79.4 | 0.008 |
| E-wave velocity at the tricuspid valve, cm/s | 11     | −11.586       | −20.850 to −2.321 | 0.019* | 79.3 | <0.001 |
| E-wave duration at the tricuspid valve, ms | 4        | −7.077        | −33.700 to 19.545 | 0.460 | 85.3 | <0.001 |
| E-wave deceleration at the tricuspid valve, ms | 8    | −14.507       | −34.448 to 5.434 | 0.129 | 91.5 | <0.001 |
| A-wave velocity at the tricuspid valve, cm/s | 10       | −1.204        | −5.682 to 3.274 | 0.558 | 76.2 | <0.001 |
| A-wave duration at the tricuspid valve, ms | 2      | −15.546       | −147.249 to 143.158 | 0.431 | 5.4 | 0.304 |
| E/A at the tricuspid valve             | 10               | −0.106        | −0.248 to 0.033 | 0.119 | 59.5 | 0.008 |
| E' at the tricuspid valve, cm/s        | 2                | 0.914         | −12.862 to 14.690 | 0.554 | 73.4 | 0.053 |
| A' at the tricuspid valve, cm/s        | 2                | 0.000         | 0.000 to 0.000 | N/A | 0 | 1.000 |
| E/E' at the tricuspid valve            | 2                | −0.893        | −2.161 to 0.374 | 0.071 | 0 | 0.802 |
| Moderate to severe PR                 | 3                | 1.268         | 1.090 to 1.476 | 0.021* | 0 | 0.982 |
| PR fraction, %                        | 8                | 12.662        | 8.912 to 16.411 | <0.001* | 56.3 | 0.025 |
| PR duration, ms                       | 7                | 46.569        | −100.462 to 7.323 | 0.079 | 95.1 | <0.001 |
| Other                                  |                  |               |         |       |            |
| QRS duration, ms                      | 18               | 4.983         | −4.296 to 14.262 | 0.272 | 89.9 | <0.001 |
| BNP, pg/mL                             | 3                | 13.264        | −10.052 to 36.581 | 0.134 | 66.8 | 0.049 |
| NT-proBNP, pg/mL                      | 3                | 61.125        | −25.398 to 147.647 | 0.093 | 0 | 0.479 |
| Peak VO2%, %                           | 7                | 8.433         | −0.050 to 16.916 | 0.051 | 87.5 | <0.001 |
| Peak VO2, mL/kg per min                | 6                | 0.648         | −3.857 to 5.153 | 0.727 | 98.0 | <0.001 |

A’ indicates annulus velocity during late atrial filling; BNP, brain natriuretic peptide; BT, Blalock-Taussig; CPB, cardiopulmonary bypass; E’, annulus velocity during early filling; E/A, ratio between early (E) and late atrial (A) ventricular filling velocity; EDFF, end-diastolic forward flow; ICU, intensive care unit; LVEDVi, left ventricular end-diastolic volume indexed; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume indexed; LVSVi, left ventricular stroke volume indexed; MD, mean difference; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CR, odds ratio; PR, pulmonary regurgitation; RAAi, right atrial area indexed; RAVi, right atrial volume indexed; rToF, repaired tetralogy of Fallot; RVESP, right ventricular end-systolic pressure; RVEF, right ventricular ejection fraction; RVESVi, right ventricular end-systolic volume indexed; RVi, right ventricular mass indexed; RVPA, right ventricle–pulmonary artery; RVSVi, right ventricular stroke volume indexed; and VO2, oxygen consumption.

*P<0.05.
analyses were performed. The findings of these analyses are presented in Data S1.

**DISCUSSION**

**Summary of Evidence**

The current meta-analysis summarizes the available evidence on associations of EDFF with patient characteristics, hemodynamic findings, and surgical properties in patients with rToF. Our findings, summarized in Figure 2, are as follows: (1) EDFF occurred in 46.5% of all patients, (2) the use of a transannular patch was significantly more common among patients with EDFF, (3) intensive care unit length of stay for these patients was longer, (4) EDFF was associated with greater RV indexed volumes and mass, as well as smaller E-wave velocity at the tricuspid valve, and (5) PR fraction was greater, and moderate to severe PR was more common with EDFF. Overall, these results suggest that EDFF is associated with dilated, hypertrophied RVs experiencing longstanding PR. However, as no clear indicators of poor RV compliance were found, EDFF may have multiple causes and might not correspond precisely with RVRP.

**EDFF Is Not a Specific Marker of RVRP and May Occur Under Several Other Conditions**

Ever since the initial reports on EDFF, it has been regarded as a hallmark feature of RVRP. Indeed, studies conducted thereafter, which were included in the present meta-analysis, defined RVRP solely based on the presence of EDFF. Strictly speaking, however, restrictive physiology implies poor ventricular compliance, or its reciprocal increased myocardial stiffness, which may be either a manifestation of primary cardiomyopathy or secondary to other cardiovascular diseases.

The gold standard measure of LV myocardial stiffness is the slope of the end-diastolic pressure-volume relationship, but is less practical for the RV, given the trapezoidal nature of the normal RV pressure-volume relationship. Furthermore, a prerequisite of pressure-volume analysis is a closed system, meaning that the semilunar valve should be closed such that changes within the ventricle reflect muscle mechanics. As the right heart is a low-pressure system, RA pressures can at times exceed pulmonary artery pressures, promoting transmission of RA outflow into the pulmonary arteries and thus opening the system. Nonetheless, when this antegrade diastolic pulmonary artery flow occurs, it suggests that the resistance to RV filling is greater than the resistance to pulmonary artery filling; this concept has been the rationale for using EDFF as a surrogate for RVRP.

EDFF is a convenient marker that is readily available from conventional Doppler echocardiography or CMR. However, there are several limitations to its value for diagnosis of RVRP, because other factors may modulate EDFF (Table 3). For example, the absence of atrial systole and other conditions that decrease preload...
may attenuate EDFF. Conversely, increased pulmonary arterial bed capacitance decreases the resistance to pulmonary artery filling and might thereby increase or induce EDFF, even when RV compliance and filling pressures are normal. As shown in our meta-analysis, the severity of PR and the use of the transannular patch during primary repair of ToF are both significantly associated with EDFF, possibly because of lower pulmonary diastolic pressure. With pressure gradients of only 1 to 2 mm Hg governing EDFF, it is highly susceptible to small changes in preload, pulmonary artery bed capacitance, and PR.

More important, this meta-analysis found no significant associations of EDFF with typical markers of restrictive filling of the RV, including decreased tricuspid E-wave deceleration, decreased early diastolic tricuspid annular velocity, increased E/A ratio, increased E/E’ (ratio between early ventricular filling velocity (E) and annulus velocity during early filling (E’)), or RA enlargement, based on random-effects models (main analysis) and only limited effects based on fixed-effects models (sensitivity analysis). This is in accordance with findings by DiLorenzo et al, who found that invasive evaluation of diastolic function with catheter-based RV end-diastolic pressure did not correlate with EDFF or any other echocardiographic parameters of diastolic function in patients with ToF. Similarly, Mori et al reported that EDFF was inconsistently associated with RVRP, noting its presence in some patients with low pulmonary diastolic pressure (attributable to severe PR) and normal RA pressure. In fact, our meta-analysis revealed a lower early (E) inflow velocity through the tricuspid valve in patients with EDFF, in contrast to increased E in the conventional restrictive pattern. This finding could well be a manifestation of the Bernoulli principle, where transtricuspid velocities drop secondary to widening of the tricuspid annulus. However, Sjöberg et al suggested that these decreased velocities might contribute to the lower diastolic kinetic energy observed on 4-dimensional flow CMR in patients with EDFF.
kinetic energy reflects ventricular performance, it might be a potential early marker of ventricular dysfunction. In summary, clinicians are encouraged to look beyond EDFF to determine if their patients have RV diastolic dysfunction.

A Unifying Theory About the Physiological and Clinical Correlates of EDFF

To reconcile the conflicting results in the literature, the observation of Lee et al.39 revealing that EDFF most commonly occurs at the ends of the RVEDVi spectrum (at \( \leq 115 \) and \( \geq 200 \) mL/m²), is key. Consider that there may be 2 main phenotypes of ToF in which EDFF is observed (Table 4). Representative pressure-volume curves for each of these phenotypes are presented in Figure 3. The first, which we refer to as early-onset, “primary” EDFF, matches the original phenotype 1. Preventing further progression of PR and limiting the extent of volume overload. Usually disappears days to months after the primary repair, but may be maintained into midterm follow-up in a subset of patients. Associated with repair at older age as seen in the initial era of development of ToF repair. Corresponds closest to actual RVRP. Small RVs with abnormal diastolic filling following directly after primary repair of ToF and probably related to fibrosis, myocardial injury, and other perioperative factors. Preventing further progression of PR and limiting the extent of volume overload. Usually disappears days to months after the primary repair, but may be maintained into midterm follow-up in a subset of patients. Associated with repair at older age as seen in the initial era of development of ToF repair. Corresponds closest to actual RVRP. Dilated RVs at late follow-up after primary repair of ToF, or may occur as a late stage of phenotype 1. Pronounced volume overload attributable to longstanding PR, whereby filling of the RV becomes limited and RV pressure becomes larger than pulmonary artery pressure. Usually is maintained during long-term follow-up but may disappear after PVR. Associated with repair at younger age as seen in more contemporary management. Only a subset of patients might have actual RVRP. EDFF indicates end-diastolic forward flow; ICU, intensive care unit; PR, pulmonary regurgitation; PVR, pulmonary valve replacement; RV, right ventricular; RVRP, RV restrictive physiology; ToF, tetralogy of Fallot; and VO₂, oxygen consumption.
More research is required to further elucidate how EDFF and different hemodynamics relate to prognosis and anticipated clinical needs. Machine learning techniques could be harnessed to identify phenotypical clusters among patients with EDFF. In addition, the relevance of EDFF for risk stratification for common procedures in rToF, such as placement of implantable cardioverter-defibrillator and pulmonary valve replacement, should be investigated. As an example of the latter, Tominaga et al showed that EDFF may disappear after pulmonary valve replacement but signals worse prognosis when it persists. It might be important to interpret this in conjunction with RV size, as patients with smaller RVs (<170 mL/m²) have not consistently shown an effect of persistent EDFF on the risk of arrhythmias. Current surgical practices with more valve-sparing operations and fewer transannular patches for ToF are likely already influencing the context in which EDFF is observed, so research into the implications of EDFF may differ from the historical baselines established in this analysis.

