The Impact of Preexisting Myocardial Remodeling on Ventricular Function Early after Tetralogy of Fallot Repair

Maria Cecília Knoll Farah, MD, PhD, Cláudia Regina Pinheiro Castro, MD, Valéria de Melo Moreira, MD, Maria Angélica Binotto, MD, PhD, Vitor Coimbra Guerra, MD, Arlindo de Almeida Riso, MD, PhD, Miguel Barbero Marcial, MD, PhD, Antonio Augusto Lopes, MD, PhD, Wilson Mathias, Jr., MD, PhD, FASE, and Vera Demarchi Aiello, MD, PhD, *São Paulo, Brazil*

Background: Twenty-three patients (median age 23 months) who underwent Fallot's tetralogy repair were investigated prospectively to detect a possible association between histopathologic myocardial remodeling and echocardiographic findings of systolic or diastolic ventricular dysfunction.

Methods: Intraoperatively resected infundibular bands and subendocardial biopsy samples from the right ventricle (RV) and left ventricle were obtained for histopathologic evaluation. Tissue Doppler echocardiographic interrogation of the ventricles was performed before surgery and in the postoperative period.

Results: Histopathologic data revealed hypertrophy of the RV cardiomyocytes and increased interstitial collagen in both ventricles. Mean values of RV isovolumic acceleration decreased significantly at the third evaluation compared with the preoperative values (P = .006). RV myocardial fibrosis greater than 8.3% was associated with a probability of altered E' of at least 0.7 (odds ratio = 2.31).

Conclusion: Preoperative histologic myocardial remodeling influenced the postoperative RV function in this group of patients with late repair. Further studies are necessary to evaluate the myocardium in younger patients and to define its influence in the long-term follow-up. (J Am Soc Echocardiogr 2010;23:912-8.)

Keywords: Fibrosis, Hypertrophy, Myocardial remodeling, Tetralogy of Fallot, Tissue Doppler imaging

Early repair of tetralogy of Fallot is generally advised to minimize the effects of chronic hypoxia and to reduce long-standing pressure overload to the right ventricle (RV) and its consequences. The surgical correction currently is achieved in children aged less than 1 year, with low mortality and excellent long-term survival in the majority of centers.[1–5] However, the optimal timing for total correction is still controversial. In Brazil, because of the socioeconomic conditions of the population, some children may reach surgical correction later than patients from developed countries. This late correction could bring additional myocardial remodeling that would affect the postoperative evolution.

It is also well known that alterations in RV function may be present early after surgery, sometimes causing a prolonged, troublesome postoperative recovery,[6–8] and in the long-term.[9–14] Moreover, some studies have also shown impaired left ventricle (LV) systolic function after tetralogy of Fallot correction.[15,16] Tissue Doppler imaging (TDI) associated with dobutamine stress echocardiography was used to evaluate the contractile reserve of the RV after tetralogy of Fallot repair. Impaired ventricular reserve could be predicted by TDI indices at rest.[17]

A few studies have described the histopathology of the myocardium in hearts with tetralogy of Fallot. Findings include myocyte hypertrophy and fiber disarray, fibrosis, edema, and degenerative changes, which become more pronounced in older patients subjected to long-standing cyanosis and pressure overload. Those changes may account for ventricular dysfunction and arrhythmias in the long term.[18–20] However, to our knowledge, the implications of preexisting myocardial abnormalities in the ventricular dysfunction seen early after repair have not been objectively addressed before.

The objectives of this prospective study were to analyze histomorphometric features of myocardial remodeling in the RV and LV in patients with tetralogy of Fallot, to identify whether any of these features may predispose patients to a higher risk of myocardial dysfunction before surgery and in the early and middle postoperative periods, and to look for possible associations between the histomorphometric aspects and other variables, such as age at operation, systemic arterial oxygen saturation, hematocrit, previous use of propranolol, electrocardiographic findings, surgical technique, and residual lesions.

From the Heart Institute (InCor), University of São Paulo Medical School, Brazil (C.R.P.C., V.M.M., M.A.B., V.C.G., A.A.R., M.B.M., A.A.L., W.M., V.D.A.); and Medical School, Health and Biological Sciences Center, University of Mato Grosso, Brazil (M.C.K.F.).

Supported by Fundação de Amparo à Pesquisa do Estado de São Paulo, grant 05/01476-2.

Reprint requests: Vera Demarchi Aiello, MD, PhD, Laboratory of Pathology, Heart Institute (InCor), University of São Paulo Medical School, Av. Dr Enéas C. Aguiar, 44, 05403-000, São Paulo SP Brasil (E-mail: *vera.aiello@incor.usp.br*).

0894-7317/$36.00

doi:10.1016/j.echo.2010.06.008

Abbreviations
IVA = Isovolumic acceleration
LV = Left ventricle, left ventricular
RV = Right ventricle, right ventricular
SD = Standard deviation
TDI = Tissue Doppler imaging

MATERIALS AND METHODS

Patient Population

We enrolled 23 consecutive patients with tetralogy of Fallot who were electively admitted for corrective surgery at the Heart Institute (InCor), University of São Paulo Medical School, from March 2005 to April 2007. Patient ages ranged from 12 to 186 months (mean = 39.6 months, median = 23 months), and 14 were male (60.9%). Patients with pulmonary atresia or associated atrioventricular septal defect were excluded from the study. Those presenting small atrial septal defects were included.

