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Editorial

Challenges and Opportunities for Patients With Tetralogy of Fallot Across the Lifespan

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More than 70 years after the description of its first successful surgical repair, tetralogy of Fallot (ToF) remains a challenging but fascinating form of congenital heart disease. Patients born with ToF can be expected to live into adulthood with a 30-year survival that exceeds 95%.[1] Nevertheless, residual cardiac lesions after repair are nearly ubiquitous. These residual lesions include pressure-loading or volume-loading conditions, sometimes both. Consequently, considerable heterogeneity in sequelae can be seen with a wide spectrum of presenting features.[2] This has made risk stratification difficult, especially as our understanding of the complex interaction between the right and the left ventricle continues to evolve. Indeed, there needs to be a balance between preventing long-term complications and avoiding unnecessary interventions. However, there remain many uncertainties pertaining to the optimal management strategy particularly in asymptomatic individuals with progressive changes in imaging and electrical parameters.

In this focus issue of *CJCPC*, we assembled a collection of articles that review the state-of-the-art evidence pertaining to ToF management. Included are important topics that are central to our understanding of this congenital heart malformation: genotyping, phenotyping, risk stratification, arrhythmias, sudden death, interventions and surgery, access to care, patient advocacy, prevention, trajectory of care, heart failure, and the evolving field of machine learning.

Genotype, Phenotype, and Risk Stratification

The importance of genetic applications in patients with ToF is increasingly being recognized as the knowledge base in this domain continues to rapidly expand. Bassett et al.[3] provide a comprehensive overview of the evolution of genetic testing, genotype-phenotype correlations, and the association between genetic profiling and clinical outcomes. They also further detail genetic profiling in contemporary clinical practice and potential applications for molecular and personalized medicine.

Cardiopulmonary exercise testing is routinely used in the surveillance of children and adults with repaired ToF to characterize cardiorespiratory fitness. Although management guidelines incorporate cardiopulmonary testing in patient care algorithms given the association between exercise measures and clinical outcomes, thresholds for intervention based on the variety of exercise measurements available have not been clearly elucidated. Leonardi and Cifra[4] provide us with a thoughtful review of the available evidence pertaining to the use of various exercise test parameters to stratify risk of adverse clinical outcomes after ToF repair.

Cardiac imaging has contributed greatly to our understanding of the implications of haemodynamic sequelae after ToF repair, making this anatomy one of the best-characterized lesions across the spectrum of congenital heart diseases. Specifically, more than 2 decades of cardiovascular magnetic resonance imaging (CMR) research has provided us with a deepening understanding of the significance of chamber enlargement, ventricular dysfunction, increased mass, and myocardial scar.

In this issue, 2 articles expand on cardiac imaging applications in the population with ToF. Crean[5] reviews multimodality imaging, with a focus on contributions from CMR and cardiac computed tomographic imaging. This illustrative introductory article is followed by an elegant and thought-provoking review by Ghonim and Babu-Narayan,[6] detailing the association between CMR parameters and outcomes including a description of established risk scores and the emerging role of artificial intelligence.

Finally, Schäfer and Mawad[7] explore the promise of advanced imaging technologies such as 4D-flow CMR and high-frame-rate echocardiography. Studying and quantifying blood flow dynamics and ventricular energetics enable us to

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better assess the impact of adverse haemodynamics caused by flow patterns, energy loss, and vorticity. The authors discuss how these tools may allow earlier detection of suboptimal flow dynamics compared with conventional markers, and how this may help to better guide treatment.

Arrhythmias and Sudden Death

Patients with repaired ToF may face a spectrum of arrhythmias, impacting their health and quality of life. These include bradyarrhythmias, such as postoperative complete atrioventricular block, often necessitating lifelong pacing, junctional ectopic tachycardia, and various tachyarrhythmias, including intra-atrial re-entry tachycardia, nonautomatic focal atrial tachycardia, atrial fibrillation, and life-threatening ventricular arrhythmias. Indeed, ventricular arrhythmias pose a significant risk, underscoring the need for thorough screening and effective management in high-risk individuals. Vô et al.[8] discuss these arrhythmias and their specific management, highlighting the connection between haemodynamics and arrhythmias.

Advances in preventing sudden cardiac death in patients with repaired ToF involve proactive risk assessment and management of ventricular arrhythmias. Our understanding of predictive risk factors has improved over the past 25 years, shifting towards personalized risk prediction that incorporates extensive data. Kakarla et al.[9] delve into these risk stratification strategies in repaired ToF. Accurate characterization of disease complexity and anatomic repair strategy significantly affects sudden death risk, emphasizing the need for routine risk stratification. This informs primary prevention measures, such as defibrillator implantation, and prompts consideration of proactive invasive approaches, including ventricular tachycardia ablation and pulmonary valve replacement. Multidisciplinary teams of congenital heart disease experts play a crucial role in assessing and stratifying risk.

