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ORIGINAL ARTICLE

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Long-term respiratory outcomes after primary total correction for tetralogy of Fallot and absent pulmonary valve in patient with respiratory symptoms

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Abstract

Objective: To review long-term respiratory outcomes for tetralogy of Fallot and absent pulmonary valve (TOF/APV) in respiratory symptomatic populations.

Methods: Of 25 consecutive patients undergoing primary total correction for TOF/APV between 1987 and 2016, Sixteen patients (64%) with a preoperative respiratory disturbance were enrolled. The median age at operation was 1.9 months old, including 4 neonates and 12 infants. Ten patients (62.5%) preoperatively necessitated mechanical ventilator support. During operation, dilated central pulmonary arteries (cPAs) were plicated and retracted anteriorly in all patients, except for the first patient of the study cohort. VSD was completely closed, and the right ventricular outflow tract was reconstructed with a handmade valved conduit before 1990, or a transannular patch with a handmade monocusp after 1991.

Results: The actuarial survival rate at 20 years was 86.7%. One patient without cPAs plication and another requiring mechanical ventilator support right after his delivery died. The median duration of postoperative mechanical ventilator support was 14 days (range, 1–183). Readmission for respiratory disturbance after discharge was frequently observed before five years of age, however, no patients were readmitted to the hospital after six years of age, during the median follow-up period of 14.7 years, with a maximum of 27.2 years. Although persistent dilatation of cPAs was common, respiratory symptoms never recurred.

Conclusions: Prognostic and respiratory outcomes after primary total correction for TOF/APV in respiratory symptomatic populations were good. Successful relief of tracheal/main bronchial compression by primary total correction at the neonatal or infantile period provided delayed, but nonrecurrent improvement of respiratory disturbances.

KEYWORDS

absent pulmonary valve, tetralogy of Fallot, tracheal/bronchial stenosis

1 | INTRODUCTION

Tetralogy of Fallot with absent pulmonary valve (TOF/APV) is a rare congenital heart anomaly and presents a wide spectrum of clinical severity.[1] Whereas some patients are free from any symptoms and are

Abbreviations: cPAs, central pulmonary arteries; PA, pulmonary artery; PV, pulmonary valve; RV, right ventricle; RVOT, right ventricular outflow tract; TOF/APV, tetralogy of Fallot with absent pulmonary valve.

TABLE 1 Patients' characteristics

	Number or Median	(% or Range)
Female:male	10:6	
Prenatal diagnosis	6	(37.5)
Gestational age (week)	38.4	(37–41)
Age at total correction (days old)	56	(26–223)
Neonates	4	(25.0)
Body weight at total correction (kg)	3.2	(2.4–6.2)
Preoperative mechanical ventilator support	10	(62.5)
22q11.2 microdeletion syndrome	2	(12.5)
CHARGE association	1	(6.3)
Preoperative transthoracic echocardiography	16	(100)
Left ventricular diastolic diameter (% of normal)	86	(66–101)
Left ventricular ejection fraction (%)	73	(48–84)
Pulmonary valve diameter (mm)	5.0	(3.5–8.9)
RVOT flow velocity (m/s)	3.7	(2.9–5.0)
Pulmonary regurgitation flow velocity (m/s)	2.6	(1.9–3.3)
Right PA diameter (mm)	15.0	(10.6–18.1)
Left PA diameter (mm)	13.0	(8.0–19.2)
Preoperative cardiac catheter examination	13	(81.3)
Pulmonary to systemic blood flow ratio	2.3	(0.7–7.3)
Pressure gradient across RVOT (mm Hg)	58	(37–89)
Mean PA pressure (mm Hg)	14.5	(8–20)
PA index (mm^2/m^2)	1968	(1,231–3,984)
Right PA index	1140	(285–1,885)
Left PA index	1477	(611–2,223)
Right ventricular end-diastolic volume index (%N)	160	(115–3)
Right ventricular ejection fraction (%)	56	(42–82)
Left ventricular end-diastolic volume index (%N)	112	(64–175)
Left ventricular ejection fraction (%)	65	(41–84)
Cardiac Index (l/min/m2)	3.1	(1.8–5.6)

PA, pulmonary artery; RVOT, right ventricular outflow tract.

