Age-Related Changes in Right and Left Ventricular Function in Tetralogy of Fallot

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Age-related changes in right (RV) and left (LV) ventricular myocardium in tetralogy of Fallot (TF) are analyzed with regard to pre- and postoperative ventricular function. In RV, preoperative function was better in patients under 4 years of age in terms of ejection fraction and compliance, but no significant change was seen in LV function. Postoperatively, patients who underwent corrective surgery at age less than 4 years showed no significant difference compared to those at operative age above 4 years in terms of RV and LV functions at rest. However, stress tests for RV by isoproterenol and LV using methoxamine revealed some masked ventricular dysfunction in both ventricles in the older groups. The relationships between these functional abnormalities and previously described histological changes of right and left ventricular myocardium in TF are discussed.

IN tetralogy of Fallot (TF), the myocardium of the right ventricle (RV) is burdened from birth by both pressure load and hypoxia. These burdens may cause structural and functional changes with age resulting in myocardial dysfunction, and may influence early and late results of corrective surgery. In terms of age-related myocardial changes of TF, differences between the ventricles may exist because the left ventricle (LV) is affected by hypoxia without pressure load and with less volume load. Morphologically, age-related change in the myocardium has been studied in both RV¹⁻³ and LV^{4,5}. There has been less investigation of functional changes in relation to pre- and postoperative stages. This report attempts to elucidate age-related changes in ventricular function of RV and LV before and after surgery.

Key Words:

Tetralogy of Fallot
Myocardial hypertrophy
Ventricular function
Age-related myocardial changes.

MATERIALS AND METHODS

Patients: Three groups of randomly selected patients were utilized for the ventricular function studies (Table I). Group A, comprising 15 preoperative patients, was analyzed for RV and LV function by separating patients into 2 subgroups according to age at the time of study: Group A-1 (< 5 yrs, n = 7, average 2.6 ± 1.3 yrs) and A-2 (≥ 5 yrs, n = 8, average 13.4 ± 10.1 yrs). The arterial oxygen saturation was $78 \pm 9\%$ in Group A-1 and $78 \pm 10\%$ in Group A-2 (ns). Of the patients who underwent corrective surgery by trans-pulmonary and trans-atrial repair,⁶ 29 patients (Group-B) were selected for postoperative RV function study. Those with severe pulmonary regurgitation were excluded. Group-C consisted of 21 patients who had undergone repair by the conventional or the new method and received postoperative LV function study. Groups B and C were each further divided into 2 subgroups according to age at the time of surgery: Group B/C-1 (< 4 yrs) and Group B/C-2 (≥ 4 yrs). Between Group B-1 (n = 19, average

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age at surgery, 2.2 ± 0.5 yrs) and B-2 ($n = 10$, average age at surgery, 6.9 ± 2.6 yrs), there were no significant differences in follow-up periods to the study (10 ± 8 vs 21 ± 14 months) or in postoperative RV/VL pressure ratio (0.46 ± 0.20 vs 0.44 ± 0.10), respectively. Between Group C-1 ($n = 10$, average age at surgery, 2.2 ± 0.5 yrs) and C-2 ($n = 11$, average age at surgery, 9.0 ± 4.6 yrs),

there were no significant differences in RV/LV pressure ratio (0.38 ± 0.07 vs 0.45 ± 0.17), preoperative hemoglobin level or postoperative periods to the study.

Ventricular Function Studies: End-diastolic pressure (EDP) of RV and LV were obtained during cardiac catheterization studies. Ventricular volume studies were performed by cineangiography using the area-length method. End-diastolic volume (EDV) was measured and expressed by EDVI (EDV/body surface area) or % of normal.⁷ Ventricular ejection fraction (EF) and specific compliance ($dV/dp \times EDVI$ mmHg⁻¹) were also measured. For the stress test in the postoperative RV function study in Group-B, isoproterenol (ISP) was utilized in 14 patients. To increase afterload in the LV function study for Group-C, methoxamine (MX) was utilized. Kps (mmHg/ml/m²), a contractile index of the LV, was obtained from 2 points on the pressure-volume curve at peak systolic pressure at rest and during MX.

