RESPONSE TO ISOPROTERENOL INFUSION IN PEDIATRIC PATIENTS FOLLOWING ATRIAL REPAIR OF TRANSPOSITION OF THE GREAT ARTERIES

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The postoperative function of the right (systemic) ventricle (SV) was evaluated in eight pediatric patients who had undergone intra-atrial switching for simple transposition of the great arteries (TGA). SV function was evaluated at rest and during isoproterenol (ISP) infusion and compared with left ventricular function in the control group. The control group consisted of five patients including two with postoperative pulmonary stenosis, two with mild pulmonary stenosis and one with postoperative partial anomalous pulmonary venous drainage. SV-graphy was performed at rest. During ISP infusion, the TGA group showed a significant increase in cardiac index (3.50 ± 0.68 (mean ± SD) L/min/m² to 4.94 ± 1.53 L/min/m², p < 0.05) and no significant changes in stroke volume index (SVI). Similar changes were observed in the control group. Resting SV-ejection fraction was 0.37 ± 0.05 in the TGA group. In regard to the relationship between SV end-diastolic pressure and SVI, all but one of the TGA patients showed normal response to the stress.

These results indicated that the right ventricle in TGA showed an acceptable response to ISP stress and acted as a systemic ventricle for at least two years after surgery.

The Mustard and Senning procedures are well established operative methods for simple transposition of the great arteries (TGA). These procedures, however, require the anatomical right ventricle (RV) to also function as the systemic ventricle (SV) after surgery. Doubts may arise as to whether the RV can maintain normal pump function in the late postoperative period. Several reports have indicated that RV function was depressed with lower RV ejection fraction (EF) and larger RV end-diastolic volume after the intra-atrial switch operation. Most of these studies were based on the assessment of RV function at rest. However, resting hemodynamics may not accurately predict the reserve of RV function. In this study, the postoperative RV function and its reserve were evaluated under pharmacologic stress induced by isoproterenol (ISP) in patients with TGA via the Mustard or Senning procedure.

MATERIALS AND METHODS

Eight asymptomatic postoperative pediatric patients with simple TGA were studied to evaluate SV function under a stress condition induced by ISP (Table I). Six patients had undergone intra-atrial switch repair by the Mustard procedure, and two by the Senning

Key Words:
- Transposition of the great arteries
- Isoproterenol
- Right ventricular function
- Right ventricular reserve

(Received May 7, 1986; accepted June 21, 1986)
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**Control**

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| 1a  | 2.3        | 129        | 178         | 96           | 125          | 1664         | 696          | 8              | 8           | 4.23           | 6.09 | 32.8 | 34.2 | 0.70 | 57  | – |
| 2b  | 1.7        | 2.8        | 138         | 176         | 94           | 120          | 1126         | 913            | 8           | 8              | 4.12 | 5.08 | 30.0 | 29.0 | 0.62 | 57  | – |
| 3c  | 8.3        | 10.6       | 116         | 138         | 108          | 120          | 1101         | 1443           | 9           | 5              | 3.63 | 4.82 | 31.3 | 34.9 | 0.60 | 69  | – |
| 4b  | 3.8        | 9.8        | 84          | 138         | 132          | 140          | 2709         | 1391           | 6           | 5              | 3.10 | 5.52 | 36.9 | 40.0 | 0.59 | 83  | – |
| 5a  | 7.0        | 7.0        | 111         | 159         | 124          | 160          | 1693         | 1333           | 12          | 7              | 4.30 | 5.10 | 38.7 | 40.6 | 0.60 | 54  | – |
| mean| 4.6        | 6.5        | 116         | 158         | 111          | 133          | 1659         | 1155           | 9           | 7              | 3.88 | 5.32 | 33.9 | 35.7 | 0.62 | 64  | – |
| ±SD | 3.4        | 3.9        | 21          | 20          | 17           | 17           | 652          | 331            | 2           | 2              | 0.51 | 0.50 | 3.7  | 4.8  | 0.04 | 12  | – |

**R vs ISP**

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**Abbreviations:** Age 1 = age at repair, Age 2 = age at study, CI = cardiac index, HR = heart rate, ISP = isoproterenol, M = Mustard, OP = operative technique, Pt = patient, R = rest, S = Senning, SVEDP = systemic ventricular end-diastolic pressure, SVEDVT = systemic ventricular end-diastolic volume index, SVEF = systemic ventricular ejection fraction, SVT = systemic ventricular stroke volume index, SVR = systemic vascular resistance, SVSP = systemic ventricular peak systolic pressure, TGA = transposition of the great arteries, Tr = mild tricuspid regurgitation (+ = Tr was observed, = = Tr was not observed.), yr = year.

