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Title: Infundibular Sparing vs Transinfundibular Approach to the Repair of Tetralogy of Fallot

Running Head: Infundibular sparing repair for TOF

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Abstract:

Introduction: The right ventricular infundibular sparing approach (RVIS) to the repair of Tetralogy of Fallot (TOF) avoids a full-thickness ventricular incision, typically utilized in the transinfundibular (TI) method.

Methods: We performed a retrospective, age-matched cohort study of patients who underwent RVIS at Texas Children's Hospital or TI at Children's Hospital Medical Center in Nebraska and subsequently underwent cardiac MRI (CMR). We compared right ventricular end-diastolic and systolic volumes indexed to body surface area (RVEDVi and RVESVi) and right ventricular ejection fraction (RVEF) as primary endpoints. Secondary endpoints were indexed left ventricular diastolic and systolic volume (LVEDVi and LVESVi), left ventricular ejection fraction (LVEF), RV sinus EF and RV outflow tract EF (RVOT EF).

Results: Seventy-nine patients were included in the analysis; 40 underwent RVIS and 39 underwent TI repair. None of the patients in the TI repair group had an initial palliation with a systemic to pulmonary arterial shunt compared to 7 (18%) in the RVIS group ($p<0.01$). There was no appreciable difference in RVEDVi (122±29cc/m^2 vs 130±29cc/m^2,$p= 0.59$) or pulmonary regurgitant fraction (40±13 vs 37±18,$p=0.29$) between the RVIS and TI groups. Compared to the TI group, the RVIS group had higher RVEF (54±6% vs 44±9%,$p<0.01$), lower RVESV (57±17cc/m^2 vs 67±25cc/m^2,$p=0.03$), higher LVEF (61±11% vs 54±8%,$p<0.01$), higher RVOT EF (47±12% vs 41±11%,$p=0.03$) and higher RV sinus EF (56±5% vs 49±6%,$p<0.01$)

Conclusions: In this selected cohort, patients who underwent RVIS repair for TOF had higher right and left ventricular ejection fraction compared to those who underwent TI repair.

Keywords: tetralogy of Fallot, right ventricular infundibular sparing repair, cardiac MRI

Introduction:

Childhood surgical correction of tetralogy of Fallot (TOF) results in low short-term mortality and morbidity[1,2]. RV dysfunction is associated with long-term morbidities, and related to chronic pulmonary regurgitation, RV fibrosis and RV obstruction, obesity and gender[3-8]. Infundibular scarring has been associated with worsening RV dilation and dysfunction in an animal model[9].

The optimal surgical strategy to the repair of TOF is an area of controversy. Many institutions perform early elective repair[10,11]. This transinfundibular (TI) approach relieves RV obstruction and cyanosis early, but requires a full-thickness incision in the infundibulum of the RV[12]. In contrast, the RV infundibular sparing technique (RVIS) avoids a full-thickness infundibular incision (Figure 1). The proposed benefit of this strategy is preservation of infundibular contractility[13]. The aim of the present study was to compare RV size and function by cardiac MRI (CMR) in patients who underwent RVIS repair to those who underwent TI approach.

Methods:

We performed an age-matched; multi-institutional retrospective cohort study comparing CMR measurements of RV size and function in patients with TOF repaired via RVIS at Texas Children's Hospital (TCH) or TI at Children's Hospital and Medical Center, University of Nebraska (CHMC). Pediatric (<18 years of age) patients with repaired TOF who underwent CMR evaluation prior to any repeat surgical intervention between January 2004 and April 2014 were identified. RVIS approach was defined by avoidance of a full-thickness infundibular incision and transatrial, transpulmonary approach to VSD closure and resection of infundibular muscle[11, 12]. When the pulmonary annulus was inadequate, the pulmonary arteriotomy extended across the annulus by ≤5mm. Repair via the RVIS approach is typically performed at 6-8 months of age. An intervening systemic to pulmonary artery shunt is necessary prior to complete repair in approximately 17%, and a transannular patch in approximately 75% of cases[12]. Three patients underwent TI at TCH due to the desire to avoid shunt physiology due to the presence of concomitant lung disease (extreme prematurity, congenital diaphragmatic hernia, and/or multiple respiratory infections), and were excluded from the study. The TI approach was defined by a full thickness incision of the infundibulum. In cases with significant infundibular hypoplasia, a transinfundibular patch was utilized to relieve obstruction. Otherwise, infundibulotomies were closed primarily. Throughout the study period, ventriculotomies were typically performed via a vertical incision.

Patients in both RVIS and TI groups were excluded if they had pulmonary atresia or if they received an RV to pulmonary artery conduit during initial repair. Patients were categorized based on age at the time of CMR as follows: 3-5 years, 5-9 years, 9 – 13 years, and 13 – 18 years. To control for the effect of age on RV size and function, patients were matched 1:1 within these age categories. When the number of TI vs RVIS patients in each age category were disparate, patients were selected for inclusion with the use of a random number generator.