Interventions and Surgery

Multidisciplinary collaboration is essential to determine optimal surgical and interventional approaches, addressing staged repairs, reinterventions, and pulmonary valve replacement throughout a patient's life. Mosa et al.[10] review existing and persisting controversies regarding the timing of primary repair and staged approached in both the asymptomatic and symptomatic patients.

The spectrum of transcatheter interventions across the lifespan is discussed by Wong et al.[11] These treatments are increasingly used before surgical repair, offering palliative procedures through catheter-based methods. After initial surgical relief of right ventricular outflow tract obstruction, there may still be varying degrees of right ventricular outflow tract obstruction, pulmonary regurgitation, or both. Primary transcatheter pulmonary valve replacement is becoming a viable option, alongside surgical pulmonary valve replacement, due to their similar safety profile and effectiveness. The introduction of self-expanding platforms has expanded the spectrum of patients who can be treated percutaneously. With technological advances and growing expertise, catheter-based interventions are expected to play a greater role in the lifelong management of patients with ToF.

Vanderlaan and Barron[12] outline how the wide clinical spectrum of ToF represents a challenge for optimal surgical management. They discuss how multidisciplinary decision-making is central to an optimal surgical management that will maximize survival, minimize reintervention, and preserve right ventricular function across the lifespan.

Access to Care, Patient Advocacy, and Physical Activity Promotion

ToF require lifelong specialized congenital heart disease care. Mackie et al.[13] reviewed how access to such specialized care remains unequal. The reality of inconsistent access to care can paradoxically impact those who need it the most. The authors offer their recommendations on how to improve access to care, which is an essential step in reducing morbidity and improving quality of life.

In the last 2 decades, we have seen a very fortunate paradigm shift of exercise restriction to one of exercise prescription and promotion for patients with congenital heart disease. ToF is no exception. Buchanan et al.[14] reviewed the current knowledge on physical activity promotion and offer strategies for improving physical activity in patients with ToF.

Ross and Verstappen[15] offer their perspective on how advocacy by patient organizations has had a significant impact on patients' lives. Speaking with a common voice reflecting lived experience with congenital heart disease, patient organizations can uniquely and successfully influence research priorities, advocate for programmes and resources, and help ensure that important issues such as access to care, discrimination, and mental health support are prioritized by policymakers and care providers.

Lifespan Trajectories, Pregnancy, and Machine Learning

ToF is a lifelong chronic condition and a truly integrated lifespan approach has great potential to further our understanding of the various trajectories that these patients follow.

Alonso-Gonzalez et al.[16] provide a comprehensive map of the complex journey of the right ventricle in ToF. They start at the cellular and microarchitectural levels and detail the specificities of the right ventricle, its complex interaction with the left ventricle, and its various mechanisms for adaptation and remodelling in the face of significant residual lesions. They then explore the various tools that are available to identify the often insidious onset of right heart failure and discuss the current therapies—and their limitations—in dealing with heart failure, or in trying to prevent it.

Jacquemyn et al.[17] provide an overview of the opportunities and challenges of artificial intelligence and machine learning for the diagnosis and prognostic prediction of patients with ToF. There are several promising developments for machine-learning–based diagnostic aid through the lifespan for patients with congenital heart disease, including patients with ToF. Perhaps the most encouraging and valuable feature of machine learning will be its ability to identify markers of increased long-term risk that are not apparent through traditional analyses, or from datasets too big or too complex to be analysed by humans. Many hurdles need to be overcome before these tools are incorporated into routine care, but we

suspect that early adopters may get a head start in enhancement of patient care when there are so many different patient profiles that need to be considered.

In the growing population of adult patients with ToF, many will want to have children. Garagiola et al.[18] reviewed how pregnancy-related changes may impact the maternal and fetal risk in patients with ToF. They rightfully underscore that while a personalized approach by a multidisciplinary team optimizes outcome, most patients with ToF will tolerate the cardiovascular demands of pregnancy even in the presence of significant valvular regurgitation. They also review how considerations around reproductive care should start in the teenage years, with age-appropriate discussions regarding fertility, childbearing, and contraception.

Conclusion and Perspectives

ToF is the archetype of moderately complex congenital disease where huge strides have been made over recent decades such that survival in the contemporary era is excellent. And yet, there is still much to learn and to accomplish so that people living with ToF can enjoy the same quality of life, exercise tolerance, and life expectancy as the general population. There is a need for more precise phenotyping of large patient cohorts with lifelong follow-up, with a focus on ventricular structural and functional parameters, reintervention-related morbidity, and patient-reported outcome measures. Priorities should be refinement and improvement of risk stratification, personalization of timing of interventions, optimization of material for valve replacement or reconstruction, and advancing precision medicine and genomics approaches to tailor treatment.

Ethics Statement

This work complies with the Canadian Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans.

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