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Editorial

The Aging Patient With Tetralogy of Fallot: Out of the Blue and Into the Pink

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In 1673, the Danish anatomist Nils Stensen (also known as Steno) described the typical anatomic features of a tetralogy in a stillborn infant for the first time.[1] Over the centuries that followed, anatomists and physicians have sought to improve their understanding of the anatomy and physiology of "blue babies." In 1888, Étienne-Louis Arthur Fallot,[2] a French physician, published a series of papers linking the anatomy of a tetralogy with the cyanotic phenotype. Arthur Fallot was the first to challenge the prevailing notion that cardiac cyanosis was always caused by a patent foramen ovale.[3] Maude Abbott[4] was the first to call it tetralogy of Fallot (ToF). ToF was untreatable until the development of the Blalock-Taussig-Thomas shunt. The observation that children with ToF who also had a patent ductus arteriosus had less cyanosis led to the idea of creating a shunt between a great vessel and the pulmonary artery to improve blood flow to the lungs. The Blalock-Taussig shunt increases pulmonary blood flow in cyanotic infants with pulmonary stenosis, transforming a "blue baby" into a pink one within minutes.[5]

Arthur Fallot recognized tetralogy as the most common form of all cyanotic heart defects. This finding has been confirmed by contemporary epidemiologic studies.[6] ToF accounts for 4.4% of all congenital heart defects, with a global birth prevalence of 0.356 per thousand.[6] Also among adults with congenital heart disease (CHD), corrected ToF is the most prevalent heart defect.[7] If not treated surgically, only one quarter of the children born with ToF would reach the age of 10 years.[8] However, 93% of the newborns with ToF currently undergo surgical repair, with the majority of surgeries performed at the age of 3-6 months.[9] Palliation with the Blalock-Taussig-Thomas shunt is declining over time, with only 5% of the children with ToF currently receiving palliative shunt.[9] If a shunt is placed, this is mainly done in neonates (0-30 days of life). Primary repair is the treatment of choice. The most prevalent primary repairs nowadays are ventriculotomy with transanular patch (44.6%), ventriculotomy with non-transanular patch (29.1%), and no ventriculotomy (24.8%).[9] Primary surgical repair offers promising life prospects for afflicted children. More than three-quarters of children with corrected ToF can survive into adulthood,[10] and three-quarters of adults with corrected ToF can live to the age of 60 years.[11] Therefore, it can be inferred that more than half of the population with ToF can reach the age of 60 years or older to date. This proportion is likely to grow because life expectancy is further improving in the younger cohorts of patients with ToF.[10]

Although exercise capacity in ToF is among the best of all CHDs,[12,13] aging with ToF[9] is associated with a decline in cardiac function and exercise capacity.[14] This decline corresponds to reduced self-reported physical functioning in older patients,[14,15] which also has been observed in the broader population of people with CHD.[16] In addition, older patients with CHD develop cardiac and noncardiac morbidities.[17] For instance, in the international APPROACH-IS cohort of 4028 adult patients with CHD from 15 countries,[18,19] there were 594 patients with repaired ToF.[20] Of these patients with ToF, 4.7% were found to have current heart failure, and 8.6% had a history of heart failure.[20] When breaking this down in different age cohorts, the prevalence of current or past heart failure was 8.7%, 14.6%, 26.3%, and 39.3% in patients aged ≤40 years, >40 to ≤50 years, >50 to ≤60 years, and >60 years, respectively (data on file), confirming the positive relationship between heart failure and aging in ToF. Importantly, heart failure in ToF is mostly right ventricular failure, which is in many cases associated with chronic pulmonary regurgitation.[21] Assessment of the right ventricular function remains a challenge, because access to cardiac magnetic resonance imaging is limited in certain areas. Nonetheless, it is not the right ventricular function that determines patients' functioning or symptoms.[14]

Another age-related issue in ToF is premature cognitive deterioration. Indeed, early brain aging is expected in people with CHD due to the cumulative impact of

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neurodegeneration and brain injuries throughout adult life, in addition to the well-known neurodevelopmental issues in childhood and adolescence.[22] Brain magnetic resonance imaging has shown that patients with ToF tend to have smaller brain volumes and larger white matter hyperintensity volumes compared with healthy controls.[23] Patients also exhibit a greater number of microbleeds, which are specific signs of brain injury.[23] These brain injuries have functional consequences. In APPROACH-IS II, one objective was to assess frailty and cognitive functioning in a subgroup of patients.[24] A total of 814 adult patients with CHD aged 40 years or older from 17 centers in 11 countries were included, 39% of whom had cognitive dysfunction.[25] Among the 188 individuals with ToF in this sample, 33.3% exhibited cognitive dysfunction, and the prevalence increased with age (30.9% in 40-50 years, 31.6% in 51-60 years, and 40.5% in >60 years) (data on file).