CMR studies were performed using a 1.5-T whole body scanner using a cardiac or thoracic coil and previously published protocols[14]. ECG-gated, breath-held or free-breathing cine imaging was performed in the short axis plane using balanced steady-state free precession sequences. The stated indications for CMR in each patient were to evaluate biventricular size and systolic function and to evaluate pulmonary regurgitant fraction in the context of repaired TOF. Referrals for CMR were dependent upon the individual practitioners at each institution. Generally speaking, patients were referred as part of the standard assessment of a patient with repaired TOF. CMR studies from both institutions were anonymized and loaded onto an independent workstation (CMR 42, Circle CVI Inc., Calgary, Canada). Measurements were performed by a radiology technician with expertise in post-processing CMR studies in patients with congenital heart disease (NAD) and reviewed by a pediatric cardiologist with expertise in CMR (SAM). Both observers were blinded to surgical technique, institution, and clinical outcome. The RV was traced to the level of the pulmonary valve annulus, and trabeculations were included in cavity size. The RV was divided into the RV sinus and the RV outflow tract (RVOT) in both diastole and systole. The RVOT/MPA border was defined by the pulmonary valve annulus. The border RVOT/RV sinus border was defined by the septal and parietal bands, similar to prior studies[15-17]. RV sinus and RVOT ejection fractions (EF) were calculated. Phase contrast imaging was employed to calculate pulmonary regurgitant fraction (PRF)[18]. The main pulmonary artery is often significantly dilated in the setting of repaired TOF. As peak velocity in the main pulmonary artery is underestimated by cross-sectional phase contrast imaging in this setting, this value was not recorded. In-plane phase contrast imaging of the RVOT obtained in a minority of the studies, and therefore was not collected as part of this study.

Primary endpoints were: RVEF, indexed RV end-diastolic volume (RVEDVi), and indexed RV end-systolic volume (RVESVi). RV systolic dysfunction was defined as EF<45%, as this is a previously identified risk factor for major adverse events[4,19]. Data were expressed as mean ± standard deviation when parametric and median and inter-quartile range (IQR) when non-parametric. Shapiro-Wilk test was applied to determine normality. Statistical analyses were carried out using SPSS (SPSS IBM, Chicago IL, Version 23). Categorical variables were analyzed using chi-square test. Continuous variables were compared using Student's T-test (parametric) or Mann Whitney U test (non-parametric). Stepwise multivariable linear regression was used to evaluate the primary outcome measures of RVEF, RVEDVi, and RVESVi using the following independent variables: RVIS repair, transannular patch, age at CMR, and gender. Independent variables were removed from the regression analysis in a stepwise fashion for P values greater than 0.15. The assumptions of linearity, homoscedasticity, independence of errors, and unusual points and normality of residuals were met. There was independence of residuals, as assessed by a Durbin-Watson statistic of 2.08. As later age at repair and the possible use of an intervening systemic to pulmonary artery shunt are inherent characteristics of the RVIS approach, these variables were not controlled for in the model.

This project was supported by the cardiovascular research institute at Texas Children's Hospital. Approval was obtained from the Internal Review Boards at the Baylor College of Medicine and University of Nebraska College of Medicine. Consent was waived.

Results:

Patients underwent TOF repair between February 1994 and May 2011. Information on surgical volume was not available from either center prior to 1995. From 1995-2011, the total number of cardiopulmonary bypass cases and TOF repairs performed were 7,384 and 491 (TCH) and 2,669 and 134 (CHMC). At both institutions, surgical volume increased steadily across time. Surgical mortality rates following repair of TOF were 1.2% (TCH) and 2.0% (CHMC). No patients who received an intervening systemic to pulmonary artery shunt died prior to TOF repair. A total of 112 patients who met inclusion criteria underwent CMR at either TCH (N=67, 14%) or CHMC (N=45, 34%) during the study period. Patients who underwent TOF repair and were followed clinically at other institutions were not included. After age-matching, there were 40 patients in each cohort. After patient selection had concluded and data analysis had begun, one subject was identified in the TI group was excluded due to insufficient CMR images for analysis. Table 1 displays baseline demographic and surgical data. The median age at TOF repair was significantly younger in the TI group. None of the patients in the TI group required a staged surgical approach. Median age at CMR was not different between the two groups (Table 2).