a: Mild pulmonary stenosis, pressure gradient = 22 ± 6 mmHg.
b: Postoperative pulmonary stenosis, pressure gradient = 7 ± 1 mmHg.
c: Postoperative partial anomalous pulmonary venous drainage.
Fig.1. Systemic ventricular end-diastolic pressure (SVEDP), from rest (R) to ISP infusion in the TGA (open circle) and control (closed circle) groups. Data are expressed as mean ± standard deviation.

procedure. The ages at operation ranged from 0.6 to 1.2 years with an average of 0.9 ± 0.2 (±SD) years. The ages at postoperative study ranged from 1.3 to 5.5 years with an average of 2.8 ± 1.8 years. The interval between repair and study ranged from 0.4 to 4.6 years with an average of 1.9 ± 1.7 years. The control group consisted of five patients including two with postoperative pulmonary stenosis, two with mild pulmonary stenosis and one with postoperative partial anomalous pulmonary venous drainage (Table I). The control group was considered to have normal left ventricular (LV) function. The ages of the control group at study ranged from 2.4 to 10.6 years with an average of 6.5 ± 3.9 years, and LV (SV) function was studied for comparison. Informed consent was obtained from their parents.

Cardiac catheterization was performed under sedation with intramuscular pethidine hydrochloride (1 mg/kg) and atropine sulfate (0.01 mg/kg). Pressure measurement was performed using a strain gauge transducer (Statham P23Db) zeroed at the patient's mid-chest level. Cardiac output was measured by the dye dilution method and expressed by cardiac index (CI L/min/m²). After measurement of basic pressures and oxygen saturation, RV graphy in the TGA group and LV graphy in the control group were performed. Infusion of ISP was then started, and its rate was increased until the heart rate (HR) increased to approximately 150% of that at rest. The ISP dose ranged from 0.05 to 0.09 μg/kg/min with an average of 0.06 ± 0.02 μg/kg/min. Hemodynamic studies were carried out repeatedly during ISP infusion, however, SV graphy was not attempted during the infusion. The systemic vascular resistance (SVR, dyne-sec·cm⁻⁵) was calculated as (Aom-RAm)/CI, where Aom is mean aortic pressure (mmHg) and RAm is mean systemic venous atrial pressure (mmHg). RV volume of the TGA group was calculated using the area-length method described by Shimazaki et al.⁷ LV volume of the control group was calculated according to the area-length method of Dodge et al.⁸ SVEF was calculated as (SVEVI–SVESVI)/SVEVI, where SVEVI is SV end-diastolic volume index (ml/m²) and SVESVI is SV end-systolic volume index (ml/m²). Data are expressed as mean ± standard deviation.

The statistical analysis was performed using the unpaired test for the unpaired samples and by the paired test for the paired samples. A p-value < 0.05 was considered significant.

RESULTS

HR, SV peak systolic pressure (SVSP), and SVR are shown in Table I. SVSP in the TGA group was lower than that in the control group during ISP infusion. In HR and SVR, no difference existed between the two groups under either condition.

SV end-diastolic pressure (SVEDP) did not change significantly during ISP infusion in the TGA group. There was no significant difference between TGA and control groups either at rest or during ISP infusion (Fig. 1).

CI increased significantly (p < 0.05) from 3.50 ± 0.68 L/min/m² at rest to 4.94 ± 1.53 L/min/m² during ISP infusion in the TGA group. In the control group, CI registered 3.88 ± 0.51 L/min/m² at rest and 5.32 ± 0.50 L/min/m² during ISP infusion. There was no significant difference between TGA and control groups either at rest or during ISP infusion (Fig. 2).

SV stroke volume index (SVI) did not change in the TGA group, with 30.6 ± 8.7 ml/beat/m² at rest and 29.1 ± 8.0 ml/beat/m² during ISP
Fig. 2. Cardiac index (CI) and systemic ventricular stroke volume index (SVI), from rest (R) to ISP infusion in the TGA (open circle) and control (closed circle) groups. Data are expressed as mean ± standard deviation.

infusion. SVI was 33.9 ± 3.7 ml/beat/m² at rest and 35.7 ± 4.8 ml/beat/m² during ISP infusion in the control group. No difference in SVI was seen in the two groups either at rest or during ISP infusion (Fig. 2).

SVEF at rest was 0.37 ± 0.05 in the TGA group and 0.62 ± 0.04 in the control group (p < 0.001) (Table I). SVEDV at rest was 109 ± 33 ml/m² in the TGA group and 64 ± 12 ml/m² in the control group (p < 0.02) (Table I). Mild tricuspid regurgitation (Tr) was observed in two of the TGA patients (Table I). Residual shunt was not observed in any of the TGA patients.

