



Published in final edited form as:

JACC Cardiovasc Imaging. 2016 January ; 9(1): 11–13. doi:10.1016/j.jcmg.2015.08.017.

Is Biventricular Fibrosis the Mediator of Late Complications in Tetralogy of Fallot?*

Michael R. Zile, MD and David Gregg, MD

Division of Cardiology, Medical University of South Carolina, Charleston, South Carolina

Keywords

cardiac magnetic resonance imaging; congenital heart disease; diffuse fibrosis; extracellular volume fraction; tetralogy of Fallot

Childhood repair of tetralogy of Fallot (TOF) is one of the great successes of congenital heart surgery, with now >90% of patients surviving to adulthood (1). Late complications including sudden death, atrial and ventricular arrhythmias, and heart failure, however, persist. After childhood repair, most patients with TOF are left with pulmonary regurgitation. Initially, even severe pulmonary regurgitation is well tolerated with usually a relatively asymptomatic period for 20 to 30 years, but then late complications arise (2). It is not clear what changes mediate the onset of symptoms and late decompensation. Most studies have shown a link to residual pulmonary regurgitation with resultant right ventricular enlargement, but what triggers the development of symptoms, ventricular failure, and poor outcomes has been unclear. Increasing evidence suggests that extracellular matrix (ECM) changes and ventricular fibrosis may play an important role mediating the decline and could be either a potential target for intervention or a guide to the ideal timing of targeting late pulmonary valve replacement or other therapeutic interventions.

Using magnetic resonance imaging (MRI) late gadolinium enhancement (LGE) to quantify focal fibrosis, increased LGE has shown correlation with severity of disease (3). LGE, however, does not show the extent of diffuse extracellular changes in the myocardium and likely underestimates ECM changes. Increasingly, MRI T1 mapping has been used to calculate extracellular volume (ECV) fraction in a variety of cardiovascular states including heart failure, arrhythmia, and pulmonary hypertension. MRI-derived ECV correlates well with histological global fibrosis and can be a useful marker of myocardial fibrosis, and T1-derived ECV has been correlated with worse prognosis in heart failure and arrhythmia (4).

In this issue of *iJACC*, 2 papers provide insight into the possible mechanisms of late complications in TOF and give insight into left and right ventricular interaction in biventricular dysfunction. Both papers look at diffuse ventricular fibrosis using MRI T1

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. David Gregg, Division of Cardiology, Medical University of South Carolina, 25 Courtenay Drive, Charleston, South Carolina 29425. greggda@musc.edu.

Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

mapping to calculate ECV in repaired TOF and evaluate the relationship to clinical status and hemodynamics. Chen et al. (5) look at biventricular fibrosis calculating extracellular volume fraction in both the left and right ventricles, whereas Broberg et al. (6) limit themselves to an evaluation of the left ventricle, interested in the importance of left- and right-sided interdependence in TOF. We are intrigued to see studies validating in particular right heart MRI-derived ECV, as the thin-walled right ventricle may present unique imaging challenges.

The populations studied by each group are quite different, which may affect conclusions and findings. Perhaps, most importantly, the cohort in the Broberg et al. (6) study is a much older group (mean age 40 years) than the cohort of Chen et al. (5) (mean age 23 years) and the age at initial repair is also considerably later. The Broberg et al. (6) cohort with delayed initial surgical treatment is therefore more reflective of historical care and the cohort of Chen et al. (5) is closer to contemporary care, with early repair of TOF now the standard of care.

Both studies demonstrate increased myocardial ECV in TOF compared with control subjects. Chen et al. (5) additionally found that right ventricular (RV) and left ventricular (LV) ECV directly correlates with each other and that LV ECV was a strong independent predictor of arrhythmia. This seems to reinforce the concept that LV dysfunction in TOF may arise from RV and LV interdependence (7) and provides new insight that ECM changes may be important in the pathophysiology. Extending the observation that pulmonary regurgitation with progressive RV dilation is linked to complications in TOF (8), Chen et al. (5) also found that patients with primary volume overload and the most severe pulmonary regurgitation had increased RV ECV, whereas patients with less regurgitation and residual pulmonary stenosis did not have the same increase in RV ECV. This may mirror the observation that some patients with TOF and mild residual stenosis fare better with less RV dilation and dysfunction, perhaps resulting in less ECV expansion (9). Although Chen et al. (5) show a weak negative correlation between RV outlet tract gradient and RV ECV, the range of gradients shown are fairly modest, and in repaired TOF, increased RV outlet tract gradient is also associated with a smaller regurgitant volume. We, therefore, urge caution, concluding that severe RV hypertension either from pulmonary stenosis or other abnormalities is not a driver of increased ECV, and, in fact, studies of pulmonary hypertension have shown a relationship to increased fibrosis by LGE (10), and animal models of pulmonary hypertension have shown increased fibrosis, both histologically and using T1 mapping (11). The findings of Chen et al. (5) would support a theory that ongoing pulmonary regurgitation with ongoing RV volume overload triggers increased biventricular fibrosis, which may mediate late complications. Although the left ventricle is not directly volume overloaded, left-sided dysfunction and fibrosis appear to correlate with hemodynamic changes from right-sided overload and dysfunction. We do not know the mechanism of biventricular interaction, but possible mediators are mechanical linkage through the shared septum, electrical mediation from dyssynchrony, and indirect stimulation through right heart dysfunction triggering deleterious neurohormonal activation. In repaired tetralogy, LV injury may also be remote, with the left ventricle prone to premature fibrosis with aging as a result of childhood surgical or pre-repair loading injury that is unmasked with time.

