Arrhythmias Late After Repair of Tetralogy of Fallot
— A Japanese Multicenter Study —

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**Background** Arrhythmia is a major late complication in adults with repaired tetralogy of Fallot, although a large-scale study has not been carried out in Japan.

**Methods and Results** A nationwide multicenter study with 512 operative survivors was performed. Actuarial survival rate at 30 years (maximum follow-up) was 98.4%. Fifty-four patients (10.5%) had clinically important arrhythmias, including 23 patients with bradycardia caused by sick sinus syndrome or atrioventricular block (AVB). A patient with complete AVB (CAVB) without pacemaker implantation (PMI) died later. Two patients had sustained ventricular tachycardia (VT) and syncope was reported in 18 patients with ventricular arrhythmias (VA). Atrial tachyarhythmias were observed in 13 patients. Older age at operation was a risk factor for atrial fibrillation/flutter, longer postoperative survival duration for VA, and QRS duration >120 ms for VT. Perimembranous ventricular septal defect was related to CAVB. Right ventricular outflow patch was not a risk factor. Importantly, 60% of the subjects had QRS duration <120 ms.

**Conclusion** The prevalence of serious arrhythmias is low in Japanese TOF patients as compared with the results from Western countries. CAVB without PMI and VT are the major risk factors for late morbidity and mortality. The excellent result could be related to the narrow QRS after surgery. (Circ J 2004; 68: 126–130)

**Key Words:** Atrial tachyarrhythmias; Complete AV block; Postoperative arrhythmia; Tetralogy of Fallot; Ventricular tachycardia

Over the past 30 years, mortality from congenital heart diseases in general has declined dramatically, and from tetralogy of Fallot (TOF) in particular, the incidence of death has declined by approximately 60% because of improvements in medical and surgical treatment. Accordingly, the most current issue in the management of TOF is the long-term result and arrhythmia is a major problem in such patients late after surgical repair. Several studies from Western countries have reported the prevalence of late arrhythmias and their significance in long-term prognosis and quality of life in this patient population. In Japan, Kobayashi et al reported a single institute’s experience of arrhythmias analyzed by Holter monitor in postoperative TOF and recently, Niwa et al reported a Japanese survey on the quality of life in adult patients with postoperative TOF, including some data on arrhythmias. These Japanese studies, however, are not comparable with the studies from Western countries in terms of the number of subjects and length of follow-up. We therefore organized a multicenter study group in Japan in order to demonstrate the prevalence of clinically important arrhythmias, the risk factors of the arrhythmias, and the significance of the arrhythmias in major morbidity and late mortality in patients after repair of TOF.

**Methods**

**Subjects**

The study group comprised 10 institutes, which are listed in Appendix 1. The national fund organization recruited them from throughout Japan in order to avoid an area-difference bias. We included only the classical TOF in non-heterotaxic situs, and excluded extreme types or pulmonary atresia with ventricular septal defect (VSD), TOF associated with endocardial cushion defect and TOF with heterotaxia. Because the funding period was limited and the amount of the data from some participating institutes was huge, data were collected for all patients who survived a total correction in the years of 1970, 1975, 1980, 1985, 1990 and 1995. We identified all patients with repaired TOF and obtained the available records after this period to year 2000, and we reviewed the data at the end of 2000. Demographic variables, current status and information about the arrhythmias of patients were obtained from hospital records and clinic visits by co-authors in each institute who were experienced pediatric cardiologists. We constructed a data file sheet on disk using commercially available software (File Maker Pro 5.0, Filemaker Inc) distributed it to participant investigators for them to fill in the relevant data. We excluded patients from further analysis for whom we could not get sufficient follow-up data (n=121). Finally, 512 patients with data obtained from the 10 participating institutes constituted the study population. We consider that this research method is acceptable for our...
pressure, 8, 10, 12–14 tricuspid and/or pulmonary regurgitation.

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Circulation Journal Vol. 68, February 2004

The primary purpose of demonstrating an overall view of the prevalence, risk factors and clinical relevance of arrhythmias in the late postoperative period of repaired TOF.

The method of detecting arrhythmias that we adopted was the same as that used in the international multicenter study that was conducted by Dr Gatzoulis and in which the chair (NM) of the present study participated. Briefly, an arrhythmia was registered when it was first found on either a standard ECG or a Holter recording. Holter recordings were available and reviewed from only 30 patients, and the majority of them were applicable only when any arrhythmias were detected on standard ECG recordings. We have defined ‘clinically important’ arrhythmias as sick sinus syndrome, 2nd or 3rd degree atrioventricular block, atrial tachyarhythmias, premature ventricular beats more than couplet, and non-sustained or sustained ventricular tachycardia. We did not include single (no couplet or non-sustained) premature beats. The definitions of these arrhythmias were based on the established criteria. The information was analyzed centrally at the Tokyo Women’s Medical University, and the final diagnoses of those arrhythmias were established after consensus was obtained among the members of the ALTAS-CHD working group.