incidentally diagnosed in the adolescent period, respiratory failure can progress early after birth in a certain number of patients.[2] The prognostic outcomes after total correction for TOF/APV have improved recently; however, outcomes in patients who suffered from preoperative respiratory failure and therefore underwent the operation within the first year of life were not satisfactory.[3–9]

Preoperative respiratory failure in patients with TOF/APV is thought to be derived from the following facts. Fetuses with TOF/APV typically have dilated central pulmonary arteries (cPAs) due to free pulmonary insufficiency, which compresses trachea and main bronchus.[10] If mild pulmonary valve (PV) stenosis under the presence of relatively sized rudimentary PV coexists, cPAs are further dilated by the effect of post stenotic dilatation, as Momma et al. clearly demonstrated by the small animal experiment.[11] Respiratory failure usually can develop after birth, along with the increase of pulmonary blood flow; however, recent development of prenatal diagnosis identified cases of intrauterine fetal death or death right after delivery.[12]

So, the purpose of this study is to review long-term respiratory outcomes of primary total correction for TOF/APV in patient with respiratory symptoms.

2 | METHODS

2.1 | Patients

The National Cerebral and Cardiovascular Center Institutional Review Board approved this retrospective study and waived the need to obtain patient consent. Of the 25 consecutive patients who underwent total correction for TOF/APV at our center between 1987 and 2016, 16 patients (64%) with preoperative need for continuous positive airway pressure or mechanical ventilator support were enrolled in this study (Table 1). During the study period, no patient died in the prenatal period or without surgery after birth.

2.2 | Surgical procedures

Our institutional policy was primary total correction. At the operation, VSD was completely closed with a patch. The anterior wall of the cPAs was plicated, then the PA trunk was divided and retracted anteriorly, and the posterior wall was anastomosed to the conus septum to relieve tracheal/main bronchial compression. The Le compte maneuver was not

applied. The right ventricular outflow tract (RVOT) was reconstructed using a handmade valved conduit in six patients before 1990, or a transannular patch with a handmade monocusp in nine patients after 1991. The latest patient underwent operation using a handmade trileaflet valved conduit, because the transannular patching was impossible due to the presence of the left main trunk running across the anterior right ventricular outflow tract, just below the pulmonary valve annulus.

2.3 | Statistical methods

This study was a single institutional, retrospective study. Pre- and postoperative data were expressed by median (range) or mean ± standard deviation, as appropriate. Evaluated variables were: (1) Preoperative findings mainly assessed by cardiac catheter examination, (2) Perioperative/in-hospital outcomes and hemodynamic assessment by a cardiac catheter examination one year after the total correction; (3) Overall mortality and freedom from reoperation rate for RVOT by the Kaplan-Maier method; and (4) Respiratory outcomes assessed by the frequency of readmission for respiratory disturbance after discharge and long-term airway assessment by three-dimensional enhanced thoracic computed tomography. Interviews with patients' parents at outpatient clinics and reports from patients' caregivers were carefully analyzed to count the frequency of readmission for postoperative respiratory failure; therefore, not only readmission to our hospital, but all readmissions to other hospitals all over the country were completely recorded.

To assess the dilatation of cPAs, the right PA Index and left PA Index were calculated according to the PA Index,[13] as shown in the following formula:

$$\text{Right PA Index} = \pi \times (\text{right PA diameter (mm)}/2)^2/\text{body surface area } (\text{m}^2)$$

$$\text{Left PA Index} = \pi \times (\text{left PA diameter (mm)}/2)^2/\text{ body surface area } (\text{m}^2)$$

The data were analyzed using PASW Statistics 18 software (SPSS Inc., Chicago, IL). Differences were considered statistically significant when the *P* value was less than.05.

3 | RESULTS

3.1 | Preoperative findings

Six current patients (37.5%) were prenatally diagnosed. Because respiratory symptoms always progress during the neonatal or infantile period, the median age at total correction was 56 days old, and ranged from 26 to 223 days, including four neonates. Ten out of 16 patients (62.5%) required mechanical ventilator support preoperatively and the remaining 6 patients required continuous positive airway pressure.

Thirteen of 16 patients underwent preoperative cardiac catheter examination (Table 1). The pulmonary to systemic blood flow ratio was typically increased, with a median value of 2.3. The median pressure gradient across the RVOT was 58 mm Hg, and ranged from 37 to 89 mm Hg. Both branch pulmonary arteries were extremely dilated, so the median pulmonary artery index was 1968 mm^2/m^2.

3.2 | Early postoperative outcomes

There were no 30-day mortalities and one in-hospital mortality (6.3%) (Table 2). Two patients required perioperative extracorporeal life support, both of whom were successfully weaned two and four days after the operation and have survived to date. Median lengths of the intensive care unit and hospital stays were 15 and 34 days. The median duration of postoperative mechanical ventilator support was 14 days (1–183), including one patient who transferred to a regional hospital after tracheostomy, with ventilator support. As the re-operation for respiratory failure, tracheostomy was performed in one patient, as described above. Two patients, including one in-hospital mortality, required left PA suspension for persistent significant airway tract obstruction. No patients required pneumonectomy or tracheal/bronchial stenting.

TABLE 2 Early surgical outcomes

	Number or Median	(% or Range)
Perioperative outcomes		
Cardiopulmonary bypass time (minutes)	194	(150–380)
Aortic cross clamp time (minutes)	80	(44–117)
In-hospital outcomes		
In-hospital mortality	1	(6.3)
Extracorporeal life support	2	(12.5)
Mechanical ventilator support (days)	14	(1–183)
Length of intensive care unit stay (days)	15	(5–161)
Length of hospital stay (days)	34	(86–932)
Re-operation for respiratory failure		
Tracheostomy	1	(6.3)
Left PA suspension	2	(12.5)

PA, pulmonary artery; RVOT, right ventricular outflow tract.

TABLE 3 Early hemodynamic assessment by cardiac catheter examination

	Number or Median	(% or Range)
Number of patients	14	
Right to left systolic ventricular pressure ratio	0.56	(0.33–1.20)
Mean PA pressure (mm Hg)	17.5	(7–40)
PA index (mm^2/m^2)	848	(416–1,390)
Right PA index (mm^2/m^2)	338	(149–640)
Left PA index (mm^2/m^2)	413	(162–995)
Right ventricular end-diastolic volume index (%N)	132.5	(99–349)
Right ventricular ejection fraction (%)	52	(28–71)
Left ventricular end-diastolic volume index (%N)	104	(75–161)
Left ventricular ejection fraction (%)	63	(52–75)
Cardiac Index ($L/min/m^2$)	3.4	(1.7–6.7)

PA, pulmonary artery.

3.3 | Early hemodynamic evaluation by cardiac catheter examination

All 14 patients who were followed for more than one year underwent postoperative cardiac catheter examination at the median duration of 1.0 year from the total correction surgery date (0.1–3.9) (Table 3). The right to left ventricular systolic pressure ratio was 0.56, and ranged from 0.33 to 1.20. The median mean PA pressure was 17.5 mm Hg. The median PA index, right PA index, and left PA index remained above normal range (848, 338, and 413 mm^2/m^2, respectively)[13]; however, all of those indices were significantly lower when compared to preoperative measurements (Figure 1).

3.4 | Overall survival

Follow up was completed on 15 patients (93.8%) and the median follow up period was 14.7 years, with the maximum follow-up period of 27.2 years. The actuarial survival rate at 25 years after the total correction was 86.7% (Figure 2). There was one in-hospital mortality as described above and one mortality soon after discharge. Both of the patients associated with 22q11.2 microdeletion syndrome survived to date.

The in-hospital mortality was a prenatal diagnosed case and required mechanical ventilator support just after birth for his severe respiratory failure. The operation was performed at 26 days of age, but the postoperative obstructive respiratory failure persisted. Left PA suspension was attempted two days after the total correction, without any improvement of respiratory failure. He completely depended on the mechanical ventilator support and died 161 days after the total correction due to septic shock, probably due to acute panperitonitis.

The late mortality was the first enrolled patient in this study cohort. Her cPAs were not plicated at the total correction, so postoperative obstructive respiratory failure continued and left PA suspension was performed two days after the initial surgery. She was extubated

