前期報告：兩側右心房症病兒之猝死與心不整脈之關聯

一、中文摘要

兩側右心房症之病兒不但常合併有複雜先天性心臟病，例如肺靜脈回流異常、單一心房、心內膜墊缺損、單一心室及肺動脈狹窄等，導致新生兒期之發紺或心衰竭，同時也常合併心臟傳導系統異常，如多重房室結及竇房結。這些傳導系統之異常經常導致上心室頻脈。至於這些不整脈的發生是否會影響這些病兒之預後，目前仍不清楚。本研究以 20 年之病兒長期追蹤為研究對象，發現即使在接受心臟之輔助手術治療，這些病兒極高的概率發生猝死，這些猝死只有 9%與心律不整有關。最重要的仍是心肺功能不足(68)%，**猛暴性感染**(23)%。

關鍵詞：心律不整、複雜先天心臟病、傳導系統異常

Abstract

Sudden death in patients with right atrial isomerism after palliation

Objectives. This longitudinal study sought to define the risk of sudden death in patients with right atrial isomerism (RAI, asplenia) after palliation.

Study design. A total of 154 patients with RAI were identified from 1980 to 1999 based on a combination of various imaging techniques. Open-heart surgery or autopsy in 52 cases confirmed the diagnosis. Sudden death was defined as acute cardiovascular collapse from which biological death occurred within 24 hours.

Results. A total of 620 patient-years were derived. The one-year and five-year survival was 72% and 50%, respectively. There were a total of 22 sudden unexpected deaths (14%, 35 events/1,000 patient-years). Sudden death tended to occur in the infancy or early childhood (12±9 mo., median, 9 mo.). The mechanisms were classified as sudden tachyarrhythmic in 2 (9%), sudden cardiac but nontachyarrrhythmic(sudden onset severe cyanosis) in 15 (68%), and sudden noncardiac in 5 (23%)(fulminant sepsis with positive blood culture: streptococcus pneumonia 3, E. coli 1 and yeast-like organism 1). Freedom from sudden death steadily decreased with age until the age of 3 years.

Conclusions. The incidence of sudden death in RAI patients after initial palliation was still very high. The sudden death was related to the complex cardiac anomalies *per se*, a susceptibility to fulminant infection, and arrhythmia.

Keywords: Sudden death, complex congenta heart disease, conduction system anomalies

二、緣由與目的

It has been estimated that about 40% of sudden cardiac death in pediatric patients occurs in the patients with unoperated congenital heart disease or acquired heart disease.[1] Congenital heart disease with abnormal conduction system, e.g., corrected transposition of great arteries and Ebstein's anomaly is also associated with a higher risk of sudden death.[2] Patients with congenital heart disease still carry the risk of sudden death after total repair operation. Sudden cardiac death may occur in 2-5% of patients following repair of tetralogy of Fallot .[3,4] The sudden death was attributed to ventricular arrhythmias that originated at the site of ventricular incision and right ventricular scar. Earlier age of surgical repair and intra-atrial repair without a right ventriculotomy were all factors likely to reduce the incidence of sudden death in these patients.[5]

As to patients with complex congenital heart disease, although the long-term data were still limited, the incidence of sudden death was in general higher than that for common congenital heart disease.[6-9] The incidence of sudden death in the patients with tricuspid atresia was around 9% and most of them occurred before the age of 4 years.[7] For patients with double inlet ventricle who were potential candidates for Fontan type

operation, the incidence of sudden death was about 10%.[8] Most of the sudden death occurred early and were with ill-defined mechanisms. In patients with hypoplastic left heart syndrome who died after the first stage operation, the autopsy results suggested a sudden cardiac death due to presumed arrhythmias in 5% of the patients.[9]

Right atrial isomerism, which is a form of heterotaxy syndrome and also called as asplenia, is commonly associated with complex congenital heart disease.[10, 11] Most common combination includes total anomalous pulmonary venous return, common atrium, atrioventricular canal, double outlet right ventricle and pulmonary stenosis or atresia.[12, 13] It has been shown that without treatment about half of the patients with RAI will die before the age of 2 years.[14] Therefore, most of the patients need early palliations to increase the pulmonary flow or to relieve the pulmonary venous obstruction. With the advances in transcatheter and surgical palliations, the prognosis has been greatly improved recently.

The previous pathological studies of RAI patients also showed the presence of abnormal cardiac conduction system, which may predispose the patients to arrhythmia during the long-term follow-up. Patients with RAI may have paired sinus and AV nodes and thereby a susceptibility to reentrant tachycardia.[15-17] The presence of congenital abnormalities of the cardiac conduction system is suggested to be a risk factor for sudden death in the patients with or without congenital heart disease.[18] Therefore, it is imperative to define more clearly the risk of sudden death in RAI patients after they survive various initial palliations to have acceptable hemodynamics. The present study based on a large patient cohort of RAI disclosed a high risk of sudden death during the long-term follow up even after various palliations. The sudden death was closely related to the complex congenital heart disease *per se*, a susceptibility to infection, or arrhythmia.

三、結果與討論

Patient Cohort

The patients of RAI were identified from the files of pediatric cardiology of this hospital from January 1980 to December 1999. The diagnosis was made based on the combination of various imaging techniques, including echocardiography, angiography, MRI and ultrafast computerized tomography (19-21). Open-heart surgery or autopsy in 52 cases confirmed the diagnosis. Patients with RAI had ipsilateral descending aorta and inferior vena cava, bilateral atrial appendage with right atrial appendage morphology and bilateral epiarterial bronchus. Telephone interview or mailed questionnaire was sent to those patients who lost to follow-up.

Definition

Sudden cardiac death was defined as acute cardiovascular collapse from which biological death occurred within 24 hours or from which the patient never regained consciousness[22]. The mechanisms of sudden death were classified according to a modification of criteria proposed by the Cardiac Arrhythmia Pilot Study: 1) sudden cardiac and tachyarrhythmic; 2) sudden cardiac but nontachyarrhythmic; and 3) sudden noncardiac death[23].

Statistical analysis

Survival and the event-free curves were estimated by the Kaplan-Meier analysis[24]. *Chi-square* test was used to examine the significance between the morphological characteristics or the types of preexisting rhythms and the occurrence of sudden death. Statistical significance was established at a p-value less than 0.05.

RESULTS

Patients

According to the aforementioned criteria, a total of 154 RAI patients were identified, from them a total follow-up of 620 patient-years was derived. Among them, 70 patients were ended with death (mortality rate, 45%). The actuarial survival estimated by Kaplan and Meier analysis is shown in

Figure 1A. One-year and 5-year survival was 72% and 51%, respectively. Most of the patients have a combination of complex cardiac defects, including anomalous pulmonary venous return, common atrium, AV canal, double outlet right ventricle and pulmonary stenosis or atresia (Table 1). Therefore, early interventions were usually indicated to increase the pulmonary flow or to relief the pulmonary venous obstruction (Table 2).

Sudden Death Events

There were a total of 22 sudden unexpected deaths during the 620 patient-years (14%, 35 events/1,000 patient-years). The age of sudden death ranged from 1 to 36 months (10±9 months, median 6 months). The temporal analysis of sudden death is shown in Figure 1. The survival of the patients decreased with age. The freedom from sudden death also decreased with age but it remained stationary after the age of 3 years.

Some observations were made among the 21 RAI patients who died suddenly and the mechanisms were therefore classified as **1)** ***sudden cardiac and tachyarrhythmic*** 2 (9%); one with ventricular tachyarrhythmias and one with undefined tachyarrhythmia. **2)** **S*udden cardiac but nontachyarrhythmic*** 15 (68%); seven occurred at hospital and were manifested as sudden onset of severe cyanosis (7) and bradycardia (1). Another 8 cases died suddenly at home and the reported symptoms were sudden onset of cardiac arrest, severe cyanosis and apnea. Three of the 8 patients were waiting for the scheduled operation (2 for a systemic to pulmonary shunt and one for Glenn operation). **3)** ***Sudden noncardiac*** 5 (23%); in these patients aged 5, 6, 9, 16 and 18 months, positive bacterial (4: streptococcal pneumonia in 3 and E. coli in one) or fungi (1, yeast-like organism) culture was reported. The course of infection was fulminant and all died within 24 hours after admission. Although prophylactic antibiotics had been suggested in some patients, the drug compliance was poor and none of the study population had received adequate dosage and duration. None of them had received vaccination against H. influenza or streptococcal pneumonia because of the unavailability of vaccines during the study period.

