Sudden Death of the Young with Cardiovascular Diseases

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Sudden death due to cardiovascular diseases was studied in 142 children who died suddenly during the period from 1969 to 1981. The age-distribution analysis showed that death occurred most frequently in infancy and it decreased with age. The subjects were divided into 7 groups, of which the hypoxemic group, consisting of 45 cases (32%), was the largest, followed by the congestive heart failure (CHF) group (33 cases, 23%), the primary endomyocardial disease (PMD)-coronary heart disease (CorHD) group (21 cases, 15%), the postoperative group (18 cases, 13%), the pulmonary vascular obstruction group (17 cases, 12%), the arrhythmia group of 3 cases and the miscellaneous group of the remaining cases. In the hypoxemic, CHF and arrhythmia groups, the majority of the cases were infants, while in the other groups the cases were distributed among all age groups. The relative incidence of each group showed that non-surgical and inoperable cases and postoperative cases increased with age and this increase has occurred in the last few years. This change has been brought about by the recent advances in medical and surgical treatments for infants with congenital heart diseases. It is hoped that in the future the number of cases which are too late for treatment will decrease further.

Sudden death is one of the major types of death in cardiovascular diseases. In adults coronary heart disease has been attracting extensive attention. Although it is less common in children, ischemic heart disease secondary to Kawasaki disease is sometimes responsible for sudden death in children in our country. It is well known that certain types of congenital heart disease and myocardial disease are likely to induce sudden death. However, the anatomical, physiological and chronological features of cardiovascular disease related to sudden death have been changing in accordance with the progress of medical and surgical treatments. This study was undertaken to clarify 1) the type of cardiac diseases responsible for sudden death, 2) the age distribution in cases of sudden death, 3) the seasonal variation of death, 4) changes in the type of disease with age and 5) the effects of medical and surgical interventions on sudden death.

SUBJECTS AND METHODS

The subjects of this study were 142 cases with a known cardiovascular disease who visited our clinic for the first time between the ages of 2 weeks and 15 years and who died suddenly during a period from 1969 to 1981.

Sudden death was defined as 1) instantaneous death, 2) acute death (death within 24 hours after the onset of the related symptoms), 3)
TABLE 1 INCIDENCE AND DIAGNOSIS OF EACH CATEGORY

<table>
<thead>
<tr>
<th>Category</th>
<th>Incidence</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Hypoxemic Group — 45 cases (32%)</td>
<td></td>
<td>TOF: 17, asplenic heart: 15, DORV with PS: 3, complete TGA-VSD-PS: 2, SV with decreased pulmonary flow: 2, pure PS with atrial R-L shunt: 2, TA-PS: 1, MA-PS: 1, corrected TGA-VSD-PS: 1, complete TGA with small VSD: 1</td>
</tr>
<tr>
<td>Congestive Heart Failure Group — 33 cases (23%)</td>
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<td>VSD: 14, ECD: 6, corrected TGA-VSD: 3, CoA complex: 2, PDA: 1, TOF with absent pulmonary valve: 1, TAPVR: 1, Scimitar syndrome: 1, SV: 1, DORV: 1, AS: 1, Ebstein’s anomaly: 1</td>
</tr>
<tr>
<td>Primary Endomyocardial Disease-Coronary Heart Disease Group — 21 cases (15%)</td>
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<td>HCM: 7, DCM: 2, EFE: 2, cardiac tumor: 1, not-classified PMD: 3, MCLS: 4, Bland-White-Garland syndrome: 1, LAD stenosis: 1</td>
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<td>Postoperative Group — 18 cases (13%)</td>
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<td>complete TGA: 6, TOF: 3, corrected TGA: 1, MVR: 1, AVR: 1, DORV: 1, AS: 1, Ebstein’s anomaly: 1, VSD post PA banding: 1, common atrium: 1</td>
</tr>
<tr>
<td>Pulmonary Vascular Obstruction Group — 17 cases (12%)</td>
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<td>primary PH: 5, PVO secondary to ASD: 3, VSD: 2, PDA: 1, complete TGA-VSD: 1, corrected TGA-VSD: 1, MA-DORV: 1, truncus arteriosus: 1</td>
</tr>
<tr>
<td>Arrhythmia Group — 3 cases (2%)</td>
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<td>QT prolongation: 1, complete A-V block: 1, Af: 1</td>
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Abbreviations: TOF = tetralogy of Fallot, DORV = double outlet of the right ventricle, PS = pulmonary stenosis, TGA = transposition of the great arteries, VSD = ventricular septal defect, SV = single ventricle, TA = tricuspid atresia, MA = mitral atresia, ECD = endocardial cushion defect, CoA = coarctation of the aorta, PDA = patent ductus arteriosus, TAPVR = total anomalous pulmonary venous return, AS = aortic stenosis, HCM = hypertrophic cardiomyopathy, DCM = dilated cardiomyopathy, EFE = endocardial fibroelastosis, PMD = primary endomyocardial disease, MCLS = mucocutaneous lymphnode syndrome, LAD = left anterior descending coronary artery, MVR = mitral valve replacement, AVR = aortic valve replacement, ASD = atrial septal defect, PA = pulmonary artery, PH = pulmonary hypertension, PVO = pulmonary vascular obstruction, Af = atrial fibrillation.

