Long-Term Survival and Unnatural Deaths of Patients With Repaired Tetralogy of Fallot in an Asian Cohort

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Background—Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease in Taiwan. This study investigates the long-term survival and risks of TOF in an Asian cohort.

Methods and Results—This study enrolled 819 consecutive patients with TOF (61.1% male), who received total correction between 1970 and 2002, as participants. Patient medical records were reviewed, and the survival status of those out of contact was confirmed by death records retrieved from the National Health database. The mean (±SD) patient age at cardiac repair was 6.5±7.6 years, and a prior shunt operation was performed in 119 (14.5%) of the patients. At cardiac repair, a transannular patch for right ventricle outlet reconstruction was required in 444 (54.2%) of the patients. After 13 808 patient-years of follow-up, the 30-year survival rate was 90.5%. The annual mortality rate increased from 0.123% in the initial 15 years after repair to 0.395% thereafter (P<0.05). The presence of major aortopulmonary collateral arteries, older operative age, and previous shunt operation are independent risks of late cardiac deaths. Secondary to cardiac mortality, unnatural deaths (accident and suicide) accounted for 27.6% of late deaths, significantly higher compared with that of the general population (odds ratio, 2.18; P=0.028).

Conclusions—In this Asian TOF cohort, except for a late decrease after 15 years, long-term survival after cardiac repair was satisfactory. Although cardiac death was the most common cause of late death, accidents or suicide may also be associated with late mortality, suggesting a potential role for psychosocial support. (Circ Cardiovasc Qual Outcomes. 2012;5:120-125.)

Key Words: tetralogy of Fallot ■ survival analysis ■ Asian ■ unnatural death

Lillehei et al1 reported the first total repair of tetralogy of Fallot (TOF) in 1955. With advances in operative techniques and perioperative care, surgical outcomes have greatly improved over the past 2 decades.2 As shown in several recent reports, the long-term survival (≥30 years) in patients with repaired TOF is ≈90%.3–7 According to a nationwide survey of the incidence of congenital heart disease (CHD) between 2000 and 2006, TOF is the leading type of cyanotic CHD in Taiwan, with an incidence rate of 63 per 100 000 live births.8 The total repair of TOF started circa 1965 in Taiwan. An acute surgical outcome was reported by a small patient cohort (n=51), one third of whom had a subpulmonary ventricular septal defect (VSD).9 In Taiwan, after implementation of the national health insurance program in 1995, which covers >98% of the population, almost every patient can receive full medical service. To delineate medical needs and the strategy for refining TOF treatment, this longitudinal study investigates the long-term survival and risk factors for late mortality using a single medical center cohort with >800 patients with TOF.

Methods

From January 1970 to December 2002, 827 patients received total repair of TOF at the National Taiwan University Hospital. Data were collected according to regulations and approved by the hospital institutional review board. This study included only patients with simple TOF in the assessment. Patients with pulmonary atresia, absent pulmonary valve, and combined endocardial cushion defects were excluded. Subjects’ medical records were reviewed, including details of their echocardiographic, electrocardiographic, cardiac catheterization, and operation records. Of the 827 patients, 819 had complete preoperative and operative data and were enrolled in this study. Total correction was defined as the accomplishment of right ventricular outlet tract (RVOT) reconstruction and VSD repair. RVOT reconstruction methods include transannular patch repair, RVOT patch without a transannular incision, transatrial-transpulmonary approach without an RVOT patch, and Rastelli conduit operation. The McGoon index was defined as the sum of the diameters of the left and right pulmonary arteries, divided by the descending aorta diameter at diaphragm level. The McGoon index was determined using angiographic data from 722 patients before the operation. If angiographic data were unavailable, the computed tomographic or echocardiographic data were analyzed instead.10 The MAPCAs were defined as large collateral arteries branching from the aorta and
supplying segments of the lungs. The presence of MAPCAs was determined using angiographic or computed tomographic data. The VSD types used in this study followed the classification of Soto and Anderson. For the subarterial type, the defect is located immediately beneath the pulmonary valve, with the aortic valve and pulmonary valve in fibrous continuity. For the perimembranous type, the defect is located in the membranous septum and may extend toward the pulmonary valve or to inlet portion. For muscular outlet VSDs, the defect is located in the outer portion of the muscular septum with an intact subpulmonary infundibulum. In this study, patients were categorized according to surgical findings.

WHAT IS KNOWN

- Tetralogy of Fallot is the most common cyanotic congenital heart disease in Taiwan.
- Important improvements in operative technique have occurred over the past 50 years, enabling more ill patients to undergo repair. However, the long-term success of the procedure in Taiwan has not been demonstrated.
- Moreover, the causes of death among long-term survivors in this Asian cohort have not been reported.

