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SYSTEMATIC REVIEW AND META-ANALYSIS

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.[1] Although great strides have been made in the initial management of this condition, patients with repaired ToF (rToF) carry significant residual hemodynamic burden.[2] 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.[3,4] 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[5] and chronically at late follow-up.[6] Initial reports[5–10] 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.[6]

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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 perioperative 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.

Nonstandard Abbreviations and Acronyms

EDFF	end-diastolic forward flow
MD	mean difference
PR	pulmonary regurgitation
RA	right atrial
rToF	repaired tetralogy of Fallot
RVEDVi	right ventricular end-diastolic volume indexed
RVRP	right ventricular restrictive physiology
ToF	tetralogy of Fallot

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.

METHODS

Data used for the analyses in this article will be made available from the corresponding author on reasonable request.

Eligibility Criteria, Databases, and Search Strategy

We followed 2 internationally recognized protocols: Preferred Reporting Items for Systematic Reviews and Meta-Analyses[17] 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

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.[19] 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 initial ToF repair, mean interval between ToF 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. I^2, 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 χ^2 test of the Cochran Q heterogeneity statistic.[20] The MD and OR were combined across the studies using a random-effects method (DerSimonian and Laird inverse variance).[21] 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 Begg and Mazumdar's rank correlation method[22] and Egger's linear regression method, using the "funnel" and "metabias" functions of the R package "meta" (version 4.19-0).[23] 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). No attempts were made to correct for multiple testing, given the exploratory nature of this study. All analyses were completed with R Statistical Software (version 4.0.5; Foundation for Statistical Computing, Vienna, Austria).

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[5–8,11–16,24–58] 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.[26,36] 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 initial ToF 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%; I^2=80.9%). 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%; I^2=80.7%), 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

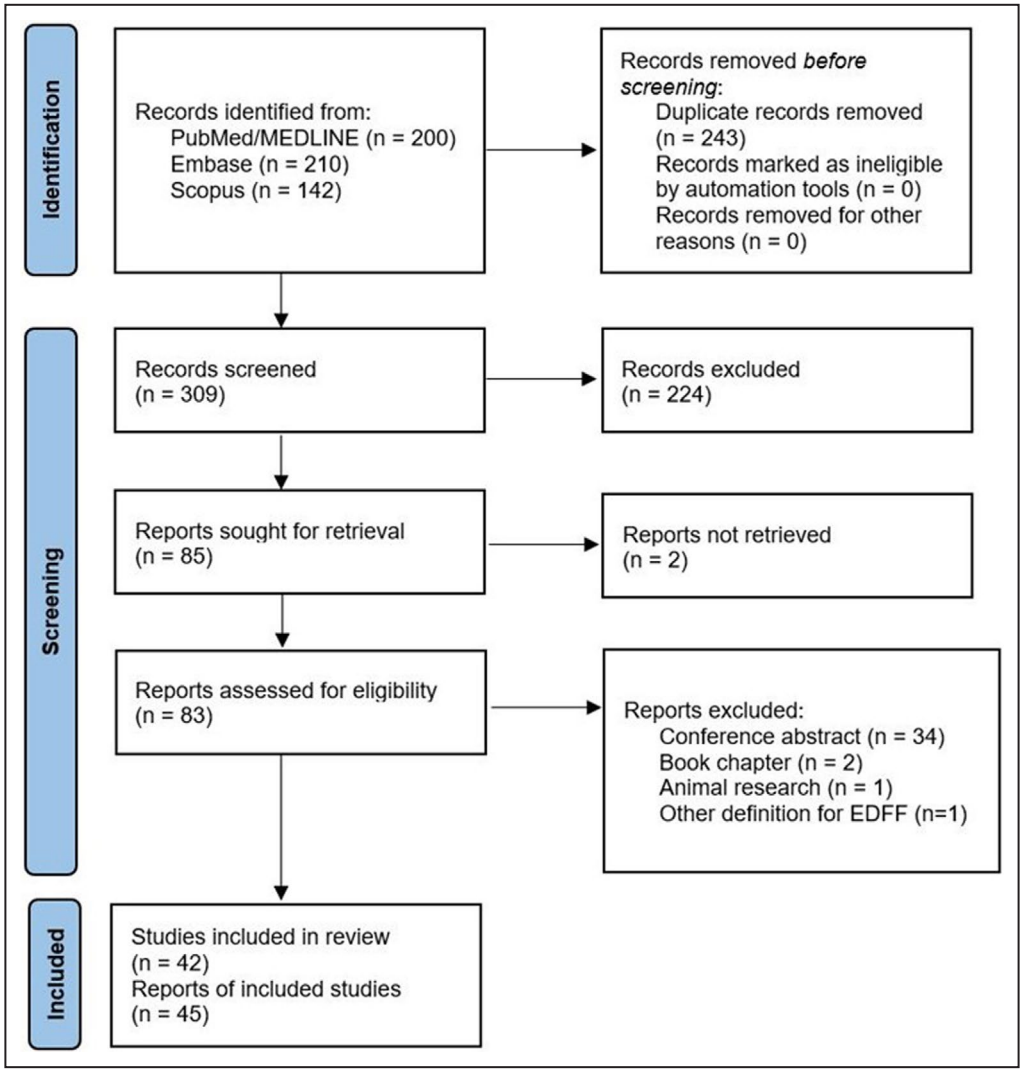

Figure 1. Flow diagram of studies included in data search.
EDFF indicates end-diastolic forward flow.

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/m^2; 95% CI, 4.57–24.8 mL/m^2; *P*=0.007), greater RV end-systolic volume indexed (random-effects model: MD, 16.1 mL/m^2; 95% CI, 1.01–31.3 mL/m^2; *P*=0.039), and greater RV stroke volume indexed (random-effects model: MD, 9.57 mL/m^2; 95% CI, 0.67–18.5 mL/m^2; *P*=0.040). Correspondingly, RV mass indexed was greater in patients with EDFF (random-effects model: MD, 2.87 g/m^2; 95% CI, 0.14–5.61 g/m^2; *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.

Table 1. Study and Patient Characteristics

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
Aburawi 2014[24]	Sweden	Prospective	NR	20	CMR	9/20 (45.0)	NR	NR	10.2
Ahmad 2012[15]	Canada	Retrospective	2008–2010	112	Doppler echocardiography	58/112 (51.8)	0.9	NR	12.9
Apitz 2010[25]	Germany	Prospective	NR	25	CMR	8/25 (32.0)	NR	7.1	17.9
Babu-Narayan 2012[26] (overlap with Krupickova 2018)	United Kingdom	Prospective	2002–2005	64	Doppler echocardiography	27/64 (42.2)	6.0	25.1	30.1
Bonello 2013[27]	United Kingdom	Prospective	2002–2008	148	Doppler echocardiography	38/148 (25.7)	4.8	NR	32.1
Cardoso 2003[28]	Brazil	Prospective	2000	30	Doppler echocardiography	19/30 (63.3)	3.0	3.2	8.7
Chaturvedi 1999[29]	United Kingdom	Prospective	NR	11	Doppler echocardiography	4/11 (36.4)	NR	NR	1.7
Cheng 2019[30]	United States	Retrospective	1999–2014	38	CMR	15/38 (39.5)	NR	NR	13.2
Cheung 2003[31]	Australia	Prospective	1981–1990	45	Doppler echocardiography	24/45 (53.3)	2.1	12.5	15.0
Choi 2008[32]	Korea	Retrospective	1997–2000	43	Doppler echocardiography	15/43 (34.9)	2.1	5.4	4.8
Clark 1995[33] (overlap with Gatzoulis 1995)	United Kingdom	Prospective	1958–1979	30	Doppler echocardiography	18/30 (60.0)	NR	21.8	27.8
Cullen 1995[5]	United Kingdom	Prospective	1992–1993	35	Doppler echocardiography	17/35 (48.6)	NR	NR	1.9
Eroglu 1999[8]	Turkey	Prospective	1986–1996	44	Doppler echocardiography	25/44 (56.8)	4.0	NR	7.7
Gatzoulis 1995[6] (overlap with Clark 1995)	United Kingdom	Prospective	1958–1979	38	Doppler echocardiography	20/38 (52.6)	5.2	NR	28.8
Gatzoulis 1998[34] (overlap with Norgard 1996)	United Kingdom	Retrospective	1985–1994	92	Doppler echocardiography	36/92 (39.1)	NR	4.5	14.7
Helbing 1996[11]	The Netherlands	Prospective	NR	19	Doppler echocardiography	13/19 (68.4)	1.5	10.0	12.0
Kordybach-Prokopiuk 2018[35]	Poland	Prospective	NR	83	Doppler echocardiography	16/83 (19.3)	11.9	21.6	31.5
Krupickova 2018[36] (overlap with Babu-Narayan 2012)	United Kingdom	Prospective	2002–2005	64	Doppler echocardiography	26/64 (40.6)	6.1	25.1	31.1
Kutty 2018[37]	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[12]	United States	Prospective	2008–2009	59	CMR	40/59 (67.8)	11.0	NR	35.0
Luijnenburg 2013[40]	The Netherlands	Prospective	2007–2010	51	CMR	31/51 (60.8)	2.8	NR	21.0
Maskatia 2013[41]	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[16]	Japan	Retrospective	2009–2016	62	Doppler echocardiography	23/62 (37.1)	3.1	NR	15.7
Munkhammar 1998[44]	United Kingdom	Prospective	1985–1996	47	Doppler echocardiography	13/47 (27.7)	0.7	NR	4.4
Munkhammar 2013[45]	Sweden	Prospective	NR	31	Doppler echocardiography	16/31 (51.6)	1.0	9.2	10.2
Norgard 1996[46] (overlap with Gatzoulis 1998)	United Kingdom	Retrospective	1985–1994	92	Doppler echocardiography	36/92 (39.1)	11.5	NR	14.7
Norgard 1998[7] (early restriction)	United Kingdom	Prospective	1992–1995	34	Doppler echocardiography	16/34 (47.1)	5.9	1.8	NR
Norgard 1998[7] (late restriction)	United Kingdom	Prospective	1992–1995	32	Doppler echocardiography	10/32 (31.3)	5.6	1.8	NR
Peng 2012[47]	United Kingdom	Prospective	NR	18	Doppler echocardiography	4/18 (22.2)	1.6	NR	1.6
Pijuan-Domenech 2014[48]	Spain	Prospective	2009–2012	20	Doppler echocardiography	16/20 (80.0)	7.7	NR	35.0
Rathore 2006[49]	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[13]	United States	Prospective	2008–2009	29	Doppler echocardiography	12/29 (41. 4)	1.4	14.0	16.3
Sandeep 2019[51]	China	Prospective	2017–2018	50	Doppler echocardiography	28/50 (56.0)	NR	NR	2.2
Sani 2020[52]	Iran	Prospective	2015–2016	30	CMR	18/30 (60.0)	NR	20.2	26.5
Shekerdemian 1999[53]	United Kingdom	Prospective	NR	23	Doppler echocardiography	8/23 (34.8)	NR	NR	2.5

