

Effect of beta-blockade on aortic dilatation in adults with repaired tetralogy of Fallot

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A. Study Purpose and Rationale

Tetralogy of Fallot (ToF) comprises 10% of all congenital heart disease and is the most common form of congenital heart disease among adults.¹ Aortic root dilatation occurs in approximately 15% of the adult patients with repaired tetralogy of Fallot (ToF).² This is postulated to result from volume overload from early right-to-left shunting through the ventricular septal defect.³ This may be mitigated by early (before 1 year of age) surgical repair,⁴ but recent cross-sectional studies have found that progressive aortic root dilation and aortic regurgitation can occur later in life despite complete surgical repair of ToF.^{5,6} In addition, it has been hypothesized that aortic dilatation may also occur secondary to intrinsic aortic histopathology. Tan et al. demonstrated that there are marked histological abnormalities, including fibrosis, elastic fragmentation, and disruption of the elastic lamellae, in the aortic root and ascending aorta of patients with ToF.⁷ This histopathology is thought to predispose to increased aortic stiffness and reduced aortic distensibility,⁶ and potentially contribute to the progressive dilatation of the aorta in patients with repaired ToF.⁸

As the population of adults with repaired ToF ages, the progression of aortic dilatation is increasingly important for several reasons. First, aortic root dilatation can result in dilation of the aortic annulus with subsequent aortic regurgitation and left ventricular dysfunction, which may necessitate surgery (aortic valve replacement +/- aortic root repair/replacement).³ Second, progressive aortic dilatation may lead to formation of aortic aneurysms, which can be complicated by dissection or aortic rupture.⁹ In 2004, the first case of marked aortic aneurysm and aortic dissection in a patient with surgically-repaired ToF was reported.^{10,11} Therefore, it is imperative to closely monitor this patient population and establish management guidelines in order to avoid the potentially devastating consequences of aortic dilatation.

A retrospective study by Niwa et al. examined the progression of aortic root dilatation in adults who had undergone surgical repair of ToF (mean age at complete repair =14 years) over a period of 5.2 +/- 3.8 years. The study found that adults with normal aortic size dilated 0.03 +/- 1.6mm/year. In contrast, adults with dilated aortas (defined as ratio of observed to expected aortic size by standard nomogram >1.5) progressed an average of 1.7 +/- 3.8 mm/year after initial repair, particularly in patients with pulmonary atresia, right aortic arch, and a longer shunt-to-repair interval.²

In the asymptomatic adult patient (without congenital heart disease) with mild-to-moderate aortic root enlargement, medical treatment with beta-blocker therapy and serial follow-up with echocardiography once or twice a year is recommended.⁹ Beta-blockers have negative inotropic and chronotropic effects, which lessens the rate and rise of the arterial pulse over time, and therefore reduces the amount of sheer stress in the aorta. Beta-blockers have been shown to retard aortic root dilatation, decrease dissection, and lower mortality in both adults and children with Marfan syndrome, a connective tissue

disease with a propensity to affect the aortic root with high rates of aneurysmal dilatation, aortic regurgitation and dissection.^{12,13}

The use of beta-blockade in patients with repaired ToF is not standard of care and the effect of beta-blockade on aortic dilatation in patients with repaired ToF is not known. It is hypothesized that beta-blockers will retard the rate of aortic dilatation in patients with repaired tetralogy of Fallot and potentially decrease the incidence of aortic dissection in this population. I propose a prospective trial to study the effects of beta-blockade on aortic dilatation in patients with repaired tetralogy of Fallot.

B. Study Design and Statistical Analysis

This is a prospective, blinded, randomized trial of beta-blockade (metoprolol) vs. placebo in individuals with repaired tetralogy of Fallot. Participants will be stratified according to aortic root size (normal vs. dilated) as assessed by the initial transthoracic echocardiogram. Age, sex and body surface area (BSA) are known determinants of aortic root dimensions.¹⁴ Therefore, standard nomograms for aortic root size will be used (adapted from Roman et al),¹⁵ which are indexed by age, sex and body surface area. Aortic root dilatation will be defined as the ratio of observed to expected aortic root diameter >1.5.

Once participants have been stratified into two groups, each group will be randomized to receive either beta-blocker therapy or placebo. Patients will be followed for three years and monitored with yearly transthoracic echocardiogram. The primary endpoint is the rate of change in aortic diameter over time, defined as the absolute difference in aortic diameter per year.

A change in aortic root diameter of 0.5 mm per year is likely to be clinically significant. This value is more than 2 times greater than intraobserver variability of aortic root size. [This was calculated from observations by Niwa et al.²: intraobserver variability in aortic root size = 0.7 +/- 0.3%; expected aortic root size in adults 40 years of age and older is 28.3 +/-1.3 mm; expected aortic root size in adults younger than 40 years is 25.8 +/- 1.8mm. Therefore, assuming an average expected aortic root size of 27mm for the study population: $27\text{mm} \times 0.007 = 0.189\text{mm}$.] To detect a difference of this magnitude (0.5 mm/year), with an alpha of $p=0.05$ and 80% power, would require a sample size of 161 subjects in each group based on an unpaired t-test comparing a continuous variable (aortic diameter) in two groups. (**Note: This power calculation was performed using an estimated standard deviation of 3.8mm for the group of patients with dilated aortas and a mean rate of change of 1.7mm year in the study by Niwa et al.² However after reviewing this previously published data, the distribution about this mean was likely to be skewed and thus the standard deviation overestimated. Therefore, a smaller sample size may be sufficient but difficult to calculate.)

Results will be evaluated by an intention-to-treat analysis. A multivariate logistic regression analysis will be used to identify predictors of aortic dilatation. Variables to be assessed are outlined in Table 1.