Although each study used slightly different thresholds for abnormal left-sided ECV and techniques to measure ECV, the Broberg et al. (6) cohort also had a significantly greater percentage of patients with “abnormal” LV ECV than the Chen et al. (5) cohort. This may reflect the age of the population with more time to develop or may reflect distant injury to the LV delayed age of repair and different surgical care in older repairs. It is therefore difficult to know whether we will see as much LV fibrosis with current care. Correlating with late clinical complications, Broberg et al. (6) found a strong correlation between ECV and age and age at repair and functional status as well as increased ECV, wider QRS, and increased markers of congestive heart failure. Followed prospectively, increased ECV also predicted worse clinical outcome, suggesting a possible future prognostic role for ECV in TOF.

Together these papers show the intriguing role of increased biventricular fibrosis in repaired TOF as a possible mediator and predictor of worse clinical outcome. These findings likely have implications for noncongenital heart failure where biventricular dysfunction also predicts worse outcome than isolated left heart failure, yet the role of the right ventricle is often ignored. Although many questions remain, this work introduces rich investigations into myocardial fibrosis to include the right side of the heart and show the perhaps underappreciated interdependence between the left and right heart. The right heart is unique from the left and will likely require unique therapy to preserve function, and greater interest in understanding the process of RV ECM changes is an important step. These 2 studies are likely to stimulate future studies seeking to understand the role of fibrosis in RV pathology, not only by imaging but also through serum biomarker studies. Future studies in TOF may show evaluation of ECV and ECM activity to be a prognostic marker, a guide to timing of late pulmonary valve replacement, or potentially new therapeutic targets. More broadly, we hope that a greater understanding of RV fibrosis and its role in clinical outcomes in congenital heart disease can be extrapolated and enlighten us about the role of the right ventricle in left-sided failure, pulmonary hypertension, and arrhythmia.

References

1. Nollert G, Fischlein T, Bouterwek S, Böhmer C, Klinner W, Reichart B. Long-term survival in patients with tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. *J Am Coll Cardiol.* 1997; 30:1374–83. [PubMed: 9350942]
2. Simazaki Y, Blackstone EH, Kirklin JW. The natural history of isolated congenital pulmonary valve incompetence: surgical implications. *Thorac Cardiovasc Surg.* 1984; 32:257–9. [PubMed: 6207619]
3. Babu-Narayan SV, Kilner PJ, Li W, et al. Ventricular fibrosis suggested by cardiovascular magnetic resonance imaging in adults with repaired tetralogy of Fallot and its relationship to adverse markers of clinical outcome. *Circulation.* 2006; 113:405–13. [PubMed: 16432072]
4. Burt JR, Zimmerman SL, Kamel IR, Halushka M, Bluemke DA. Myocardial T1 mapping: techniques and potential applications. *Radiographics.* 2014; 34:377–95. [PubMed: 24617686]
5. Chen C-A, Dusenbery SM, Valente AM, Powell AJ, Geva T. Myocardial ECV fraction assessed by CMR is associated with type of hemodynamic load and arrhythmia in repaired tetralogy of Fallot. *J Am Coll Cardiol Img.* 2016; 9:1–10.
6. Broberg CS, Huang J, Hogberg I, et al. Diffuse LV myocardial fibrosis and its clinical associations in adults with repaired tetralogy of Fallot. *J Am Coll Cardiol Img.* 2016; 9:86–7.
7. Broberg CS, Aboulhosn J, Mongeon FP, et al. Prevalence of left ventricular systolic dysfunction in adults with repaired tetralogy of Fallot. *Am J Cardiol.* 2011; 107:1215–20. [PubMed: 21349477]

8. Gregg D, Foster E. Pulmonary regurgitation is the nexus of complications in tetralogy of Fallot. *Curr Rep Card.* 2007; 9:315–22.
9. Latus H, Gummel K, Rupp S, et al. Beneficial effects of residual right ventricular outflow tract obstruction on right ventricular volume and function in patients after repair of tetralogy of Fallot. *Pediatr Cardiol.* 2013; 34:424–30. [PubMed: 22915139]
10. Freed BH, Gomberg-Maitlin M, Chandra S, et al. Late gadolinium enhancement cardiovascular magnetic resonance imaging predicts clinical worsening in patients with pulmonary hypertension. *J Cardiovasc Magn Reson.* 2012; 14:11. [PubMed: 22296860]
11. Garcia-Alvarez A, et al. Association of myocardial T1-mapping CMR with hemodynamics and RV performance in pulmonary hypertension. *J Am Coll Cardiol Img.* 2015; 8:75–82.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript