Histopathologic changes in ascending aorta and risk factors related to histopathologic conditions and aortic dilatation in patients with tetralogy of Fallot

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Supplemental material is available online.

Objective: The purposes of this study were to evaluate the histologic characteristics of the aortic wall and the risk factors related to histopathology and aortic dilatation in patients undergoing intracardiac repair of tetralogy of Fallot.

Methods: Operatively excised full-thickness aortic wall tissue from 98 consecutive patients undergoing intracardiac repair of tetralogy of Fallot aged 6 months to 47 years (mean 104.5 ± 102.8 months; median 72 months) were studied by light microscopy. The receiver operating characteristic curve analysis was done to quantify the diagnostic accuracy of loss of lamellar counts and multiple logistic regression models.

Results: Twenty-five (25.5%) aortic tissue specimens were indicated as histologically normal and were used as normal controls. The incidence of elastic fragmentation, increased ground substance, medionecrosis, smooth muscle disarray, and fibrosis was 74.5%, 54%, 39.8%, 26.5%, and 57.1%, respectively. A lamellar count of less than 60 was associated with a sensitivity of 80% and a specificity of 87.67%. Area under the receiver operating characteristic curve indicated that 93.37% (standard error ± 0.039) of the time the value of lamellar count was lower for the abnormal histopathology group than for the normal group ($P < .001$). The risk of aortic dilatation was 15.97 times higher in patients with histopathologically abnormal aorta.

Conclusions: The majority of aortic media of the ascending aorta in cyanotic tetralogy of Fallot indicates significant loss of lamellar units and pre-existing intrinsic aortopathy. The changes are present since infancy and are more pronounced in older patients subjected to long-standing cyanosis and volume overload and may account for or may coexist with the higher incidence of aortic dilatation encountered in these patients.

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Received for publication Feb 6, 2007; revisions received May 19, 2007; accepted for publication June 1, 2007.

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J Thorac Cardiovasc Surg 2008;135:69-77

0022-5223/$34.00

doi:10.1016/j.jtcvs.2007.06.011

Dilatation of the aortic root with or without aortic regurgitation is a well-described feature in patients with tetralogy of Fallot (TOF) and pulmonary stenosis or pulmonary atresia.[1-3] A subset of adult patients with TOF exhibit ongoing dilatation of the aortic root even after repair, necessitating aortic valve and aortic root surgery.[1-7] It is hypothesized that a medial abnormality coupled with increased aortic blood flow might be the cause for aortic root dilatation in untreated patients.[2-4,6,8-13] However, histopathologic or ultrastructural studies to lend credence to this hypothesis have been limited because of limited number of patients and restricted observations.[1,7-13]

This prospective study aims to (1) elucidate the histopathologic characteristics of the aortic wall in patients with TOF and to identify the relationship, if any, between the lamellar counts and appearance of histopathologic changes; (2) correlate any identifiable pathologic changes with known risk factors such as age at operation,

Abbreviations and Acronyms

CI = confidence interval
MAPCA = major aortopulmonary collateral artery
OR = odds ratio
ROC = receiver operating characteristic
RVEDP = right ventricular end-diastolic pressure
SD = standard deviation
SE = standard error
TOF = tetralogy of Fallot

previous systemic–pulmonary arterial shunting procedures, systemic arterial oxygen saturation, hematocrit, right ventricular end-diastolic pressure (RVEDP), degree of aortic override, and aortic regurgitation; (3) identify the histopathologic characteristics that may predispose patients to the higher risk of aortic dilatation seen in these patients; and finally (4) to evaluate the sensitivity, specificity, and predictive accuracy of a low lamellar count as a possible predictor of histopathologically abnormal aorta.

Patients and Methods

Patients were enrolled for this prospective study after approval by the institutional ethics committee and after informed written consent had been obtained from parents/guardians. Between January 2004 and June 2006, specimens of excised aortic wall from 108 consecutive patients undergoing intracardiac repair for TOF at AIIMS, New Delhi, India, were subjected to histopathologic analysis. Of these, 98 samples from 98 patients (71 male subjects) were found suitable for analysis (10 were excluded either because of insufficient tissue material or because of morphologic artifacts resulting from inadequate fixation and/or poor orientation). The examiners were blind to demographic, procedural, and hemodynamic data.

