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*Heart* 2006;92;1827-1830: originally published online 14 Jun 2006; doi:10.1136/hrt.2006.091199

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Central and peripheral arterial stiffness in patients after surgical repair of tetralogy of Fallot: implications for aortic root dilatation

Y F Cheung, X Ou, S J Wong

OBJECTIVES: To test the hypotheses that (1) the central conduit arteries stiffen preferentially over the peripheral conduit arteries in patients with repaired tetralogy of Fallot (ToF); and (2) central arterial stiffening is related to aortic root dilatation.

Design and patients: Heart–femoral pulse wave velocity (PWV), femoral–ankle PWV, carotid augmentation index and body surface area-adjusted aortic sinotubular dimension were determined in 31 children after ToF repair and compared with those in 31 age-matched controls after left-to-right shunt repair. In addition, the PWVs and augmentation index were related to the sinotubular junction dimension.

Results: Compared with controls, patients had significantly greater heart–femoral PWV (mean 666 (SD 151) v 587 (81) cm/s, p = 0.021) and carotid augmentation index (14.1 (17.0)% v 25.2 (14.6)%, p = 0.016), whereas the right 888 (202) v 845 (207) cm/s, p = 0.42) and left 918 (227) v 851 (215) cm/s, p = 0.25) femoral–ankle PWVs were similar between the two groups. The sinotubular junction z score of patients was significantly greater than that of controls (4.7 (1.5) v 1.1 (1.4), p < 0.001). Univariate analysis showed that the sinotubular junction z score correlated positively with heart–femoral PWV (r = 0.43, p = 0.001) and carotid augmentation index (r = 0.46, p = 0.001). Multiple linear regression similarly identified heart–femoral PWV (β = 0.30, p = 0.04) and carotid augmentation index (β = 0.31, p = 0.04) (model R² = 0.26) as significant determinants of sinotubular junction z score.

Conclusions: The aorta stiffens in patients with repaired ToF, which may contribute to progressive dilatation of the aortic root in the long term.

METHODS

Participants
Thirty-one patients with surgically corrected ToF were recruited from the paediatric cardiac clinic over a three-month period. The following data were collected from the medical records: previous palliative shunt operation, age at total surgical repair, duration of follow up since operation and residual cardiac lesions as documented by serial echocardiography. Thirty-one patients with previous surgical repair of left-to-right shunt, but without aortic valve complications, were recruited as controls to adjust for the potential influence of cardiopulmonary bypass on the arterial mechanical properties due to chronic endothelial dysfunction. The body weight and height of the participants were measured, and the body surface area was calculated accordingly. All of the participants and the parents of minors gave written, informed consent.

Echocardiographic examination
Transesophageal echocardiography was performed with a 2–4 MHz or 3–8 MHz phased-array scanner, interfaced to a Sonos 5500 ultrasound machine (Philips Medical Systems, Andover, Massachusetts, USA). M mode echocardiography in the short-axis view was used to measure the left ventricular systolic and end diastolic dimensions, and the right ventricular end diastolic dimension. The left ventricular fractional shortening was calculated according to the formula:

\[ \text{Fractional Shortening} = \left( \frac{\text{Diastolic Diameter} - \text{Systolic Diameter}}{\text{Diastolic Diameter}} \right) \times 100 \]
Assessment of arterial stiffness

The regional stiffness of the arterial segments was determined by the PWV along the segment of interest, which is related to the square root of the elastic modulus according to the Moens–Korteweg equation.\(^1\)\(^5\) Hence, the stiffer the arterial segment, the faster the PWV. Central and peripheral arterial stiffness was therefore assessed by measuring the heart–femoral and femoral–ankle PWV, respectively, with an automatic device (VP-2000; Colin Medical Technology, Komaki, Japan). Briefly, the device measured simultaneously ECGs, phonocardiograms, bilateral brachial and ankle pressures, and carotid and femoral arterial pulse waves. The arterial pressures of the four limbs were measured with an oscillometric sensor method, and the carotid and femoral arterial pressures of the four limbs were measured with an automatic device (VP-2000; Colin Medical Technology, Komaki, Japan). Briefly, the device measured simultaneously ECGs, phonocardiograms, bilateral brachial and ankle pressures, and carotid and femoral arterial pulse waves. The arterial pressures of the four limbs were measured with an oscillometric sensor method, and the carotid and femoral arterial pressures were obtained by applanation tonometry.\(^16\) The transit time was determined by the foot-to-foot method, and the path length was calculated automatically according to the patient’s height on the basis of oriental anthropometric data.\(^16\) The PWV was calculated as path length divided by transit time. Additionally, from the carotid arterial waveform, the augmentation index was calculated as the ratio of the amplitude of the pressure wave above its systolic shoulder to the total pulse pressure.\(^15\) Augmentation of the systolic pulse contour is related to wave reflection and stiffness of the arterial tree. Earlier arrival of the reflected wave to the central arteries in a stiff arterial tree increases augmentation of pressure in late systole. Intraobserver variability for the measurement of heart–femoral PWV, femoral–ankle PWV, and carotid augmentation index, as determined from the mean and SD of differences in two consecutive results from magnetic optical disks for offline analyses. The measurements were made in three cardiac cycles and the average was calculated for subsequent analyses.