(*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
Shin 2016[54]	Korea	Retrospective	2005–2015	116	Doppler echocardiography	35/116 (30.2)	2.3	14.2	NR
Sjöberg 2018[55]	Sweden	Prospective	NR	15	CMR	10/15 (66.7)	NR	NR	29.0
Tominaga 2021[56]	Japan	Retrospective	2003–2019	46	Doppler echocardiography	23/46 (50.0)	3.4	31.0	37.0
van den Berg 2007[14]	The Netherlands	Prospective	2002–2004	36	Doppler echocardiography	24/36 (66. 7)	0.9	15.3	16.0
Vukomanovic 2006[57]	Serbia and Montenegro	Prospective	1995–2004	60	Doppler echocardiography	18/60 (30.0)	4.3	NR	9.0
Xu 2014[58]	China	Retrospective	2011–2012	80	Doppler echocardiography	30/80 (37.5)	1.2	NR	1.2

CMR indicates cardiac magnetic resonance; EDFF, end-diastolic forward flow; NR, not reported; and ToF, tetralogy of Fallot.

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-diastolic 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-diastolic volume indexed (fixed-effects model: MD, −4.15 mL/m^2; 95% CI, −4.86 to −3.44 mL/m^2; P<0.001), smaller LV end-systolic volume indexed (fixed-effects model: MD, −2.97 mL/m^2; 95% CI, −3.43 to −2.52 mL/m^2; P<0.001), smaller LV stroke volume indexed (fixed-effects model: MD, −1.65 mL/m^2; 95% CI, −2.05 to −1.24 mL/m^2; 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 cm^2/m^2; 95% CI, 0.42–0.74 cm^2/m^2; 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, 0.82–5.03 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	Studies, N	Summary measures			Heterogeneity	
		OR/MD	95% CI	*P* value	I^2, %	χ^2 *P* value
Patient characteristics						
Age at repair, y	16	0.329	−0.419 to 1.077	0.363	95.2	<0.001
Time of follow-up since repair, y	9	0.318	−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/m^2	16	14.706	4.572 to 24.840	0.007*	91.0	<0.001
RVESVi, mL/m^2	11	16.146	1.012 to 31.280	0.039*	94.9	<0.001
RVSVi, mL/m^2	6	9.570	0.674 to 18.466	0.040*	98.3	<0.001
RVMi, g/m^2	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/m^2	5	0.005	−6.334 to 6.344	0.998	87.7	<0.001
LVESVi, mL/m^2	2	−1.728	−27.074 to 23.618	0.546	57.3	0.126
LVSVi, mL/m^2	2	−1.179	−12.443 to 10.086	0.411	91.9	<0.001
LVEF, %	9	−0.195	−1.256 to 0.866	0.682	74.3	<0.001
RAAi, cm^2/m^2	3	1.083	−0.319 to 2.484	0.080	92.8	<0.001
RAVi, mL/m^2	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	−174.249 to 143.158	0.431	5.4	0.304
E/A at the tricuspid valve	10	−0.106	−0.246 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 VO_2, %	7	8.433	−0.050 to 16.916	0.051	87.5	<0.001
Peak VO_2, 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; OR, odds ratio; PR, pulmonary regurgitation; RAAi, right atrial area indexed; RAVi, right atrial volume indexed; rToF, repaired tetralogy of Fallot; RVEDP, right ventricular end-diastolic pressure; RVEDVi, right ventricular end-diastolic volume indexed; RVEF, right ventricular ejection fraction; RVESP, right ventricular end-systolic pressure; RVESVi, right ventricular end-systolic volume indexed; RVMi, right ventricular mass indexed; RVPA, right ventricle–pulmonary artery; RVSVi, right ventricular stroke volume indexed; and VO_2, oxygen consumption.

*$P<0.05$.

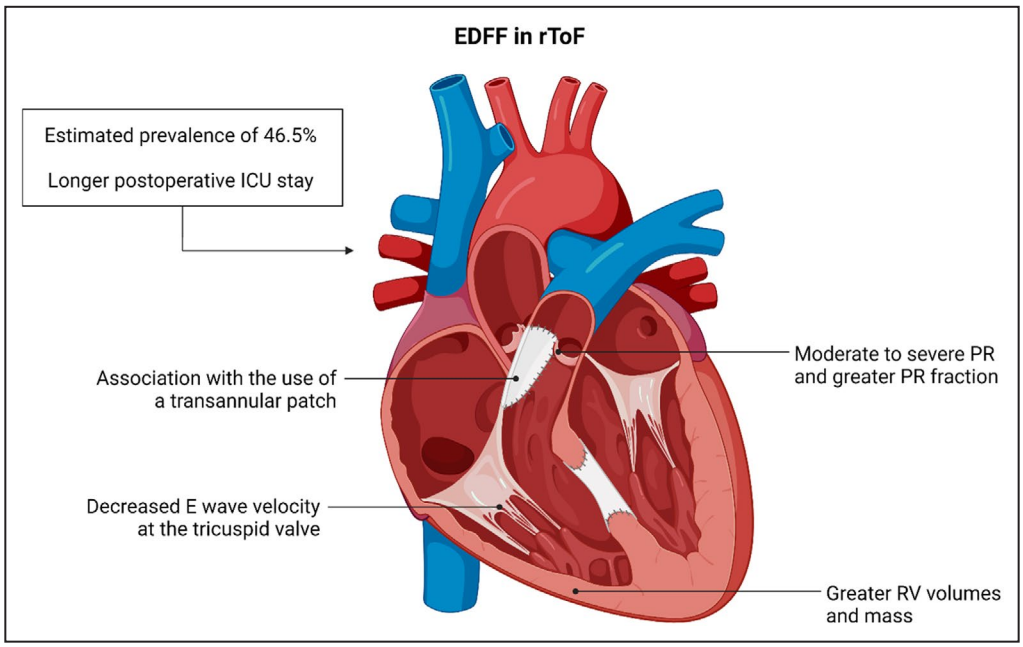

Figure 2. Summary of the main findings about end-diastolic forward flow (EDFF) in repaired tetralogy of Fallot (rToF) in the present meta-analysis.
ICU indicates intensive care unit; PR, pulmonary regurgitation; and RV, right ventricular.

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,[5–10] 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.[59] The gold standard measure of LV myocardial stiffness is the slope of the end-diastolic pressure-volume relationship,[60] 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.[61]

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).[62] For example, the absence of atrial systole and other conditions that decrease preload

Table 3. Framework to Think About Factors Influencing EDFF

Factor	Main findings
Atrial contractility	• Morbidity related to atrial arrhythmias is 3-fold more common among patients with EDFF, further interfering with hemodynamics[27] • Increased RA pressure can lead to EDFF, although EDFF can also occur in patients with low pulmonary diastolic pressure and normal RA pressure[16]
RV volumes	• EDFF most commonly occurs at the ends of the spectrum of RVEDVi (at ≤115 and ≥200 mL/m^2), supporting the hypothesis that 2 distinct phenotypes might exist[39]
RV compliance and diastolic function	• Acute EDFF in the postoperative setting is associated with greater myocardial injury and oxidative stress[29] • The slope of the end-diastolic pressure-volume relationship is increased in EDFF, indicating increased diastolic RV stiffness[25] • Peak diastolic strain rate is decreased at the interventricular septum but increased at the RV free wall of patients with EDFF[13,35] • In a porcine model, EDFF only occurred if PR was accompanied by RV hypertrophy, supporting the role of the latter in the pathophysiology of EDFF[62] • Fibrosis of the RVOT is associated with EDFF and correlated with the degree of PR and RV volumes[45]
Myocardial perfusion	• EDFF is associated with increased basal coronary flow, probably because of increased systolic workload against a stiff fibrotic myocardium and increased RV volumes. This might, in turn, explain the decreased coronary flow reserve and impaired exercise capacity[24]
Ventricular-ventricular interactions	• LA size was larger and pulmonary venous flow reversals were more pronounced in patients with EDFF, suggesting increased LV filling pressures. This might be attributable to septal flattening, the induction of LV fibrosis, and/or interventricular diastolic dyssynchrony in the setting of progressive RV dilatation[15] • The ACE inhibitor ramipril led to an improvement in both LA and LV function in patients with EDFF[26,36]
Pulmonary regurgitation	• EDFF is typically associated with the transannular patch but is not usually present in patients in whom the pulmonary valve had been preserved during primary repair[8]
Residual obstruction	• Some degree of residual RVOT obstruction after ToF repair may be beneficial by protecting the RV from enlarging even in the presence of large PR[38,41]
Pulmonary arterial bed capacitance and respiration	• The respiratory cycle acts as an additional hemodynamic pump, which becomes more important when effective pulmonary flow attributable to RV contraction decreases and acts as a "suction" mechanism predisposing to EDFF[33] • EDFF increases during normal inspiration and during the expiratory phase of positive pressure ventilation, probably because of increased systemic venous return[5] • EDFF is less common among patients with pulmonary atresia, despite their predilection to RV noncompliance, as they have stiff, diminutive pulmonary arteries with poor arborization.[37] Similarly, EDFF may be attenuated by aging. Conversely, increased pulmonary artery capacitance may contribute to EDFF

ACE indicates angiotensin-converting enzyme; EDFF, end-diastolic forward flow; LA, left atrial; LV, left ventricular; PR, pulmonary regurgitation; RA, right atrial; RV, right ventricular; RVEDVi, RV end-diastolic volume indexed; RVOT, RV outflow tract; and ToF, tetralogy of Fallot.