Limitations and Sources of Heterogeneity

Our meta-analysis was limited to univariate analyses. Residual confounding by year of publication or enrollment, age at initial repair, timing of assessment or pulmonary valve replacement relative to initial repair, as well as anatomical and functional characteristics cannot be excluded. More important, patients from older cohorts underwent initial repair with different techniques and perioperative management compared with contemporary practice. Although subgroup analyses of all investigated factors comparing studies with large RVEDVi versus those with low RVEDVi might have corroborated our framework including the 2 phenotypes, these data were not consistently reported in a sufficient number of studies to perform such analyses. Meta-regression analyses were conducted instead, but these were likewise limited by modest power. Similarly, subgroup analyses based on the timing of initial repair and subsequent interventions could further enhance our understanding of EDFF and may be the subject of future clinical investigations. Furthermore, it should be considered that our analyses were not corrected for multiple testing given the exploratory nature of our study, such that our estimates might need to be validated in future studies. Finally, the technical limitations of echocardiography and CMR to identify EDFF might have affected our findings. In this regard, of the studies that primarily defined EDFF based on CMR ascertained their results based on Doppler echocardiography. Sani et al found a comparable prevalence of EDFF with both echocardiography (56.7%) and CMR (60.0%; P=0.792). In contrast, Lee et al found that CMR identified a higher prevalence.
of EDFF (64.4%) compared with Doppler echocardiography (44.4%; \( P=0.039 \)), with only 58.6% of the CMR cases being confirmed on Doppler echocardiography. Furthermore, they found that Doppler-based EDFF correlated less well with peak oxygen consumption percentage (\( r=0.381; \ P=0.026 \)) than did CMR-based EDFF (\( r=0.536; \ P=0.001 \)). Kutty et al\(^\text{37} \) found a modest correlation between both modalities (Fleiss’ \( \kappa=0.597 \)). The finding of our subgroup analysis that overall there was only a marginally higher EDFF prevalence with CMR compared with Doppler echocardiography (50.8% versus 45.7%; \( P=0.332 \)) is reassuring, although future investigations directly comparing both modalities will likely advance our understanding.

**CONCLUSIONS**

In this meta-analysis, EDFF occurred in 46.5% of patients with rToF and is associated with the use of a transannular patch, longer intensive care unit length of stay, greater RV indexed volumes and mass, smaller E-wave velocity at the tricuspid valve, and greater PR. EDFF is not specific of RVRP and has multiple alternative causes. Our review supports a specific reconciliation of the conflicting EDFF literature, based on the presence of 2 main phenotypes: (1) early-onset, “primary” EDFF and (2) late-onset, “secondary” EDFF. The latter has become more prevalent in contemporary practice, with improved peripartum neonatal and diastolic function but progressive dilatation resulting from longstanding PR. Future studies should refine the diagnostic criteria for RVRP and clarify the potential prognostic relevance of EDFF in various settings.

**ARTICLE INFORMATION**

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**REFERENCES**

1. van der Linde D, Konings EEM, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJM, Roos-Hesselink JW. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol. 2011;58:2241–2247. doi: 10.1016/j.jacc.2011.08.025
2. Apitz C, Webb GD, Redington AN. Tetralogy of Fallot. Lancet. 2009;374:1462–1471. doi: 10.1016/S0140-6736(09)60857-7
3. Carvalho JS, Shinebourne EA, Busst C, Rigby ML, Redington AN. Exercise capacity after complete repair of tetralogy of Fallot: deleterious effects of residual pulmonary regurgitation. Heart. 1992;67:470–473. doi: 10.1136/hrt.67.6.470
4. Dennis M, Moore B, Kotchetkova I, Pressley L, Cordina R, Celemajer DS. Adults with repaired tetralogy: low mortality but high morbidity up to middle age. Open Heart. 2017;4:e000564. doi: 10.1136/openh eart-2016-000564
5. Cullen S, Shore D, Redington A. Characterization of right ventricular diastolic performance after complete repair of tetralogy of Fallot. Circulation. 1995;91:1782–1789. doi: 10.1161/01.CIR.91.6.1782
6. Gatzozius MA, Clark AL, Cullen S, Newman CGH, Redington AN. Right ventricular diastolic function 15 to 35 years after repair of tetralogy of Fallot: restrictive physiology predicts superior exercise performance. Circulation. 1995;91:1775–1781. doi: 10.1161/01.CIR.91.6.1775
7. Norgård G, Gatzozius MA, Josen M, Cullen S, Redington AN. Does restrictive right ventricular physiology in the early postoperative period predict subsequent right ventricular restriction after repair of tetralogy of Fallot? Heart. 1998;79:481–484. doi: 10.1136/hrt.79.5.481
8. Eroglu AG, Sarigolua A, Sarigolub T. Right ventricular diastolic function after repair of tetralogy of Fallot: its relationship to the insertion of a “transannular” patch. Cardiol Young. 1999;9:384–391. doi: 10.1017/S1047951100005187
9. Gibbs JL, Wilson N, Witsenburg M, Williams GJ, Goldberg SJ. Diastolic forward blood flow in the pulmonary artery detected by doppler echocardiography. J Am Coll Cardiol. 1985;6:1322–1328. doi: 10.1016/S0735-1097(85)80220-5
10. Redington AN, Penny D, Rigby ML, Hayes A. Antegrade diastolic pulmonary arterial flow as a marker of right ventricular restriction after complete repair of pulmonary atresia with intact septum and critical pulmonary valvar stenosis. Cardiol Young. 1992;2:382–386. doi: 10.1017/S1047951100007988
11. Helbing WA, Niezen RA, Le Cessie S, van der Geest RJ, Ottenkamp J, de Roos A. Right ventricular diastolic function in children with pulmonary regurgitation after repair of tetralogy of Fallot: volumetric evaluation by magnetic resonance velocity mapping. J Am Coll Cardiol. 1996;28:1827–1835. doi: 10.1016/S0735-1097(96)00387-7
12. Lu JC, Cotts TB, Agarwal PW, Attili AK, Dorfman AL. Relation of right ventricular dilation, age of repair, and restrictive right ventricular physiology with patient-reported quality of life in adolescents and adults with repaired tetralogy of fallot. Am J Cardiol. 2010;106:1788–1802. doi: 10.1016/j.amjcard.2010.08.021
13. Samyn MM, Kwon EN, Gorenz JS, Yan K, Danduran MJ, Cava JR, Simpson PM, Frommeil PC, Tweddell JS. Restrictive versus non-restrictive physiology following repair of tetralogy of Fallot: is there a difference? J Am Soc Echocardiogr. 2013;26:746–755. doi: 10.1016/j.echo.2013.03.019
14. Van den Berg J, Wielopolski PA, Meijboom FJ, Witsenburg M, Bogers AJJC, Pattynama P, Helbing WA. Diastolic function in repaired tetralogy of fallot at rest and during stress: assessment with MR imaging. Radiology. 2007;243:212–219. doi: 10.1148/radiol.2431060213
SUPPLEMENTAL MATERIAL
Supplemental Methods

Search strategy.

PubMed (n=200 on March 8, 2021)

("Tetralogy of Fallot"[Mesh] OR fallot* tetralogy OR tetralogy of fallot) AND (restrictive OR end-diastolic forward flow OR end diastolic forward flow OR antegrade diastolic pulmonary flow OR antegrade diastolic pulmonary artery flow OR antegrade diastolic flow) in all fields

Embase (n=210 on March 8, 2021)

('fallot tetralogy'/exp OR 'fallot* tetralogy' OR 'tetralogy of fallot') AND ('restrictive' OR 'end-diastolic forward flow' OR 'end diastolic forward flow' OR 'antegrade diastolic pulmonary flow' OR 'antegrade diastolic pulmonary artery flow' OR 'antegrade diastolic flow') in all fields

Scopus (n=142 on March 8, 2021)

( TITLE-ABS-KEY ("fallot's tetralogy" OR "fallot* tetralogy" OR "tetralogy of fallot") AND TITLE-ABS-KEY ("restrictive" OR "end-diastolic forward flow" OR "end diastolic forward flow" OR "antegrade diastolic pulmonary flow" OR "antegrade diastolic pulmonary artery flow" OR "antegrade diastolic flow") )
Supplemental Results

Subgroup analyses

Subgroup analysis revealed that significantly different results were observed by prospective and retrospective studies for the following variables: right ventricular mass indexed (RVMi), right ventricular end-diastolic pressure (RVEDP), left ventricular stroke volume indexed (LVSVi), and left ventricular ejection fraction (LVEF). Prospective studies reported a significantly greater RVMi in end-diastolic forward flow (EDFF) (mean difference [MD] 3.81 g/m², 95% 1.42-6.21, 6 studies), whereas a retrospective study reported lower RVMi (MD -0.70 g/m², 95% CI -1.21;-0.18, 1 study) (p<0.001). Furthermore, retrospective studies reported higher RVEDP in patients with EDFF (MD 1.78, 95% CI 0.93-2.63, 3 studies), as well as lower LVSVi (MD -2.03, 95% CI -2.48;-1.57, 1 study) and higher LVEF (MD 0.95%, 95% 0.60-1.30, 6 studies). In contrast, prospective studies found no significant differences in either RVEDP (MD 0.00 mmHg, 95% CI -0.75-0.75, 1 study), LVSVi (MD -0.25 ml/m², 95% CI -1.13-0.63, 1 study), or LVEF (MD -1.08%, 95% CI -2.37-0.21, 3 studies) (test for subgroup differences: all p<0.001). Lastly, the association between transannular patch repair and EDFF found by prospective studies (odds ratio [OR] 2.46, 95% 1.47-4.13, 14 studies) was greater than that found by retrospective studies (OR 1.38, 95% CI 0.51-3.73, 7 studies) (test for subgroup differences: p=0.001). No other significant interaction effects were observed.