Statistical analysis

Data are presented as mean (SD). The differences in demographic data, echocardiographic indices and arterial stiffness indices between patients and control participants were compared by unpaired Student’s t test and Fisher’s exact test where appropriate. The Pearson correlation analysis was used to assess for possible relationships between the sinotubular junction z score and the demographic data, systemic blood pressure, echocardiographic parameters and arterial stiffness indices for the entire cohort. Stepwise multiple linear regression analysis was used to identify significant determinants of the sinotubular junction z score. A value of p < 0.05 was considered significant for each individual comparison but was adjusted by Bonferroni correction for multiple comparisons. All data were statistically analysed with SPSS V.11.5 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Patients

Table 1 summarises the demographic and clinical data of the patients. Of the 31 patients with ToF, 11 (35%) had palliative shunt operations performed before definitive surgery. Of the

| Table 1 Demographic and clinical data of tetralogy of Fallot group (ToF) and controls |
|---------------------------------|-----------------|-----------------|------------------|
|                                | ToF (n = 31)    | Controls (n = 31) | p Value         |
| Age at study (years)           | 15.3 (5.7)      | 16.2 (5.5)       | 0.53            |
| Age at surgery (years)         | 4.1 (3.6)       | 7.6 (6.4)        | 0.014*          |
| Duration of follow up (years)  | 11.2 (6.0)      | 8.8 (6.4)        | 0.15            |
| Sex (men:women)                | 16:13           | 14:17            | 0.80            |
| Body mass index (kg/m\(^2\))  | 18.9 (4.3)      | 20.1 (4.0)       | 0.29            |
| Systolic blood pressure (mmHg) | 110 (13)        | 109 (12)         | 0.77            |
| Diastolic blood pressure (mmHg)| 62 (8)          | 61 (8)           | 0.60            |

Data are mean (SD). \(^*\)Significant difference (p<0.05).

Figure 1 Box plots of (A) heart–femoral pulse wave velocity and (B) carotid augmentation index in tetralogy of Fallot group (ToF) and controls.
Aortic root size and arterial stiffness

The sinotubular junction $z$ score of patients with ToF was significantly greater than that of controls ($4.7 (1.3)\,\text{vs}\,1.1 (1.4), p<0.001$). By univariate analysis, the sinotubular junction $z$ score correlated positively with heart–femoral PWV ($r = 0.43, p = 0.001$; fig 2A) and carotid augmentation index ($r = 0.46, p = 0.001$) (fig 2B), but not with demographic variables, systemic blood pressure and echocardiographic parameters. In patients with ToF, the sinotubular junction $z$ score was similar between patients with (4.9 (1.0)) and those without (4.6 (1.8), $p = 0.73$) a previous palliative shunt operation and was not related to the age at surgery ($p = 0.36$).

Multiple linear regression of the entire cohort was used to identify significant determinants of the sinotubular junction $z$ score. The independent variables included were only those found to be significantly associated with sinotubular junction $z$ score by univariate analysis. The significant determinants identifiable were heart–femoral PWV ($\beta = 0.30, p = 0.04$) and carotid augmentation index ($\beta = 0.31, p = 0.04$) (model $R^2 = 0.26$).

DISCUSSION

This study shows preferential stiffening of the central over the peripheral conduit arteries in patients with repaired ToF. The increased carotid augmentation index reflects stiffening of the arterial tree with earlier arrival of the reflected wave to the central arteries and augmentation of pressure in late systole. An increase in heart–femoral PWV without a concomitant increase in femoral–ankle PWV suggests central arterial stiffening in patients after ToF repair. More important, the heart–femoral PWV, and hence the aortic stiffness, is shown to be a significant determinant of aortic root size.

The clinical significance of aortic root dilatation in patients after repair of ToF is increasingly recognised. Limited longitudinal data from adult patients suggest that the dilatation is progressive despite surgery, which may result in significant aortic regurgitation and necessitate prosthetic valve replacement. Niwa and colleagues recently reported that 15% of their cohort of 216 adult patients after repair of ToF had aortic root dilatation, with dilatation increasing at a rate of 17 mm/year in this subgroup. Of even greater concern are the recent case reports of aortic dissection late after repair of ToF in two adults whose aortic roots exceeded 60 mm in diameter.