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,[63] 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[16] 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[55] suggested that these decreased velocities might contribute to the lower diastolic kinetic energy observed on 4-dimensional flow CMR in patients with EDFF. As

Table 4. Unifying Theory About Physiological and Clinical Correlates of EDFF

Phenotype 1: early-onset, "primary" EDFF	Phenotype 2: late-onset, "secondary" EDFF
Physiological correlates	
Small RVs with abnormal diastolic filling following directly after primary repair of ToF and probably related to fibrosis, myocardial injury, and other perioperative factors	Dilated RVs at late follow-up after primary repair of ToF, or may occur as a late stage of phenotype 1
Preventing further progression of PR and limiting the extent of volume overload	Pronounced volume overload attributable to longstanding PR, whereby filling of the RV becomes limited and RV pressure becomes larger than pulmonary artery pressure
Usually disappears days to months after the primary repair, but may be maintained into midterm follow-up in a subset of patients	Usually is maintained during long-term follow-up but may disappear after PVR
Associated with repair at older age as seen in the initial era of development of ToF repair	Associated with repair at younger age as seen in more contemporary management
Corresponds closest to actual RVRP	Only a subset of patients might have actual RVRP
Clinical correlates	
Longer ICU length of stay attributable to increased central venous pressure and low cardiac output state	Independent predictor of rapid RV enlargement
Improved exercise tolerance (higher peak VO_2) because of improved oxygenation, as EDFF contributes to forward flow and shortens duration of PR	Related to functional deterioration and worse exercise tolerance
Lower risk of arrhythmias and sudden death	Associated with increased risk of adverse outcomes, such as ventricular dysfunction and arrhythmias; persistent EDFF after PVR indicates worse prognosis

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 VO_2, oxygen consumption.

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 ≤115 and ≥200 mL/m^2), 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 cohorts described by Cullen et al[5] and Gatzoulis et al.[6] This phenotype more closely resembles a "true" RVRP, and occurs in association with small RVs with abnormal diastolic filling.[34] EDFF in these patients has its onset in the period around primary ToF repair. Cardiopulmonary bypass, myocardial edema, ventriculotomy, endomyocardial fibrosis, and the insertion of nonfunctional patches in the ventricular septum and across the right ventricular outflow tract might all be expected to impair RV diastolic performance.[8] Although increased central venous pressure and low cardiac output lead to longer intensive care unit length of stay in these patients, RVRP is eventually beneficial as it prevents further progression of PR, thereby improving exercise tolerance and reducing the risk of adverse outcomes.[6–8] Early-onset EDFF usually disappears days to months after the primary repair, although it may be maintained into midterm follow-up in a subset of patients.[5,7]

The first phenotype was more commonly observed in earlier ToF cohorts, when patients were operated at a later age and perioperative ventricular dysfunction was common.[44] Improvements in surgical techniques and myocardial preservation have led to improved diastolic function in the early and midterm period after repair, but might also have promoted a higher prevalence of a second phenotype.[44] Late-onset, "secondary" EDFF is a consequence of an overdistended ventricle and rightward shift of the pressure-volume curve.[16,39] The lack of RVRP in early follow-up allows for continuing RV remodeling and enlargement in the presence of longstanding PR. The severely dilated RV eventually becomes stiff or encounters space constraints attributable to the pericardium and the capacity of the thoracic cavity. In this setting, EDFF occurs without restricted RV filling or decreased RV volume.[12] This dilatation-related phenotype has been linked to severe PR,[16] fibrosis,[45] accelerated RV enlargement,[54] and increased risk of adverse outcomes.[56] Corroborating these observations, Lee et al[39] demonstrated that EDFF was associated with improved exercise tolerance (peak oxygen consumption) in patients with RVEDVi <170 mL/m^2, but not in those with RVEDVi ≥170 mL/m^2.

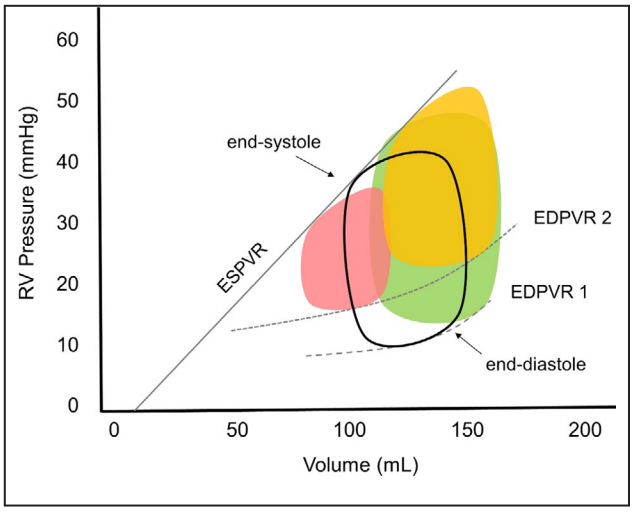

Figure 3. Representative pressure-volume curves for the different phenotypes of end-diastolic forward flow (EDFF). The pressure-volume curve of the normal right ventricle (RV), which is characterized by its trapezoidal shape, is depicted in the middle (black contours). The early-onset, "primary" type of EDFF is associated with a small, restrictive RV (red shape on the left) with decreased myocardial compliance (end-diastolic pressure-volume relationship [EDPVR] 2 is shifted upward compared with EDPVR 1). In contrast, the late-onset, "secondary" type of EDFF presents as a dilated RV with a rightward shift of the pressure-volume relationship, either without (green shape on the right at EDPVR 1) or with marked myocardial stiffening (yellow shape on the right at EDPVR 2). ESPVR indicates end-systolic pressure-volume relationship.

Perspectives for Future Research and Clinical Practice

EDFF was invariably treated as a binary feature in all studies. However, it is possible that characteristics, such as EDFF duration, mean and peak velocity, velocity time integral, and percentage of contribution to the stroke volume, may have their own implications. Although a few studies have reported such characteristics,[8,30,34,37,45,48,57] it will be a task for future investigations to determine how they correlate with patient characteristics, cardiac morphology and function, and outcomes. Having said that, it is clear that EDFF is an imperfect surrogate for poor RV compliance, so future studies should aim to identify more reliable markers for RVRP. Multiple parameters may be required, including tricuspid inflow characteristics, tricuspid valve annulus, hepatic veins, right atrial size, and collapsibility of the interior vena cava.[64] In addition, more investigations using invasive measurements of filling pressures are warranted to validate findings from noninvasive modalities. Of interest, recent advances have made it possible to measure RV pressure-volume loops more routinely in clinical and research settings, as described in an outstanding recent review by Brener et al.[65]

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.[66,67] As an example of the latter, Tominaga et al[56] 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/m^2) have not consistently shown an effect of persistent EDFF on the risk of arrhythmias.[68] 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.[69]

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, 2 of the studies that primarily defined EDFF based on CMR ascertained their results based on Doppler echocardiography. Sani et al[52] found a comparable prevalence of EDFF with both echocardiography (56.7%) and CMR (60.0%; P=0.792). In contrast, Lee et al[39] 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[37] found a modest correlation between both modalities (Fleiss' κ=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 perioperative ventricular 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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Supplemental Material

Data S1
Figures S1–S15

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SUPPLEMENTAL MATERIAL

Data S1.

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[37] 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[37]) 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[25]), LVSVi (MD -0.25 ml/m², 95% CI -1.13-0.63, 1 study[27]), 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.

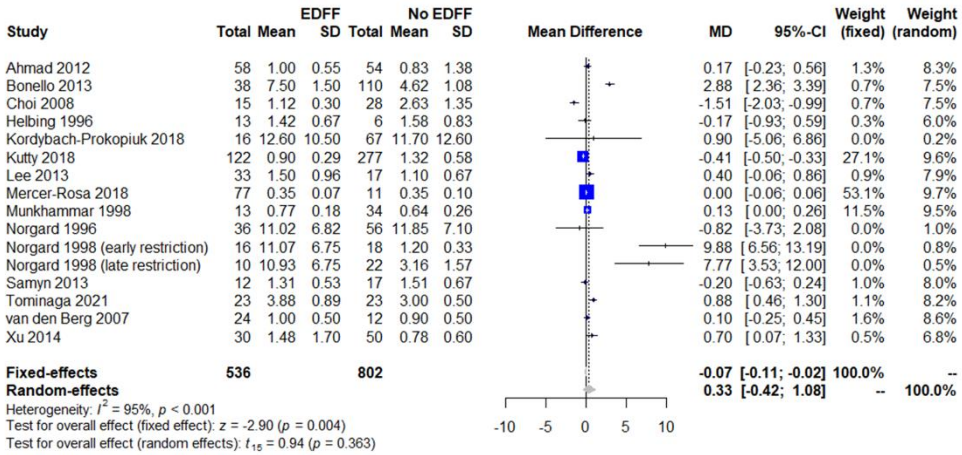
Meta-regression analyses

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

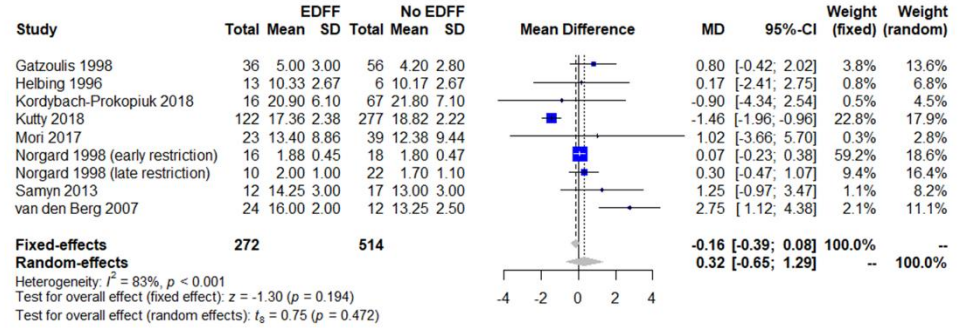
ventricular stroke volume indexed (RVSVi) (regression coefficient 0.465, 95% CI 0.144-0.786, p=0.016, 6 studies) and pulmonary regurgitation fraction (regression coefficient 0.214, 95% CI 0.003-0.424, p=0.048, 8 studies). Lastly, it was found that older age at evaluation was associated with smaller MD 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)



