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Clinical Research

Rationale and Design of the Canadian Outcomes Registry Late After Tetralogy of Fallot Repair: The CORRELATE Study

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ABSTRACT

Background: Chronic hemodynamically relevant pulmonary regurgitation (PR) resulting in important right ventricular dilation and ventricular dysfunction is commonly seen after tetralogy of Fallot (TOF) repair. Late adverse clinical outcomes, including exercise intolerance, arrhythmias, heart failure and/or death accelerate in the third decade of life and are cause for considerable concern. Timing of pulmonary valve replacement (PVR) to address chronic PR is controversial, particularly in asymptomatic individuals, and effect of PVR on clinical measures has not been determined.

Methods: Canadian Outcomes Registry Late After Tetralogy of Fallot Repair (CORRELATE) is a prospective, multicentre, Canada-wide cohort study. Candidates will be included if they are $\geq$ 12 years of age, have had surgically repaired TOF resulting in moderate or severe PR, and are able to undergo cardiovascular magnetic resonance imaging. Enrollment of $>$ 1000 individuals from 15 participating centres (Toronto, Montreal, Quebec City, Sherbrooke, Halifax, Calgary, Edmonton, and Vancouver) is anticipated. Clinical data, health-related quality of life metrics, and adverse outcomes will be entered into a web-based database. A central core lab will analyze all cardiovascular magnetic resonance studies (PR severity, right ventricular volumes, and ventricular function). Major adverse outcomes (sustained ventricular tachycardia and cardiovascular cause of death) will be centrally adjudicated.

Results: To the best of our knowledge, CORRELATE will be the first prospective pan-Canadian cohort study of congenital heart disease in children and adults.

Conclusions: CORRELATE will uniquely link clinical, imaging, and functional data in those with repaired TOF and important PR, thereby enabling critical evaluation of clinically relevant outcomes in those managed conservatively compared with those referred for PVR.

RÉSUMÉ

Introduction : Une régurgitation pulmonaire (RP) chronique pertinente sur le plan hémodynamique qui entraîne une importante dilatation ventriculaire droite et une dysfonction ventriculaire est fréquemment observée après la réparation de la tétralogie de Fallot (TF). Les résultats cliniques défavorables tardifs, à savoir l'intolérance à l'effort, les arythmies, l'insuffisance cardiaque ou la mort s'accélèrent au cours de la troisième décennie de la vie et sont la cause de problèmes considérables. Le moment du remplacement valvulaire pulmonaire (RVP) pour lutter contre la RP chronique est controversé, particulièrement chez les individus asymptomatiques. De plus, l'effet du RVP sur les mesures cliniques n'a pas été déterminé.

Méthodes : L'étude CORRELATE (*Canadian Outcomes Registry Late After Tetralogy of Fallot Repair*) est une étude de cohorte prospective et multicentrique pancanadienne. Les candidats seront sélectionnés s'ils ont $\geq$ 12 ans, ont subi une réparation chirurgicale de la TF entraînant une RP modérée ou grave, et sont aptes à subir une imagerie cardiovasculaire par résonance magnétique. L'inscription de $>$ 1000 individus de 15 centres participants (Toronto, Montréal, Québec, Sherbrooke, Halifax, Calgary, Edmonton et Vancouver) est anticipée. Les données cliniques, les mesures de la qualité de vie liée à la santé et les résultats défavorables seront entrés dans la base de données en ligne. Un laboratoire central analysera toutes les études cardiovasculaires par résonance magnétique (gravité de la RP, les volumes du ventricule droit et a fonction ventriculaire). Les résultats défavorables majeurs (tachycardie ventriculaire soutenue et cause cardiovasculaire de décès) seront centralement confirmés.

Résultats : À notre connaissance, l'étude CORRELATE sera la première étude de cohorte prospective pancanadienne sur la cardiopathie congénitale chez les enfants et les adultes.

Conclusions : L'étude CORRELATE reliera uniquement les données cliniques, fonctionnelles et d'imagerie des individus ayant subi une réparation de la TF et une importante RP, permettant ainsi l'évaluation critique des résultats cliniquement pertinents des individus qui sont pris en charge de manière conservatrice comparativement à ceux qui sont orientés pour subir le RVP.

The most common form of cyanotic congenital heart disease (CHD), tetralogy of Fallot (TOF) is commonly encountered in contemporary CHD practice. In Canada, more than 100,000 adults currently live with CHD and 1/3 of those classified as having "severe" CHD have a diagnosis of TOF.[1] The number of survivors will continue to increase over time, because of the immensely successful outcomes of pediatric cardiac surgery in recent decades.[2,3] Although survival into adult life after early repair is excellent, morbidity and mortality rates increase with time, and cardiovascular events and/or need for repeat surgery become more common during the third decade of life.[4]

Anatomic repair of TOF typically involves augmentation of the pulmonary outflow tract through repair/removal of the pulmonary valve, excision of the subvalvar muscle, and pulmonary artery (PA) enlargement. These surgical procedures render the pulmonary valve chronically regurgitant in most cases and pulmonary regurgitation (PR) is ubiquitous in adult survivors notwithstanding early TOF repair. Although once thought to be inconsequential, chronic PR is now known to be directly related to morbidity and mortality. Despite the ongoing hemodynamic insult to the right ventricle (RV) imposed by chronic hemodynamically relevant (moderate or severe) PR, most remain asymptomatic.[5] Nevertheless, we now appreciate that the consequences of ongoing moderate or severe valvular insufficiency can result in a cascade of progressive RV dilation and dysfunction, associated left ventricular (LV) dysfunction and ultimately adverse clinical outcomes (including exercise intolerance, tachyarrhythmias, and/or death).[4,6-10]

Important PR is treated with pulmonary valve replacement (PVR) surgery, which is the most frequent form of surgical reintervention after initial TOF repair.[11] Results of PVR in the symptomatic patient (evidenced by the presence of significantly diminished exercise capacity, clinical arrhythmias, and/or heart failure) tend to be disappointing, because of failure of RV reverse remodelling and persisting arrhythmia in many,[12] suggesting that a conservative approach to timing of PVR is likely too late. These observations have prompted a move toward performance of earlier "preventive" repair, before the development of overt symptoms, using physiologic parameters, including measures of ventricular volumes and function, as thresholds for intervention.[13-15] Nevertheless, robust data to support the benefits of early PVR are remarkably limited and the effect of PVR on measures of clinical well-being and adverse outcomes are largely unknown.