The association between the intracardiac anomalies and the occurrence of sudden death was analyzed. None of the morphological characteristics, including the presence of pulmonary stenosis or atresia (22/22 *versus* 119/132, $p > 0.05$) and total anomalous pulmonary venous return to systemic veins (6/22 *versus* 57/132, $p > 0.05$), was found to be significantly associated with sudden death. The history of supraventricular tachycardia was not associated with the occurrence of sudden death, either (4/22 *versus* 34/132, $p > 0.05$). The tendency remained the same even we excluded those with noncardiac sudden death from the analysis. After the Fontan-type operation, one patient with RAI developed incisional atrial flutter, which was controlled by transcatheter radiofrequency ablation and amiodarone. Another RAI patient had severe right heart failure, which was complicated by the protein-losing enteropathy and atrial fibrillation. However, none of these post-Fontan patients experienced sudden death during the study period.

DISCUSSION

With the advances in interventions, the long-term prognosis of the RAI patients is improved. However, the present study showed that the RAI patients, in the presence of fair hemodynamics after palliation, still carried a high risk of sudden death. Sudden death was most likely related to the underlying complex cardiac anomalies, which may be associated with an abnormal pulmonary vascular bed. Sudden arrhythmic death, although not common, may occur in some cases. The high incidence (23%) of fulminant infection was unique for the RAI patients.

Sudden death in the patients with RAI had only rarely been reported[25-27]. In an early familial case report, three sudden deaths occurred during the infancy and two with evidences of sepsis [25]. In a recent study of 20 RAI patients, only one late sudden death was identified [26]. The patient died 3 years after the shunt operation. This present study based on a large cohort of RAI patients, showed a high incidence of sudden death even after the palliation. The incidence was as high as 14%. The incidence of sudden death in other types of complex congenital heart disease after the initial palliation is generally reported around 10%[7-9]. Franklin et al reported an incidence of 9% for sudden death in the patients with tricuspid atresia[7]. As to patients with double inlet ventricle, the incidence of sudden death was reported as 10%[8]. These patients usually, just like patients with heterotaxy syndrome, need a Fontan type operation as the final palliation. Most of the sudden death occurred before the timing of Fontan type operation. Although the number of sudden death was not few, the mechanisms had not been well defined. In a pathology series of 122 cases that died after the Norwood stage I operation, the cause of death was attributed to sudden arrhythmic death in 5% of the patients[9]. This issue pointed out the potential risk of sudden arrhythmic death in complex congenital heart disease.

As compared to the long-term data of postoperative congenital heart disease, the event rate of sudden death in the RAI patients after palliation was also significantly higher[22]. The event rate of sudden death in common postoperative congenital heart disease was 0.9/1,000 patient-years. For postoperative transposition of great arteries and aortic stenosis patients, the event rate was 5/1,000 patient-years. The risk of sudden death was relatively constant. For postoperative tetralogy of Fallot, the risk increased primarily after 20 years of follow up with an event rate of 1.5/1,000 patient-years. As to the sudden death in the patients after Fontan-type operation, which is usually performed for complex congenital heart disease, the data were still limited. The risk was considered high in those who developed atrial flutter[28]. In a large series of 270 post-Fontan patients, 29% of the patients developed late atrial arrhythmias and one died suddenly due to ventricular fibrillation. In another report of 18 post-Fontan patients with atrial flutter, two died suddenly during the follow-up[29]. In this series, two RAI patients (20%) developed atrial arrhythmias after total cavopulmonary connection operation. The lack of sudden death in these patients might be related to the small number of the patient population who survived the operation and the relatively short period of the follow-up after the Fontan type operation.