Average RVEF was higher in the RVIS group compared to the TI group (55±5% vs 48±6%, p=<0.01). The odds of RV dysfunction (RVEF<45%) were 8.5x (1.7-48) higher in the TI group compared to the RVIS group. RVOT EF and RV sinus EF were higher in the RVIS group compared to the TI group (47±12% vs 40±12%, p=0.01 and 56±5% vs 49±6%, p<0.01 respectively, Figure 2). LVEF was higher in the RVIS group compared to the TI group, 59±4% compared to 56±8% (p=0.04). There was a modest correlation between LVEF and RVEF, with R=0.56, p<0.01 (Figure 3). Figure 4 displays average RVEF for both groups within each age category. RVESVi was significantly lower in the RVIS group compared to the TI group (P=0.02), while RVEDVi, and LVEDVi were not significantly different between the two groups (Figure 5 and Table 3).

On univariable analysis, within the RVIS cohort, there was slightly lower RVEF in males compared to females (53±4% vs 56±4%, p=0.04). Within the TI cohort, there was no significant difference in RVEF between males and females (47±6% vs 49±7%, p=0.63). Within the RVIS cohort, RVEDVi in males was 136±32 ml/m^2 compared to 122±23 ml/m^2 in females (p=0.15), and within the TI cohort the average RVEDVi in males was 148±45 ml/m^2 compared to 120±41 ml/m^2 in females (p=0.07). The presence of a transannular incision did not have a significant association with global or segmental ventricular size or function (Table 4). Patients who underwent transannular incision had higher PRF compared to those who did not. Within the RVIS cohort, older age at CMR correlated with higher RVESVi (R=0.5, p=0.001) and RVEDVi (R=0.6, p< 0.01). There was no appreciable association between age and RVEF or LVEF in the RVIS group; we found no appreciable association between age and any outcome variable within the TI group. Within the RVIS group, there was no significant difference in RVEF, RVEDVi, RVESVi, RVOT EF or RV body EF between patients who did or did not receive a systemic to pulmonary artery shunt. Within each cohort, there were no significant associations between age at TOF repair and any of the outcome variables.

In a multivariable model that included surgical strategy (RVIS vs. TI), age at CMR, and gender, female gender (B=2.1, p=0.11) and RVIS repair (B=6.6, p<0.005) were associated with higher RVEF with an adjusted R^2=0.28. Female gender (B=9.8, p=0.07), younger age at CMR (B=1.2, p=0.03), and RVIS repair (B=10.0, p=0.03) were associated with lower RVESVi with an adjusted R^2 of 0.19. Younger age at CMR (B=2.2, p=0.01) and female gender (B=15.5, p=0.08) were associated with lower RVEDVi with an adjusted R^2 of 0.12.

Discussion:

We performed a retrospective cohort study comparing RV size and function between patients who underwent the RVIS with those who underwent TI. This represents the first direct comparison of

CMR-based measurements of ventricular size and function in this setting. The RVIS cohort had higher average RVEF, an 8-fold reduction in odds of RV dysfunction, and lower average RVESVi than the TI group. RVOT EF, RV sinus EF and LVEF were higher in the RVIS vs the TI group. Multivariable analyses revealed the RVIS approach to be associated with higher RVEF when accounting for female gender and age. Transannular incision was associated with higher PRF.

Prior studies have demonstrated a 25-year survival of 96.8% in patients who underwent transatrial/transpulmonary repair of TOF, with higher freedom from reoperation compared to classic repair, suggesting a lower incidence of pulmonary valve replacement[1]. Recently, Lee et al identified transinfundibular incision of ≥1 cm an independent risk factor for RV dysfunction[20]. The same group investigated whether patients with a "limited" ventriculotomy(<1cm) had improved RV size and function compared to those who had a "conventional" ventriculotomy(>1cm), and found no difference between the two groups[21]. Importantly, our study compared patients who underwent any infundibulotomy (TI) to those in whom no infundibulotomy was performed (RVIS). Within this context, our findings suggest that the presence of even a "limited" (1cm) infundibulotomy imparts a long-term maladaptive effect on RV function.

We speculate that the higher RVEF we observed in the RVIS group is due to preservation of a contractile infundibulum. In a porcine model, an infundibulotomy results in greater RV dilation and reduced RV function[9]. In the setting of patients with TOF, delay in RVOT excursion correlates with QRS duration, suggesting that scarring of the RVOT leads to mechanical dyssynchrony[22], a known risk factor for RV dysfunction and sudden cardiac death[23]. RVOT dysfunction correlates with overall RV dysfunction, LV dysfunction, and exercise capacity[24,25]. Our findings of lower RVOT EF and global EF in the TI group are consistent with the hypothesis that early infundibular injury has lasting consequence. One unexpected finding was higher RV sinus EF in the RVIS group. The presence of an infundibular incision and subsequent scar may result in increased wall stress and subsequent adverse remodeling distal to the incision itself. Alternatively, the transinfundibular incision in TI cases may have been extended inferior to where we defined the boundary of the RVOT.