Before surgery, 47% of the patients had at least one episode of hypoxemic spell; 65% were receiving daily oral propranolol (mean dosage 1.8 mg/kg/day). Mean room air oxygen saturation was 88.1% ± 5.4%, and mean hematocrit was 40.22% ± 6.24%. Median preoperative Doppler gradient across the RV outflow tract was 74 mm Hg, ranging from 43 to 120 mm Hg. Three patients had undergone palliative Blalock–Taussig shunt previously.

The patients and their parents were informed about the research purpose of the data collection and gave their informed consent. The study was approved by the Ethics and Scientific Committee of the Heart Institute.

Clinical Assessment

All patients had a complete clinical assessment, including evaluation of oxygen saturation measured in room air using finger pulse oximetry. A blood sample was collected preoperatively for determination of hematocrit. All patients had a 12-lead surface electrocardiogram performed using a Hewlett-Packard recorder (Hewlett-Packard, Palo Alto, CA), at a speed of 25 mm/s and 1 mV/cm standardization, and the previous use of propranolol was registered.

Echocardiography

A complete two-dimensional and Doppler echocardiographic examination was performed using echocardiography equipment (Philips-Sonus 5500 or Philips-HDI 5000, Andover, MA) with a 3.5- or 5.0-MHz transducer. Pulsed-wave TDI was performed by activating the TDI function in the same unit. Filters were set to exclude high-frequency signals. Gains were minimized to allow a clear tissue signal with minimal background noise. The TDI velocities were obtained from the four-chamber view of each patient. A 2-mm sample volume was placed at the lateral angle of the tricuspid or the mitral valve annulus. The peak myocardial velocities during early and late diastole, systole, and isovolumic contraction were recorded from both ventricles. The myocardial isovolumic acceleration (IVA) was measured by dividing the myocardial peak velocity during isovolumic contraction time to the time from the onset to peak of this wave (Figure 1). The IVA time was measured from the end of the myocardial velocities during late diastole to the beginning of the myocardial velocities during systole.

Persistent (residual) pulmonary valvar stenosis was considered present when the maximal systolic gradient at the RV outflow tract was greater than 30 mm Hg. Residual pulmonary insufficiency was considered mild when the regurgitant jet was detected near the valve in the pulmonary artery and holodiastolic in duration, moderate when the regurgitant jet was detected up to the medial portion of the pulmonary trunk, and severe when the jet flow was protodiastolic and present up to the pulmonary branches.

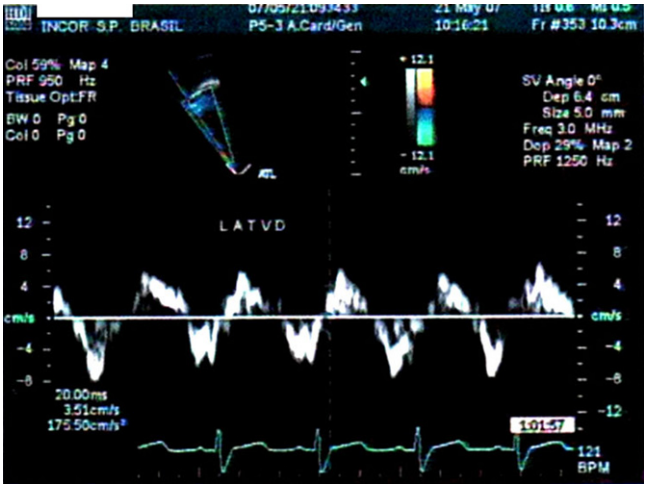

Figure 1 Typical tissue Doppler tracing obtained at the base of the RV. Wave during IVA precedes the S wave and begins before the peak of the R wave on electrocardiogram. IVA was measured by dividing peak velocity by the time interval from onset of the wave (zero-crossing) during IVA to the time at peak velocity of this wave.

All measurements were performed three times, and the mean value was used for analysis. Echocardiographic studies were performed by the same investigator before surgery, within the first 72 hours after surgery, and 30 to 90 days after surgery.

Histologic and Morphometric Analyses

Tissue samples were obtained for histology from the RV infundibular muscle bands resected as part of the surgical relief of the subpulmonary obstruction (23 cases), as endomyocardial biopsies obtained during surgery from the RV inlet (22 cases) and, when technically feasible, from the free wall of the LV through the ventricular septal defect before its closure (20 cases). Tissue was processed routinely for histology, and 5-μm–thick sections were stained with hematoxylin–eosin and Sirius red for collagen quantification and submitted to immunohistochemistry against factor VIII antigen to label endothelial cells of capillaries.

The morphometric measurements were carried out with the aid of an interactive computer-assisted image analyzer (Leica Quantimet; Leica Cambridge, Cambridge, UK).[21] To avoid interobserver variation, a single investigator operated the analyzer.

Cardiomyocyte Diameter

The smallest transverse cardiomyocyte diameter was measured at the level of the nucleus at a final magnification of 400×. The number of required measurements was determined after analyzing the evolution of the mean values and variance in 20, 40, 60, 80, 100, 120, 140, 180, and 200 observations. Finally, the option was made to measure 60 cardiomyocytes per section, in a minimum of 10 microscopic fields. The results obtained were compared with normal values for age published previously.[22,23] Mean values of cardiomyocyte diameter greater than the normal value for age plus one standard deviation (SD) were considered as histologic hypertrophy.