TABLE 1: Patient characteristics and clinical variables:

- Anatomical variants: right/left aortic arch, type of VSD, bicuspid AV
- Age at palliative shunt procedure
- Type and duration of previous palliative shunt (BT, Potts, Waterston)
- Time from shunt to definitive surgical correction
- Age at surgical correction
- Method of surgical correction: transventricular vs. transatrial/transpulmonary
- Residual VSD or subsequent VSD repair
- Presence and severity of aortic regurgitation
- History of infective endocarditis
- Left ventricular ejection fraction (%)

C. Study Procedure

After consultation with the patient's adult congenital cardiologist, potential study participants will be approached about participation by a study researcher. A brief description of the study and the inclusion/exclusion criteria are explained. If patients are eligible and willing to participate, a researcher will explain the study in detail and written informed consent will be obtained. Data obtained on study participants will include: demographic data, previous medical and surgical treatment, echocardiographic imaging data, and information on adverse drug reactions and adverse event. Patients will be instructed on how and when to take the experimental study medication (metoprolol or placebo). Patients will be instructed on the importance of adherence to the medical regimen and pill counting will be used to assess compliance. Participants will be informed of potential side effects of the study drug and whom to contact should these occur. The subjects, the study investigators, and the patient's cardiologist will be blinded to treatment regimen. Patients will be asked to return for a brief follow-up every four months in order to assess for adverse effects of the study drug, monitor drug compliance and adjust the dosage if indicated.

Patients will undergo an initial echocardiogram at the Schneeweiss Adult Congenital Heart Center, followed by routine (non-experimental) yearly echocardiograms over the course of the study (3 years). The transthoracic echocardiograms are performed in the left lateral decubitus position by an experienced technologist. Two-dimensional measurements of the aortic root will be made at end-diastole in parasternal long-axis views perpendicular to the long axis of the aorta at 4 levels: (1) annulus (defined echocardiographically as the hinge points of the aortic cusps); (2) sinuses of Valsalva; (3) sino-tubular junction (supra-aortic ridge); (4) proximal ascending aorta. Measurements of the aortic root diameter will be made using the leading edge technique. All echocardiographic interpretations and analysis will be done offline and no additional time will be imposed upon the subject for experimental echocardiographic data collection.

D. Study Drugs

This study intends to achieve beta-blockade with metoprolol tartrate (tradename: Lopressor), a cardioselective beta-adrenergic blocker. Patients with contraindications to the use of beta-blockers will be excluded. Patients will be started on an initial dose of 25mg po bid to be taken with or immediately after meals. The dose will be uptitrated to achieve a target heart rate of 60-70 bpm or a maximum dose of 450mg/day. The dose can also be reduced to minimize side effects. Common adverse effects include: bradyarrhythmia (3-16%), heart block (5%), heart failure (27%), hypotension (27%), pruritis (5%), rash (5%), constipation (1%), diarrhea (5%), indigestion (1%), nausea (1%), dizziness (10%), fatigue (10%), depression (5%), dyspnea (1-3%) and wheezing (1%). Serious bronchospasm occurs in approximately 1%. Patients will be advised of the potential harm with abrupt withdrawal including exacerbation of angina pectoris and myocardial infarction. A copy of the package insert will be provided to all research participants.

E. Medical Device

N/A

F. Study Questionnaires

N/A

G. Study Subjects

Inclusion criteria:

- 18 years of age or older
- Met criteria for the diagnosis of tetralogy of Fallot: (1) a non-restrictive ventricular septal defect; (2) an overriding aorta; (3) obstruction of the right ventricular outflow tract which may be infundibular, valvar, or both, with or without supra-valvular or branch pulmonary artery stenosis; and (4) consequent right ventricular hypertrophy.
- Had definitive surgical correction for tetralogy of Fallot

Exclusion criteria:

- Contraindication to beta-blockade: bradycardia (heart rate <60bpm), acute heart failure, heart block (first, second or third degree) or sick-sinus syndrome, hypersensitivity to metoprolol, asthma or chronic obstructive pulmonary disease, severe peripheral arterial circulatory disorder, pheochromocytoma, and systolic blood pressure less than 90mmHg.

H. Recruitment of Subjects

Approximately 250 adult patients with repaired tetralogy of Fallot are followed at the Schneeweiss Adult Congenital Heart Center at Columbia University. Patients will be recruited if they meet the above inclusion criteria and are willing to participate in the research protocol.

I. Confidentiality

Each subject enrolled in the study will be assigned a study identification (ID) number so that study information will remain confidential. The link between subject name and ID number will be stored in a secure location with access granted only to study investigators.

J. Potential Conflict of Interest

No conflicts of interest exist. This is not a pharmaceutical-sponsored study, nor do the investigators have a relationship with the manufacturer of the study drug.

K. Location of the Study

The study will be conducted in the Schneeweiss Adult Congenital Heart Disease Center.

L. Potential Risks

Treatment with metoprolol may rarely induce adverse drug reactions including symptomatic bradycardia, dizziness, postural hypotension, fatigue, lethargy, mental depression, headache, nausea, diarrhea, sleep disturbances, and asthma exacerbation or bronchospasm. To minimize the potential risks, the starting dose of the study drug is relatively low and will be up-titrated slowly. Subjects will be followed closely for adverse drug reactions.

M. Potential Benefits

The potential benefit of participation in the proposed study is those randomized to beta-blocker therapy may have decreased rates of aortic dilatation.

N. Alternative Therapies

The alternative is to not participate in the study.

O. Compensation to Subjects

Patients will be compensated with \$100 after the initial evaluation and echocardiogram and \$50 at each of the two subsequent yearly visit requiring follow-up echocardiograms.

P. Costs to Subjects

There is no cost to study participants.

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