There was no difference in RVEDVi and PRF between the RVIS and TI group, and this may be impacted by the inherent selection bias within the study design. The lower RVESVi in the RVIS group is not surprising, and may be indictive of improved compensatory mechanisms to volume overload in this cohort. The development of RV dysfunction is multifactorial, and while chronic pulmonary regurgitation and RV volume overload are initially well tolerated, eventually compensentory mechanisms of the ventricle to volume overload fail, resulting in increased end-systolic volume and reduced EF [19].

There may be further hemodynamic effects of the RVIS approach that were not specifically elucidated during this study but which also lead to the observed difference in RVEF. While we did not assess the degree of residual obstruction in each group, no patient underwent repeat surgery for RV obstruction. It is possible that patients in the RVIS cohort had mild, subclinical RVOT obstruction which may impart a hemodynamic benefit in the setting of repaired TOF[26]. Patients who undergo RVIS are often treated with beta blockade in the postoperative period to protect against tachycardia which may impair RV filling and worsen RVOT obstruction. However, the degree of residual RVOT obstruction in patients who undergo the RVIS approach is rarely clinically significant in the long-term[12]. While older age at repair may be seen as a disadvantage of the RVIS approach, the myocardium earlier in infancy may be more at risk for injury than later in infancy. Although later increase in RV mass as measured by CMR is a risk factor for poor clinical outcome in the setting of repaired TOF, RV hypertrophy has been correlated with improved contractility in an animal model[5,27]. The correct degree of mild RV obstruction and hypertrophy may preserve contractility and limit maladaptive RV remodeling.

Other potential consequences of the RVIS approach may include surgical approaches that are altered in order to preserve the infundibulum. While there were no statistically significant differences in transannular incision and PRF between RVIS and TI groups, these analyses may suffer from lack of power. The authors believe that the presence of annular hypoplasia determines the need to perform a transannular incision. However, there may be differences in surgical approach related to the preservation of the infundibulum that have long-term consequence and are unaccounted for by our analyses.

Our finding of a higher LVEF in the RVIS group is likely secondary to favorable ventricular-ventricular interactions. Davlouros et al showed that RVOT akinesis resulted in decreased RVEF, and found a correlation between RVEF and LVEF, similar to our study[7,24]. Transannluar incision did not appear to be associated with worsened RVOT EF, although it was associated with higher PRF. This supports the hypothesis that sparing the infundibulum and the pulmonary valve annulus are both important to long-term RV health, via different mechanisms. RV dysfunction and volume overload have been linked to long-term outcomes in patients with repaired TOF[4,5,7]. The degree of volume overload may not be modified by the RVIS approach, preservation of the infundibulum appears mechanistically important for overall RV systolic function.

The impact of gender on outcomes in congenital heart disease has been difficult to establish due to the infrequency of cardiac lesions and heterogeneity within malformations. While data on children suggest that males are at higher risk for high risk congenital heart disease, females are at higher risk for mortality when high risk disease exists[28]. Sarikouch et al reported higher RV end-systolic and end-diastolic volumes and lower RVEF in male patients with repaired TOF compared to females. However, when standardized to healthy controls, females actually demonstrated higher z-scores for RV volumes and lower z-scores for RVEF[8]. Our findings of higher RVEDVi and lower RVEF in male patients may be reflective of the characteristic gender differences seen in the general population.

Limitations

There are some inherent limitations of this study. As they reflect differences inherent to the approach, age at repair and the need for an intervening systemic to pulmonary artery shunt were not controlled for in the multivariable model. On univariate analysis, these factors did not appear to be associated with any of the outcome measures within each cohort. Early in the RVIS experience, repair was delayed until later in infancy. For this reason, the median age at TOF repair was 9.8 months. Other confounding differences in intraoperative and perioperative management may exist between and among the two institutions. While substantial differences exist between the centers in surgical volume, both are high volume centers with low surgical mortality. We did not analyze these other potential confounding factors, as the detail in the medical record did not allow for this. A certain degree of variability exists when measuring RV volumes, especially in the context of an immobile patch. We accounted for this by using a single, blinded, observer to measure RV volumes. Selection bias likely exists, with increased referral of patients for CMR in the presence of worsening RV dilation or dysfunction on echocardiogram, especially in younger age groups. The decision of when to provide pulmonary valve competency in the setting of chronic pulmonary insufficiency is somewhat subjective. These sources of bias may have contributed to the negative finding of differences in PRF and RVEDVi between the two cohorts and to the relatively high rates of transannular incision. Although we did not have sufficient data to match patients based on characteristics of their preoperative anatomy, patients with significant pulmonary valve hypoplasia who required a right ventricule to pulmonary artery conduit were excluded from the analysis. Additionally, patients were enrolled based on the clinical indication to obtain a cardiac MRI, therefore the study population is likely biased towards patients with significant preoperative RV outflow tract obstruction. . After study planning and data collection had begun, more recent data on risk factors for adverse events in TOF have identified RVEF cutoffs of 50% (female) and 48% (male)[5]. These values are slightly higher than the 45% cutoff value used in this study.

