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Editorial

Looking to the Left to Get It Right: Left Ventricular Systolic Dysfunction and Risk Stratification Late After Tetralogy of Fallot Repair

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See article by Egbe et al., pages 1784–1790 of this issue.

Much of the tetralogy of Fallot (TOF) story has been told from the perspective of the right heart. Embryologically, TOF develops as a right heart obstructive lesion arising secondary to anterior and superior deviation of the infundibular septum. Consequently, the anatomic substrate at birth, surgical repair in early childhood, and sequelae in later life are determined by early development and subsequent integrity of the right ventricular outflow tract (RVOT), pulmonary valve, and pulmonary arteries. The volume loaded right ventricle (RV) from chronic pulmonary valve regurgitation (PR) is the current archetype of subpulmonic ventricular failure in congenital heart disease.[1] As a result, much of the existing literature has been centred on preservation of myocardial health of the RV, specifically with respect to timing of pulmonary valve intervention to address chronic PR.[2] In this issue of the *Canadian Journal of Cardiology*, Egbe et al. provide a meta-analysis of the data pertaining to the association between systolic dysfunction of the left ventricle (LV) and adverse cardiovascular outcomes and suggest that we refocus our attention on the prognostic relevance of the left heart late after TOF repair.[3]

Tetralogy of Fallot: Both a Right and a Left Heart Disease

Knowledge of risk stratification in congenital heart disease typically builds in an incremental fashion and the conclusions drawn by Egbe et al. elaborate on important prior observations. The predictive value of LV systolic dysfunction in adults with repaired TOF (rTOF) has long been recognized. The association between moderate or severe LV dysfunction (LV ejection fraction [EF] $<$ 40% on echocardiography) and sudden cardiac death in adults with rTOF was first described by investigators in Toronto almost 2 decades ago.[4] Of note, these authors determined that the predictive value was strengthened with incorporation of a prolonged QRS duration ($\geq$ 180 ms). In a subsequent cardiovascular magnetic resonance imaging (CMR) study from Boston, moderate or severe LV systolic dysfunction (defined as LVEF $<$ 40%) was independently associated with impaired clinic status (New York Heart Association functional class III or IV).[5] In their cross-sectional single-centre study, Geva et al. highlighted the correlation between RV and LV systolic dysfunction, providing supportive evidence of the concept of ventricular-ventricular interactions in rTOF.

Ventricular interdependence, particularly the impact of alterations in size and function of the LV on RV integrity, was first described by Bernheim more than 100 years ago.[6] The converse, or the "reversed Bernheim effect," has been applied to rTOF.[7] Given the pervasive finding of chronic PR with associated RV enlargement and systolic dysfunction in the context of a shared ventricular septum, common myocardial fibres, and a single pericardial sac, it is not surprising that hemodynamically relevant RV disease would have a detrimental effect on the LV.[8,9] Importantly, following pulmonary valve replacement (PVR), LV filling and systolic function has been shown to improve,[10,11] with the greatest impact demonstrated in patients with moderate or severe impairment in LV systolic function before surgery.[12]

Tetralogy of Fallot Is More Than Ventricular Dilation and Dysfunction of the Right Heart

The prevailing morphology in the published literature is that of RV dilation secondary to chronic residual PR late after TOF repair, but other phenotypes which have received less attention include myocardial dysfunction related to diastolic disease and tissue injury secondary to replacement scar or diffuse fibrosis (as a result of necrosis secondary to chronic hypoxia of the myocardium before surgical repair, injury at the time of surgery, or coronary artery insufficiency [congenital or acquired]). An expanding body of literature relates to the contributions of ventricular conduction

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characteristics and electrical-mechanical associations.[13] Certainly, identification of the precise etiology of LV dysfunction should be sought to maximize the effect of the treatment strategy selected: surgical, interventional, medical, or a combination thereof. This level of granularity, though highly desirable, is largely absent from the published literature and therefore could not be featured in the meta-analysis by Egbe et al.[3]

What Does This Study Tell Us?