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



C. Age at study (years)

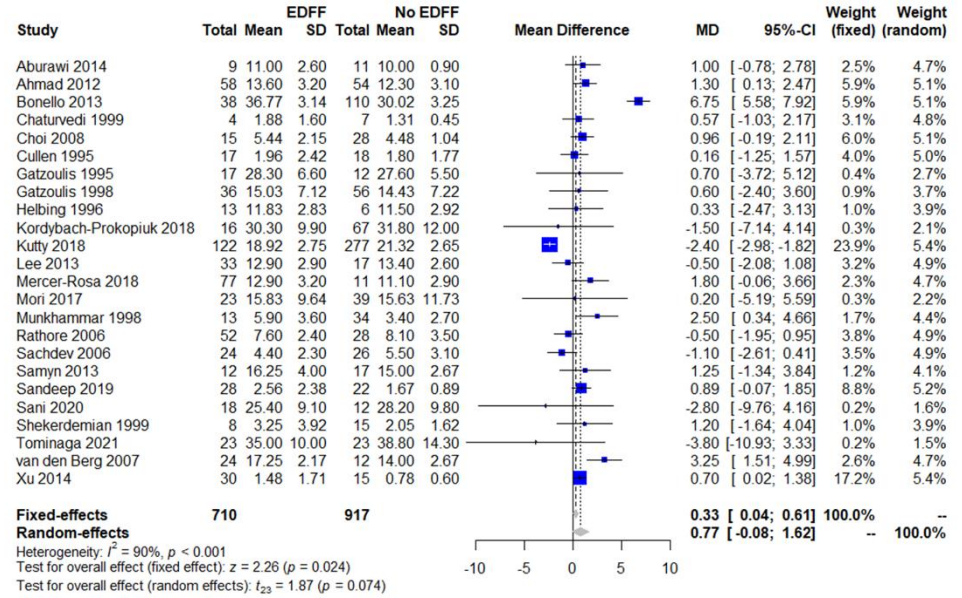
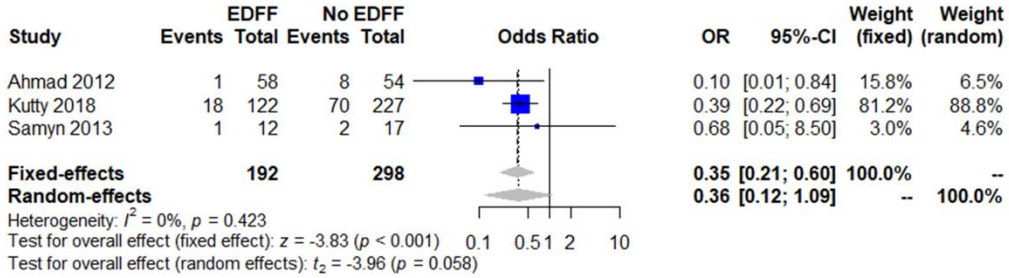
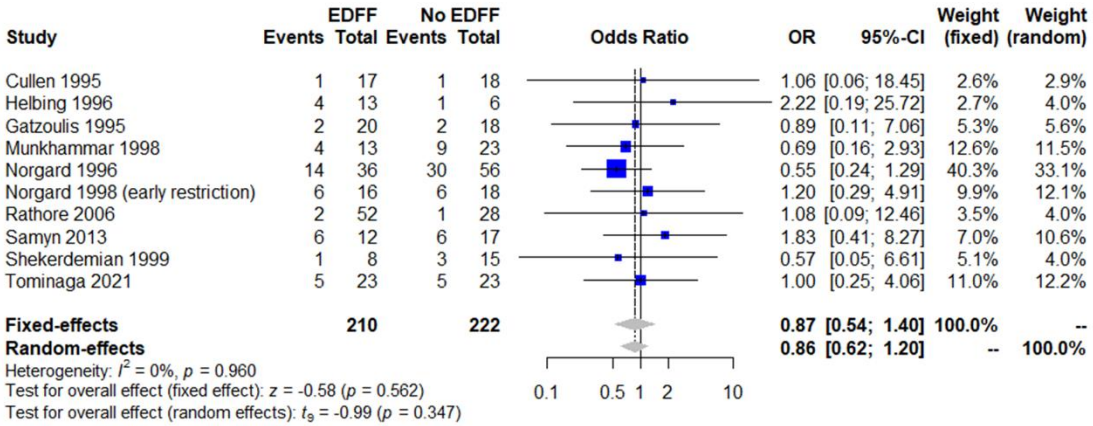


Figure S2. Forest plots. BT, Blalock-Taussig; CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; OR, odds ratio; RVPA, right ventricle-pulmonary artery; SD, standard deviation.

A. Previous RVPA shunt



B. Previous BT shunt



C. Aortic cross-clamp time (min)

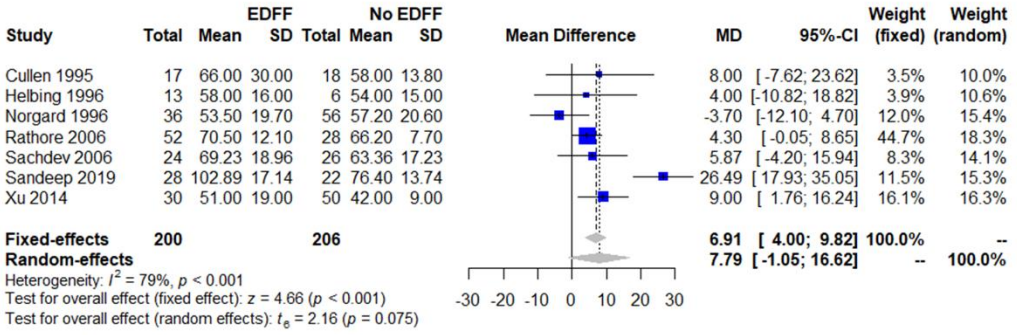
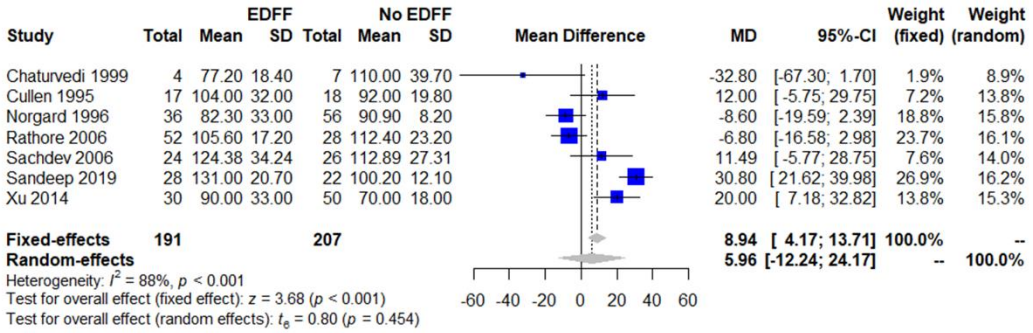
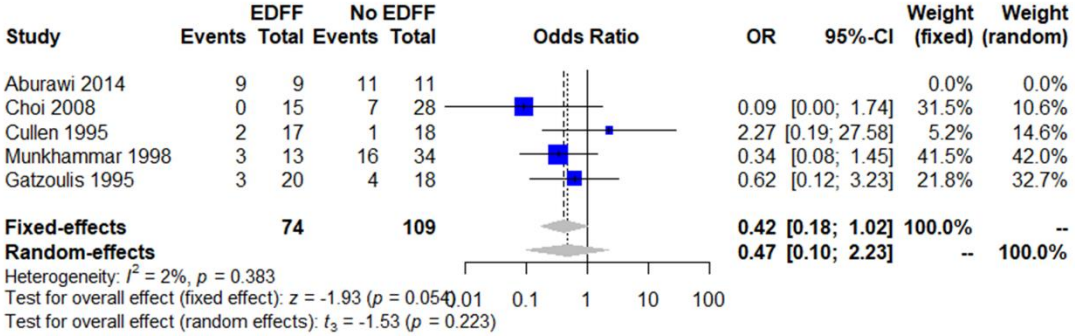


Figure S3. Forest plots. CI, confidence interval; CPB, cardiopulmonary bypass; EDFF, end-diastolic forward flow; MD, mean difference; OR, odds ratio; SD, standard deviation.