WHAT THE STUDY ADDS

- Among 819 operations at a single Taiwanese center from 1970 to 2002, the 10-, 20-, and 30-year survival rates were 95.8%, 92.7%, and 90.5%, respectively.
- A multivariable model of later mortality found that age (odds ratio [OR], 1.06; 95% CI, 1.002–1.12), previous shunt operation (OR, 3.4; 95% CI, 0.99–11.7), and the presence of major aortopulmonary collateral arteries (MAPCAs; OR, 10.5; 95% CI, 1.17), and the presence of major aortopulmonary collateral arteries, there were 21 missing cases; for type of ventricular septal defect, there were 53 missing cases; and for the saturation and hemoglobin data, there was 73 missing cases.

In addition to reviewing medical records, questionnaires or telephone interviews were conducted with patients who had not received follow-up for >2 years. The survival status of patients who were out of contact was checked using the death records of the National Health database. Early mortality was defined as death ≤1 year after the operation, and late death was defined as death >1 year after the operation.

This study used the χ² and Fisher exact tests to compare the clinical characteristics between groups. An independent Student t test was used for other numeric data comparisons. The CI of the incidence rate was calculated using the Midp exact method. The Kaplan-Meier survival curve was adopted for survival analysis, and the log-rank test was used to compare the results. Logistic and Cox regressions were applied for regression analyses. Statistical significance was defined as P < 0.05.

Results

Table 1 shows the basic clinical characteristics of the patient cohort. The male/female ratio was 500:319. The mean (±SD) patient age at operation was 6.5±7.6 years; 155 patients (18.9%) underwent the operation when >10 years. A systemic-to-pulmonary shunt was performed before cardiac repair in 119 (14.5%) of the patients. The shunt operation rate decreased in 1974, and has remained stationary thereafter (Figure 1). The mean (±SD) preoperative hemoglobin level was 16.1±3.1 g/dL, and the mean (±SD) preoperative arterial saturation was 83.4±9.0%. Preoperative cardiac catheterization or computed tomography data identified the MAPCAs in 23 patients (2.9%). The McGoon index was >2.0 in 11.4% of the patients, 1.5–2.0 in 31.8% of the patients, and <1.5 in 11.4% of the patients. The VSD type was subarterial in 14.1% of the patients, and the perimembranous type in 83.3% of the patients. At cardiac repair, 444 patients (54.2%) received a transannular patch, 235 (28.7%) received an RVOT patch, 127 (15.5%) received the transatrial-transpulmonary approach without an RVOT patch, and 13 (1.6%) received a Rastelli conduit operation.

The total follow-up period of the study cohort was 13 808 patient-years. The mean (±SD) follow-up period was

### Table 1. Basic Clinical Characteristics of 819 Patients With Repaired Tetralogy of Fallot

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female ratio</td>
<td>500:319</td>
</tr>
<tr>
<td>Age at operation, y</td>
<td>6.5±7.6</td>
</tr>
<tr>
<td>&lt;3</td>
<td>337 (41.1)</td>
</tr>
<tr>
<td>3–10</td>
<td>327 (39.9)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>155 (18.9)</td>
</tr>
<tr>
<td>Syndromic combination</td>
<td>42 (5.1)</td>
</tr>
<tr>
<td>DiGeorge syndrome</td>
<td>13 (1.6)</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>9 (1.1)</td>
</tr>
<tr>
<td>Pulmonary artery size, McGoon index*</td>
<td></td>
</tr>
<tr>
<td>&lt;1.5</td>
<td>91 (11.4%)</td>
</tr>
<tr>
<td>1.5–2</td>
<td>254 (31.8)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>453 (56.8)</td>
</tr>
<tr>
<td>Presence of major aortopulmonary collateral artery*</td>
<td>23 (2.9)</td>
</tr>
<tr>
<td>Type of ventricular septal defect*</td>
<td></td>
</tr>
<tr>
<td>Subarterial</td>
<td>108 (14.1)</td>
</tr>
<tr>
<td>Muscular outlet</td>
<td>20 (2.6)</td>
</tr>
<tr>
<td>Perimembranous</td>
<td>637 (83.3)</td>
</tr>
<tr>
<td>Saturation, %</td>
<td>83.4±9.0</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>16.1±3.1</td>
</tr>
<tr>
<td>Previous shunt operation</td>
<td>119 (14.5)</td>
</tr>
<tr>
<td>Operation method</td>
<td></td>
</tr>
<tr>
<td>Transannular patch</td>
<td>444 (54.2)</td>
</tr>
<tr>
<td>Tight ventricular outlet tract patch</td>
<td>235 (28.7)</td>
</tr>
<tr>
<td>Transatrial-transpulmonary without patch</td>
<td>127 (15.5)</td>
</tr>
<tr>
<td>Rastelli conduit</td>
<td>13 (1.6)</td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>16.9±9.2</td>
</tr>
</tbody>
</table>

Data are given as mean (±SD) or number (percentage), unless otherwise indicated.

*Missing data: for pulmonary artery size and presence of major aortopulmonary collateral arteries, there were 21 missing cases; for type of ventricular septal defect, there were 53 missing cases; and for the saturation and hemoglobin data, there was 73 missing cases.
16.9±9.2 years. The 10-, 20-, and 30-year survival rates were 95.8%, 92.7%, and 90.5%, respectively (Figure 2). Early mortality occurred in 27 patients (3.3%), of whom 19 (2.3%) died within 1 month of the operation. These patient deaths were mostly attributed to perioperative mortality. Regarding the other 8 patients, 2 died from postoperative heart failure, 1 from arrhythmia, 1 from cardiac tamponade, 2 from neurological complications, and the other 2 from infection occurring within 1 year after operation. Multivariate logistic regression analysis using factors, including sex, pulmonary artery size, MAPCA existence, previous shunt operation, age at operation, operation year, syndromic combination, VSD type, and RVOT reconstruction method, identified the presence of MAPCAs as the only risk factor for early mortality (OR, 5.06; 95% CI, 1.40–18.32; \( P < 0.014 \)). Of the 23 patients with MAPCAs, 2 received transcatheter coil embolization before operation, 3 received unifocalization at the operation because of interruption or hypoplasia of 1 pulmonary artery, and 2 received MAPCA ligation during the operation. Of the 23 patients with MAPCAs, 3 died shortly after the operation.

Late mortality occurred in 29 patients, with an increasing trend in mortality correlated to the postoperative follow-up years. The annual mortality rate was 0.123% (95% CI, 0.05%–0.195%) in the first 15 years, and increased to 0.395% (95% CI, 0.212%–0.577%) 15 years after cardiac operation (\( P < 0.05 \)). Cardiovascular death accounted for 51.7% of late mortality, and unnatural death (accidents or suicide) accounted for 27.6% (Table 2). For patients who survived the first year after operation, the 10-, 20-, and 30-year survival rates were 99%, 95.9%, and 93.7%, respectively. Multivariate Cox regression analysis of the previously described factors identified patient age at operation, presence of MAPCA, and previous shunt operation as significant independent risk factors of late cardiovascular mortality (Table 3). Figure 3 shows the patient survival curves according to age at operation and presence of MAPCAs. The 20-year survival rate of patients with and without MAPCAs was 95.9% and 88.9%, respectively (Figure 3A). Two patients with MAPCAs died late after the operation; both were associated with hypoplasia or interruption of 1 pulmonary artery, and received unifocalization of MAPCAs during the operation. Stratifying the patients into 3 groups according to their age at operation (<3, 3–10, and >10 years) elucidated the impact of age at operation on long-term survival. When comparing the late survival of patients in the group aged <3 years with those of the groups aged 3 to 10 years and >10 years, the 20-year survival rates were 97.1%, 97.1%, and 91.2%, respectively (Figure 3B).

In this study, accident (n=5) or suicide (n=3) was the second most common cause of late death, accounting for

**Table 2. Cause of 29 Late Deaths in Patients With Repaired Tetralogy of Fallot**

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular origin</td>
<td>15 (51.7)</td>
</tr>
<tr>
<td>Heart failure or pulmonary hypertension</td>
<td>7 (24.1)</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td>Accident or suicide</td>
<td>8 (27.6)</td>
</tr>
<tr>
<td>Suicide</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td>Accident</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>Hepatic or gastrointestinal cause</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td>Infection</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (3.4)</td>
</tr>
</tbody>
</table>
27.6% of total deaths. The 3 suicides involved falling several floors, drug intoxication, and gas intoxication. The 5 patients who experienced accidents all died of multiple fractures from car accidents and other accidents. The annual incidence of mortality from accidents or suicide was 57.9 per 100,000 persons (95% CI, 26.9–110.0 per 100,000 persons) in this repaired TOF cohort. According to the Department of Health’s annual report in 2009, the annual accident and suicide mortality rates of a sample of the same age from the general population in Taiwan was 16.3 and 10.3 per 100,000 persons, respectively. The mortality rates of these unnatural deaths in this TOF patient cohort were significantly higher, with an OR of 2.18 (P=0.028).

Discussion

This study determined the following: (1) The early mortality and long-term survival rates of an Asian TOF cohort from a tertiary care center in Taiwan are comparable to those of Western countries. (2) Older patient age at operation, presence of MAPCAs, and shunt operation history are independent risk factors of late cardiovascular death. (3) Although cardiovascular death accounted for most late deaths, unnatural deaths (suicides and accidents) were also significant causes of late mortality. The annual mortality from unnatural causes was considerably higher in patients with repaired TOF than in the general age-comparable population. This demonstrates an urgent need to provide better psychosocial care for adult patients with CHD.