Meta-regression analyses

Meta-regression analysis revealed that in more recent samples (higher mean year of enrollment) reported a larger MD for right ventricular end-diastolic volume indexed (RVEDVi) (regression coefficient 1.762, 95% CI 0.395-3.129, p=0.018, 10 studies) and aortic cross-clamp time (regression coefficient 0.844, 95% CI 0.138-1.550, p=0.029, 6 studies) in EDFF compared to no EDFF. Furthermore, larger MD for RVEDVi were associated with larger MD for right
ventricular stroke volume indexed (RVSVi) (regression coefficient 0.465, 95% CI 0.144-0.786, p=0.016, 6 studies) and pulmonary regurgitation fraction (regression coefficient 0.214, 95% CI 0.003-0.424, p=0.048, 8 studies). Lastly, it was found that older age at evaluation was associated with smaller MD for RVSVi (regression coefficient -1.142, 95% CI -1.610;-0.674, p=0.003, 6 studies) and greater MD for N-terminal pro-brain natriuretic peptide (NT-proBNP) (regression coefficient 15.324, 95% CI 0.797-29.850, p=0.047, 3 studies). No other significant associations were found.
Figure S1. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; SD, standard deviation.

A. Age at repair (years)

| Study               | EDFD | No EDFD | Mean Difference | Weight (fixed) | Weight (random) |
|---------------------|------|---------|-----------------|----------------|-----------------|
| Ahmad 2012          | 58   | 1.00    | 0.50            | 0.83           | 1.38            |
| Bonello 2013        | 38   | 5.00    | 1.00            | 6.00           | 4.00            |
| Chio 2008           | 15   | 1.00    | 0.30            | 2.63           | 3.15            |
| Heitberg 1996       | 13   | 4.00    | 0.67            | 6.18           | 0.83            |
| Kordbach-Prokop 2012| 16   | 10.00   | 10.00           | 11.70          | 12.60           |
| Kuty 2018           | 122  | 0.56    | 0.29            | 1.32           | 0.58            |
| Lee 2013            | 33   | 2.00    | 0.10            | 1.30           | 0.10            |
| Mercier-Rosa 2018   | 77   | 0.50    | 0.07            | 0.35           | 0.10            |
| Markham 1998        | 13   | 0.77    | 0.15            | 4.64           | 0.26            |
| Norgard 1996        | 36   | 11.02   | 6.82            | 11.85          | 7.10            |
| Norgard 1998 (early restriction) | 10 | 1.07    | 6.75            | 1.20           | 0.33            |
| Norgard 1998 (late restriction) | 10 | 10.03  | 6.75            | 2.19           | 1.57            |
| Saphir 2013         | 12   | 1.31    | 0.53            | 1.51           | 0.67            |
| Tommasi 2007        | 23   | 3.98    | 0.09            | 2.01           | 0.38            |
| van den Berg 2007   | 24   | 1.00    | 0.50            | 1.30           | 0.50            |
| Xu 2004             | 30   | 1.48    | 1.70            | 0.50           | 0.78            |

Fixed-effects: 536 802  
Random-effects: Heterogeneity: $I^2 = 95\%, p < 0.001$  
Test for overall effect (fixed effect): $z = -2.60$ ($p = 0.004$)  
Test for overall effect (random effects): $I^2 = 94\%$ ($p = 0.363$)

B. Time of follow-up since repair (years)

| Study               | EDFD | No EDFD | Mean Difference | Weight (fixed) | Weight (random) |
|---------------------|------|---------|-----------------|----------------|-----------------|
| Gatouzos 1996       | 36   | 0.00    | 5.00            | 4.20           | 2.86            |
| Heitberg 1996       | 13   | 0.00    | 10.33           | 6.07           | 2.67            |
| Kordbach-Prokop 2012| 16   | 0.00    | 20.90           | 67.21          | 7.10            |
| Kuty 2018           | 122  | 0.00    | 17.36           | 23.18          | 18.82           |
| Mar 2017            | 13   | 0.00    | 11.60           | 23.39          | 7.44            |
| Norgard 1998 (early restriction) | 16 | 1.00    | 18.80           | 18.90          | 0.47            |
| Norgard 1998 (late restriction) | 10 | 2.00    | 1.00            | 2.00           | 1.00            |
| Samyn 2013          | 12   | 0.00    | 12.14           | 3.00           | 1.00            |
| van den Berg 2007   | 24   | 0.00    | 16.00           | 2.00           | 12.25           |

Fixed-effects: 272 514  
Random-effects: Heterogeneity: $I^2 = 93\%, p < 0.001$  
Test for overall effect (fixed effect): $z = -1.30$ ($p = 0.194$)  
Test for overall effect (random effects): $I^2 = 75\%$ ($p = 0.472$)

C. Age at study (years)

| Study               | EDFD | No EDFD | Mean Difference | Weight (fixed) | Weight (random) |
|---------------------|------|---------|-----------------|----------------|-----------------|
| Abursou 2014        | 9    | 11.00   | 2.60            | 11.00          | 0.90            |
| Ahmad 2012          | 38   | 13.60   | 3.20            | 54.12          | 3.10            |
| Bonello 2013        | 38   | 37.77   | 3.14            | 11.30          | 0.25            |
| Chio 2008           | 15   | 5.44    | 2.15            | 28.48          | 1.04            |
| Colen 1995          | 17   | 1.96    | 2.42            | 18.10          | 1.77            |
| Gatouzos 1995       | 17   | 28.30   | 6.60            | 12.60          | 5.50            |
| Gatouzos 1996       | 36   | 15.03   | 7.12            | 56.143         | 7.22            |
| Heitberg 1996       | 13   | 11.88   | 2.83            | 6.11.50        | 3.92            |
| Kordbach-Prokop 2012| 16   | 30.30   | 9.00            | 67.310         | 12.00           |
| Kuty 2018           | 22   | 19.52   | 2.75            | 277.21         | 2.65            |
| Lee 2013            | 33   | 12.50   | 2.90            | 17.13          | 2.40            |
| Menage-Rosa 2013    | 77   | 12.89   | 3.20            | 11.11          | 2.90            |
| Mon 2017            | 23   | 16.33   | 9.64            | 39.1563        | 11.73           |
| Munkhammer 1996     | 13   | 5.00    | 3.60            | 34.30          | 2.70            |
| Rathorn 2006        | 52   | 7.60    | 2.40            | 28.10          | 2.50            |
| Sachoer 2006        | 24   | 4.40    | 2.30            | 26.55          | 3.10            |
| Schröder 2015       | 13   | 10.25   | 4.00            | 17.03          | 2.67            |
| Sander 2019         | 28   | 2.56    | 2.38            | 22.167         | 0.89            |
| Sani 2020           | 18   | 20.40   | 9.10            | 12.280         | 1.90            |
| Shekendi 2015       | 8    | 3.25    | 3.02            | 15.20          | 1.62            |
| Tommasi 2021        | 23   | 35.00   | 10.00           | 23.380         | 14.30           |
| van den Berg 2007   | 24   | 17.25   | 2.17            | 12.140         | 2.67            |
| Xu 2014             | 30   | 1.48    | 1.71            | 15.078         | 0.69            |

Fixed-effects: 710 917  
Random-effects: Heterogeneity: $I^2 = 93\%, p < 0.001$  
Test for overall effect (fixed effect): $z = 2.26$ ($p = 0.024$)  
Test for overall effect (random effects): $I^2 = 8.17\%$ ($p = 0.047$)
Figure S2. Forest plots. BT, Blalock-Taussig; CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; OR, odds ratio; RVPA, right ventricle-pulmonary artery; SD, standard deviation.

### A. Previous RVPA shunt

| Study       | EDFF Events | EDFF Total | No EDFF Events | No EDFF Total | Odds Ratio | OR (95% CI) | Weight (fixed) | Weight (random) |
|-------------|-------------|------------|----------------|---------------|------------|-------------|----------------|-----------------|
| Ahmad 2012  | 1           | 58         | 2              | 54            | 0.10       | [0.01; 0.84] | 15.8%          | 6.5%            |
| Kutty 2018  | 18          | 122        | 27             | 127           | 0.39       | [0.22; 0.69] | 81.2%          | 88.8%           |
| Samyn 2013  | 1           | 12         | 1              | 17            | 0.68       | [0.06; 8.56] | 3.0%           | 4.6%            |

**Fixed-effects:** 192

**Random-effects:** 298

**Fixed-effects:** 0.35 [0.21; 0.60] 100.0% --

**Random-effects:** 0.36 [0.12; 1.09] -- 100.0%

Test for overall effect (fixed effects): $z = -3.83$ (p = 0.001)

Test for overall effect (random effects): $t_2 = -3.96$ (p = 0.058)

### B. Previous BT shunt

| Study       | EDFF Events | EDFF Total | No EDFF Events | No EDFF Total | Odds Ratio | OR (95% CI) | Weight (fixed) | Weight (random) |
|-------------|-------------|------------|----------------|---------------|------------|-------------|----------------|-----------------|
| Cullen 1995 | 1           | 17         | 1              | 18            | 1.06       | [0.06; 18.45] | 2.6%           | 2.9%            |
| Helbing 1996 | 4           | 13         | 1              | 16            | 2.22       | [0.19; 25.72] | 2.7%           | 4.0%            |
| Gatzoulis 1995 | 2       | 20         | 2              | 22            | 0.89       | [0.11; 7.06]  | 5.3%           | 5.6%            |
| Munkhammar 1998 | 4 | 13         | 3              | 16            | 0.69       | [0.16; 2.93]  | 12.6%          | 11.5%           |
| Norgard 1996 | 14          | 36         | 30             | 56            | 0.55       | [0.24; 1.29]  | 40.3%          | 33.1%           |
| Norgard 1998 (early restriction) | 6 | 16 | 6              | 18            | 1.20       | [0.29; 4.91]  | 9.9%           | 12.1%           |
| Rathore 2006 | 2           | 52         | 1              | 28            | 1.08       | [0.09; 12.46] | 3.5%           | 4.0%            |
| Samyn 2013   | 6           | 12         | 6              | 17            | 1.83       | [0.41; 8.27]  | 7.0%           | 10.6%           |
| Shekhereman 1999 | 1 | 8         | 3              | 15            | 0.57       | [0.05; 6.61]  | 5.1%           | 4.0%            |
| Tominaga 2021 | 5          | 23         | 5              | 23            | 1.00       | [0.25; 4.08]  | 11.0%          | 12.2%           |

**Fixed-effects:** 210

**Random-effects:** 222

**Fixed-effects:** 0.87 [0.54; 1.40] 100.0% --

**Random-effects:** 0.86 [0.62; 1.20] -- 100.0%

Test for overall effect (fixed effect): $z = -0.58$ (p = 0.562)

Test for overall effect (random effects): $t_2 = 0.99$ (p = 0.347)

### C. Aortic cross-clamp time (min)

| Study       | EDFF Mean | EDFF SD | No EDFF Mean | No EDFF SD | Mean Difference | MD (95% CI) | Weight (fixed) | Weight (random) |
|-------------|-----------|---------|--------------|-----------|----------------|-------------|----------------|-----------------|
| Cullen 1995 | 66.00     | 30.00   | 58.00        | 13.80     | 8.00 [7.62; 23.62] | 3.5%        | 10.0%          |                 |
| Helbing 1996 | 13        | 58.00   | 60.00        | 15.00     | 4.00 [10.82; 18.82] | 3.9%        | 10.0%          |                 |
| Norgard 1996 | 53.50     | 19.70   | 56.50        | 20.60     | -3.70 [12.10; 47.70] | 12.0%       | 15.4%          |                 |
| Rathore 2006 | 52        | 70.00   | 12.10        | 7.70      | 4.30 [1.05; 8.63]  | 44.7%       | 18.3%          |                 |
| Sandeep 2019 | 28        | 102.69  | 17.14        | 22        | 26.49 [17.93; 35.05] | 11.5%       | 15.3%          |                 |
| Xu 2014      | 30        | 51.00   | 19.00        | 50        | 9.00 [17.60; 24.24] | 16.1%       | 10.3%          |                 |

**Fixed-effects:** 200

**Random-effects:** 206

**Fixed-effects:** 6.91 [4.00; 9.82] 100.0% --

**Random-effects:** 7.79 [-1.06; 16.82] -- 100.0%

Test for overall effect (fixed effect): $z = 4.66$ (p < 0.001)

Test for overall effect (random effects): $t_2 = 2.16$ (p = 0.075)
Figure S3. Forest plots. CI, confidence interval; CPB, cardiopulmonary bypass; EDFF, end-diastolic forward flow; MD, mean difference; OR, odds ratio; SD, standard deviation.

A. CPB time (min)

| Study          | EDFF Total | Mean (SD) | EDFF Mean (SD) | No EDFF Total | Mean (SD) | No EDFF Mean (SD) | Mean Difference | MD (95%-CI) | Weight (fixed) | Weight (random) |
|----------------|------------|-----------|----------------|---------------|-----------|-------------------|----------------|-------------|----------------|----------------|
| Chaturvedi 1999 | 4          | 77.20 (18.40) | 710.00 (39.70) | -32.80        | [67.30; 1.70] | 1.9%              | 10.9%           |            |                |                |
| Cullen 1996    | 17         | 104.60 (32.00) | 92.00 (19.80)  | -12.00        | [4.75; 29.75] | 7.2%              | 13.8%           |            |                |                |
| Norgard 1996   | 36         | 82.30 (33.00)  | 58 (9.09)       | -8.60         | [10.58; 2.93] | 18.8%             | 15.8%           |            |                |                |
| Rathore 2006   | 52         | 106.60 (17.20) | 82 (4.20)       | -8.60         | [16.58; 23.88] | 23.7%             | 16.1%           |            |                |                |
| Sachdev 2006   | 24         | 124.30 (34.24) | 20 (11.89)      | -11.40        | [3.77; 28.75] | 7.0%              | 14.0%           |            |                |                |
| Sandeep 2019   | 28         | 131.00 (20.70) | 22 (10.20)      | -30.80        | [21.62; 39.08] | 26.9%             | 16.2%           |            |                |                |
| Xu 2014        | 30         | 90.00 (33.00)  | 50 (7.00)       | 20.00         | [7.18; 32.82]  | 13.8%             | 15.3%           |            |                |                |

Fixed-effects 191 207
Random-effects

Test for overall effect (fixed effect): z = 3.68 (p = 0.001)
Test for overall effect (random effects): t = 8.00 (p = 0.454)

B. Transatrical repair

| Study         | EDFF Events Total | Events Total | No EDFF Events Total | Odds Ratio | OR (95%-CI) | Weight (fixed) | Weight (random) |
|---------------|--------------------|--------------|----------------------|------------|-------------|----------------|----------------|
| Aburawi 2014  | 9                  | 9            | 11                   | 11         | 0.09        | [0.00; 1.74]   | 0.0%           |                |
| Choi 2008     | 0                  | 15           | 7                    | 28         | 0.09        | [0.00; 1.74]   | 0.0%           |                |
| Cullen 1995   | 2                  | 17           | 1                    | 18         | 2.27        | [0.19; 27.58]  | 5.2%           |                |
| Munkhammar 1998 | 3                | 13           | 16                   | 34         | 0.34        | [0.08; 1.45]   | 41.5%          |                |
| Gatzioulis 1995 | 3             | 20           | 4                    | 18         | 0.62        | [0.12; 3.23]   | 21.8%          |                |

Fixed-effects 74 109
Random-effects

Test for overall effect (fixed effect): z = 1.93 (p = 0.05) 1.01
Test for overall effect (random effects): t = 1.53 (p = 0.223)

C. Transannular patch repair

| Study          | EDFF Events Total | Events Total | No EDFF Events Total | Odds Ratio | OR (95%-CI) | Weight (fixed) | Weight (random) |
|----------------|--------------------|--------------|----------------------|------------|-------------|----------------|----------------|
| Aburawi 2014   | 5                  | 9            | 2                    | 11         | 5.62        | [0.75; 42.36]  | 0.7%           |                |
| Ahmad 2012     | 36                 | 58           | 26                   | 54         | 1.76        | [0.83; 3.74]   | 8.7%           |                |
| Bonello 2013   | 23                 | 38           | 62                   | 110        | 1.19        | [0.56; 2.52]   | 10.7%          |                |
| Chaturvedi 1999 | 1                | 4            | 7                    | 12         | 0.83        | [0.05; 13.63]  | 0.9%           |                |
| Choi 2008      | 13                 | 15           | 9                    | 28         | 13.72       | [2.54; 74.13]  | 0.7%           |                |
| Cullen 1995    | 8                  | 17           | 5                    | 18         | 2.31        | [0.57; 9.41]   | 2.2%           |                |
| Gatzioulis 1995 | 1             | 20           | 0                    | 18         | 2.85        | [0.11; 74.38]  | 0.4%           |                |
| Hebing 1996    | 9                  | 13           | 1                    | 6          | 11.25       | [0.97; 130.22] | 0.4%           |                |
| Kordybach-Prokopik 2018 | 6 | 10 | 27 | 67 | 0.89 | [0.09; 2.73] | 5.6% | 5.9% |                |
| Kutty 2018     | 75                 | 122          | 147                  | 227        | 0.87        | [0.55; 1.37]   | 33.8%          |                |
| Lee 2013       | 25                 | 33           | 12                   | 17         | 1.30        | [0.35; 4.84]   | 3.3%           |                |
| Mercier-Rosa 2018 | 77            | 77           | 11                   | 11         | 0.50        | [0.21; 1.20]   | 0.0%           |                |
| Norgard 1996   | 20                 | 36           | 40                   | 56         | 8.75        | [1.52; 50.31]  | 0.8%           |                |
| Norgard 1998 (early restriction) | 14 | 16 | 8 | 18 | 1.07 | [0.40; 2.86] | 6.5% | 6.5% |                |
| Rathore 2006   | 36                 | 52           | 19                   | 28         | 1.07        | [0.40; 2.86]   | 6.5%           |                |
| Sachdev 2006   | 14                 | 24           | 5                    | 26         | 5.88        | [1.65; 20.91]  | 1.7%           |                |
| Sandeep 2019   | 22                 | 29           | 6                    | 22         | 9.78        | [2.06; 35.96]  | 1.2%           |                |
| Samn 2013      | 4                  | 12           | 4                    | 17         | 1.62        | [0.31; 8.39]   | 1.9%           |                |
| Shekerdemian 1999 | 4            | 8            | 4                    | 15         | 2.75        | [0.46; 16.59]  | 1.2%           |                |
| Torniai 2021   | 8                  | 23           | 9                    | 23         | 0.63        | [0.25; 2.75]   | 5.0%           |                |
| van den Berg 2007 | 17      | 24           | 6                    | 12         | 2.43        | [0.58; 10.18]  | 2.0%           |                |
| Xu 2014        | 30                 | 30           | 42                   | 50         | 12.20       | [0.68; 219.48] | 0.4%           |                |

Fixed-effects 675 841
Random-effects

Heterogeneity: $I^2 = 56\%$, $p < 0.001$
Test for overall effect (fixed effect): $z = 3.07$ ($p < 0.001$)
Test for overall effect (random effects): $t = 3.17$ ($p = 0.005$)
Figure S4. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; ICU, intensive care unit; MD, mean difference; OR, odds ratio; SD, standard deviation.