Conclusion

In this study, the RVIS approach to repair of TOF was associated with higher RVEF, RVOT EF, RV sinus EF, and LVEF, lower RVESVi, and an 8-fold reduction in the odds of RV dysfunction compared to the TI approach. These potential benefits must be balanced against the need to delay the TOF repair to 6-8 months of age and occasional need for a systemic to pulmonary artery shunt.

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Author Contributions:

M. Olive: concept and design, data collection, drafting of the manusciprt, approval of the article

C. Fraser: concept and design, critical revision of the article, approval of article

S. Kutty: Data collection, concept and design, critical revision of the article, approval of the article

D. McKenzie: concept and desing, critical revision of the article, approval of the article

J. Hammel: concept and design, critical revision of the article, approval of the article

R. Krishnamurthy: concept and design, critical revision, approval of the article

N. Dodd: data collection, critical revision, approval of the article

S. Maskatia: concept and design, critical revision of the article, statistics, approval of the article

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Figure Legends:

Figure 1: Comparison of the right ventricular infundibular sparing repair (left) and the transinfundibular repair (right).

Figure 2: Average global RV ejection fraction, RVOT ejection fraction and RV sinus EF for the transinfundibular (dark blue) and RVIS (light blue) groups. Error bars represent 1 SD.

Figure 3: Association between left and right ventricular ejection fraction (entire cohort).

Figure 4: Average right ventricular ejection fraction for the TI and RVIS groups within each age category. Error bars represent 1 SD.

Figure 5: Average right ventricular end-diastolic and end-systolic volume for the TI (dark blue) and RVIS (light blue) groups. Error bars represent 1 SD.

Table 1

Table 1: Demographic and Surgical Data			
	Transinfundibular N=39	RVIS N=40	P-value
Male	27 (69%)	24 (60%)	0.40
Trisomy 21	2 (5%)	1 (3%)	0.54
22q11 deletion syndrome	3 (8%)	3 (8%)	0.98
Median (IQR) age at repair in months	4.0 (2.5-5.8)	9.8 (6.2-14.8)	<0.01
Systemic to pulmonary artery shunt	0	7 (18%)	<0.01
Transannular patch	29 (74%)	35 (88%)	0.14

RVIS: Right ventricular infundibular sparing approach

Table 2

Table 2: Age Distribution			
	Transinfundibular N=39	RVIS N=40	P-value
Median (IQR) age at CMR in years	11.5 (4.4-15)	9.7 (6.0-14)	0.65
Age category 1 (< 5 years)	8	8	
Age category 2 (5 – 9 years)	7	8	
Age category 3 (9–13 years)	9	9	
Age category 4 (13 – 18 years)	15	15	

RVIS: Right ventricular infundibular sparing approach

CMR: Cardiac MRI

Table 3

Table 3: Endpoints Stratified by Surgical Strategy			
	Transinfundibular N=39	RVIS N=40	P-value
Pulmonary regurgitant fraction (%)	35±17	41±13	0.08
RVEDVi (ml/m^2)	139±45	130±29	0.32
RVESVi (ml/m^2)	73±28	60±17	0.01
RV Sinus EDVi (ml/m^2)	113±37	105±24	0.31
RV Sinus ESVi (ml/m^2)	57±22	46±13	0.01
RVOT EDVi (ml/m^2)	26±10	25±8	0.45
RVOT ESVi (ml/m^2)	16±8	13±5	0.08
LVEDVi (ml/m^2)	78±19	71±13	0.07
LVESVi (ml/m^2)	35±9	29±7	<0.01

RVEDVi (indexed right ventricular end-diastolic volume)

RVESVi (indexed right ventricular end-systolic volume)

RV Sinus EDVi (indexed right ventricular sinus end-diastolic volume)

RV Sinus ESVi (indexed right ventricular sinus end-systolic volume)

RVOT EDVi (indexed right ventricular outflow tract end-diastolic volume)

RVOT ESVi (indexed right ventricular outflow tract end-systolic volume)

LVEDVi (indexed left ventricular end-diastolic volume)

LVESVi (indexed left ventricular end-systolic volume)

All volumes indexed to body surface area

Table 4: Endpoints Stratified by Transannular Patch			
	Transannular patch (N=64)	No patch (N=15)	P-value
Pulmonary regurgitant fraction (%)	40±15	30±15	0.03
RVEDVi (ml/m^2)	134±39	136±34	0.85
RVESVi (ml/m^2)	66±24	69±23	0.60
RV Sinus EDVi (ml/m^2)	108±32	111±26	0.80
RV Sinus ESVi (ml/m^2)	51±19	55±17	0.54
RVOT EDVi (ml/m^2)	26±9	25±10	0.94
RVOT ESVi (ml/m^2)	15±7	15±8	0.88
LVEDVi (ml/m^2)	73±18	80±12	0.13
LVESVi (ml/m^2)	31±9	35±7	0.10