A. CPB time (min)



B. Transatrial repair



C. Transannular patch repair

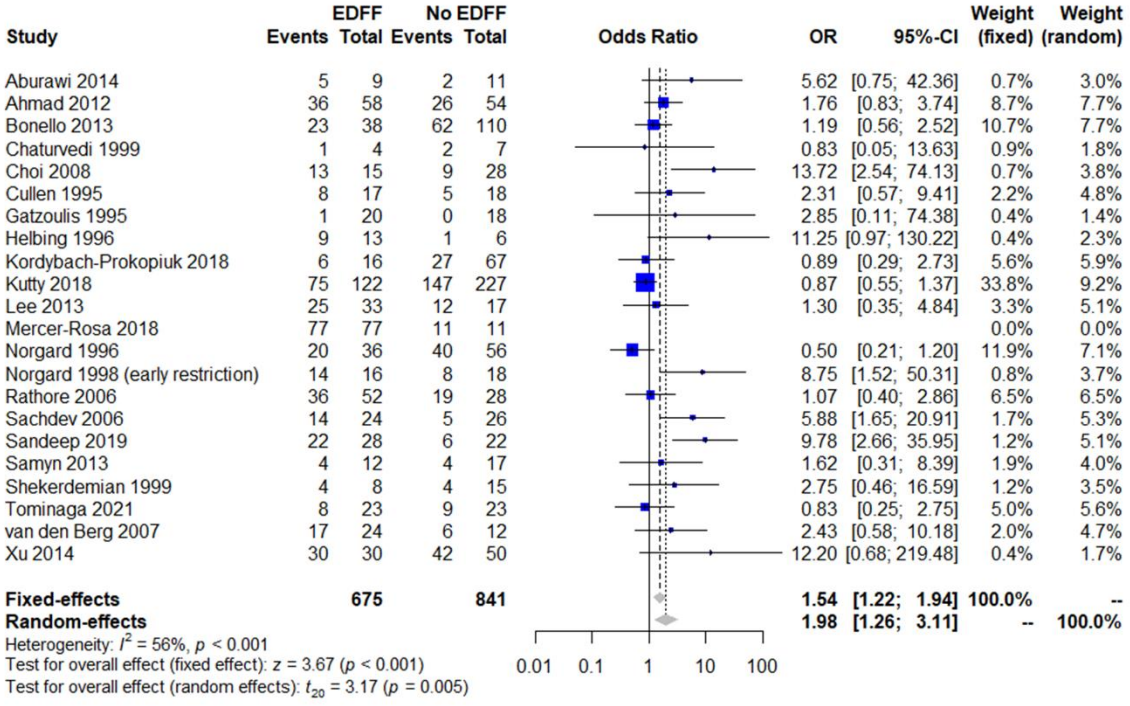
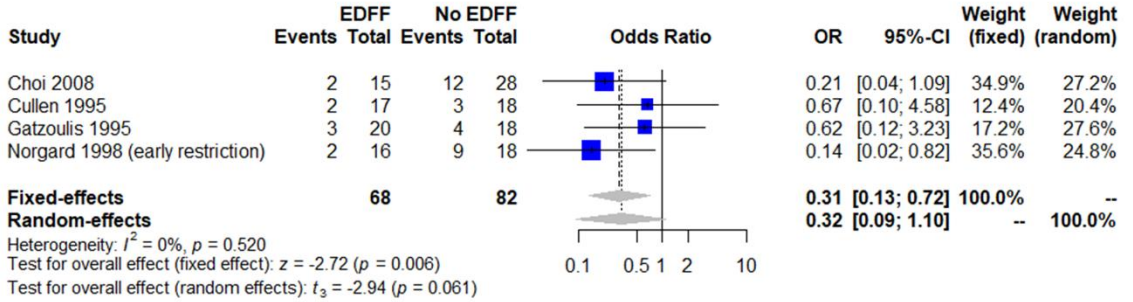


Figure S4. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; ICU, intensive care unit; MD, mean difference; OR, odds ratio; SD, standard deviation.

A. Outflow patch repair



B. ICU Length of stay (days)

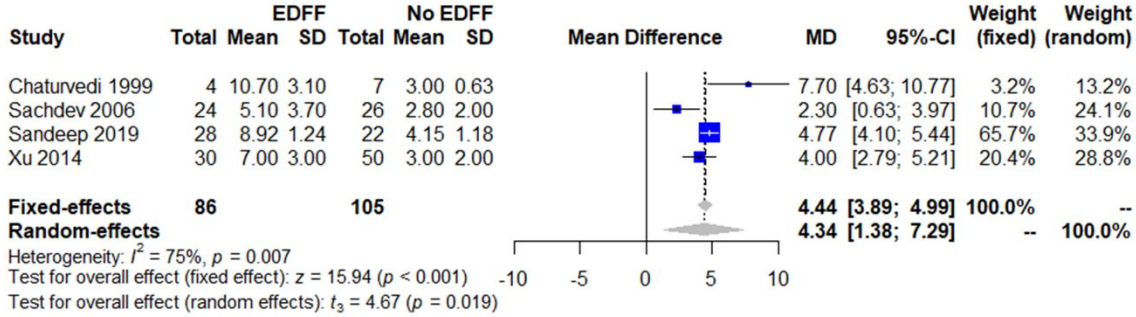
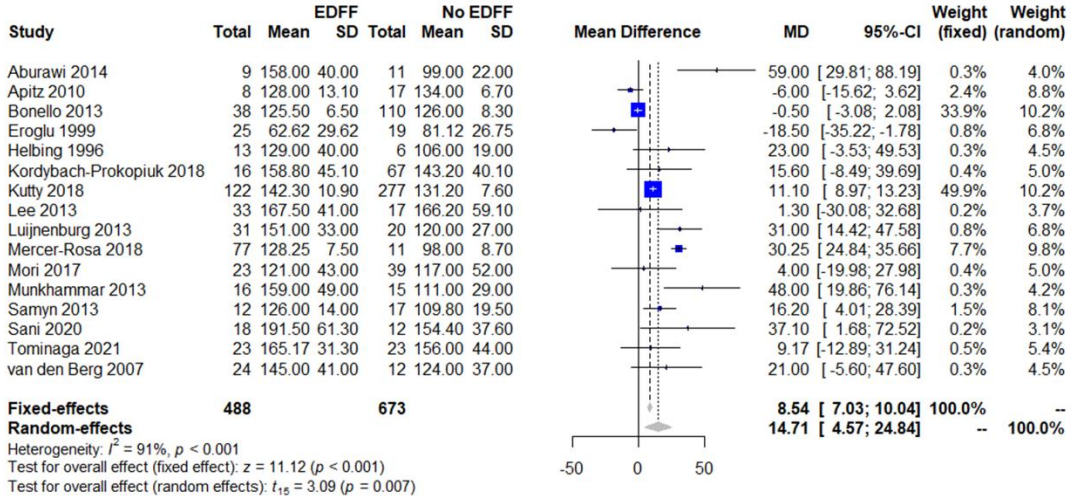
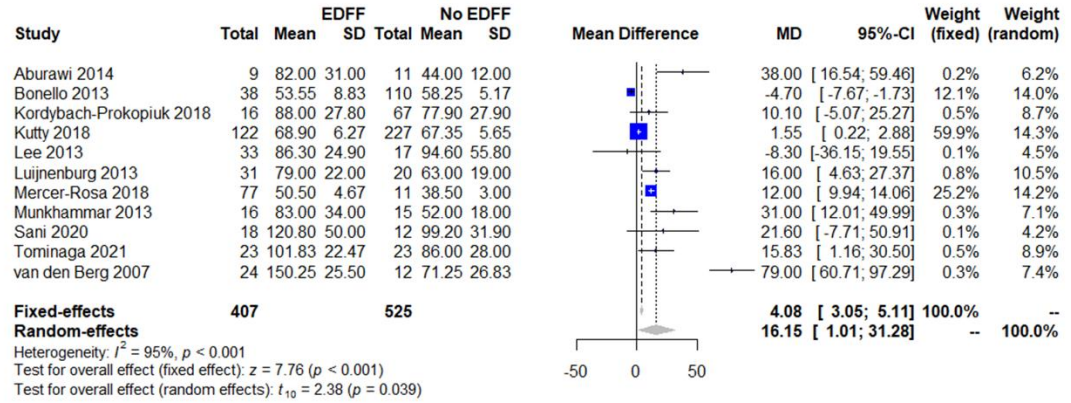


Figure S5. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; RVEDVi, right ventricular end-diastolic volume indexed; RVESVi, right ventricular end-systolic volume indexed; RVSVi, right ventricular stroke volume indexed; SD, standard deviation.

A. RVEDVi (mL/m²)



B. RVESVi (mL/m²)



C. RVSVi (mL/m²)

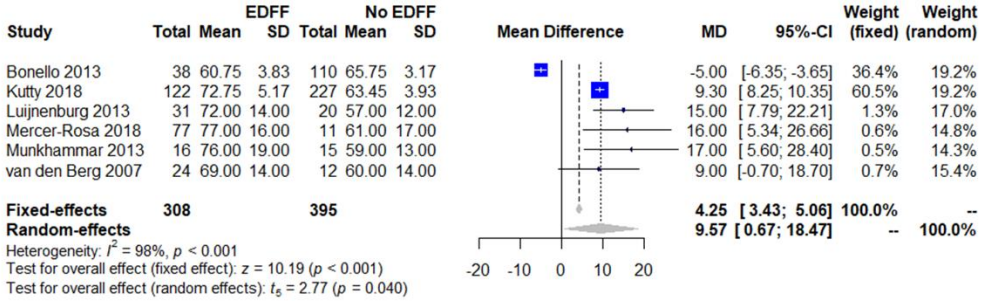
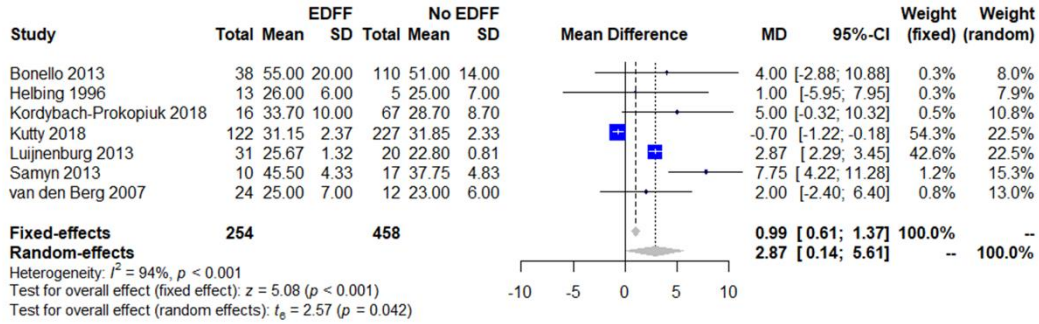
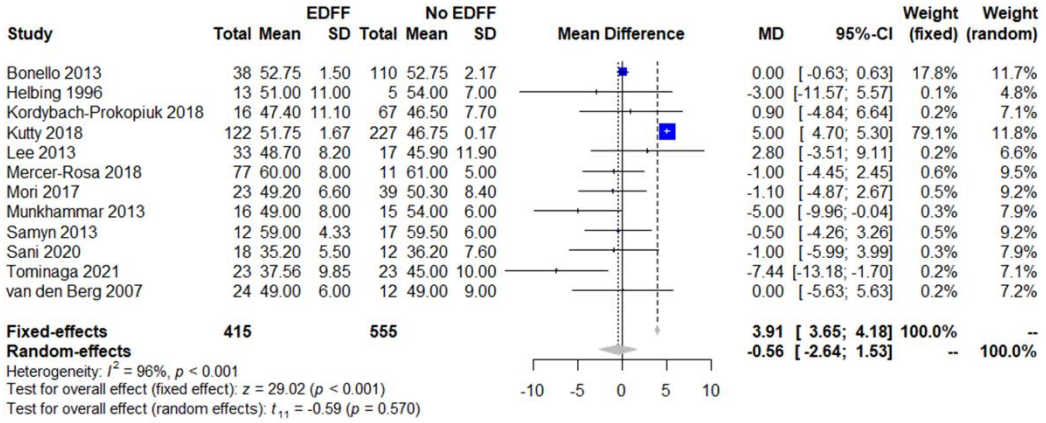


