Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 23, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.07.100

STATE-OF-THE-ART PAPER

Hot Topics in Tetralogy of Fallot

Juan Villafañe, MD,* Jeffrey A. Feinstein, MD,† Kathy J. Jenkins, MD, MPH,‡ Robert N. Vincent, MD, CM,§ Edward P. Walsh, MD,‡ Anne M. Dubin, MD,† Tal Geva, MD,‡ Jeffrey A. Towbin, MD,‖ Meryl S. Cohen, MD,¶ Charles Fraser, MD,# Joseph Dearani, MD,** David Rosenthal, MD,† Beth Kaufman, MD,† Thomas P. Graham, Jr, MD,†† on behalf of the Adult Congenital and Pediatric Cardiology Section, American College of Cardiology

Lexington, Kentucky; Palo Alto, California; Boston, Massachusetts; Atlanta, Georgia; Cincinnati, Ohio; Philadelphia, Pennsylvania; Houston, Texas; Rochester, Minnesota; and Nashville, Tennessee

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect. We explore "hot topics" to highlight areas of emerging science for clinicians and scientists in moving toward a better understanding of the long-term management of patients with repaired TOF. From a genetic perspective, the etiology of TOF is multifactorial, with a familial recurrence risk of 3%. Cardiac magnetic resonance is the gold standard assessment tool based on its superior imaging of the right ventricular (RV) outflow tract, pulmonary arteries, aorta, and aortopulmonary collaterals, and on its ability to quantify biventricular size and function, pulmonary regurgitation (PR), and myocardial viability. Atrial re-entrant tachycardia will develop in more than 30% of patients, and high-grade ventricular arrhythmias will be seen in about 10% of patients. The overall incidence of sudden cardiac death is estimated at 0.2%/yr. Risk stratification, even with electrophysiologic testing and cardiac magnetic resonance, remains imperfect. Drug therapy has largely been abandoned, and defibrillator placement, despite its high risks for complications and inappropriate discharges, is often recommended for patients at higher risk. Definitive information about optimal surgical strategies for primary repair to preserve RV function, reduce arrhythmia, and optimize functional status is lacking. Post-operative lesions are often amenable to transcatheter intervention. In selected cases, PR may be treated with transcatheter valve insertion. Ongoing surveillance of RV function is a crucial component of clinical assessment. Except for resynchronization with biventricular pacing, no medical therapies have been shown to be effective after RV dysfunction occurs. In patients with significant PR with RV dilation, optimal timing of pulmonary valve replacement remains uncertain, although accepted criteria are emerging. (J Am Coll Cardiol 2013;62:2155–66) © 2013 by the American College of Cardiology Foundation

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect, occurring in approximately 1 in 3,500 births and accounting for 7% to 10% of all congenital cardiac malformations. This exploration of a few "hot topics" is not intended to be a comprehensive review, but to present areas of emerging science for clinicians and scientists in moving toward a better understanding of the long-term management of patients with repaired TOF. Specifically, the following topics are presented: 1) genetics; 2) the crucial role of cardiac magnetic resonance (CMR) imaging; 3) recent advances in echocardiography (ECHO); 4) arrhythmias and sudden cardiac death (SCD); 5) surgical considerations and catheter-based therapy; 6) exercise performance; 7) ventricular function and heart failure; and 8) timing of and indications for pulmonary valve replacement (PVR).

Genetics

The etiology of TOF is multifactorial. Up to 25% of patients have chromosomal abnormalities, with trisomy 21 (Online Mendelian Inheritance in Man [OMIM][1] 190685) and

From the *Department of Pediatrics (Cardiology), University of Kentucky, Lexington, Kentucky; †Department of Pediatrics (Cardiology), Lucile Packard Children's Hospital, Stanford University Medical Center, Palo Alto, California; ‡Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts; §Children's Healthcare of Atlanta, Atlanta, Georgia; ‖The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; ¶Division of Cardiology, Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; #Texas Children's Hospital, Houston, Texas; **Department of Surgery, Mayo Clinic, Rochester, Minnesota; and the ††Division of Pediatric Cardiology, Vanderbilt Children's Hospital, Nashville, Tennessee. Dr. Villafane is a consultant for Biomedical Systems. Dr. Jenkins is the primary investigator at the Data Coordinating Center of a Johns Hopkins Medical Center–sponsored study of Melody valve implantations (Medtronic, Inc., Minneapolis, Minnesota). Dr. Dubin has received educational support funding for a fellow-in-training at her institution from Medtronic. Dr. Rosenthal is a member of the clinical events committee for the Berlin Heart Post-Approval study. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received February 15, 2013; revised manuscript received June 26, 2013, accepted July 1, 2013.

[1]OMIM (Online Mendelian Inheritance in Man) is an online catalog of human genes and genetic disorders developed by the National Center for Biotechnology Information (NCBI) (http://www.omim.org/).