RVEDVi (indexed right ventricular end-diastolic volume)

RVESVi (indexed right ventricular end-systolic volume)

RV Sinus EDVi (indexed right ventricular sinus end-diastolic volume)

RV Sinus ESVi (indexed right ventricular sinus end-systolic volume)

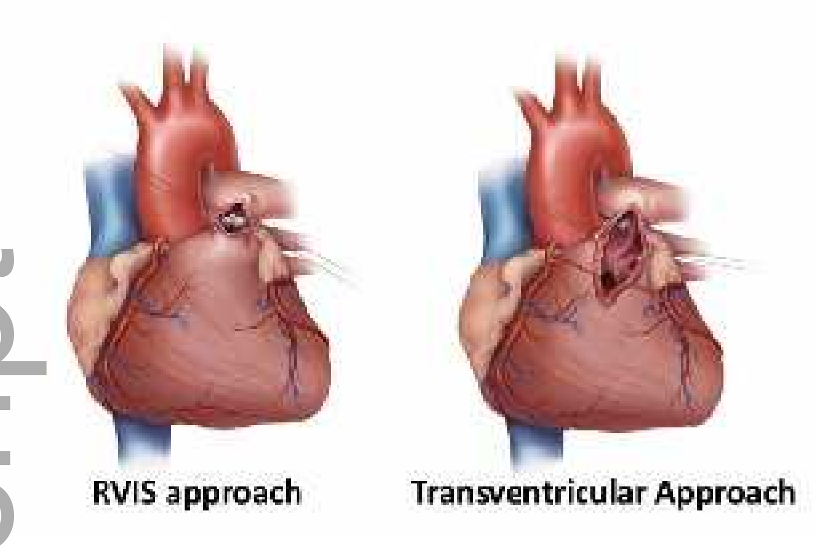
RVOT EDVi (indexed right ventricular outflow tract end-diastolic volume)

RVOT ESVi (indexed right ventricular outflow tract end-systolic volume)

LVEDVi (indexed left ventricular end-diastolic volume)

LVESVi (indexed left ventricular end-systolic volume)

All volumes indexed to body surface area



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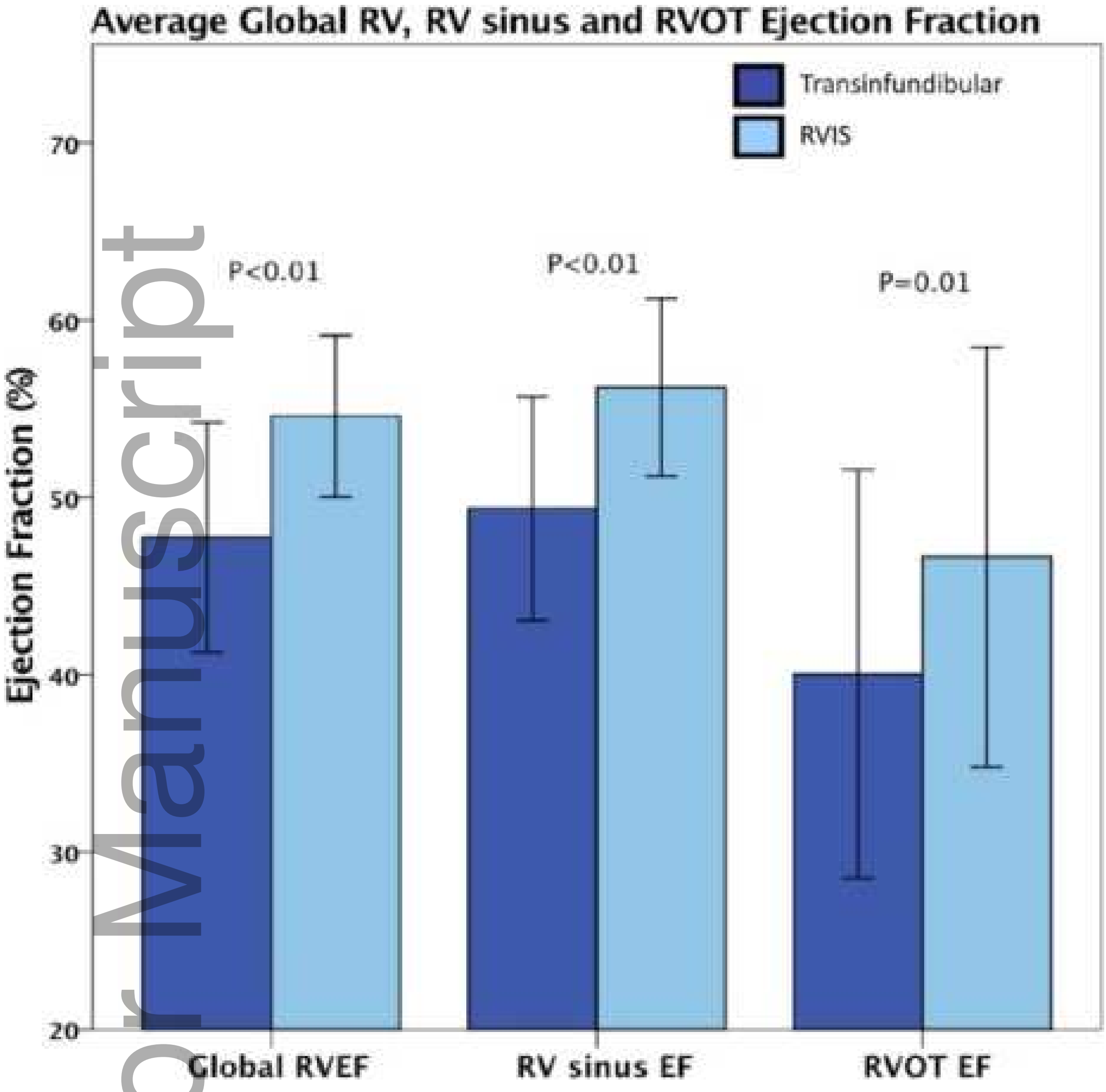