Previous studies have shown that the clinically important arrhythmias are associated with older age at repair, large ventriculotomy, high postoperative right ventricular pressure, tricuspid and/or pulmonary regurgitation, premature ventricular beats more than couplet, and non-sustained or sustained ventricular tachycardia. We did not include single (no couplet or non-sustained) premature beats. The definitions of these arrhythmias were based on the established criteria. The method of detecting arrhythmias that we adopted was the same as that used in the international multicenter study that was conducted by Dr Gatzoulis and in which the chair (NM) of the present study participated. Briefly, an arrhythmia was registered when it was first found on either a standard ECG or a Holter recording. Holter recordings were available and reviewed from only 30 patients, and the majority of them were applicable only when any arrhythmias were detected on standard ECG recordings. We have defined ‘clinically important’ arrhythmias as sick sinus syndrome, 2nd or 3rd degree atrioventricular block, atrial tachyarhythmias, premature ventricular beats more than couplet, and non-sustained or sustained ventricular tachycardia. We did not include single (no couplet or non-sustained) premature beats. The definitions of these arrhythmias were based on the established criteria. The information was analyzed centrally at the Tokyo Women’s Medical University, and the final diagnoses of those arrhythmias were established after consensus was obtained among the members of the ALTAS-CHD working group.

Prevalence of Arrhythmias

There were 54 patients (10.5%) who had clinically important arrhythmias at follow-up. Only 1 patient had both non-sustained ventricular tachycardia and 2nd degree atrioventricular block, and this patient was included only in the group of ventricular arrhythmias. There were 438 patients whose ECG did not show clinically important arrhythmias, or showed only simple premature supraventricular or ventricular premature beats. Those 438 patients served as the arrhythmia-free control group in the following analysis. The other 20 patients had transient clinically important arrhythmias as described later, and they were not included in the control group.

Sick sinus syndrome was seen initially in 7 patients, and was transient in 3 of them. Twenty patients had 2nd degree atrioventricular block, which was already present before operation and continued in 1, disappeared late after operation in 7, and progressed to complete block in 2. Sixteen patients had complete atrioventricular block, which was restored to sinus rhythm in 10 of them. As mentioned earlier, 2nd degree block progressed to complete block in the 2 patients at 1 and 12 years after repair, respectively, resulting in permanent complete block in 8 patients. All but 1 of these patients had perimembranous ventricular septal defect (VSD). A patient with complete block who had not undergone permanent pacemaker implantation died at 27 years after repair. None of the patients who had perioperative transient complete block developed complete block later.

Persistent transient ventricular arrhythmias were seen in 18 patients: premature ventricular beats of couplet type in 10 patients, non-sustained ventricular tachycardia in 6 patients, and sustained ventricular tachycardia in 2 patients. The 18 patients were older at operation (6.6±12.4 years) compared with the control group (4.0±5.4 years, p<0.05). The ventricular arrhythmias as a whole increased at around 10 from 1 month to 30 years with an average of 11.7±7.2 years.

There were 8 late deaths. Their age at operation averaged 9.2±8.7 years and follow-up period was 23.4±9.3 years, both of which were significantly larger than those of survivors (4.0±5.9 years and 11.2±7.0, respectively) (p<0.01). Only 1 death was directly related to an arrhythmia, which was postoperative complete atrioventricular block with no pacemaker implantation. The causes of death of the other 7 patients were liver dysfunction in 2, severe systemic infection in 2, and unknown in 3. Actuarial survival for the patients who survived total repair was 99.8% at 10 years, 99.6% at 20 years, and 98.4% at 30 years (Fig 1).

Results

Demographic Data

Five hundred and twelve patients were registered from 7 institutes, which provided satisfactory data for analysis. Age at operation ranged from 4 months to 54 years with an average of 4.4±6.0 years and the follow-up period ranged...
or more years after repair (Fig 2). The 2 patients with sustained ventricular tachycardia experienced Adams-Stokes attack, and one survived with severe brain damage and the other was well with an intracardiac defibrillator implantation. All 8 patients with ventricular tachycardia had QRS longer than 120 ms.