The strengths and weaknesses of the study by Egbe et al. are worthy of mention.[3] Given the infrequent occurrence of "hard" end points (death, aborted sudden death, and sustained ventricular tachycardia) on an annualized basis in rTOF, pooled data are necessary, and the present report contains data from 2854 patients published in 7 studies, for a total of 155 major adverse events. Although the common end point is termed "cardiovascular adverse event" (CAE) by the authors, it is important to note that death was all-cause mortality, and not strictly cardiovascular in nature; whether the association between LV dysfunction and adverse outcomes would be further strengthened by more stringent criteria for CAE remains speculative. Furthermore, we advise caution regarding interpretation of the data presented, because several of the studies selected may have overlapping populations (most notably the International Multicenter TOF Registry [INDICATOR] cohort outcomes, which are listed in 2 studies[14,15] as well as potential for additional overlap in a third study[16]). Moreover, adverse outcomes in adults with rTOF and recent PVR may not be directly comparable with outcomes in adults without recent PVR, because the former cohort may have adverse outcomes directly attributable to surgical reintervention.[15]

Importantly, the authors of the present study highlight that LV systolic dysfunction is likely multifactorial and a deeper understanding of contributing etiologies is necessary to direct management strategies.[3] In addition, this study supports the concept of ventricular-ventricular interaction: the right and left ventricles do not work in isolation, and impaired function, volume, or pressure load of one ventricle will ultimately affect the contralateral ventricle. The findings of this study should catalyze future research into the mechanistic underpinning of LV disease and ventricular-ventricular interaction in the rTOF cohort. It should also facilitate further research to study the effect of established heart failure therapies on LV systolic dysfunction and outcome in patients with rTOF. Although targeted surgical, catheter, or arrhythmia interventions can ameliorate LV function when systolic dysfunction is attributed to RV volume overload, coronary artery disease, or dyssynchrony, effective therapies for disease at the myocardial level have yet to be defined. The presence of diffuse myocardial fibrosis in rTOF is emerging as an important determinant of ventricular health, including the extent of reverse remodelling after PVR as well as development of major adverse cardiovascular events in the rTOF population. Non-invasive parametric imaging techniques can now be applied for detection and quantification of diffuse myocardial fibrosis through estimation of extracellular volume fraction calculation with the use of CMR T1 mapping sequences.[17-21] The value of early detection of myocardial fibrosis in rTOF requires further study, but it may allow for tailored medical therapies in an "at-risk" individual before manifest disease (including heart failure, arrhythmia, and/or sudden death) can occur. The incremental value of T1 mapping for risk stratification in rTOF requires clarification, but T1 mapping would likely carry additive prognostic value beyond traditional markers of systolic function such as EF. In line with a deepening understanding of the benefits of precision medicine, study of genetic determinants of fibrosis may allow further refinement in risk stratification and responsiveness to medical therapies in a given individual.

Future Perspectives

The treatment of TOF—from the time of pioneering cross-circulatory repair to the current era of percutaneous pulmonary valve implantation—is widely regarded as one of the greatest successes of congenital heart disease management. Notwithstanding successful intervention in pediatric life, these patients have a worse survival as compared with the normal population, principally from heart failure, arrhythmia, and sudden death, with increasing morbidity and mortality with advancing age. The identification of patients at risk of adverse events is highly desirable. Given the relatively rare occurrence of major adverse cardiovascular events, pooled data, preferably prospective in nature, are necessary to draw meaningful conclusions regarding prediction of risk and is the topic of ongoing study.[22,23] Although LV systolic dysfunction appears to be a strong independent risk factor for adverse cardiovascular events, as highlighted by the Egbe et al. study,[3] further clarification regarding contributing etiologies will be necessary before successful therapies can be initiated to treat, or better yet to prevent, left heart disease and related sequelae in rTOF.

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Disclosures

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