Aging and age-related issues represent a new frontier in CHD research.[26] However, they are indispensable components of long-term trajectories and a life course epidemiology.[27] The CHD research agenda should encompass thorough investigations into the biology of aging in CHD, the functional impact of aging, interventions to slow down the aging process, and supportive strategies (Fig. 1).[17] Specifically, in patients with ToF, research on the optimal timing of interventions, considering age, will be crucial. Indeed, the evidence regarding the clinical benefits of pulmonary valve replacement is accumulating.[28,29] With reduced surgical risks and the emergence of transcatheter pulmonary valve replacement, an increasing number of patients are becoming eligible for this procedure.[30] However, the optimal timing and outcomes of pulmonary valve replacement in ToF remain subjects of research, especially within this aging population, where early-onset comorbidities are arising. Further, surgical pulmonary valve replacement beyond the age of 35 years is associated with higher mortality.[31] Another concern for patients with ToF is the risk of infective endocarditis. This condition occurs more frequently in patients with ToF who have undergone pulmonary valve replacement compared with those without the procedure.[32] In addition, infective endocarditis is common in patients who have undergone transcatheter pulmonary valve replacement.[33] In conclusion, alongside the age-related issues that are commonly observed in CHD, patients with ToF face specific challenges as they age. Gaining insights will be crucial in preparing for the emerging

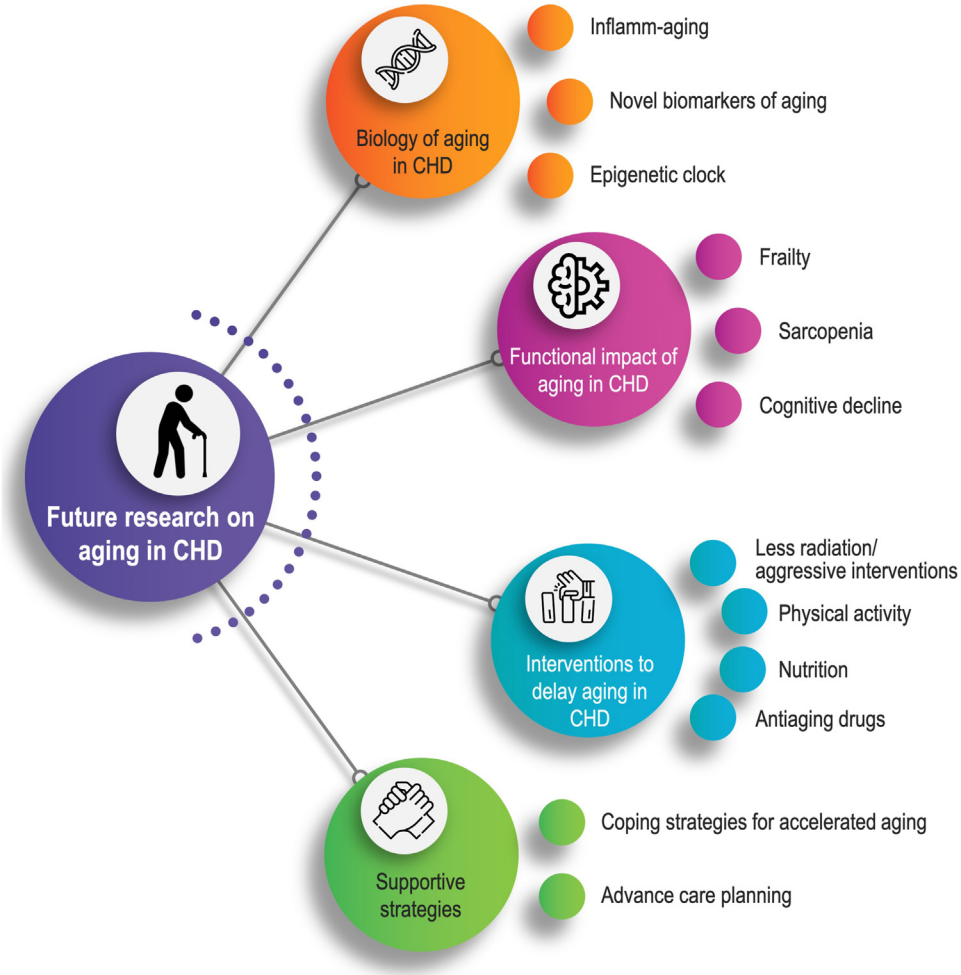

Figure 1. Research directions on aging in congenital heart disease (CHD). Reproduced from Moons and Marelli[17] (published under the CC BY-4.0 license).

challenges associated with the treatment and care of older individuals with ToF, as well as addressing the concerns that matter most to the patients.[34]

Ethics Statement

No new data are reported here. Hence, ethics approval was not needed.

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