Atrial tachyarrhythmias persisted in 13 patients: 8 had atrial fibrillation/flutter and 5 had paroxysmal atrial or supraventricular tachycardia. The age at operation of these patients was 16.1±15.2 years, which was significantly (p<0.05) older than that of the control group (4.0±5.4 years).

**Arrhythmias and Risk Factors**

The prevalence of the arrhythmias was not related to preoperative data such as oxygen content (n=185) or oxygen saturation (n=344), hematocrit or hemoglobin concentration (n=422), or pulmonary artery size (n=478).

The type of VSD was reported in 410 patients. Complete atrioventricular block was induced at operation in 5 of 300 patients (1.7%) with perimembranous VSD, which was significantly more frequent than in patients with subarterial or conus defect (0/110). A patient with subarterial defect developed complete block that progressed from 2nd degree block at 12 years after repair (Table 1).

Right ventricular outflow patch repair was performed in 456 patients, and 104 patients of them had a transannular patch. Fifty-seven patients underwent valvotomy and 456 patients, and 104 patients of them had a transannular patch. None of the arrhythmias was related to these surgical procedures (Table 1).

The postoperative QRS duration was shorter than 120 ms in 60% of the patients and was equal to or longer than 120 ms in the rest, and ventricular tachycardia was more frequent in the latter than the former group. The arrhythmias were not related to other postoperative parameters such as bifascicular block (left axis deviation plus complete right bundle branch block), or right ventricular pressure evaluated by cardiac catheterization or echocardiography. Ventricular and atrial tachyarrhythmias seemed to be associated with cardiomegaly, although the difference did not reach statistical significance (Table 1).

**Discussion**

This is the first large-scale multicenter study in Japan of late arrhythmia in patients with repaired TOF. The present study has demonstrated that the prevalence of clinically important arrhythmias was 10.5% at follow-up up to 30 years after repair of TOF, and that late morbidity and mortality related to the arrhythmias, especially ventricular tachycardia, were less than those reported in the literature.

Surgical complete atrioventricular block was seen only in patients who had perimembranous VSD. Hokanson et al have reported that perioperative transient complete block is a risk of late sudden death, implying that the block may recur later and therefore we should repeat the ambulatory ECG recordings in the 10 patients with transient complete block in the present study. It has also been emphasized that bifascicular block can progress to trifascicular or complete block and sudden death; however, there were no such patients among the present subjects and also none in the recent report of Gatzoulis et al.

Transmural or right ventricular outflow patch is a risk factor for late arrhythmias. Kirklin et al reported that transmural repair was a factor for early mortality but not for late mortality, implying that transmural patch itself is not a major factor for fatal arrhythmias. Our data support their view. Inappropriate enlargement of the right ventricular outflow tract, however, obviously causes a hemodynamically significant pulmonary regurgitation that dilates the right ventricle and further causes tricuspid regurgitation, creating a vicious circle that further results in enlargement of the right atrium. They are well-known risk factors for both ventricular tachycardia and atrial fibrillation/flutter, and are clinically evident in patients with a wide QRS interval and a large heart. We emphasize that Harrison et al have reported that late mortality and morbidity from atrial tachyarrhythmias were much higher than originally thought, although there was no late death because of atrial tachyarrhythmias in the present study.

It is worth pointing out that the duration of the postoperative QRS was less than 120 ms in 60% of the present patients, which is less than that reported in the previous studies, the majority of which were from Western countries. In Japan, surgery to prevent complete right bundle branch block has been a strong trend since the early 1970s.

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**Table 1 Late Arrhythmias and Major Factors (Only in Patients Who Had Relevant Data on File)**

<table>
<thead>
<tr>
<th>Arrhythmia free</th>
<th>SSS</th>
<th>≥2 AVB</th>
<th>≥3 AVB</th>
<th>Atrial tachycardia</th>
<th>Ventricular tachycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of VSD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subarterial</td>
<td>110</td>
<td>2</td>
<td>1</td>
<td>1*</td>
<td>1</td>
</tr>
<tr>
<td>Perimembranous</td>
<td>300</td>
<td>2</td>
<td>8</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Outflow tract repair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No patch</td>
<td>50</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Outflow patch</td>
<td>317</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Transannular repair</td>
<td>87</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>QRS duration &lt;120 ms</td>
<td>253</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>≥120 ms</td>
<td>122</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Cardiothoracic ratio ≤50%</td>
<td>160</td>
<td>3</td>
<td>7</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>≥60%</td>
<td>136</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

SSS, sick sinus syndrome; ≥2 AVB, 2nd degree atrioventricular block; ≥3 AVB, 3rd degree (complete) atrioventricular block; VSD, ventricular septal defect; *Atrial tachycardia included atrial fibrillation and flutter, ectopic atrial tachycardia, and re-entrant supraventricular tachycardia; †ventricular tachycardia included non-sustained and sustained ventricular tachycardia.