Figure S6. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; RVEDP, right ventricular end-diastolic pressure; RVEF, right ventricular ejection fraction; RVESP, right ventricular end-systolic pressure; RVMi, right ventricular mass indexed; SD, standard deviation.

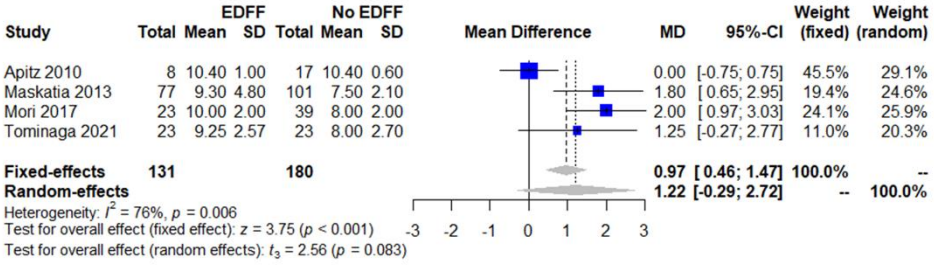
A. RVMi (g/m²)



B. RVEF (%)



C. RVEDP (mmHg)



D. RVESP (mmHg)

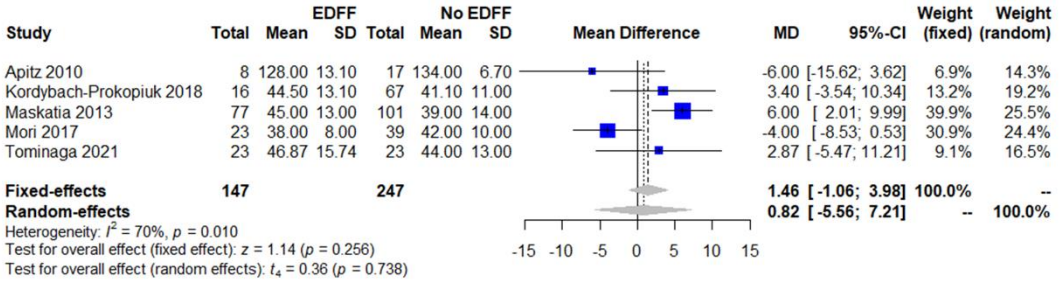
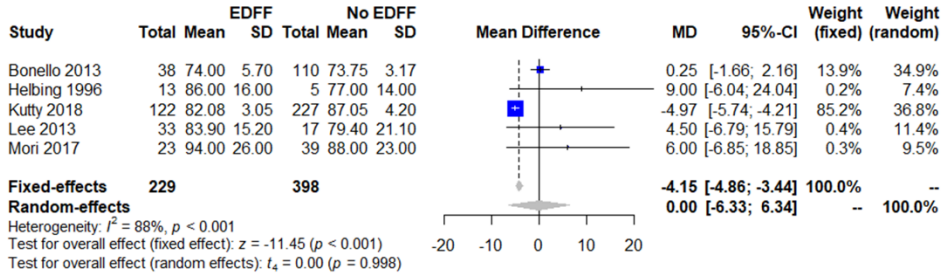
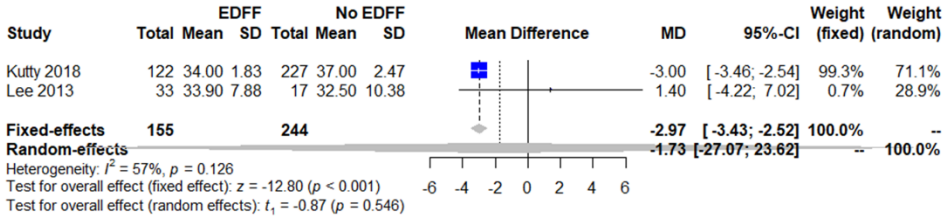


Figure S7. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; LVEDVi, left ventricular end-diastolic volume indexed; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume indexed; LVSVi, left ventricular stroke volume indexed; MD, mean difference;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

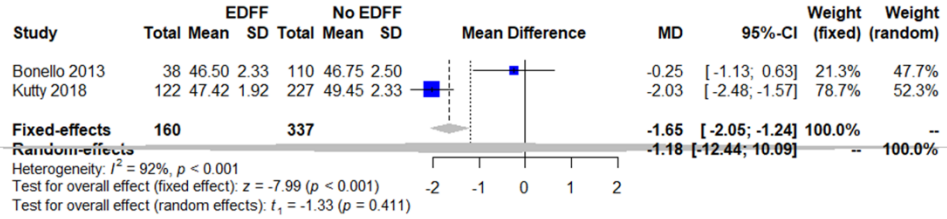
A. LVEDVi (mL/m²)



B. LVESVi (mL/m²)



C. LVSVi (mL/m²)



D. LVEF (%)

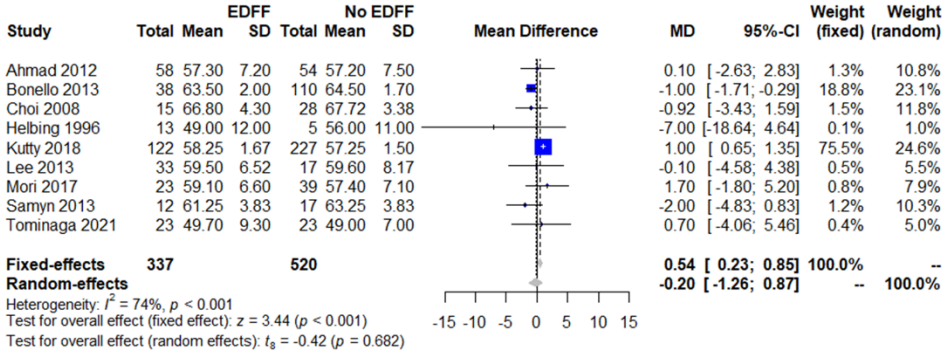
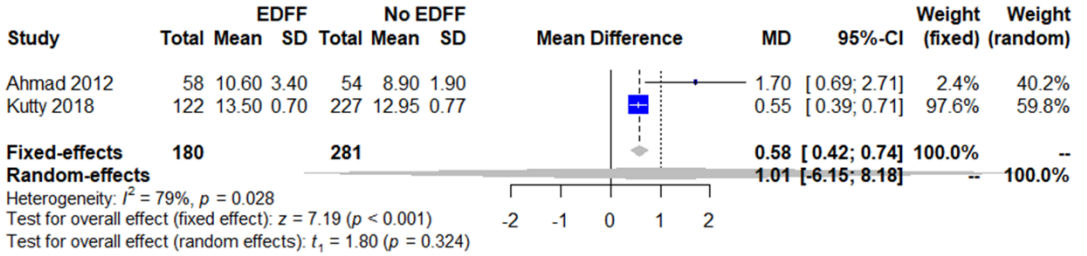


Figure S8. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; RAAi, right atrial area indexed; RAVi, right atrial volume indexed; SD, standard deviation.