Long-Term Survival

Several previous cohort studies reported satisfactory long-term survival rates in repaired patients with TOF, with a 30-year survival rate ranging from 86% to 91.7%. This study revealed similar results: the 10- and 30-year survival rates were 95.8% and 90.5%, respectively. Nollert et al also observed that the late mortality of patients with repaired TOF increased significantly 25 years after cardiac operation. In this study, the patient survival rate declined significantly 15 years after cardiac operation, with mortality rates increasing from 0.123% per year in the first 15 years to 0.395% per year after 15 years. Late morbidities, such as ventricular arrhythmia and severe pulmonary regurgitation, may contribute to late mortality. Such trends of increased late mortality have never been observed in patients with simple CHD. Instead, the survival of patients with simple CHD after cardiac surgery frequently plateaued during long-term follow-up.

Cardiovascular Mortality Risk Factors

This study identified the risk factors for late cardiovascular mortality as increased age at operation, previous shunt operation, and the presence of MAPCAs. The association between increased age at operation and higher late mortality has been previously described and attributed to longer durations of hypoxia and right ventricular hypertension, which increase the incidence of late arrhythmia. In this study, patients’ late mortality and cardiovascular mortality were both lower in those operated on at younger ages, particularly those ≤3 years. Therefore, we suggest that cardiac repair of TOF be performed early (ie, aged ≤3 years) to avoid the long-term effects of hypoxia and right ventricle overload, which may subsequently increase the risk of late mortality.

The presence of MAPCAs in patients with simple form TOF is rare, measuring 2.9% in this series. Regarding MAPCAs, their importance to these patients with TOF has...
seldom been addressed. In this study, we found the presence of MAPCAs to be a significant predictor of early, and late, cardiac mortality in patients with TOF. The presence of MAPCAs frequently indicates relatively small and complex pulmonary arteries. In addition, long-term exposure of MAPCAs to high pressure from the aorta may cause vascular wall remodeling and lead to late pulmonary hypertension. Introduction of a Blalock-Taussig shunt before the total repair and unifocalization of MAPCAs to central pulmonary arteries may cause late pulmonary artery distortion. These factors may accentuate pulmonary regurgitation, which causes right ventricular overload, right ventricular failure, and then late arrhythmia and cardiac mortality.

Importance of Unnatural Deaths

In our patients with TOF, unnatural deaths (suicides or accidents) were the second most common cause of late death (27.6%). The annual mortality from accidents or suicides (57.9/100000 person-years) was more than 2 times the annual mortality of the general population at the same age. The reasons for such high mortality from unnatural deaths remain unclear. Medical care of these patients was optimized through government support, including National Health Insurance and Physical and Mental Disability Support. However, several problems exist. First, previous studies revealed that the likelihood of full-time employment for adult patients with CHD, especially males, was lower. This may hinder economic independence among these patients. Second, neurological complications are also a common problem. Our previous study found that 3.9% of patients presented major neurological sequelae (as hypoxic ischemic encephalopathy, stroke, or seizure) early after operation and before discharge. Adult patients with CHD, even after correction of CHD, may display lower academic abilities, including in language expression, intelligence, and motor skills. With these handicaps, psychosocial functioning may be jeopardized and the risk of suicide or accidental death may increase. Third, depression is also a common problem in adult patients with CHD, and may significantly affect their quality of life and late mortality. The incidence of depression is reported to be higher in patients with repaired CHD, which may be underestimated by the difficulty of selecting appropriate diagnosis instruments.

In addition, undertreatment is common in these patients. In Asian populations with traditional cultures, depression is typically underdiagnosed and undertreated. These observations strongly indicate that the provision of integrated care remains far from adequate to meet the complicated requirements of patients with CHD, especially in Asian populations. Thus, this study advocates the development of an organized medical care program, incorporating psychological and educational support, to improve the long-term outcomes of adult patients with repaired CHD.

Study Limitation

Although the proportion of unnatural deaths is high, only 8 patients experienced unnatural deaths, which may reduce the statistical power and was a limitation.

Surgical strategies for treating patients with TOF have changed over the past 10 years. More patients with TOF received direct total repair instead of staged shunt operations. However, a certain percentage of the patients who participated in this study had received a staged shunt operation, even after 2000. In addition, 18.9% of the patients received a total repair when aged >10 years. Therefore, this study may overemphasize the impact of shunt operations and patient age at operation on long-term surgical outcomes.

Conclusion

The long-term survival rate of patients with repaired TOF in this Asian cohort was comparable to that in Western reports, and was characterized by a late decrease 15 years after repair. Although cardiac death was the most common cause of mortality, accidents or suicides were also associated with late deaths, demonstrating the urgent need to provide better psychosocial support.

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Disclosures

None.

References


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