Figure 3 shows the relationship between SVEDP and SVI at rest and during ISP infusion. The control group showed a decrease or no change in SVEDP and a variable change in SVI. Seven TGA patients exhibited a decrease in SVEDP and variable changes in SVI, but one TGA patient showed an increase in SVEDP and a decrease in SVI.

DISCUSSION

The intra-atrial switch operation, including the Mustard¹ or Senning² procedure, requires the RV to also function as SV after the repair. In patients with simple TGA, the operative mortalities of the Mustard or Senning procedure are lower than those of the Jatene repair³ which utilizes the left ventricle as SV. Therefore, the former procedures are generally performed in TGA where the ventricular septum is intact. The cause of this postoperative RV abnormality has been attributed to the unsuitability of the RV for pumping blood into the higher pressure system due to its morphological structure⁴; further, the RV is supplied by only one coronary artery⁵ and there are no collateral or anastomotic vessels⁶. Therefore, when the RV is exposed to the stress, an imbalance between myocardial oxygen demand and supply can occur. Selden et al⁷ reported that in two cases with isolated corrected TGA who had anginal pain, the pain might have been due to an imbalance between

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myocardial oxygen demand and supply, since no stenotic lesions were observed in their coronary arteries.

Previous reports on poor RV function in postoperative TGA were based on hemodynamic assessment at rest. Most patients do well clinically after repair of TGA, and thus, it is difficult to explain the discrepancy between the clinical and hemodynamic status. Therefore, it is important to evaluate hemodynamics under stress conditions, but, to date, there has been little information regarding hemodynamics during stress. Cooperative required in exercise stress is difficult when the patients are young children. In this study, the ISP stress test was performed in place of exercise stress to assess RV function and its reserve. The stress test by ISP infusion has been utilized as a test simulating exercise for evaluating cardiac function in patients with congenital heart disease.

SVSP was lower in the TGA group than in the control group during ISP infusion. However, SVR showed no difference in the two groups under either condition. Neither was there any difference in afterload between both groups. In the TGA group, three patients showed a high value in SVEDP at rest. In seven patients, including these three patients, SVEDP decreased during ISP infusion. Compliance of SV is preserved in the TGA patients. CI increased significantly and SVI did not change in the TGA group during ISP infusion. The increase of CI was due to the elevated HR. No difference was seen between TGA and control groups in CI and SVI either at rest or during ISP infusion. The changes in CI were similar to data previously reported by Godman et al.

The relationship between SVEDP and SVI correlated with Frank-Starling’s curve. ISP increases myocardial contractility, so the curve shifts to the left during ISP infusion. An abnormal response is an increase in SVEDP during ISP infusion. In the control group, no patients showed an increase in SVEDP. All but one TGA patients displayed a decrease in SVEDP. Ross et al. demonstrated the relationship between EDP and SVI that occurred with exercise; abnormal LV dynamics were associated with an increase in SVI and EDP; depressed LV function was characterized by no change or a fall in SVI and EDP.
an increase in LVEDP. On the basis of the relationship, only one TGA patient showed an abnormal response. Thus in this study, most of the TGA patients showed a normal response to ISP.

Recently, there have been studies of hemodynamic response to exercise after the intra-atrial switch operation in older patients. Parrish et al.20 reported that despite abnormal RVF response to exercise, no significant differences were detected in exercise tolerance between normal patients and TGA patients (9 ± 3 years at study) who had undergone the Mustard repair. Based on these findings, they suggested that for most patients with TGA, the abnormalities of ventricular function were not clinically important in childhood. Graham21 pointed out that patients with repaired TGA whose resting RVF was less than 0.33 had some clinical impairment in exercise tolerance. But patients with resting RVF of approximately 0.43 usually had no clinically evident problems in exercise impairment. In our study, the response to ISP was almost normal, although resting RVF (SVEF) was lower, averaging 0.37 ± 0.05, and resting RVVEDV (SVEVDV) was larger, averaging 109 ± 33 ml/m². The pump function, therefore, is considered to be well compensated.

In conclusion, postoperative RV in patients who had undergone the Mustard or Senning procedure for TGA showed a response to ISP stress considered acceptable as a systemic ventricle at least for two years after surgery.

REFERENCES

2. SENNING A: Surgical correction of transposition of the great vessels. Surgery 45: 966, 1959
10. SHAKER RM, PUDDU GC: Coronary arterial anatomy in complete transposition of the great vessels. Am J Cardiol 17: 355, 1966
20. PARRISH MD, GRAHAM TP Jr, BENDER HW, KATO H et al.

Japanese Circulation Journal Vol. 50, October 1986