A. Outflow patch repair

| Study                  | EDFF Events | No EDFF Events | Odds Ratio | OR   | 95%-CI      | Weight (fixed) | Weight (random) |
|------------------------|-------------|----------------|------------|------|-------------|----------------|-----------------|
| Choi 2008              | 2           | 15             |            | 0.21 | [0.04; 1.09]| 34.9%          | 27.2%           |
| Cullen 1995            | 2           | 17             |            | 0.67 | [0.10; 4.58]| 12.4%          | 20.4%           |
| Gatzoulis 1995         | 3           | 20             |            | 0.62 | [0.12; 3.23]| 17.2%          | 27.0%           |
| Norgard 1998 (early restriction) | 2       | 16             |            | 0.14 | [0.02; 0.82]| 35.6%          | 24.8%           |

Fixed-effects 68 82
Random-effects 0.31 [0.13; 0.72] 100.0% --

Heterogeneity: $I^2 = 0\%$, $p = 0.520$
Test for overall effect (fixed effect): $z = -2.72$ ($p = 0.006$)
Test for overall effect (random effects): $t_3 = -2.94$ ($p = 0.061$)

B. ICU Length of stay (days)

| Study          | EDFF Total Mean | SD Total Mean | No EDFF Total Mean | SD No EDFF Mean | Mean Difference | MD 95%-CI      | Weight (fixed) | Weight (random) |
|----------------|-----------------|---------------|--------------------|-----------------|----------------|-------------|----------------|-----------------|
| Chaturvedi 1999| 4 10.70 3.10    | 7 3.00 0.63   |                    |                 | 7.70 [4.63; 10.77] | 3.2%          | 13.2%          |
| Sachdev 2006   | 24 5.10 3.70    | 26 2.80 2.00  |                    |                 | 2.30 [0.63; 3.97] | 10.7%         | 24.1%          |
| Sandeep 2019   | 28 8.92 1.24    | 22 4.15 1.18  |                    |                 | 4.77 [4.10; 5.44] | 65.7%         | 33.9%          |
| Xu 2014        | 30 7.00 3.00    | 50 3.00 2.00  |                    |                 | 4.00 [2.79; 5.21] | 20.4%         | 28.6%          |

Fixed-effects 86 105
Random-effects 4.44 [3.88; 4.99] 100.0% --

Heterogeneity: $I^2 = 75\%$, $p = 0.007$
Test for overall effect (fixed effect): $z = 15.94$ ($p < 0.001$)
Test for overall effect (random effects): $t_3 = 4.67$ ($p = 0.019$)
Figure S5. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; RVEDVi, right ventricular end-diastolic volume indexed; RVESVi, right ventricular end-systolic volume indexed; RVSVi, right ventricular stroke volume indexed; SD, standard deviation.

A. RVEDVi (mL/m²)

| Study         | Total Mean | Total SD | Total Mean | Total SD | Mean Difference | MD       | 95% CI       | Weight (fixed) | Weight (random) |
|---------------|------------|----------|------------|----------|----------------|----------|--------------|----------------|-----------------|
| Aburaw et al. | 9          | 158.00   | 40.00      | 11       | 99.00          | 22.00    | -59.00       | 0.3%           | 4.0%            |
| Apic et al.   | 8          | 125.00   | 13.10      | 17       | 134.00         | 6.70     | -6.00        | 2.4%           | 3.8%            |
| Bonelli et al.| 36         | 125.50   | 6.50       | 110      | 126.00         | 8.30     | -0.50        | 3.0%           | 20.8%           |
| Ergol et al.  | 25         | 62.00    | 29.62      | 19       | 81.12          | 26.75    | -18.50       | 0.8%           | 6.8%            |
| Hebing et al. | 13         | 129.00   | 40.00      | 8         | 106.00         | 59.10    | 23.00        | 3.4%           | 18.5%           |
| Kordybach et al. | 16  | 158.00   | 45.10      | 67       | 143.20         | 40.10    | 15.60        | 4.0%           | 5.0%            |
| Kutty et al.  | 122        | 142.30   | 10.50      | 277      | 131.20         | 7.60     | 11.10        | 4.9%           | 10.2%           |
| Lee et al.    | 31         | 165.00   | 51.00      | 37       | 154.00         | 37.00    | 11.00        | 4.6%           | 5.8%            |
| Lujenburger et al.| 31  | 151.00   | 33.00      | 20       | 120.00         | 27.00    | 31.00        | 4.5%           | 6.8%            |
| Mercer et al. | 77         | 128.25   | 7.50       | 11       | 98.00          | 8.70     | 30.25        | 7.7%           | 9.8%            |
| Mon et al.    | 23         | 121.00   | 43.00      | 39       | 117.00         | 52.00    | 4.00         | 4.0%           | 5.0%            |
| Munkhammar et al.| 16  | 159.00   | 49.00      | 15       | 111.00         | 29.00    | 48.00        | 1.4%           | 2.6%            |
| Santer et al. | 12         | 120.00   | 14.00      | 19       | 108.00         | 19.50    | 16.00        | 1.5%           | 1.8%            |
| Sani et al.   | 18         | 191.50   | 91.30      | 12       | 154.40         | 37.00    | 37.10        | 2.3%           | 3.1%            |
| Tominaga et al.| 23        | 165.17   | 31.30      | 23       | 156.00         | 44.00    | 9.17         | 0.5%           | 0.5%            |
| van den Berg et al.| 24  | 145.00   | 41.00      | 12       | 124.00         | 37.00    | 21.00        | 0.3%           | 0.5%            |

B. RVESVi (mL/m²)

| Study         | Total Mean | Total SD | Total Mean | Total SD | Mean Difference | MD       | 95% CI       | Weight (fixed) | Weight (random) |
|---------------|------------|----------|------------|----------|----------------|----------|--------------|----------------|-----------------|
| Aburaw et al. | 9          | 62.00    | 31.00      | 11       | 44.00          | 12.00    | 30.00        | 0.2%           | 0.2%            |
| Bonelli et al.| 38         | 53.55    | 8.83       | 110      | 58.25          | 5.17     | -4.70        | 12.1%          | 14.0%           |
| Kordybach et al.| 16  | 68.00    | 27.80      | 97       | 77.90          | 27.90    | -10.10       | 0.5%           | 0.7%            |
| Kutty et al.  | 122        | 68.00    | 6.27       | 237      | 67.35          | 5.65     | 1.65         | 0.5%           | 1.3%            |
| Lee et al.    | 33         | 86.00    | 24.90      | 17       | 94.60          | 55.80    | -8.30        | 0.1%           | 0.5%            |
| Lujenburger et al.| 31  | 79.00    | 22.00      | 20       | 63.00          | 19.00    | 16.00        | 0.8%           | 1.0%            |
| Mercer et al. | 77         | 50.50    | 4.67       | 11       | 38.50          | 3.00     | 12.00        | 25.2%          | 32.4%           |
| Munkhammar et al.| 16  | 83.00    | 34.00      | 15       | 52.00          | 18.00    | 31.10        | 0.3%           | 0.7%            |
| Sani et al.   | 18         | 180.00   | 50.00      | 12       | 99.20          | 31.90    | 21.60        | 0.1%           | 0.2%            |
| Tominaga et al.| 23        | 181.00   | 22.47      | 23       | 180.00         | 28.00    | 15.83        | 0.5%           | 0.9%            |
| van den Berg et al.| 24  | 150.00   | 25.50      | 12       | 127.00         | 26.83    | 79.00        | 0.3%           | 0.7%            |

C. RVSVi (mL/m²)

| Study         | Total Mean | Total SD | Total Mean | Total SD | Mean Difference | MD       | 95% CI       | Weight (fixed) | Weight (random) |
|---------------|------------|----------|------------|----------|----------------|----------|--------------|----------------|-----------------|
| Bonelli et al.| 38         | 60.75    | 3.83       | 110      | 65.75          | 3.17     | -5.00        | 36.4%          | 19.2%           |
| Kutty et al.  | 122        | 72.75    | 5.17       | 227      | 63.45          | 3.93     | 9.30         | 60.0%          | 19.2%           |
| Lujenburger et al.| 31  | 72.00    | 14.00      | 20       | 57.00          | 12.00    | 15.00        | 1.3%           | 1.7%            |
| Mercer et al. | 77         | 77.00    | 46.00      | 11       | 61.00          | 17.00    | 16.00        | 0.6%           | 0.6%            |
| Munkhammar et al.| 16  | 160.00   | 19.00      | 15       | 59.00          | 13.00    | 17.00        | 0.5%           | 0.5%            |
| van den Berg et al.| 24  | 69.00    | 14.00      | 12       | 60.00          | 14.00    | 9.00         | 0.7%           | 1.5%            |

Fixed-effects 

Random-effects
Figure S6. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; RVEDP, right ventricular end-diastolic pressure; RVEF, right ventricular ejection fraction; RVESP, right ventricular end-systolic pressure; RVMi, right ventricular mass indexed; SD, standard deviation.

A. RVMi (g/m²)

B. RVEF (%)

C. RVEDP (mmHg)

D. RVESP (mmHg)
**Figure S7. Forest plots.** CI, confidence interval; EDFF, end-diastolic forward flow; LVEDVi, left ventricular end-diastolic volume indexed; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume indexed; LVSVi, left ventricular stroke volume indexed; MD, mean difference; SD, standard deviation.

A. **LVEDVi (mL/m²)**

B. **LVESVi (mL/m²)**

C. **LVSVi (mL/m²)**

D. **LVEF (%)**
Figure S8. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; RAAi, right atrial area indexed; RAVi, right atrial volume indexed; SD, standard deviation.