A. RAAi (cm^2/m^2)



B. RAVi (mL/m^2)

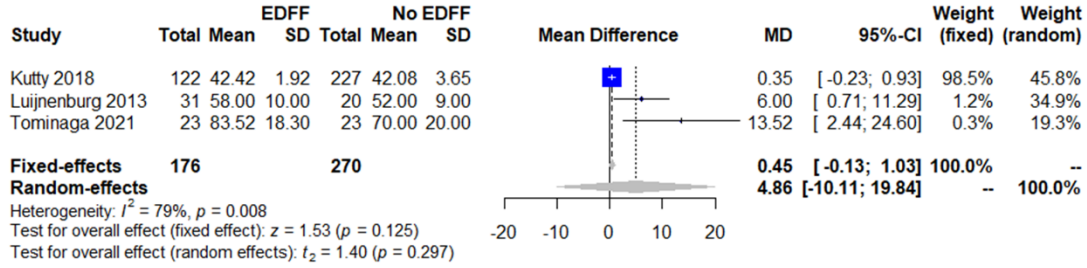
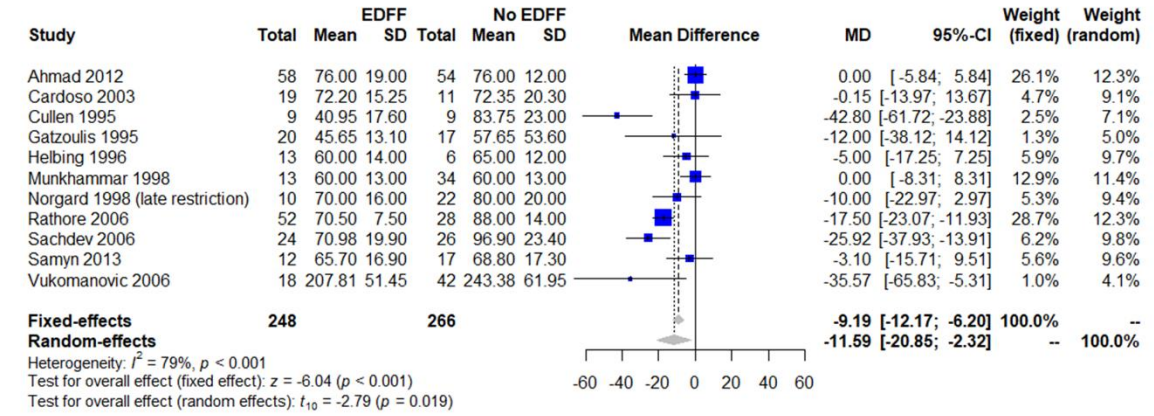
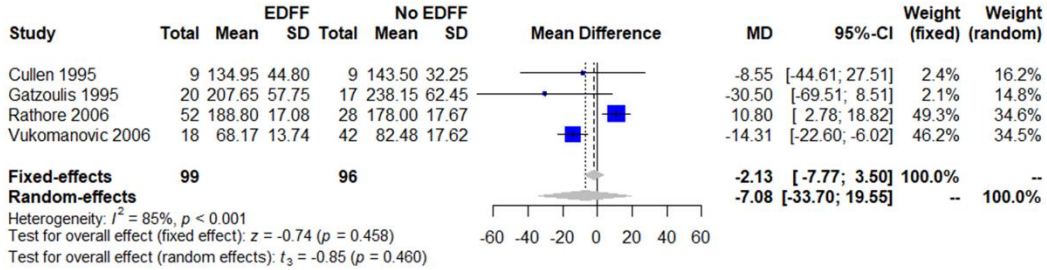


Figure S9. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; SD, standard deviation.

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



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



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

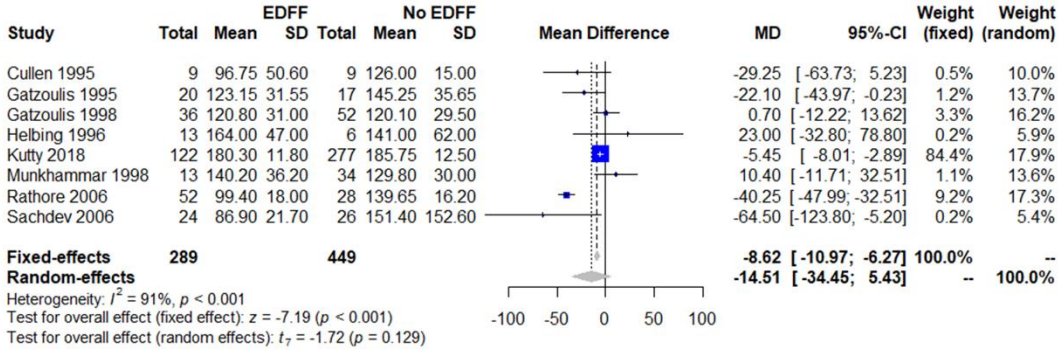
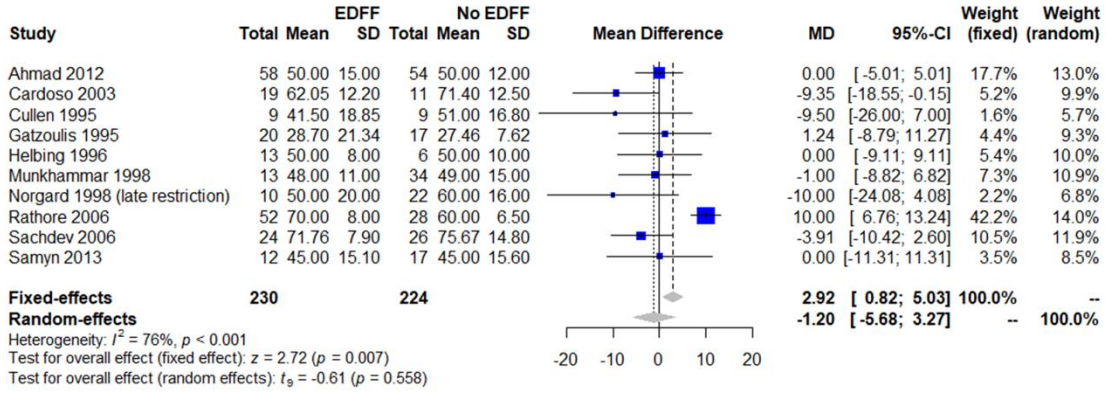
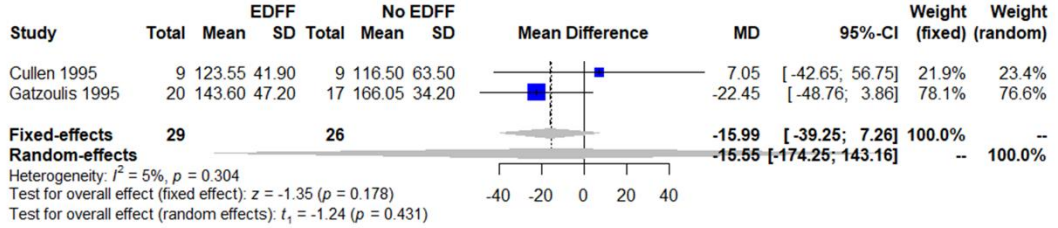


Figure S10. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; SD, standard deviation.

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



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



C. E/A at the tricuspid valve

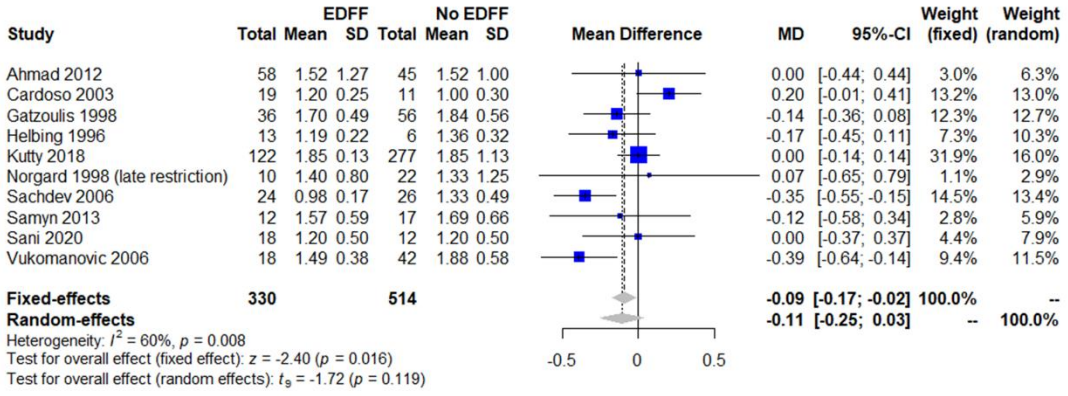
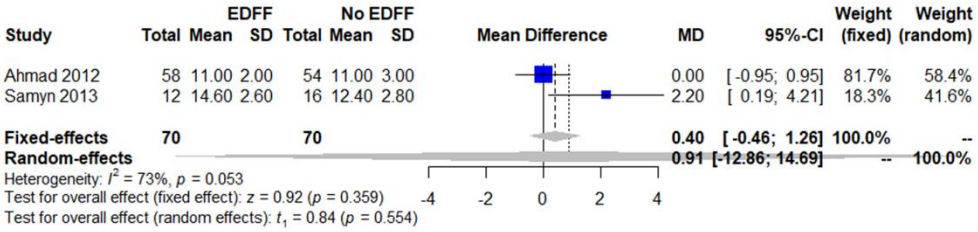
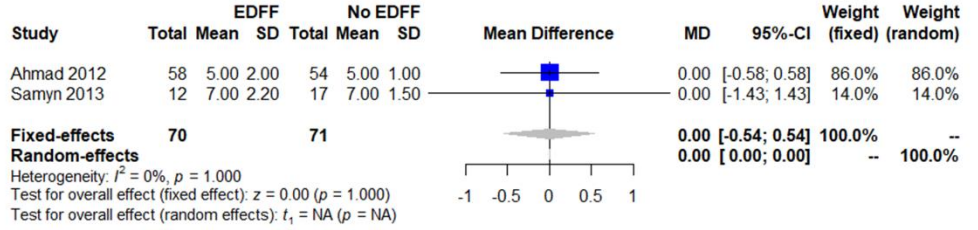


Figure S11. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; SD, standard deviation.