acute death, preceded by mild prodromal symptoms and signs not indicating to us the anticipation of sudden death and 4) death, which should have been instantaneous in itself but was averted by extensive cardiovascular support so that the patient survived for 24 hours or more but finally died.

Since the cardiovascular diseases showed some specific physiological and pathological features which can be involved as the causes of sudden death, the subjects were classified into 7 groups according to their basic disorders. In the first group, hypoxemia was a major clinical pathology; heart failure was minimal or pulmonary vascular obstruction, if any, was mild. The second group consisted of cases with congestive heart failure (CHF) caused by structural abnormalities, such as congenital cardiac anomaly or valvular lesion. The third was the primary endomyocardial disease (PMD) and coronary heart disease (CorHD) group, which included coronary anomalies and the sequelae of Kawasaki disease (MCLS). The fourth group was of primary or secondary pulmonary vascular obstruction (PVO). Postoperative (PO) cases made up one group (the fifth group) and included only cases after intracardiac repair. In the sixth (arrhythmia) group electrocardiographic abnormality was the major problem. Those cases which could not be categorized into any of these groups were classified as the miscellaneous group (the seventh group).

RESULTS

Age Distribution and Sex Difference

Forty-seven patients (33%) died under one year of age and thirty (21%) died at the age of one or two years. Fifteen (11%) died between 3 and 5 years of age, 8 (6%) between 6 and 8 years, 12 (8%) between 9 and 11 years, 10 (7%) between 12 and 14 years, 14 (10%) between 15 and 19 years and 6 (4%) at 20 years or older.

Sixty-seven (47%) were males and 75 (53%) were females. There was no age specificity in the sex difference.
Incidence of Each Group

There were 45 patients (32%) in the hypoxemic group and 33 (23%) in the CHF group. The PMD-CorHD, PO and PVO groups were next, being 21 cases (15%), 18 cases (13%) and 17 cases (12%), respectively. The arrhythmia group consisted of 3 cases (2%). The diagnoses included in each group are listed in Table I. The miscellaneous group included simple coarctation, bacterial endocarditis, small ventricular septal defect (VSD), vascular ring and functional murmur in a obese boy, one in each case.

Age Distribution in Each Group (Fig. 1)

In the hypoxemic group, 13 cases (29%) were under one year of age and 10 (22%) were one year old. Thus, more than half of the cases were under 24 months. The mean age was 3.7 ± 4.7 (SD) years and the median was one year. Twenty-five cases (76%) of the CHF group were under one year of age, with a mean of 2.5 ± 4.4 years, the median being 8 months. In the PMD-CorHD group the cases were distributed widely from infants to 19 years old. Four cases of MCLS were included in this group: 2 cases of
Fig. 2. Changes in relative incidence of each category by age: The CHF group was mainly in infancy. The hypoxemic group showed a fairly constant incidence throughout childhood. Inoperable cases increased with age. Abbreviations are the same as in Fig. 1.

Fig. 3. Seasonal variation. Throughout the whole series, sudden death was seen most frequently in winter. This is especially obvious in the CHF and PVO groups. In the hypoxemic group, the cases were found more in spring and autumn than in winter and summer. Abbreviations are the same as in Fig. 1.
Changes in Relative Incidence of Each Group with Age (Fig. 2)

Under one year of age, the CHF group of 25 cases (53% in this age group) was the largest, followed by hypoxemic group of 13 cases (28%). The others were 5 cases of the PMD-CorHD group, 3 cases of the arrhythmia group and one of the miscellaneous group. The relative incidence of the CHF group decreased sharply with age over 12 months, though a small peak was observed in its incidence between 9 and 14 years. The hypoxemic group showed a constant incidence from infants to 11 years. Over 11 years it decreased and none of these cases were older than 20 years. The incidence of the PVO and PMD-CorHD groups increased with age. The PO cases had a relatively constant incidence throughout the whole age range except for infancy.

Type of Death

In the hypoxemic group, 22 of 29 cases under one year old died from anoxic spell, while in the cases over one year instantaneous death occurred most frequently (7 of 16 cases). In the CHF group 18 of 25 infants died from the so-called “white spell” (a sudden pale and dyspneic attack). Over one year instantaneous death was the most frequent (4 of 8 cases). Three of these 4 cases had been known to have arrhythmias such as atrial fibrillation, frequent premature ventricular contraction and atrio-ventricular block, and the remaining one had Ebstein's

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anomaly which also suggests a death related to lethal arrhythmia. Of 21 cases of the PMD-CorHD group, instantaneous death occurred in 14 cases and 6 others were found dead. In 17 cases of the PVO group, 13 had an instantaneous death and 2 were found dead. In the PO group, instantaneous death occurred in 11 cases. Ten of these had had associated arrhythmias such as advanced atrio-ventricular block, frequent premature ventricular contraction and atrial tachyarrhythmias. One case in this group had a malfunction of a replaced mitral valve.

Seasonal Variation (Fig. 3)
Throughout the whole series, 42 cases (30%) died in winter, 37 (26%) in spring, 25 (18%) in summer and 38 (28%) in autumn. In the hypoxemic group, death was relatively frequent in autumn (15 cases, 33%), and in spring (14 cases, 31%). In the CHF group, 16 cases (46%) died in winter which is similar to the PVO group where 7 cases (41%) died in winter. In the other groups, there was no specific seasonal variation.

During the period from 1969 to 1981, there was no definite trend in the number of sudden death cases. The relative incidence of the CHF group, however, decreased during the last 5 years, and inoperable cases such as PVO and PMD or postoperative cases increased (Fig. 4). The hypoxemic group showed a relatively constant incidence, although the age became higher during the last 4 years (Fig. 5). The anatomical features of these older patients were characterized by pulmonary atresia and VSD with inadequate aortic-to-pulmonary collateral arteries which remained unoperated.

The 12 years from 1970 to 1981 were divided into three 4-year periods and the age distribution was analyzed in order to evaluate yearly changes of the incidence of sudden death. During the first 4 year period from 1970 to 1973, 42% of the cases were one year of age and 16% were older than 12 years. Thereafter, infant cases decreased and the latter group increased. They were 24% and 26%, respectively, during the last 4 year period (Fig. 6).

DISCUSSION
The age distribution in this study has a very similar pattern to that of the natural history of congenital heart disease suggesting that sudden death is one of the major types of death in congenital cardiac anomalies.