*Complete heart block developed from 2nd degree block at 12 years after repair; †significantly less frequent (p<0.05) compared with the other group, respectively.
because complete right bundle block depresses ventricular function. The procedure involves a small or even no right ventriculotomy with small transannular patch resulting in fairly good postoperative right ventricular function and a somewhat small pulmonary ring preventing significant regurgitation. Relatively short QRS duration, in turn, does not provide a substrate for reentrant ventricular tachycardia. Thus, the effort to preserve ventricular function has also resulted in the low prevalence of ventricular tachycardia and, as a consequence, prevented life threatening ventricular arrhythmias.

Finally, as is known, complete heart block or ventricular tachycardia is the most important risk factor for late death in this patient group. Therefore, postoperative complete heart block should be treated by permanent pacemaker implantation, when it is confirmed not to be transient, as recommended in the guidelines of the ACC/AHA. In addition, ventricular tachycardia should be treated intensively by effective medicine(s), or invasive treatments such as catheter ablation or ICD implantation if medical treatment is not effective.

Study Limitations
The study was retrospective and the surgical procedures may have changed during the study period. There was also some variation in data collection among the participating institutes. Holter ECG monitoring was done in only a small portion of the subjects, and finally, data only came from patients who survived in certain specified years. Accordingly, we were not able to include more detailed parameters such as catheterization data, ventricular volume characteristics, or details of the surgical procedures, and therefore the analysis of the study was rather simplistic. Because of this weakness, our data only demonstrate the overall trend in late arrhythmias of repaired TOF per se. Another drawback was that arrhythmias were diagnosed by a standard ECG performed during a clinic visit, not by Holter monitoring, in the majority of patients. Gatzoulis et al used the same strategy, however, and Friedli considers that the simple surface ECG gives enough information for screening clinically important arrhythmias, especially those with a high risk for morbidity or mortality. Lastly, our study protocol did not include all patients in the study periods, but we considered that this did not severely affect the purpose of our study, which was to demonstrate the overall tendency of the prevalence and clinical significance of arrhythmias in patients late after repair of TOF. Finally, the average follow-up years of the present study was 11.7 years, which was shorter than that of the study of Gatzoulis et al. As it is well known that the prevalence of arrhythmias increases as the time after repair and the age of patients increases, we have to continue careful follow-up of the present patients.

Because of the nature of a multicenter study, we were not able to analyze the precise mechanism, anatomical and electrophysiological substrates, or the cardiac anatomic nervous activity. These are very important issues and studies should be conducted in the future. We also had the same limitation as another Japanese multicenter study on Infective Endocarditis complicated with congenital heart disease.

Conclusion
This is the first large-scale multicenter study in Japan on late arrhythmia in patients with repaired TOF. The prevalence of serious arrhythmias is low in these patients, which may be related to a rather shorter duration of postoperative QRS. Unpaved complete heart block and ventricular tachycardia are the major risks for late morbidity and mortality. The excellent overall late outcome could be the result of improvements in the surgical procedure. These data may be useful for future comparative studies of arrhythmias in patients with repaired TOF.

Acknowledgments
The authors acknowledge the following investigators for their advice and effort in collecting the data for this study.

Takako Shinoohara, MD, Shigera Tateno, MD, Toshihitsu Shibata, MD, Hiroya Ushinohama, MD, Seiki Matsushita, MD, Toshihiko Yasuda, MD, Aya Miyazaki, MD, and Kenichi Kuroasaki, MD

This work was supported by a Research Grant for Cardiovascular Disease (12C-11) from the Ministry of Health, Labor, and Welfare of Japan.

References


**Appendix 1**

Institutes that participated in the ALTAS-CHD study.
Iwate Medical University Memorial Heart Center, Chiba Cardiovascular Center, Tokyo Women’s Medical University The Heart Institute of Japan, Yokohama Municipal Medical College, Shizuoka Children’s Hospital, Aichi Children’s Health and Medical Center, Chukyo Hospital, Red Cross Wakayama Medical Center, Kinki University Hospital, Osaka University Hospital, National Cardiovascular Center, Fukuoka Children’s Hospital.