The novel findings of the present study of central aortic stiffening and increased carotid augmentation index, in conjunction with the reported intrinsic aortic histological abnormalities, may perhaps shed some light on the mechanisms that underlie progressive aortic root dilatation in patients after surgical repair of ToF. Intrinsic aortopathy in patients with ToF of different age groups is manifest by varying degrees of medionecrosis, fibrosis, cystic medial necrosis and elastic fragmentation with elastic lamellae disruption. Disruption of elastic fibres causes aortic dilatation and shifts the stress to the much less distensible collagen fibre. The resultant aortic stiffening increases circumferential wall stress and stimulates vascular smooth muscle to further increase collagen synthesis. Augmentation of the central systolic and pulse pressures due to increased heart–femoral PWV and wave reflection may further amplify the increase in circumferential arterial wall stiffness.
stress, which probably causes further breakdown of the medial elastin and increases the possibility of local fatigue.²¹ Hence, the functional and structural abnormalities of the aorta in ToF may lead to the establishment of a positive feedback loop that results in progressive aortic root dilatation. In an experimental model of intact segments of human aorta, the extent of irreversible dilatation has indeed been shown to correlate negatively with aortic distensibility.²²

Chronic hypoxia, inevitable in patients with ToF before surgical correction, has been shown to generate growth factors and matrix proteins that can induce smooth muscle proliferation and remodelling, resulting in irreversible remodelling of the vasculature with smooth muscle proliferation and fibrosis.²³ Hypoxia may, in addition to intrinsic aortopathy, therefore possibly have a role in aortic stiffening. Nonetheless, the findings of similar peripheral arterial stiffness in patients and controls and the absence of a relation between aortic root dimension and the age at surgical repair of ToF in the present study do not support this proposition. The second finding concurs with that reported by Niwa and colleagues,²⁴ who found no difference in the age at repair between patients with ToF with and those without significant aortic root dilatation. Previous insertion of a systemic-pulmonary arterial shunt could have increased the flow and caused structural changes in the central arteries. Nonetheless, we found no differences in central arterial stiffness between patients with ToF with and those without previous shunt insertion.

Whereas data on the prevalence, course, risk factors and probable underlying mechanisms of progressive aortic root dilatation in patients after ToF repair are accumulating, the optimal management strategies for these patients remain controversial. Although β blockers have been reported to be effective in reducing the rate of aortic root dilatation in patients with Marfan’s syndrome,²⁵ its usefulness in patients with dilated aortic root after repair of ToF remains to be clarified. Our finding of aortic stiffening in these patients provides a basis for arterial distensifying strategies, in particular such vasodilators as angiotensin-converting enzyme inhibitors and calcium channel blockers.²⁶ Indeed, compared with β blockers, enalapril has been reported to achieve a greater reduction of aortic stiffness index and a smaller increase in aortic root diameter in patients with Marfan’s syndrome.²⁷ However, drug treatments for aortic root dilatation in Marfan’s syndrome are controversial. The aforementioned studies²⁸ ²⁹ were small, the study by Shores and colleagues³⁰ did not find any difference in end points and was followed by a number of studies with varying results, and the study reported by Yetman and co-workers³¹ was not randomised and had a significant number of treatment reassignments. Aortic root replacement has also been recommended in adult patients with ToF with aortic root size exceeding 55 mm to avoid the risk of the catastrophic outcome of aortic dissection.³² Undoubtedly, further controlled studies are required to provide evidence-based strategies for the prevention of progressive aortic root dilatation and its associated complications in patients after repair of ToF.

A potential limitation is the cross-sectional nature of the study. It would have been ideal to relate the severity of aortic stiffening to the rate of aortic root dilatation longitudinally. The findings of positive correlations between arterial stiffness indices and sinotubular junction z score do not prove causality. Nonetheless, as mentioned above, the functional and structural abnormalities of the aorta in ToF may lead to the establishment of a positive feedback loop that contributes to progressive aortic root dilatation.

In conclusion, the aorta stiffens in patients with repaired ToF, which may contribute to progressive dilatation of the aortic root. Whether arterial distensifying strategies would reduce the rate of aortic root dilatation, and hence the associated complications of aortic regurgitation and dissection in the long term, is a topic for further research.

Authors’ affiliations
Y F Cheung, X Ou, S J Wong, Division of Paediatric Cardiology, Department of Paediatrics and Adolescent Medicine, Grantham Hospital, The University of Hong Kong, Hong Kong, China

REFERENCES


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