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The applications and potential limitations of right ventricular volumes as surrogate marker in tetralogy of fallot

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ABSTRACT

Cardiac magnetic resonance imaging derived right ventricular (RV) volumes are often necessary for optimal timing of pulmonary valve replacement in patients with tetralogy of Fallot (TOF). This practice is based on previous studies that reported preoperative RV volumetric thresholds that predicted postoperative RV remodeling. As a result, pulmonary valve replacements are being performed even in asymptomatic patients based on RV volumetric thresholds that predict complete postoperative RVOT remodeling. Hence, RV volumes are now being used as surrogate markers/endpoints for future cardiovascular outcomes. Unfortunately, there are no studies showing survival benefit for performing pulmonary valve replacement at smaller RV volumes. This review underscores some of the limitations of using RV volumes as surrogate markers for clinical outcomes, and also highlights knowledge gaps about the pathophysiologic mechanism of cardiovascular death in the TOF population.

1. Background

Tetralogy of Fallot (TOF) is one of the most common congenital heart disease diagnoses [1,2], and it is an understudied cause of heart failure and cardiovascular mortality [3]. It is characterized by subaortic ventricular septal defect associated with right ventricle (RV) outflow tract obstruction and override of the aorta with RV hypertrophy which invariably leads to cyanosis [4,5]. TOF is treated surgically by relieving the RV outflow tract obstruction and closing the ventricular septal defect [4]. Surgical TOF repair is palliative and not curative, because it always results in residual or recurrent hemodynamic lesions such as pulmonary regurgitation [4,6,7]. It is postulated that chronic pulmonary regurgitation is one of the *upstream* events in the chain of causality of cardiovascular mortality after TOF repair (Fig. 1) [4–13]. The median survival in the TOF population is 55 years, and more than 80% of the deaths are due to end-stage heart failure or arrhythmia/sudden cardiac death [14–16]. Since chronic pulmonary regurgitation underpins the pathogenesis of cardiovascular mortality after TOF repair, interventions to address chronic pulmonary regurgitation should modify the natural history of disease.

2. Treatment of chronic pulmonary regurgitation

Pulmonary valve replacement, either surgical or transcatheter, is the gold standard therapy for chronic pulmonary regurgitation [12,13,15,17]. Pulmonary valve replacement is now a low risk procedure with less than 2% risk of perioperative mortality, and results in an instantaneous elimination of RV volume overload due to pulmonary regurgitation [12,13,15,17]. Unfortunately, pulmonary valve replacement is a temporizing strategy because of the limited longevity of pulmonary bioprosthetic valves which is typically 10–15 years [18–21]. As a result, the timing of pulmonary valve replacement is critical, because performing the procedure too early will result in the need for multiple reinterventions due to prosthetic valve degeneration, while performing the procedure to late may result in irreversible RV dilation and systolic dysfunction [22–24].

3. RV volumes as surrogate marker of cardiovascular outcomes

Cardiac magnetic resonance imaging is the gold standard for RV volumetric assessment, and typically measures RV end-diastolic

Abbreviations: TOF, tetralogy of fallot; RV, right ventricle; RVEDVI, right ventricular end-diastolic volume index; RVESVI, right ventricular end-systolic volume index.

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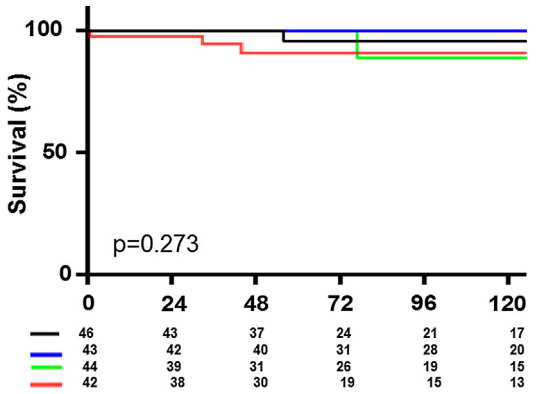

Fig. 1. Schematic showing natural history of tetralogy of Fallot (TOF) repair. Surgical TOF repair ***(left)*** leads to chronic pulmonary regurgitation (PR) and right ventricular (R) dilation and dysfunction ***(middle)*** and then to cardiovascular morbidity and mortality ***(right)***.

volume index (RVEDVI) and RV end systolic volume index (RVESVI) [22]. A landmark study by Oosterhof et al. [25] reported that complete RV remodeling (postoperative normalization of RV volumes) occur if pulmonary valve replacement is performed at RVEDVI < 160 ml/m^2 or RVESVI < 80 ml/m^2. Based on this study and several other subsequent studies, RVEDVI < 160 ml/m^{2}and RVESVI < 80 ml/m^2 became almost universally adopted as the threshold to recommend pulmonary valve replacement in order to prevent irreversible RV dilation and dysfunction [16,17,23–25]. Since it is postulated that RV dilation leads to RV systolic dysfunction which ultimately leads to cardiovascular death, RVEDVI and RVESVI which are predictors of RV remodeling, were therefore adopted as surrogate markers of cardiovascular outcomes such as mortality [16,17,23–25].