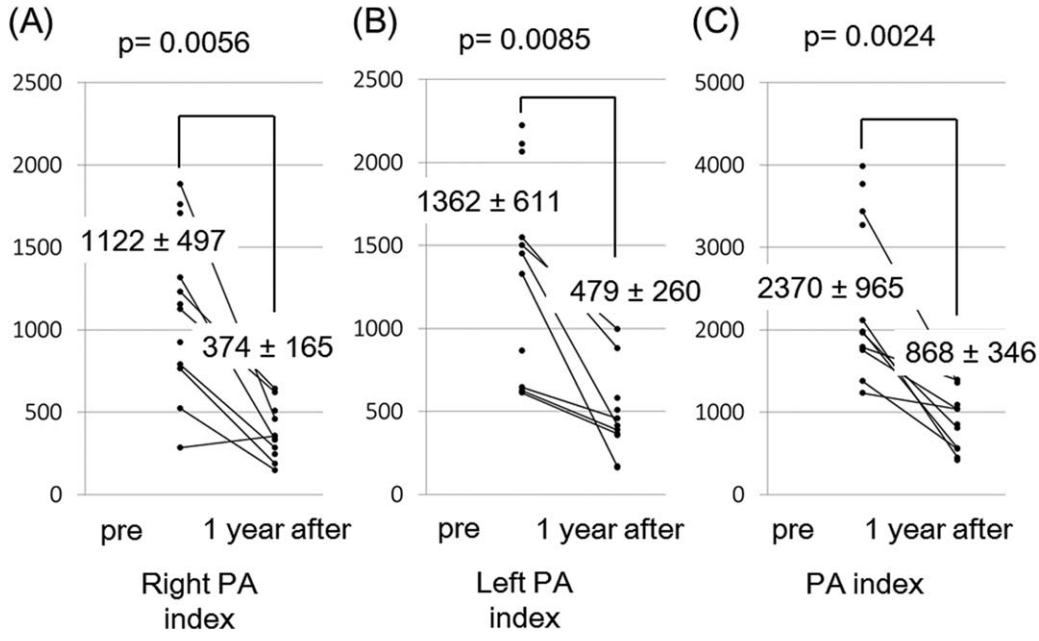

FIGURE 1 All of the right PA, left PA, and PA indexes were significantly decreased from preoperative evaluation to one year after the total correction

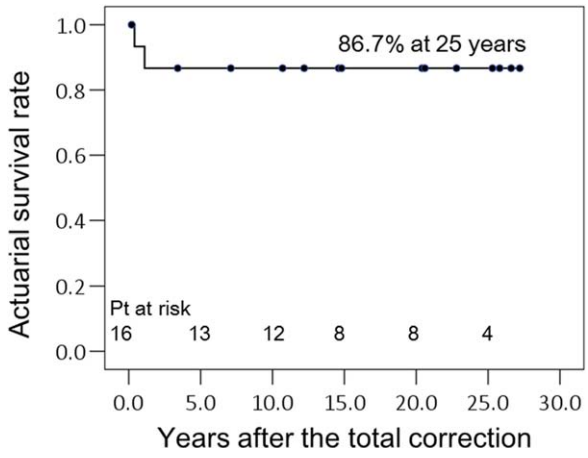

FIGURE 2 Actuarial survival rate by Kaplan–Meier curve

176 days after the initial surgery; however, cardiopulmonary resuscitation was frequently required due to recurrent apnetic spells after that. She was discharged from the hospital 299 days after the initial surgery, but required multiple emergent readmissions due to respiratory failure, then died 418 days after the initial surgery.

3.5 | Freedom from reoperation rate for RVOT

Freedom from reoperation for RVOT rate at 20 years was 52.2% (Figure 3). While patients undergoing RVOT reconstruction using the transannular patch with a handmade monocusp required reoperation for RVOT insufficiency, patients using the handmade valved conduit required reoperation for RVOT stenosis. The number of reoperation for RVOT was significantly higher in patients where handmade valved conduit was used in comparison to patients where transannular patch with a handmade monocusp was used (log-rank: $P = .0026$). Furthermore, all patients who had a handmade valved conduit placement

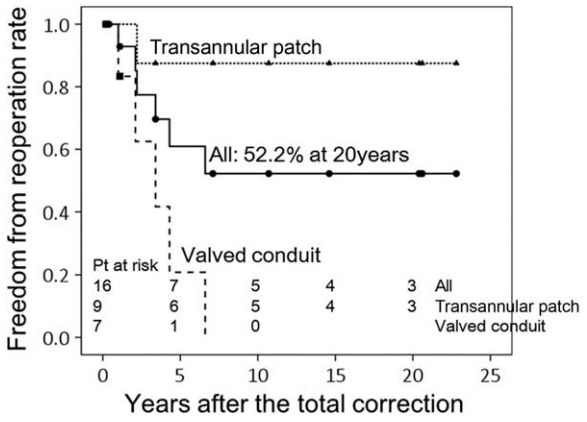

FIGURE 3 Freedom from reoperation rate for RVOT by the Kaplan-Meier curve. The solid line indicates all patients, the dotted line indicates patients treated with the transannular patch, and the dashed line indicates patients treated with the valved conduit. Patients using the handmade valved conduit required significantly frequent reoperation for RVOT (vs transannular patch, log-rank: $P = .0026$)