A. RAAi (cm²/m²)

| Study     | EDFF Total Mean | EDFF SD | No EDFF Total Mean | No EDFF SD | Mean Difference | MD   | 95%-CI       | Weight (fixed) | Weight (random) |
|-----------|-----------------|---------|--------------------|------------|----------------|------|-------------|----------------|-----------------|
| Ahmad 2012| 58 10.60 3.40   | 54      | 8.90 1.90         |            |                | 1.70 | [0.69; 2.71]| 2.4%           | 40.2%           |
| Kutty 2018| 122 13.50 1.00  | 227     | 12.95 0.77        |            |                | 0.55 | [0.39; 0.71]| 97.6%          | 59.8%           |

Fixed-effects: 180
Random-effects: 281
Mean Difference: 0.58 [0.42; 0.74] 100.0%

Heterogeneity: $I^2 = 79\%$, $p = 0.028$
Test for overall effect (fixed effect): $z = 7.19$ ($p < 0.001$)
Test for overall effect (random effects): $t_1 = 1.80$ ($p = 0.824$)

B. RAVi (mL/m²)

| Study     | EDFF Total Mean | EDFF SD | No EDFF Total Mean | No EDFF SD | Mean Difference | MD   | 95%-CI       | Weight (fixed) | Weight (random) |
|-----------|-----------------|---------|--------------------|------------|----------------|------|-------------|----------------|-----------------|
| Kutty 2018| 122 42.42 1.92  | 227     | 42.08 3.65        |            |                | 0.35 | [-0.23; 0.93]| 98.5%          | 45.6%           |
| Lujinburg 2013 | 31 58.00 10.00 | 20      | 52.00 5.00        |            |                | 0.00 | [0.71; 11.20]| 1.2%           | 34.9%           |
| Tominaga 2021| 23 83.52 18.30 | 23      | 70.00 20.00       |            |                | 13.52| [2.44; 24.60]| 0.3%           | 19.3%           |

Fixed-effects: 176
Random-effects: 270
Mean Difference: 0.45 [-0.13: 1.03] 100.0%

Heterogeneity: $I^2 = 79\%$, $p = 0.008$
Test for overall effect (fixed effect): $z = 1.53$ ($p = 0.125$)
Test for overall effect (random effects): $t_2 = 1.40$ ($p = 0.297$)
Figure S9. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; SD, standard deviation.

A. E wave velocity at the tricuspid valve (cm/sec)

| Study       | Total | EDFF Mean | EDFF SD | No EDFF Mean | No EDFF SD | Mean Difference | MD       | 95%-CI           | Weight (fixed) | Weight (random) |
|-------------|-------|-----------|---------|--------------|------------|----------------|----------|-----------------|----------------|-----------------|
| Ahn 2012    | 58    | 76.00     | 19.00   | 54           | 76.00      | 12.00          | 0.00     | [-5.84; 5.64]   | 26.1%          | 12.3%           |
| Cardoso 2003| 19    | 72.20     | 15.25   | 11           | 72.35      | 20.30          | 0.15     | [13.97; 13.67]  | 4.7%           | 9.1%            |
| Cullen 1995 | 15    | 49.05     | 17.60   | 9            | 83.75      | 23.00          | -4.20    | [-61.72; -23.68] | 2.5%           | 7.1%            |
| Gatzoulis 1995| 15   | 45.05     | 15.10   | 17           | 57.65      | 53.60          | -12.00   | [38.12; 14.12]  | 1.3%           | 5.0%            |
| Heiberg 1995| 13    | 60.00     | 14.00   | 6            | 65.00      | 9.00           | -5.00    | [17.25; 7.25]   | 5.9%           | 9.7%            |
| Hurth 1998  | 12    | 60.00     | 13.00   | 13           | 60.00      | 13.00          | 0.00     | [-8.31; 8.31]   | 12.9%          | 11.4%           |
| Norgard 1998 (late restriction) | 10   | 70.00     | 16.00   | 22           | 80.00      | 20.00          | -10.00   | [22.97; 29.77]  | 3.3%           | 9.4%            |
| Norgard 1998 (late restriction) | 10   | 70.00     | 16.00   | 22           | 80.00      | 20.00          | -10.00   | [22.97; 29.77]  | 3.3%           | 9.4%            |
| Rathiore 2006| 52   | 70.50     | 7.50    | 28           | 88.00      | 14.00          | -17.50   | [23.07; -11.93] | 28.7%          | 12.3%           |
| Sachdev 2006 | 24   | 70.98    | 19.90   | 26           | 90.90      | 23.40          | -25.92   | [37.93; 13.91]  | 6.2%           | 9.8%            |
| Same 2013   | 12    | 65.70     | 16.90   | 17           | 68.80      | 17.30          | -3.10    | [-15.71; 9.51]  | 5.6%           | 9.6%            |
| Volkanovic 2006 | 18   | 207.61  | 51.45   | 42           | 243.38     | 61.95          | -35.57   | [65.83; -5.31]  | 1.0%           | 4.1%            |

Fixed-effects: 248
Random-effects: 266
Heterogeneity: $I^2 = 79\%$, $p = 0.001$
Test for overall effect (fixed effect): $z = -8.04$ ($p = 0.001$)
Test for overall effect (random effects): $t_2 = -2.79$ ($p = 0.019$)

B. E wave duration at the tricuspid valve (msec)

| Study       | Total | EDFF Mean | EDFF SD | No EDFF Mean | No EDFF SD | Mean Difference | MD       | 95%-CI           | Weight (fixed) | Weight (random) |
|-------------|-------|-----------|---------|--------------|------------|----------------|----------|-----------------|----------------|-----------------|
| Cullen 1995| 9     | 134.95    | 44.80   | 9            | 143.50     | 32.25          | -8.55    | [44.61; 27.51]  | 2.4%           | 16.2%           |
| Gatzoulis 1995| 9    | 207.65   | 57.75   | 17           | 238.15     | 62.45          | -30.50   | [49.51; 8.51]   | 2.1%           | 14.8%           |
| Rathiore 2006| 52   | 183.80   | 17.08   | 28           | 178.00     | 17.67          | -16.60   | [2.78; 19.93]   | 49.3%          | 34.6%           |
| Volkanovic 2006 | 18 | 68.17     | 13.74   | 42           | 82.48      | 17.62          | -14.31   | [22.00; 6.02]   | 40.2%          | 34.5%           |

Fixed-effects: 99
Random-effects: 96
Heterogeneity: $I^2 = 86\%$, $p < 0.001$
Test for overall effect (fixed effect): $z = -0.74$ ($p = 0.469$)
Test for overall effect (random effects): $t_2 = -0.85$ ($p = 0.400$)

C. E wave deceleration at the tricuspid valve (msec)

| Study       | Total | EDFF Mean | EDFF SD | No EDFF Mean | No EDFF SD | Mean Difference | MD       | 95%-CI           | Weight (fixed) | Weight (random) |
|-------------|-------|-----------|---------|--------------|------------|----------------|----------|-----------------|----------------|-----------------|
| Cullen 1995| 9     | 96.75     | 50.60   | 9            | 126.00     | 15.00          | -29.25   | [-63.73; 5.23]  | 0.5%           | 10.0%           |
| Gatzoulis 1995| 9    | 123.15   | 31.55   | 17           | 145.25     | 35.65          | -22.10   | [-43.97; -0.23] | 1.2%           | 13.7%           |
| Gatzoulis 1998| 36   | 120.80   | 31.00   | 52           | 120.10     | 29.50          | 0.70     | [-12.22; 13.62] | 3.3%           | 16.2%           |
| Heiberg 1995| 13    | 164.00   | 47.00   | 6            | 141.00     | 62.00          | -23.00   | [-32.80; 7.80]  | 0.2%           | 5.9%            |
| Kutty 2018  | 122   | 190.30   | 11.80   | 277          | 185.75     | 12.50          | -4.55    | [-8.01; -2.88]  | 84.4%          | 17.9%           |
| Norgard 1998 (late restriction) | 13  | 140.20   | 36.20   | 34           | 129.00     | 30.00          | -10.40   | [-11.71; 32.51] | 1.1%           | 13.6%           |
| Rathiore 2006| 52   | 94.80    | 18.00   | 28           | 139.65     | 16.20          | -40.25   | [47.99; -32.51] | 9.2%           | 17.3%           |
| Sachdev 2006 | 24   | 80.60    | 21.70   | 20           | 151.40     | 152.60         | -64.50   | [153.80; -5.20] | 0.2%           | 5.4%            |

Fixed-effects: 289
Random-effects: 449
Heterogeneity: $I^2 = 91\%$, $p < 0.001$
Test for overall effect (fixed effect): $z = -7.19$ ($p < 0.001$)
Test for overall effect (random effects): $t_2 = -7.72$ ($p = 0.129$)
Figure S10. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; SD, standard deviation.