4. Timing of intervention based on surrogate markers

Since the publication of the landmarks study by Oosterhof et al in 2007, most outcome studies of pulmonary valve replacement now use RV volumes as surrogate marker, and similarly, some practice guidelines have endorsed the use of RV volumes for prognostication [16,17,23–25]. As a result, the number of pulmonary valve replacements performed in the United States has tripled in the last decade, and the age at the time of initial pulmonary valve replacement has decreased from median age of 30–35 years to median age of 20–22 years [18,20,26,27]. This proactive treatment paradigm is based on the premise that *optimal timing (early)* of pulmonary valve replacement will lead to RV remodeling, and thus prevent RV dysfunction and cardiovascular complications. Unfortunately, the use of RV volumes as surrogate markers for cardiovascular outcomes, which is the foundation for the current proactive treatment paradigm, creates a number of clinical problems that are addressed in the next section.

5. Limitations of RV volumes as surrogate markers

Since RV dilation and systolic dysfunction is in the chain of causality for cardiovascular mortality in the TOF population, the current proactive paradigm *assumes* that performing pulmonary valve replacement based on RVEDVI and/or RVESVI will result in a reduction in cardiovascular mortality. This concept has not been tested rigorously. In a recent observational study to assess the relationship between preoperative RV volumes and long-term postoperative survival [28], 175 adult TOF patients who underwent pulmonary valve replacement at Mayo Clinic Rochester, had preoperative RVEDVI and RVESVI of 117–208 and 57–136 ml/m^2 respective. The investigators grouped the cohort into 4 quartiles based on preoperative RVEDVI, and then compared the long-term survival between the different quartiles (Fig. 2). There was no difference in the long-term survival between the different quartiles [28]. Similar to this result, there are no studies till date that have demonstrated a long-term survival benefit based on timing pulmonary valve replacement exclusively based on RV volumes [15,17,23,24].

Apart from the questionable clinical benefit of pulmonary valve replacement based base RV volumetric remodeling as surrogate endpoint; patients are now undergoing pulmonary valve replacement at much younger age because of this treatment paradigm [27]. Since the median age for pulmonary valve replacement in the current era is around 20–22 years, and the median longevity of bioprosthetic pulmonary valve is 10–15 years [18,20,26], we will expect a patient to undergo about 4 additional interventions for pulmonary valve replacement by the age of 70 years. This will result in multiple surgical reoperations, which is associated with increased perioperative mortality because of fibrosis and scaring from prior operations [21]. Although transcatheter pulmonary valve replacement provides a less invasive alternative, the risk of patient prosthesis mismatch and the feasibility of performing multiple sequential pulmonary valve replacements have not been studied. Furthermore the presence of a prosthetic valve is associated with more than a 10-fold increase in the risk of endocarditis, and prosthetic valve endocarditis is associated with up to 30% risk of mortality even in the current era [29]. Implantation of pulmonary valve at an early age increases the at-risk period for prosthetic valve endocarditis.

6. Conclusions

The current review underscores some of the limitations of using RV volumes as surrogate markers/endpoints for clinical research

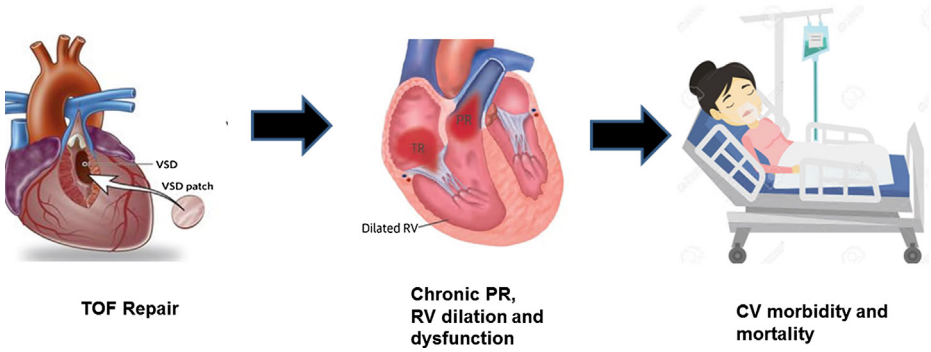

Fig. 2. Kaplan Meier curves comparing survival between all 4 quartiles: first quartile (black), second quartile (blue), third quartile (green) and fourth quartile (red).

and clinical practice. It also highlights some of the knowledge gaps in the chain of causality linking RV volumes with cardiovascular mortality (end-stage heart failure and arrhythmia/sudden cardiac death). Considering the importance of TOF in the epidemiology of congenital heart disease, its contribution to heart failure hospitalization and healthcare resources utilization, and the suboptimal long-term survival of only 5 decades, there is need for further studies to delineate the mechanism of cardiovascular death in this population.

Authors contribution

Alexander Egbe, Karim Osman and Naser Ammash: design, initial draft and final review.

Declaration of Competing Interest

The authors declare that they have no competing financial interests for this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2019.100430.

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