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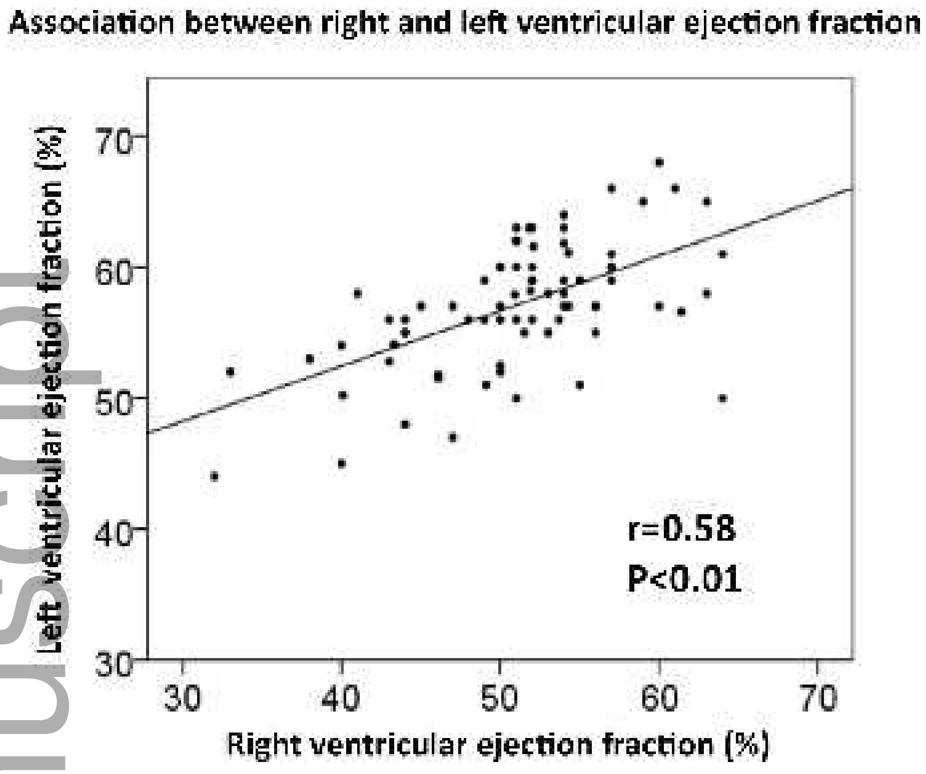

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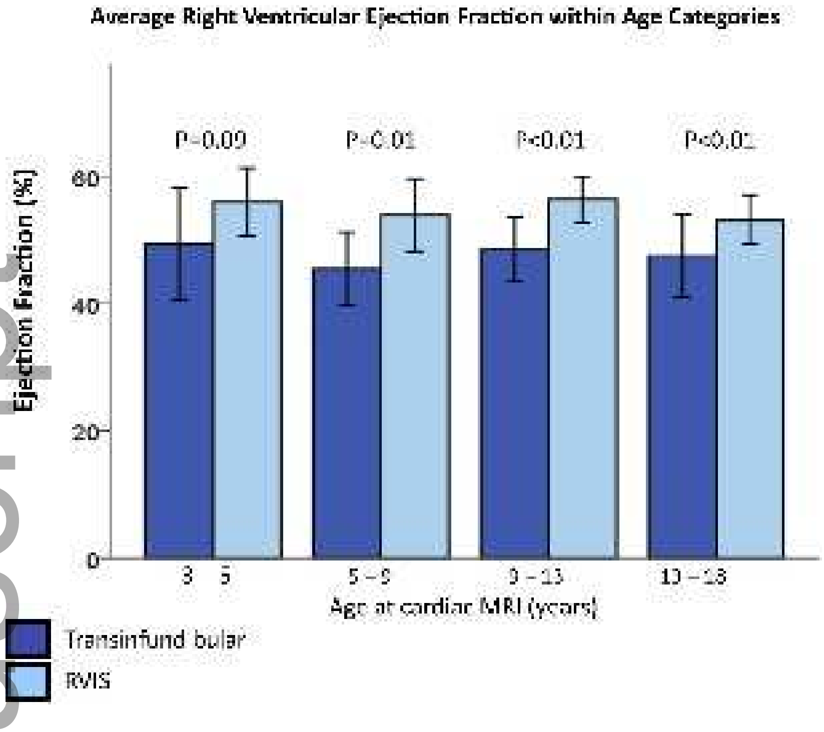