As shown in the present study, the majority of sudden death in RAI patients was manifested as sudden onset of aggravated cyanosis, which failed to be improved after resuscitation. Most of these patients (12/15, 80%) had satisfactory O_2 saturation before the sudden death and only three of them were waiting for a shunt operation (two for a systemic-to-pulmonary and one for Glenn shunt). The acutely aggravated cyanosis was due to diminished effective pulmonary flow, which may be related to acute pulmonary hypertension or shunt dysfunction. The RAI patients had a high chance of anomalous pulmonary venous return to systemic veins. For those with right atrial (right-sided or left sided) drainage of the pulmonary veins, by definition the term “intracardiac type of anomalous pulmonary venous return” still could be applied. The previous pathological report of patients with total anomalous pulmonary venous return described the existence of various degree of medial hypertrophy of the pulmonary arteries and arterioles[30-31]. In those with obstruction, the hypertrophy was pronounced and accompanied by the pulmonary edema and extravasation of red cells into alveolar space. In those without obstruction, the medial hypertrophy and intimal proliferation was also prominent. Therefore, the pulmonary vascular bed in the patients with anomalous

pulmonary venous return is deemed as abnormal. The medial hypertrophy and intimal proliferation of pulmonary arterioles may not regress or even become worse with time after the repair of anomalous pulmonary venous return. Therefore, we highly suspect the possibility of an abnormal reactivity of the pulmonary vascular bed of RAI patients, which may lead to acute pulmonary hypertension and shunt dysfunction. We nonetheless failed to demonstrate the association between the presence of anomalous pulmonary drainage to systemic veins and sudden death in this study. The reactivity of the pulmonary vascular bed in RAI patients needs to be further clarified in the future.

The associated abnormal conduction system was shown in the previous pathological studies of RAI patients[15, 16]. We have also demonstrated a high probability of supraventricular tachycardia in the RAI patients[17, 32]. The tachycardia is most likely due to a reentry between the paired AV nodes. The presence of abnormal cardiac conduction system was a risk factor for sudden death[18]. According to the pathology reports of more than 100 patients with sudden cardiac death, abnormalities in the conduction system could be identified in every case, including the 13 cases with congenital heart disease[18]. The abnormalities included various degrees of fibrosis as well as a variety of congenital anomalies, such as paired sinus node; paired or divided AV node or nodal-cell like cells. Therefore, it was suggested that patients with abnormal cardiac conduction system were at a higher risk of sudden death. However, a direct cause-effect relation between the abnormal conduction system and the sudden death was not well documented. Sudden arrhythmic death, although not common, may occur in some cases.

Furthermore, we have found that fulminant infection accounted for about one-fourth (23%) of the sudden death in RAI patients. Patients with RAI have compromised immune function and thereby a susceptibility to infection[33, 34]. The course of sepsis was often fulminant and the condition deteriorated soon. Prophylactic antibiotics, including ampicillin for the initial 6 months of life and penicillin for older infants and children, had therefore been suggested. However, we found that the drug compliance was usually poor. None of our patients received adequate dosage and duration of the prophylactic antibiotics. Therefore, the effects of prophylactic antibiotics could not be assessed. On the other hand, if available, we suggested that RAI patients should receive vaccinations against pneumococcus and hemophilus as part of the routine vaccination. Besides, routine blood cell counts and culture, and close observation are warranted during the acute febrile episodes.

In conclusion, the incidence of sudden death in RAI patients after initial palliation was still very high. The sudden death was related to the complex cardiac anomalies *per se*, a susceptibility to fulminant infection, and arrhythmia. More definitive cardiac operation at earlier age and aggressive management of infection may be helpful to reduce the risks.

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行政院國家科學委員會補助專題研究計畫成果報告

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※**複雜性先天心臟病術前術後心律不整之電生理學機轉：**※
※**以同步電位及立體結構定位法研究**(2/3) ※
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計畫參與人員：

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中 華 民 國 90 **年** 5 **月** 31 **日**