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TABLE II  CARdiovascular diseases leading to sudden death during infancy

<table>
<thead>
<tr>
<th>Disease</th>
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<tbody>
<tr>
<td>Cyanotic Heart Disease with Decreased Pulmonary Flow:</td>
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<tr>
<td>Splenecrosis, TOF, DORP-PS, SV-PS, TA-PS, etc.</td>
</tr>
<tr>
<td>Large L-R Shunt with PH:</td>
</tr>
<tr>
<td>VSD, ECD, PDA, Aortico-pulmonary window, etc.</td>
</tr>
<tr>
<td>Coarctation of the Aorta</td>
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<tr>
<td>TAPVR</td>
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<tr>
<td>Hypoplastic Left Heart</td>
</tr>
<tr>
<td>Endomyocardial Disease:</td>
</tr>
<tr>
<td>EFE, HCM, Carditis, cardiac tumor</td>
</tr>
<tr>
<td>Arrhythmias:</td>
</tr>
<tr>
<td>QT prolongation, complete A-V block</td>
</tr>
<tr>
<td>Coronary Disease:</td>
</tr>
<tr>
<td>MCLS, Bland-White-Garland syndrome, hypoplasia, anomalous origin</td>
</tr>
<tr>
<td>Semilunar Valve Stenosis (severe):</td>
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<tr>
<td>PS, AS</td>
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Abbreviations are the same as in Table I.

The mechanisms of sudden death are acute circulatory collapse due to cardiac standstill or ventricular fibrillation, acute respiratory failure or cerebral vascular accident, although the underlying conditions and the clinical course leading to death are variable and have not been completely defined as yet. This study reveals that the major conditions leading to sudden death are hypoxemia, congestive heart failure complicated with respiratory distress in infancy or with arrhythmias in older children, primary and secondary myocardial diseases, pulmonary vascular obstructive disease and postoperative status associated with persistent congestive heart failure and/or arrhythmias.

We have found in this study that hypoxemia and CHF are the most common causes of sudden death in infancy. In this stage death occurred most often due to anoxic spell in the hypoxic group. In cases with congenital cardiac anomalies, such as VSD and infundibular stenosis, the classical anoxic spell results in sudden death, and in cases dependent on patent ductus arteriosus (PDA), such as VSD, pulmonary atresia and PDA, an unexpectedly early closure of the ductus results in sudden or acute death by a cessation of pulmonary circulation. Recently, death from these conditions has been decreased by some medical advances. Anoxic spell can be managed by beta-blocker or by correcting anemia which is often present in the form of relative anemia being frequently overlooked. For keeping the ductus open a continuous administration of prostaglandin E is very effective during the newborn period. Recent advances in surgery have made it possible for a very small baby to undergo various types of palliative or even reparative operations successfully when the medical treatments fail.

Infants with a large left-to-right ventricular or ductal shunt may have an acute dyspneic attack called “white spell”. This is a clinical condition manifested by the sudden onset of ill humor, crying, marked perspiration and tachypnea followed by dyspnea, coldness of the extremities and paleness of skin. Furthermore, bradycardia, hypotension and loss of consciousness occur in extreme cases. This attack may be triggered by upper respiratory infection, sucking milk, crying when hungry and so on. These events cause a

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decrease in \( \text{PaO}_2 \) and an increase in \( \text{PaCO}_2 \), both of which have potent depressive effects on the cardiovascular system. This worsens the underlying left ventricular failure and results in a decrease of left ventricular forward flow, which stimulates the sympathetic nervous system, catecholamine release and the renin-angiotensin-aldosterone system. Thus, peripheral vasoconstriction occurs and systemic vascular resistance, in other words, the afterload to the left ventricular ejection increases, and the forward flow is impeded, thereby completing a vicious circle. This attack is the major cause of sudden death in infants with a large left-to-right shunt. The mortality rate of this group has been decreased by careful medical management using digitalis and diuretics, or by protection from, or intensive medical therapy, for infection. When indicated, surgical treatment which includes primary reparative operation for simple anomalies and various palliations for complex anomalies, can be performed effectively. As described above, recent advances in medical and surgical treatments have successfully decreased sudden death in infants with cyanotic heart disease or with cardiac anomalies causing heart failure. This, in turn, has resulted in a relative increase of older cases in the yearly change of age distribution as presented in Fig. 6.