A. A wave velocity at the tricuspid valve (cm/sec)

| Study       | Total Mean | EDFF Mean | SD EDFF | Total Mean | No EDFF Mean | SD No EDFF | Mean Difference | MD       | 95%-CI          | Weight (fixed) | Weight (random) |
|-------------|------------|-----------|---------|------------|--------------|------------|----------------|---------|----------------|----------------|----------------|
| Ahmad 2012  | 58 50.00   | 15.00     | 54 50.00| 12.00      | 0.00         | [5.01, 17.7] | 13.0%          | 1.24    | 0.02           |                | -              |
| Cardoso 2003| 19 62.05   | 12.20     | 11 71.40| 12.50      | -3.95        | [0.30, 7.00] | 5.2%           | 4.4%    | 0.00           |                | -              |
| Cullen 1995 | 9 41.50    | 18.85     | 9 51.00| 16.60      | -5.00        | [3.90, 11.8] | 4.3%           | 3.3%    | 0.00           |                | -              |
| Gatziouls 1995| 20 28.70 | 21.34     | 17 27.46| 8.62       | 0.62         | [0.20, 7.00] | 5.7%           | 4.3%    | 0.00           |                | -              |
| Helsing 1996 | 13 50.00  | 8.00      | 6 50.00| 10.00      | -5.00        | [0.01, 11.8] | 4.3%           | 4.3%    | 0.00           |                | -              |
| Munkherman 1998| 13 48.00 | 11.00     | 34 49.00| 15.00      | -1.00        | [4.00, 6.00] | 7.3%           | 5.7%    | 0.00           |                | -              |
| Norgard 1996 | 20 50.00  | 20.00     | 22 60.00| 16.00      | -10.00       | [4.00, 6.00] | 7.3%           | 4.3%    | 0.00           |                | -              |
| Rathore 2006 | 52 70.00  | 8.00      | 28 60.00| 6.50       | 10.00        | [6.00, 12.0] | 5.7%           | 5.7%    | 0.00           |                | -              |
| Sachdev 2006 | 24 71.78  | 7.90      | 26 75.67| 14.80      | -9.00        | [4.00, 6.00] | 7.3%           | 5.7%    | 0.00           |                | -              |
| Sarmyn 2013  | 12 45.00  | 15.10     | 12 45.00| 15.60      | -3.91        | [1.40, 2.60] | 5.7%           | 5.7%    | 0.00           |                | -              |

B. A wave duration at the tricuspid valve (msec)

| Study       | Total Mean | EDFF Mean | SD EDFF | Total Mean | No EDFF Mean | SD No EDFF | Mean Difference | MD       | 95%-CI          | Weight (fixed) | Weight (random) |
|-------------|------------|-----------|---------|------------|--------------|------------|----------------|---------|----------------|----------------|----------------|
| Cullen 1995| 9 123.55  | 41.90     | 9 116.50| 63.50      | 7.05         | [5.75, 12.75]| 21.3%          | 23.4%   | 0.00           |                | -              |
| Gatziouls 1995| 20 143.60| 47.20     | 17 166.05| 34.20      | -22.45       | [48.76, 3.06]| 78.1%          | 76.6%   | 0.00           |                | -              |

C. E/A at the tricuspid valve

| Study       | Total Mean | EDFF Mean | SD EDFF | Total Mean | No EDFF Mean | SD No EDFF | Mean Difference | MD       | 95%-CI          | Weight (fixed) | Weight (random) |
|-------------|------------|-----------|---------|------------|--------------|------------|----------------|---------|----------------|----------------|----------------|
| Ahmad 2012  | 58 1.52   | 1.27      | 54 1.25 | 1.00       | 0.00         | [-0.44, 0.44]| 3.0%           | 6.3%    | 0.00           |                | -              |
| Cardoso 2003| 19 1.20   | 0.25      | 11 1.00 | 0.30       | 0.20         | [-0.01, 0.41]| 13.2%          | 13.9%   | 0.00           |                | -              |
| Cullen 1995 | 9 1.20    | 0.49      | 56 1.84 | 0.50       | -0.14        | [-0.30, 0.06]| 12.3%          | 12.7%   | 0.00           |                | -              |
| Helsing 1996 | 13 1.19   | 0.22      | 6 1.36  | 0.32       | -0.17        | [-0.45, 0.11]| 3.3%           | 5.7%    | 0.00           |                | -              |
| Kutty 2008  | 122 1.65  | 1.33      | 277 1.85| 11.3       | 0.00         | [-0.14, 0.14]| 31.9%          | 10.0%   | 0.00           |                | -              |
| Norgard 1998| 10 1.40   | 0.80      | 22 1.33 | 1.25       | 0.07         | [0.05, 0.79]| 1.1%           | 2.9%    | 0.00           |                | -              |
| Sachdev 2006| 24 0.98   | 0.17      | 26 1.33 | 0.49       | -0.35        | [0.55, 0.15]| 14.5%          | 13.4%   | 0.00           |                | -              |
| Sarmyn 2013 | 12 1.57   | 0.59      | 17 1.69 | 0.66       | -0.12        | [-0.58, 0.34]| 2.6%           | 5.9%    | 0.00           |                | -              |
| Sani 2020  | 16 1.20   | 0.50      | 12 1.20 | 0.50       | 0.00         | [0.37, 0.37]| 4.4%           | 7.9%    | 0.00           |                | -              |
| Vukmanovic 2006| 18 1.49   | 0.38      | 42 1.88 | 0.58       | -0.39        | [-0.64, 0.14]| 9.4%           | 11.5%   | 0.00           |                | -              |

Heterogeneity: $I^2 = 60\%$, $p = 0.008$
Test for overall effect (fixed effect): $z = -2.40$ ($p = 0.016$)
Test for overall effect (random effects): $t_q = -1.72$ ($p = 0.119$)
Figure S11. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; SD, standard deviation.

A. *E*’ at the tricuspid valve (cm/sec)

| Study     | EDFF Total | EDFF Mean | EDFF SD | No EDFF Total | No EDFF Mean | No EDFF SD | Mean Difference | MD (95% CI) | Weight (fixed) | Weight (random) |
|-----------|------------|-----------|---------|---------------|--------------|------------|----------------|-------------|---------------|-----------------|
| Ahmad 2012 | 58         | 11.00     | 2.00    | 54            | 11.00        | 3.00       | -0.09          | [0.95, 0.96] | 81.7%         | 58.4%           |
| Samyn 2013 | 12         | 14.60     | 2.00    | 16            | 12.40        | 2.80       | 2.20           | [0.19, 4.21] | 18.3%         | 41.0%           |

Fixed-effects: 70
Random-effects: 70
Heterogeneity: τ² = 73, p = 0.053
Test for overall effect (fixed effect): z = 0.92 (p = 0.359)
Test for overall effect (random effects): t₁ = 0.84 (p = 0.554)

B. *A*’ at the tricuspid valve (cm/sec)

| Study     | EDFF Total | EDFF Mean | EDFF SD | No EDFF Total | No EDFF Mean | No EDFF SD | Mean Difference | MD (95% CI) | Weight (fixed) | Weight (random) |
|-----------|------------|-----------|---------|---------------|--------------|------------|----------------|-------------|---------------|-----------------|
| Ahmad 2012 | 58         | 5.00      | 2.00    | 54            | 5.00         | 1.00       | 0.00           | [0.58, 0.58] | 86.0%         | 86.0%           |
| Samyn 2013 | 12         | 7.00      | 2.20    | 17            | 7.00         | 1.50       | 0.00           | [1.43, 1.43] | 14.0%         | 14.0%           |

Fixed-effects: 70
Random-effects: 71
Heterogeneity: τ² = 0, p = 1.00
Test for overall effect (fixed effect): z = 0.00 (p = 1.000)
Test for overall effect (random effects): t₁ = NA (p = NA)

C. *E*/E’ at the tricuspid valve

| Study     | EDFF Total | EDFF Mean | EDFF SD | No EDFF Total | No EDFF Mean | No EDFF SD | Mean Difference | MD (95% CI) | Weight (fixed) | Weight (random) |
|-----------|------------|-----------|---------|---------------|--------------|------------|----------------|-------------|---------------|-----------------|
| Ahmad 2012 | 58         | 7.00      | 2.50    | 54            | 7.80         | 3.20       | -0.80          | [1.87, 0.27] | 53.4%         | 53.4%           |
| Samyn 2013 | 12         | 4.70      | 1.70    | 17            | 5.70         | 1.30       | -1.00          | [2.14, 0.14] | 46.6%         | 46.6%           |

Fixed-effects: 70
Random-effects: 71
Heterogeneity: τ² = 0, p = 0.802
Test for overall effect (fixed effect): z = -2.24 (p = 0.025)
Test for overall effect (random effects): t₁ = -0.95 (p = 0.071)
Figure S12. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; OR, odds ratio; PR, pulmonary regurgitation; SD, standard deviation.

A. Moderate to severe PR

| Study             | EDFF Events | Total Events | No EDFF Events | Total Events | Odds Ratio | OR 95%-CI | Weight (fixed) | Weight (random) |
|-------------------|-------------|--------------|----------------|--------------|------------|-----------|---------------|----------------|
| Ahmad 2012        | 39          | 58           | 34             | 54           | 1.21       | [0.55; 2.63]| 45.0%         | 44.1%          |
| Motl 2017         | 12          | 23           | 18             | 39           | 1.27       | [0.45; 3.57]| 24.9%         | 25.0%          |
| Xu 2014           | 19          | 30           | 28             | 50           | 1.36       | [0.54; 3.44]| 30.1%         | 30.9%          |

Random-effects

Fixed-effects

Heterogeneity: $I^2 = 0\%$, $p = 0.982$
Test for overall effect (fixed effect): $z = 0.90 (p = 0.366)$
Test for overall effect (random effects): $t_2 = 8.75 (p = 0.021)$

B. PR fraction (%)

| Study             | EDFF Total | Mean | SD Total | Mean | SD | No EDFF Total | Mean | SD | Mean Difference | MD 95%-CI | Weight (fixed) | Weight (random) |
|-------------------|------------|------|----------|------|----|---------------|------|----|-----------------|-----------|---------------|----------------|
| Aptitz 2010       | 8          | 3.86| 2.90     | 17   | 2.60| 5.20          |      |    | 10.30           | [7.11; 13.49]| 8.1%          | 19.6%          |
| Kordbach-Prokopi 2018 | 10        | 29.00| 14.00     | 67   | 23.50| 17.50         |      |    | 6.40            | [1.04; 14.44]| 1.3%          | 7.3%           |
| Katty 2016        | 222        | 36.38| 4.42     | 277  | 25.75| 5.38          |      |    | 12.62           | [11.02; 13.63]| 81.1%         | 27.3%          |
| Lee 2013          | 33         | 44.20| 8.90     | 17   | 36.70| 12.10         |      |    | 7.50            | [1.00; 14.00]| 1.9%          | 9.9%           |
| Luijenburg 2013   | 231        | 36.00| 13.00    | 20   | 15.00| 17.00         |      |    | 21.00           | [12.26; 29.74]| 1.1%          | 6.4%           |
| Munkhammar 2013   | 16         | 45.00| 9.00     | 15   | 23.00| 19.00         |      |    | 22.00           | [11.42; 32.58]| 0.7%          | 4.7%           |
| Samyn 2013        | 12         | 44.75| 5.50     | 17   | 28.00| 8.00          |      |    | 16.75           | [11.84; 21.66]| 3.4%          | 13.7%          |
| van den Berg 2007 | 24         | 33.25| 9.17     | 12   | 21.50| 8.30          |      |    | 11.75           | [5.79; 17.71]| 2.3%          | 11.0%          |