Statistical Analysis: The unpaired samples were compared by the Student-t test and the paired samples by the paired-t test. Differences were defined as significant when $p < 0.05$. The average values were expressed by mean $\pm$ SD.

TABLE I THREE GROUPS UTILIZED IN THIS STUDY. ISP IN GROUP B SHOWS

Group	n	Age at Study	Age at Operation
<i>Group A (n = 15): Preoperative RV and LV functions.</i>			
A-1	7	< 5 yrs	—
A-2	8	≥ 5 yrs	—
<i>Group B (n = 29): Postoperative RV function</i>			
B-1	19 (Isp; 9)	—	< 4 yrs
B-2	10 (Isp; 5)	—	≥ 4 yrs
<i>Group C (n = 21): Postoperative LV function.</i>			
C-1	10	—	< 4 yrs
C-2	11	—	≥ 4 yrs

Isp in Group B shows isoproterenol test. The details of each groups are described in the text.

TABLE II COMPARISONS IN VENTRICULAR FUNCTIONS BETWEEN EACH SUBGROUPS

Group	RVEDP mmHg	RVEF %	RVEDV* %	RV-Compliance mmHg ⁻¹ .m ²	LVEDP mmHg	LVEF %	LVEDV* %	LV-Compliance mmHg ⁻¹ .m ²
A-1	6 ± 2	52 ± 7	110 ± 144	0.10 ± 0.04	6 ± 2	60 ± 6	125 ± 5	0.10 ± 0.03
A-2	9 ± 4	40 ± 4	104 ± 32	0.05 ± 0.02	9 ± 6	56 ± 5	188 ± 41	0.08 ± 0.03
p	ns	< 0.01	ns	< 0.02	ns	ns	< 0.05	ns

Group	RVEDP	RVEF	RVEDV*	RVEF		
				Rest	Isp	
B-1	5 ± 2	57 ± 6	150 ± 29	57 ± 7	60 ± 6	** ₁ , p < 0.05
B-2	7 ± 3	54 ± 6	140 ± 20	56 ± 5	58 ± 5	** ₂ , ns
p	< 0.05	ns	ns	ns	ns	

Group	LVEDP	LVEF	LVEDVI ml/m ²	Kps mmHg/ml/m ²
C-1	6 ± 3	61 ± 4	82 ± 5	10.84.9
C-2	8 ± 2	60 ± 5	102 ± 22	5.5 ± 5.3
p	< 0.05	ns	< 0.025	< 0.05

* = % of normal; ** = significance between at rest and isoproterenol test; Isp = isoproterenol test

Fig. 1. The relationship between the age and the average myocardial fiber diameter of the right ventricular outflow muscle in tetralogy of Fallot, and comparison to the normal (control). This figure is reproduced from Kato's original paper.¹

RESULTS (Table II)

1) Preoperative RV and LV Functions AT Rest (Group-A)

There was no significant difference in either RVEDP or LVEDP between Groups A-1 and A-2. In EF, Group A-1 showed higher RVEF compared to Group A-2 ($p < 0.01$), but there was no significant difference in LVEF between the 2 groups. Specific compliance (mmHg^{-1}) of RV was higher in Group A-1 than in Group A-2 ($p < 0.02$), but there was no significant difference in LV compliance between the 2 groups.

2) Postoperative Right Ventricular Function (Group-B)

Group B-1 showed significantly lower RVEDP compared to Group B-2 ($p < 0.05$), but there was no significant difference in RVEDV between the 2 subgroups. In 14 patients who underwent ISP test, 9 from Group B-1 and 5 from Group B-2, there were no significant differences in RVEF and RVEDV between the 2 subgroups either at rest or at the time of the ISP test, respectively. However, Group B-1 showed a significant response in EF to ISP ($p < 0.05$), whereas no significance was seen in Group B-2.