The yearly change of relative incidence in each group has also shown that in recent years sudden death is seen primarily in non-surgical diseases, postoperative or inoperable cases. Inoperable cases include those in which no surgical treatment was indicated for anatomical reasons and those in which the initial delay of the operation resulted in an irreversible pulmonary vascular obstruction or myocardial damage. These cases were in the older age group in this study. The progression of pulmonary vascular obstruction or myocardial damage can be avoided by an early operation which now can be carried out with a fairly good result. Thus, in the future, it is hoped that no cases will be judged too late for treatment. In the postoperative group the major problems were myocardial failure associated with various arrhythmias16–20 Trifascicular block was once regarded as the most important cause of sudden death in postoperative patients, but we did not experience a single such case during this study. Gillette et al.19 documented the importance of ventricular tacharyrhythmias in postoperative sudden death, showing a similar finding to ours. With the improvement of surgical techniques including myocardial protection during cardiopulmonary bypass, postoperative residue, sequela and complications are now decreasing year by year, so that postoperative sudden death is also expected to decrease in the future. For PMD, beta-blockers or calcium antagonists are being used to prevent the patients from sudden death, although conclusive data has not been obtained as yet.1,22

Aortic stenosis has been reported to be a very common cause of sudden death5,6,8,12,13 but we found no typical case in the present study except a neonatal case with severe congestive heart failure. We have previously reviewed the files of the Tokyo Forensic Medical Office and found 31 children and adolescents who died suddenly and were autopsied to find cardiovascular pathologic findings during the period from 1962 to 19664 Six of these 31 cases died of aortic stenosis, either alone, or with mitral valvular lesions or aortic regurgitation. This shows the significance of this disease. The reason why no case was found in the present study may be that in patients with aortic stenosis their physical activity has been restricted since this disease is known to be a likely cause of sudden death, or that the incidence of aortic stenosis itself is possibly much less in Japan than in Western countries.23

In Japan mucocutaneous lymphnode syndrome (MCLS, Kawasaki disease) is now one of the major causes of sudden death in children. Although MCLS was initially considered to be a benign and selflimiting disease, it has recently become apparent that coronary artery disease, associated in 5–20% of the cases, can induce sudden death. Death results from acute myocardial infarction, acute carditis or rupture of a coronary aneurysm, which usually occurs within one or 2 months from the onset. Cases who escaped sudden death may be found to have ischemic dilated cardiomyopathy later.

Myocarditis, latent or apparent, may lead to sudden death as was seen in 3 of the 31 cases described above24 Of importance also are subtle abnormalities of the coronary arteries such as anomalous origin of the left coronary artery from the right sinus of Valsalva3,25 intramural coronary artery26,27 hypoplasia of the coronary artery and others28 It is well-known that a patient with mitral valve prolapse may die suddenly29 Furthermore, a recent report by Cooper and Abinader30 has documented that sudden death occurs among a wide range of relatives of a case with mitral valve prolapse. This condition is a clinical entity related to
various conditions such as Marfan syndrome and skeleto-muscular disorders including straight back, funnel chest or others, postcardiitic status, myocardial disease, congenital coronary artery disease or others. Oda had reported that there are some cases with mitral valve prolapse, whose left ventricular ejection fraction reduced and left ventricular end-diastolic pressure elevated during an exercise test, and he has suggested that these cases may have a risk of sudden death. A case with a small VSD was included in the miscellaneous group of the present study, and we wonder whether or not small VSD is related to sudden death. Recently, Smeeon et al have reported that conduction tissue changes were observed in a case with an enlarged membranous septum (membranous septal aneurysm) which is a process of spontaneous closure of VSD, and they have suggested that these changes may be the cause of sudden death in that case.

In summary, cardiovascular diseases which are likely to induce sudden death have specific features (Tables II and III). Recent advances in medical and surgical treatments have brought about a decrease in the frequency of sudden death in infants with simple anomalies; thus, leaving only cases, usually older ones, in which surgical treatment is not indicated.

REFERENCES
28. KUROSAWA H, WAGENAAR SS, BECKER AE: Sudden death in a youth: A case of quadricuspid