Random-effects

Fixed-effects

Heterogeneity: $I^2 = 56\%$, $p = 0.025$
Test for overall effect (fixed effect): $z = 27.07 (p < 0.001)$
Test for overall effect (random effects): $t_2 = 7.09 (p < 0.001)$

C. PR duration (msec)

| Study             | EDFF Total | Mean | SD Total | Mean | SD | No EDFF Total | Mean | SD | Mean Difference | MD 95%-CI | Weight (fixed) | Weight (random) |
|-------------------|------------|------|----------|------|----|---------------|------|----|-----------------|-----------|---------------|----------------|
| Gatziouls 1995    | 20         | 30.20| 65.40    | 18   | 44.10| 10.54         |      |    | -141.90         | [-179.93; 103.87]| 0.2%         | 14.1%          |
| Mercy-Rosa 2018   | 77         | 42.50| 2.67     | 11   | 31.25| 2.83          |      |    | 11.25           | [9.47; 13.03]| 98.7%         | 15.6%          |
| Munkhammar 1998   | 13         | 253.30| 41.90    | 34   | 353.00| 71.80         |      |    | -99.70          | [-132.88; -66.52]| 0.3%         | 14.4%          |
| Norgard 1998 (early restriction) | 16    | 171.00| 76.00    | 18   | 174.00| 39.00         |      |    | -3.00           | [44.37; 38.37]| 0.2%          | 13.9%          |
| Norgard 1998 (late restriction) | 10   | 210.90| 52.00    | 22   | 254.00| 40.60         |      |    | -34.80          | [-71.22; 102.02]| 0.2%          | 14.2%          |
| Sachdev 2006      | 24         | 166.60| 79.50    | 26   | 233.30| 88.60         |      |    | -162.60         | [-212.80; -112.40]| 0.1%         | 13.5%          |

Random-effects

Fixed-effects

Heterogeneity: $I^2 = 95\%$, $p < 0.001$
Test for overall effect (fixed effect): $z = 11.49 (p < 0.001)$
Test for overall effect (random effects): $t_2 = -2.11 (p = 0.079)$
Figure S13. Forest plots. BNP, brain natriuretic peptide; CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; OR, odds ratio; SD, standard deviation.

### A. QRS duration (msec)

| Study               | Total Mean | SD | Total Mean | SD | Total Mean | SD | Mean Difference | MD   | 95%-CI | Weight (fixed) | Weight (random) |
|---------------------|------------|----|------------|----|------------|----|-----------------|------|--------|---------------|-----------------|
| Usurwali 2014       | 9.123      | 29.00 | 11.144     | 20.00 | 12.150     | 25.00 | -2.00          | 9.00 | [15.03, 33.03] | 0.3%            | 3.9%            |
| Ahmad 2012          | 8.148      | 10.30 | 9.157      | 18.00 | 9.206      | 23.00 | 0.34          | 9.00 | [-0.60, 18.00] | 2.0%            | 6.5%            |
| Apitz 2010          | 3.146      | 27.00 | 10.114     | 20.00 | 10.116     | 30.00 | -0.96          | 9.00 | [-1.74, 2.13]  | 3.2%            | 6.8%            |
| Bonello 2013        | 19.130     | 20.00 | 10.114     | 40.00 | 11.146     | 50.00 | -0.96          | 9.00 | [-1.00, 0.06]  | 6.0%            | 6.5%            |
| Cardoso 2003        | 19.140     | 20.00 | 10.156     | 24.00 | 10.156     | 24.00 | -0.96          | 9.00 | [-1.00, 0.06]  | 6.0%            | 6.5%            |
| Eroglu 1999         | 36.123     | 16.00 | 16.123     | 18.00 | 16.120     | 18.00 | -0.21          | 9.00 | [-0.37, 0.51]  | 3.5%            | 6.9%            |
| Gatzoulis 1998      | 16.132     | 33.70 | 16.132     | 21.20 | 16.132     | 21.20 | -0.21          | 9.00 | [-0.39, 0.48]  | 6.0%            | 5.1%            |
| Kudla-Prokopciou 2018 | 122.138     | 5.70 | 122.138     | 5.70 | 122.138     | 5.70 | -0.21          | 9.00 | [-0.39, 0.48]  | 6.0%            | 5.1%            |
| Kutty 2018          | 33.137     | 19.30 | 33.137     | 19.30 | 33.137     | 19.30 | -0.21          | 9.00 | [-0.39, 0.48]  | 6.0%            | 5.1%            |
| Lee 2013            | 23.137     | 32.00 | 33.123     | 41.00 | 23.137     | 32.00 | -0.21          | 9.00 | [-0.39, 0.48]  | 6.0%            | 5.1%            |
| Morn 2011           | 112.138     | 5.70 | 112.138     | 5.70 | 112.138     | 5.70 | -0.21          | 9.00 | [-0.39, 0.48]  | 6.0%            | 5.1%            |
| Norgard 1998 (early restriction) | 16.710     | 30.00 | 16.710     | 30.00 | 16.710     | 30.00 | -0.21          | 9.00 | [-0.39, 0.48]  | 6.0%            | 5.1%            |
| Norgard 1998 (late restriction) | 22.112     | 19.30 | 22.112     | 19.30 | 22.112     | 19.30 | -0.21          | 9.00 | [-0.39, 0.48]  | 6.0%            | 5.1%            |
| Samal 2013          | 12.143     | 15.80 | 12.143     | 15.80 | 12.143     | 15.80 | -0.21          | 9.00 | [-0.39, 0.48]  | 6.0%            | 5.1%            |
| Sara 2020           | 18.156     | 13.70 | 12.145     | 14.80 | 12.145     | 14.80 | -0.21          | 9.00 | [-0.39, 0.48]  | 6.0%            | 5.1%            |
| Sara 2020           | 18.156     | 13.70 | 12.145     | 14.80 | 12.145     | 14.80 | -0.21          | 9.00 | [-0.39, 0.48]  | 6.0%            | 5.1%            |
| Tomlinaga 2021       | 23.152     | 21.80 | 23.152     | 21.80 | 23.152     | 21.80 | -0.21          | 9.00 | [-0.39, 0.48]  | 6.0%            | 5.1%            |

**Fixed-effects 484**

**Random-effects 732**

Test for overall effect (fixed effect): z = 4.18 (p < 0.001)
Test for overall effect (random effects): I² = 1.14 (p = 0.272)

### B. BNP (pg/mL)

| Study               | Total Mean | SD  | Total Mean | SD  | Total Mean | SD  | Mean Difference | MD   | 95%-CI | Weight (fixed) | Weight (random) |
|---------------------|------------|-----|------------|-----|------------|-----|-----------------|------|--------|---------------|-----------------|
| Apitz 2010          | 8.370      | 0.50 | 17.280     | 5.20 | 26.650     | 5.20 | -9.28          | 9.00 | [3.80, 14.14]  | 76.3%           | 44.4%           |
| Morn 2011           | 12.250     | 20.67 | 17.150     | 6.33 | -4.90      | 9.00 | [-12.05, 2.25]  | 1.6% | 6.3%             |                |
| Samal 2013          | 12.145     | 15.80 | 12.145     | 15.80 | -4.90      | 9.00 | [-12.05, 2.25]  | 1.6% | 6.3%             |                |

**Fixed-effects 43**

**Random-effects 73**

Heterogeneity: I² = 67%, p = 0.049
Test for overall effect (fixed effect): z = 4.81 (p < 0.001)
Test for overall effect (random effects): I² = 2.45 (p = 0.134)

### C. NT-proBNP (pg/mL)

| Study               | Total Mean | SD  | Total Mean | SD  | Total Mean | SD  | Mean Difference | MD   | 95%-CI | Weight (fixed) | Weight (random) |
|---------------------|------------|-----|------------|-----|------------|-----|-----------------|------|--------|---------------|-----------------|
| Kordbach-Prokopciou 2018 | 16.433     | 66.90 | 21.990     | 292.40 | -557.50   | 292.40 | -213.40         | 63.06 | [15.43, 110.69]  | 93.0%           | 93.0%           |
| Luinnen 2013        | 31.144     | 90.09 | 20.608     | 81.08 | -63.00    | 226.60 | -25.50          | 61.12 | [26.40, 147.66]  | 100.0%          | 100.0%          |
| Morn 2017           | 21.138     | 175.50 | 34.183     | 555.10 | -221.60   | 555.10 | -61.12          | 61.12 | [-26.40, 147.66]  | 100.0%          | 100.0%          |

**Fixed-effects 68**

**Random-effects 121**

Heterogeneity: I² = 0%, p = 0.479
Test for overall effect (fixed effect): z = 2.01 (p = 0.099)
Test for overall effect (random effects): I² = 3.04 (p = 0.093)
Figure S14. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; OR, odds ratio; SD, standard deviation; VO2, oxygen consumption.

A. Peak VO2 (%)

B. Peak VO2 (mL/kg/min)
Figure S15. Publication bias analysis by funnel plot graphic. (A) transannular patch repair. (Begg and Mazumdar’s test: p=0.025, Egger’s test: p=0.002). (B) right atrial volume indexed. (Begg and Mazumdar’s test: p=0.117, Egger’s test: p=0.014). (C) pulmonary regurgitation fraction. (Begg and Mazumdar’s test: p=0.453, Egger’s test: p=0.038). (D) A wave velocity at the tricuspid valve. (Begg and Mazumdar’s test: p=0.655, Egger’s test: p=0.005).