3) Postoperative Left Ventricular Function at Rest and During MX Test (Group-C)

At rest, LVEDP was lower in Group C-1 than in Group C-2 ($p < 0.05$), and LVEDVI was significantly lower ($p < 0.025$) in Group C-1 than

in Group C-2. However, in LVEF at rest, there was no significant difference between the 2 subgroups. Kps, which was obtained after MX infusion, was significantly higher ($p < 0.05$) in Group C-1 compared to Group C-2.

DISCUSSION

1) Age-related Changes in Histology and Function of RV

Our histological studies on right ventricular myocardium in TF have already demonstrated that RV hypertrophy commences immediately after birth, and the diameter of RV muscle fiber increases with age¹ (Fig. 1). Furthermore, irreversible histological alterations characterized by intercellular fibrosis and nuclear degeneration can be seen in patients over 4 years of age. Also, these findings showed no positive correlation to the degree of hypoxia. The approximate age in which irreversible change may occur has not been clearly indicated in other papers. Jones and his associates² also demonstrated a correlation between degenerative changes in RV outflow muscle cells and age, although there was a lack of correlation between the age and hypertrophy when the patients were divided at 15 years of age. In addition, they compared electron microscopic findings with degenerative findings entirely absent in patients under 5 years but common in older patients over 30 years.³ It was indicated that the stresses of prolonged ventricular hypertrophy and hypoxia in RV were reflected in impaired cardiac function.

Jarmakani and his associated⁸ have previously reported on preoperative right ventricular function in TF with or without palliative surgery and demonstrated the presence of decreased EF, possibly due to chronic hypoxia. There has been some analysis of preoperative RV function related to age,⁹ and age-related depression in RV function has been shown to be less remarkable. The present study shows some correlations to morphological findings, that is the RVEF and RV compliance were better in patients of younger age who were divided by the age of 5 years.

Postoperative RV function in this report, in which the group was divided according to the age of operation at 4 years, indicated a significant difference in RVEDP with a higher value in the older group of patients. While this might partly correlate to the histological findings, EDP alone may not be suitable to see the correlation. RVEF and RVEDV showed no significant

differences between the 2 subgroups divided by the age at 4 years. According to the ISP test, however, RVEF showed a slight but significant response only in the younger group. Therefore, there appears to be some correlation between morphological changes and postoperative function of RV. Drawing a definite conclusion regarding the relationship between these two factors may be difficult from this study because the number studied was small and other factors influenced the results. Further studies are required to elucidate the relationship between the age of operation and postoperative RV functions.

2) Relations between the Morphological and Hemodynamic Findings in LV

In regard to morphological studies on LV muscle in TF, Koh and his associates⁴ have shown that the degree of LV muscle hypertrophy and fibrosis was less than in RV muscle, and the muscle diameter of LV was correlated with preload, i.e. LVEDVI. Fukuda and his associates⁵ have also reported similar findings in LV muscle in TF. Therefore, occurrence of age-related changes in LV muscle seems less likely than in RV muscle, and the preoperative left ventricular function in this report showed similar results. Postoperatively, the results obtained at rest in this report showed no significant difference in LVEF between the 2 subgroups, with there being no apparent age-related changes in LV function. However, our study using methoxamine to induce afterload has unmasked dysfunction of LV as expressed by Kps. Similar results using the LV minute work index under MX test has been reported by Borow and his associates.¹⁰ Therefore, age-related changes may even develop in LV muscle from chronic hypoxia as well as from decreased preload, despite the lack of apparent histological changes.

3) Clinical Implications

This study attempted to elucidate age-related changes in the myocardium using methods of morphology and function while separating the RV and LV. The most significant age-related change was found histologically in RV muscle, with seeming correlations to pre- and postoperative RV functions. LV may exhibit fewer age-related changes in myocardium, but the stress test for the ventricular function study has shown

underlying functional abnormalities in patients with later corrective surgery. Considering the presence of postoperative myocardial dysfunctions even with recent improvements in the repair of TF,⁶ these findings indicate the necessity of early repair of TF because the combination of chronic pressure load to RV and hypoxia with decreased preload to LV appear to result in functional disturbances.

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