Age at correction was 6 months to 47 years (mean 104.5 ± 102.8 months; median 72 months), with 30.6% of patients (n = 30) being younger than 4 years of age and 20.4% (n = 20) being older than 12 years of age. Cardiac catheterization and angiocardiography were performed on all patients to confirm the diagnosis, to define coronary artery anatomy, and to identify major aortopulmonary collateral arteries (MAPCAs). The details of the patients are summarized in Table E1. In 65 (66.3%) patients, the aortic root was dilated. Dilatation was defined as the ratio of observed/expected aortic root diameter indexed to body surface area and age greater than 1.5.[14] Thirteen (20%) of 65 patients had evidence of trivial to mild aortic regurgitation.

Standard cardiopulmonary bypass and myocardial protection techniques were used in all patients. Intracardiac repair was performed with a transatrial, transpulmonary approach in 76 (77.5%) patients and a trans–right atrial approach in 22 (22.5%) patients. In 65 (66.3%) patients, a transannular patch was used. Five (5.1%) patients with TOF and pulmonary atresia required a right ventricle–pulmonary artery homograft conduit. The aortic tissues studied were operatively excised from the aortic cannulation site. A button of full–thickness aortic wall tissue (about 2-3 mm width) was excised from within the aortic purse-string suture on a side-biting aortic clamp as atraumatically as possible.

Collection and Preparation of Tissues

Excised full-thickness aortic wall tissue during intracardiac repair was subjected to histopathologic evaluation by light microscopy.

Light Microscopic Evaluation

Each biopsy specimen was fixed in 10% buffered formalin solution at room temperature, embedded in paraffin block, and thin sections of 4 to 5 μm were taken. The slides were then stained with hematoxylin and eosin. Special stains like Masson trichrome, elastic Verhoeff van Gieson, and alcian blue periodic acid–Schiff were used as and when indicated. The sections were examined with research light microscope (Nikon Optiphot; Nikon Corporation, Tokyo, Japan, magnification 40×, 100×, or 200×).

The histopathology slides were simultaneously evaluated by two independent observers and there was no interobserver disagreement on interpretation of the presence or absence of disease. The histologic evaluation of the aortic media included 6 variables: (1) lamellar count, (2) loss or fragmentation of elastic lamellae, (3) increased amount of ground substance, (4) medionecrosis, (5) smooth muscle disarray (changes in smooth muscle orientation), and (6) fibrosis. The lesions were graded 1 to 3 according to the criteria adapted from Schlatmann and Becker[15] and from de Sa and associates[16] (Table E2).

The grades were determined on the basis of the worst area observed in each specimen. The number of elastic lamellae were counted at the thickest and thinnest area in the media and the mean of these numbers was calculated. While counting, we included the longer elastic lamellae parallel to the lumen.

Definitions

Aortic root dilatation. Age, height, body weight, and sex are known to be the determinants of aortic root dimensions in the normal heart.[14,17] Therefore, we used the standard nomogram for aortic root size at the sinotubular junction adopted from Roman and associates,[14] indexed to body surface area and age.[5,16,17] Aortic root dilatation was defined as the ratio of observed/expected aortic root diameter greater than 1.5.

Apoptosis. Apoptosis is defined as a form of programmed cell death and has been recognized as a central feature of fundamental biological processes including embryonic morphogenesis, remodeling of mature tissues, and cell replacement in certain adult tissues, for example, the thymus. In contrast to necrosis, apoptosis occurs in isolated cells without any accompanying cellular reaction.[18-20]

Elastic fragmentation. Elastic fragmentation is defined as focal fragmentation of elastic lamellae in the aortic media. Three grades were recognized: grade 1, fewer than 5 foci of elastic lamellae, loss or fragmentation in one microscopic field, each focus comprising 2 to 4 neighboring elastic lamellae; grade 2, 5 to 9 foci of elastic lamellae fragmentation in one microscopic field; and grade 3, presence of 10 or more foci of elastic fragmentation in one microscopic field (Table E2).[15,16]

Accumulation of ground substance. The ground substance is a hydrated gel composed of glycosaminoglycans, proteoglycans, and adhesive glycoproteins in which elastic fibers and collagen are