Abbreviations and Acronyms

BNP = B-type natriuretic peptide
CMR = cardiac magnetic resonance
ECHO = echocardiography
EF = ejection fraction
ICD = implantable cardioverter-defibrillator
LV = left ventricular
NYHA = New York Heart Association
PR = pulmonary regurgitation
PVR = pulmonary valve replacement
RV = right ventricular
SCD = sudden cardiac death
TAPSE = tricuspid annular plane systolic excursion
TOF = tetralogy of Fallot

22q11.2 microdeletions (OMIM 188400, 192430, and 611867) most frequent. Trisomies 18 and 13, as well as other less common chromosomal abnormalities, have been reported. Chromosome 22q11.2 microdeletions occur in approximately 20% of TOF patients with pulmonary stenosis and in 40% with pulmonary atresia (1–4). DiGeorge syndrome (*DGS*; OMIM 188400), the most severe type of 22q11.2 microdeletion, also includes palatal abnormalities, dysmorphic facies, learning disabilities, immune deficiencies, and/or hypocalcemia (5). A less severe 22q11.2 microdeletion in TOF, Shprintzen (velocardiofacial) syndrome (*VCFS*; OMIM 192430), does not include the immune deficiencies or hypocalcemia of DiGeorge syndrome (5). Of the more than 40 commonly deleted 22q11.2 genes, only T-box 1 (*TBX1*) has been found in murine models to be haploinsufficient, with a phenotype convincingly similar to that of the human syndrome. *TBX1* missense and truncating mutations have been identified in up to 30% of patients with the nondeletion type and with the DGS/VCFS phenotype (6,7).

Mutations of the jagged1 gene (*JAG1*; chromosome 20p12), which cause Alagille syndrome, show clinical overlap with 22q11.2-deletion disorders and may cause isolated TOF (8). Mutations of the NK2 homeobox 5 gene (*NKX2.5*; chromosome 5q35) have been reported in 4% of nonsyndromic patients with TOF (9). Other known TOF-associated genetic variants include: zinc finger protein, multitype 2 (*ZFPM2*) (10); growth differentiation factor 1 (*GDF1*) (11); *GATA4* (12); cripto, Frl1, cryptic 1 (*CFC1*); forkhead box transcription factor 1 (*FOXH1*) (13); teratocarcinoma-derived growth factor 1 (*TDGF1*); nodal (*NODAL*) (14); and *GATA6* (15). Analysis of copy number variants has been used for identifying 11 de novo copy number variants associated with TOF (16). These regions included chromosomes 1q21.1, 3p25.1, 7p21.3, and 22q11.2. Arrington et al. (17) demonstrated that haploinsufficiency of the lipoma preferred partner protein, a member of the zyxin family of proteins, may cause TOF.

The risk for recurrence in a family is approximately 3%. If a genetic basis for TOF is identified, family members with congenital heart defects can be screened to determine the risk for passing congenital heart defects on to future children. Genetic data can also be used for risk stratification in patients regarding cardiac and noncardiac manifestations of the disease.

Screening of patients with TOF could include fluorescence in situ hybridization analysis of chromosome 22q11 microdeletions or a chromosome microarray. If the result is negative, consideration may be given to specific genetic-mutation analyses.

Cardiac Magnetic Resonance

CMR is the gold standard quantitative assessment of biventricular size and function, flow measurements, and myocardial viability (18,19). The goals of CMR in repaired TOF include: 1) quantitative assessment of left ventricular (LV) and right ventricular (RV) volumes, mass, stroke volumes, and ejection fraction (EF); 2) quantification of pulmonary regurgitation (PR), tricuspid regurgitation, cardiac output, and pulmonary-to-systemic flow ratio; 3) evaluation of regional wall motion abnormalities; 4) imaging the anatomy of the RV outflow tract, pulmonary arteries, aorta, and aortopulmonary collaterals; 5) assessment of myocardial viability, including scar tissue in the ventricular myocardium aside from sites of previous surgery; 6) evaluation for residual intra- or extracardiac shunt; 7) evaluation of the aortic valve for regurgitation and measurement of aortic size; and 8) evaluation of the coronary arteries (20,21) (Fig. 1). Despite the complex geometry and heavy trabeculations of the RV, CMR measurements of ventricular size and function in repaired TOF have shown good intra- and interobserver reproducibility (22,23).

The indications for CMR in repaired TOF vary with age. During the first decade of life, CMR is indicated only when imaging data necessary for clinical decision-making cannot be obtained on ECHO. However, if there is concern regarding the degree of RV volume load and dysfunction, CMR is preferred over computed tomography or catheterization. Beginning early in the second decade of life, CMR is indicated as a routine test for the surveillance of PR, biventricular size and function, dysfunction of other valves, and myocardial viability assessment. Little information exists regarding the optimal frequency of CMR following baseline examination. In many patients, ventricular size and function remain stable over many years. In others, the RV progressively dilates, and its function declines over a short time period. Until new data emerge to guide the frequency of CMR after baseline examination, it may be reasonable to repeat the study every 3 years, or more frequently in patients with advanced disease.

CMR has emerged as a powerful tool for risk stratification in patients with repaired TOF. In a study of 793 patients from 6 centers, Gatzoulis et al. (24) found that older age at repair and QRS duration $\geq$180 ms were independent predictors of SCD; this finding was later supported by findings from Khairy et al. (25). However, those studies lacked tools to measure RV size and function. More recently, a study utilizing CMR for measuring ventricular size and function found that severe RV dilation and RV and/or LV dysfunction were independent predictors of heart failure, sustained ventricular tachycardia, and SCD (26). In a multicenter study of 871 patients with TOF, Valente et al. (27) showed that although QRS duration $\geq$180 ms alone