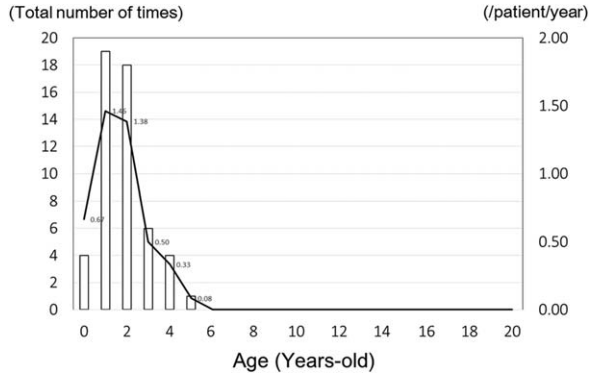

FIGURE 4 Chronological changes of readmission times for respiratory disturbances after the total correction by age. Open bars represent the total number of readmission times, and the line represents readmission times/patient/year

required repeat RVOT reconstruction within seven years after the total correction surgery. At the postoperative catheter examination, moderate or greater pulmonary insufficiency was observed in 1 of 6 patients (16.7%) who who received a valved conduit and 6 of 8 patients (75%) who received a monocusped transannular patch ($P = .03$).

3.6 | Readmission for respiratory disturbance after the total correction

Readmission for respiratory disturbances, mainly infections such as pneumonia, bronchitis, upper respiratory tract infection and asthmatic bronchitis, were counted after the operation (Figure 4). Frequent readmissions were observed until two years of age. During the first year of age, 13 patients were followed and the total number of their readmissions was 19 times (1.45 times/patient/year), and during the second year of life, 13 patients were followed and the total number of their readmissions was 18 times (1.38 times/patient/year). After that, the frequency of readmission had markedly decreased, and none of the patients were readmitted to the hospital after six years of age, during the median follow-up period of 14.7 years.

3.7 | Airway assessment by 3-dimensional computed tomography

Before the total correction, the left main bronchus was compressed by dilated cPAs, as well as the distal right main bronchus (Figure 5A). One month after the total correction, cPAs were significantly downsized and compression of the whole right main bronchus and distal left main bronchus was well relieved and only mild stenosis remained at the middle of the left main bronchus (Figure 5B). Persistent dilatation of cPAs long after the total correction was usually observed, but the airway was free from obstruction.

4 | DISCUSSION

This study demonstrated that the total correction for TOF/APV at the neonatal and infantile period in symptomatic patients successfully

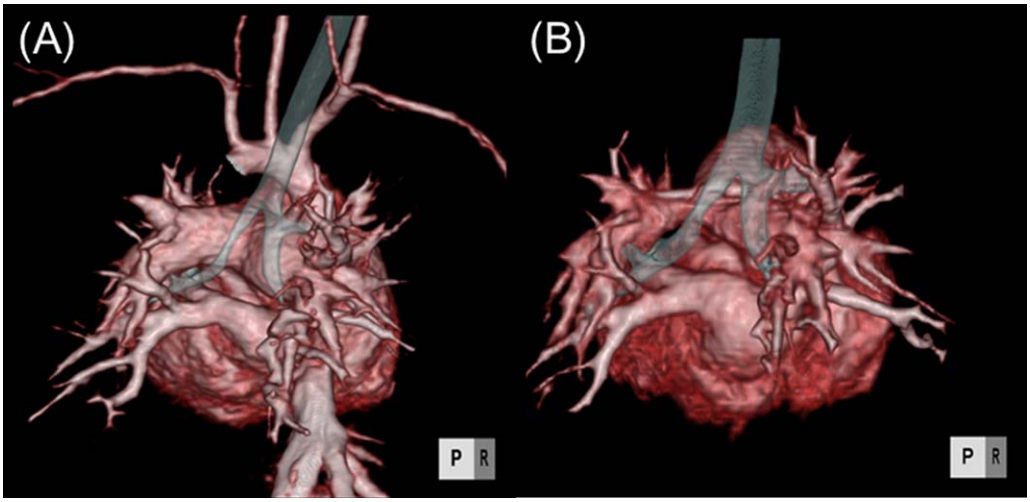

FIGURE 5 Representative three-dimensional computed tomography images. Before (A) and one month after the total correction (B) images of the same patient who underwent the operation at the neonatal period

relieved tracheal/main bronchial compression, which resulted in delayed, but complete improvement of respiratory disturbances. Although late recurrent dilatation of cPAs was commonly seen, respiratory disturbances never recurred.