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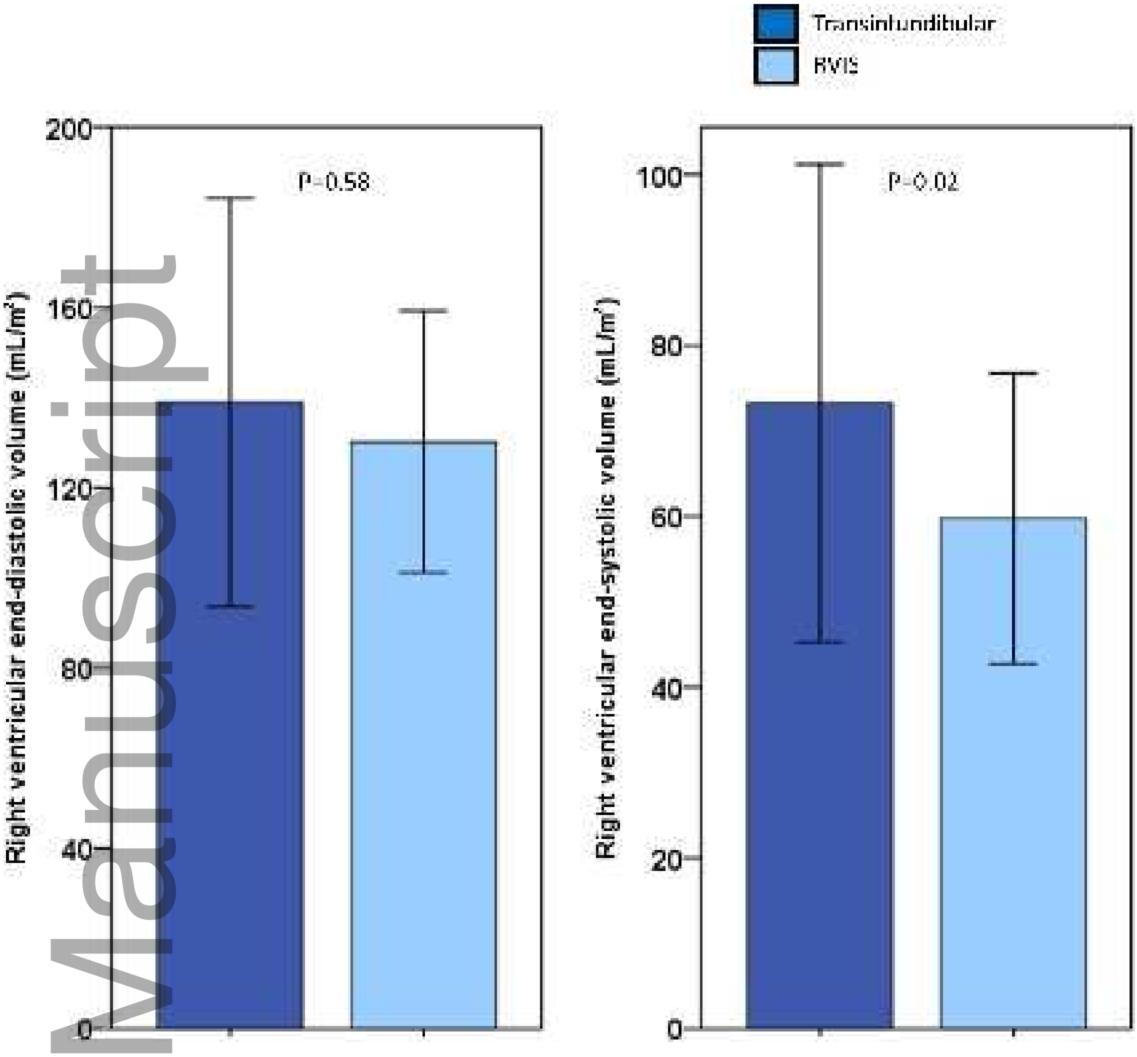

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