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



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



C. E/E' at the tricuspid valve

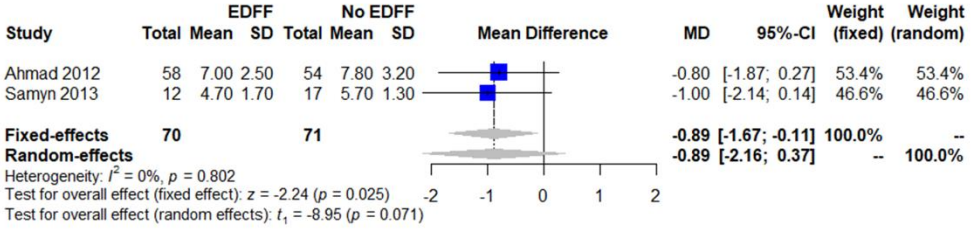
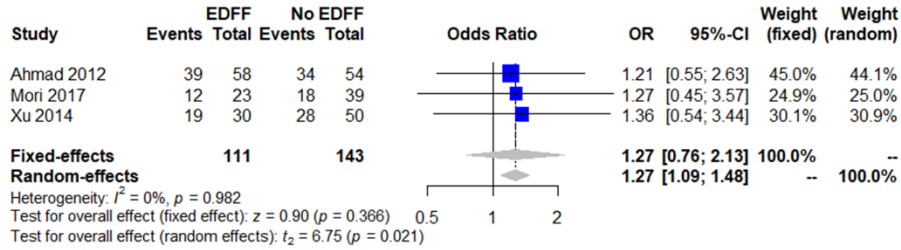
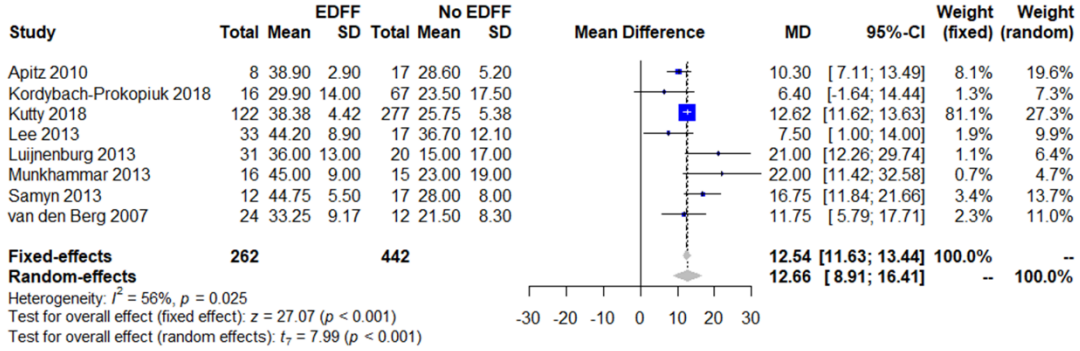


Figure S12. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; OR, odds ratio; PR, pulmonary regurgitation; SD, standard deviation.

A. Moderate to severe PR



B. PR fraction (%)



C. PR duration (msec)

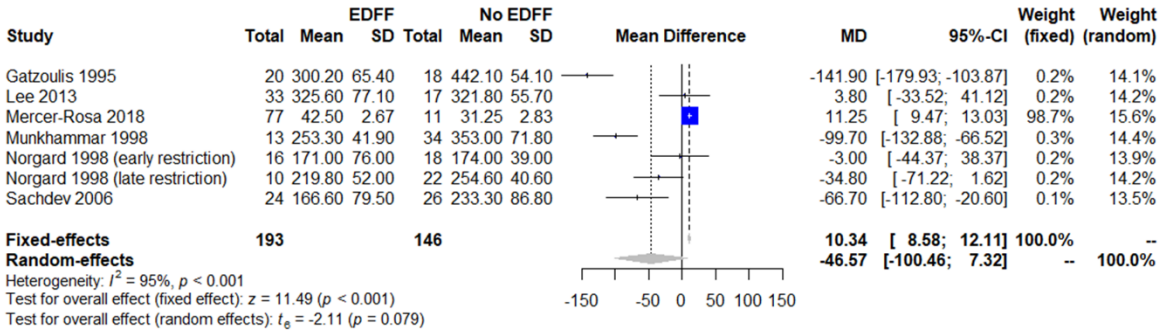
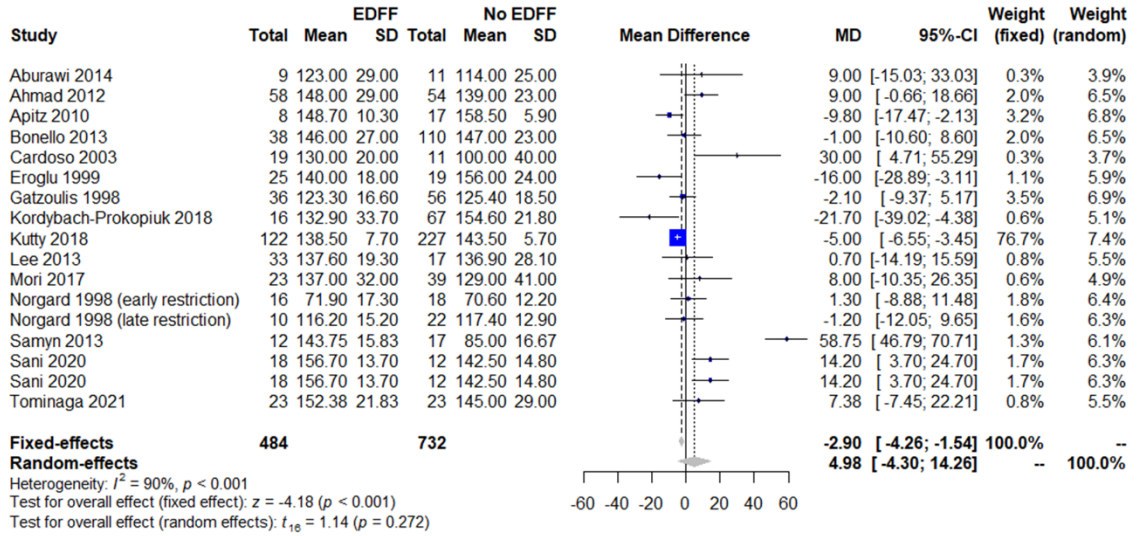
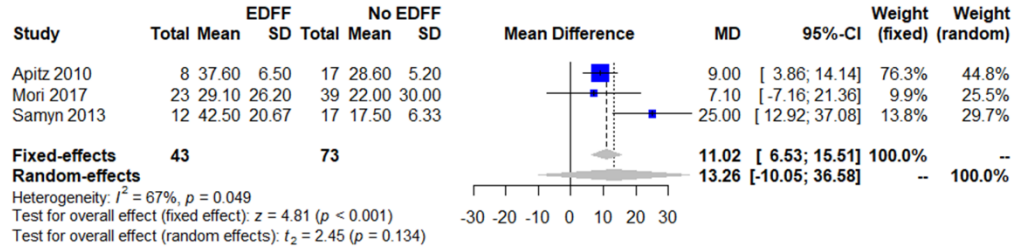


Figure S13. Forest plots. BNP, brain natriuretic peptide; CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; OR, odds ratio; SD, standard deviation.

A. QRS duration (msec)



B. BNP (pg/mL)



C. NT-proBNP (pg/mL)

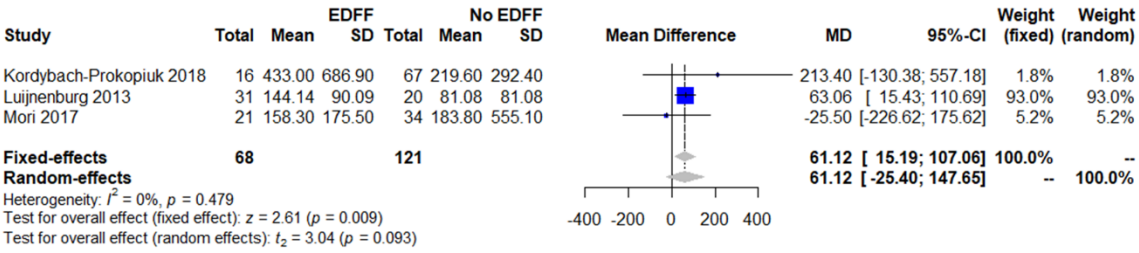
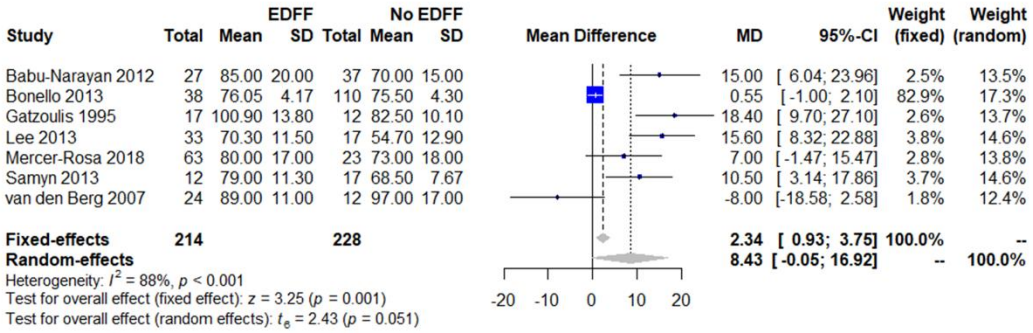


Figure S14. Forest plots. CI, confidence interval; EDFF, end-diastolic forward flow; MD, mean difference; OR, odds ratio; SD, standard deviation; VO2, oxygen consumption.

A. Peak VO2 (%)



B. Peak VO2 (mL/kg/min)

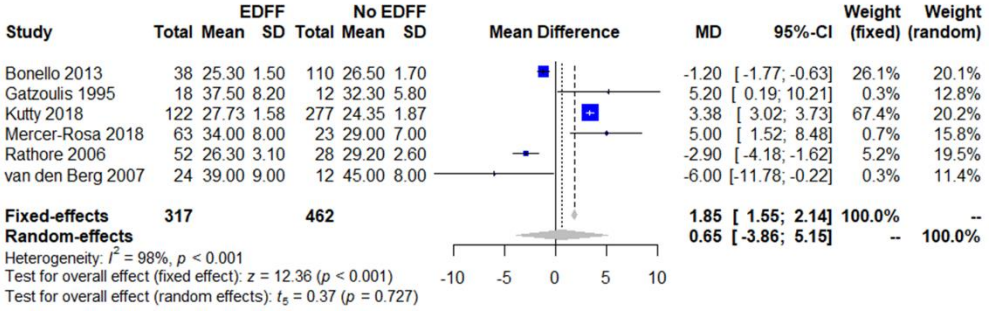


Figure S15. Publication bias analysis by funnel plot graphic. (A) transannular patch repair. (Begg and Mazumdar's test: p=0.025, Egger's test: p=0.002). **(B) right atrial volume indexed.** (Begg and Mazumdar's test: p=0.117, Egger's test: p=0.014). **(C) pulmonary regurgitation fraction.** (Begg and 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).