Both of the mortalities were caused by persistent respiratory failure, and each of them left important messages. At first, plication of cPAs was essential to rescue patients' lives and also for the relief of airway obstructions. Advantages of the Le compte maneuver and tubular resection of ascending aorta still have not been demonstrated.[14] All late survivors older than five years old in this study cohort were completely free from respiratory disturbances; nevertheless, persistent dilatation of cPAs was commonly seen. This indicates that early relief of the airway obstruction achieves delayed but complete resolution of respiratory symptoms. A similar process occurs in patients with primary bronchomalacia. Mild to moderate bronchomalacia usually resolves by the age of five years without any interventions. This was partially explained by the fact that the diameter of the trachea and bronchi tripled from birth to maturity.[15]

Second, a limited effect of surgery was proven by the other mortality case. He was the only patient in this study cohort who required mechanical ventilator support right after his delivery to treat severe respiratory failure. Although he survived to total correction at the age of 26 days with complete relief of the main bronchial obstruction, obstructive respiratory failure remained after the operation and he died in hospital. Like this case, patients born with more severe respiratory failures may be associated with untreatable intrapulmonary bronchial obstruction.[12] Plication of cPAs beyond the hilum was reported to improve surgical outcomes[9]; however, the obstruction extends to more distal intrapulmonary bronchi in such clinically critical patients. In fact, abnormal arbolization and the formation of intrapulmonary arteries such as tufts, looping, or an increase in number was observed and compressed the lobar and segmental bronchi in such patients.[2] If distal intrapulmonary bronchial obstruction is localized in a few lung segments, concomitant or subsequent pulmonary segmentectomy may be effective to resolve ventilation perfusion mismatches, but it usually exists in all segments. Based on these findings, now we think that patients born with severe respiratory failure that required mechanical ventilator support right after their delivery may not be able to be rescued by surgery.

The lack of availability of small sized homografts in Japan remains a challenge in terms of performing RVOT reconstruction surgery.[4–9] We changed the institutional strategy of RVOT reconstruction during the study period from using the handmade valved conduit to using the transannular patch with a handmade monocusp as an attempted to reduce the early reoperation rate. As expected, significant pulmonary regurgitation is inevitable after RVOT reconstruction with the transannular patch with a handmade monocusp, but respiratory outcomes in patients who received a monocusped transannular patch seemed to be similar to those who received a valved conduit. Early postoperative outcomes are reported to be similar in patients who had a valve insertion in RVOT compared to those who did not.[4] Although the conduit replacement has recently been safely done in many centers, we think RVOT reconstruction with the transannular patch with a handmade monocusp is the best procedure if anatomical conditions allow. Once again, the key element in RVOT reconstruction at the primary total correction is retraction of cPAs anteriorly, away from the airway, by division of the PA trunk and reattachment of the posterior wall to the conus septum.

4.1 | Study limitations

This study is a 30-year, long-term retrospective series consisting of a small number of patients. Only two mortalities were included, so any statistical analysis could not detect risk factors for survival. Although physical assessment of the respiratory system and the number of readmissions for respiratory disturbances revealed satisfactory improvement of postoperative respiratory functions, direct assessment of airway obstructions by bronchoscopy or a multislice CT scan was not routinely and chronologically performed.

In conclusion, survival and respiratory outcomes after primary total correction for TOF/APV in the respiratory symptomatic populations were good. Successful relief of tracheal/main bronchial compression by the primary total correction at the neonatal or infantile period provided delayed, but nonrecurrent improvement of respiratory disturbances.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept/design: Hoashi
Data analysis/interpretation: Hoashi, Kurosaki
Drafting article: Hoashi
Data collection: Iwasa, Kagisaki, Shimada
Critical revision: Shiraishi
Article approval: Ichikawa

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