Sudden Cardiac Death in Adult Congenital Heart Disease

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Background—Sudden cardiac death (SCD) is a major cause of mortality in adults with congenital heart disease (CHD). The aim of this study was to determine the adult CHD population at risk of SCD and the clinical parameters associated with SCD.

Methods and Results—We performed a multicenter case-control study. Patients who died suddenly as a result of proven or presumed arrhythmia were included (cases). For each case, 2 controls matched on diagnosis, type of surgical intervention, age, and gender were included. From 3 databases including 25 790 adults with CHD, 1189 deaths (5%) were identified, of whom 213 patients (19%) died suddenly. Arrhythmic death occurred in 171 of 1189 patients. The underlying cardiac lesions were mild, moderate, and severe CHD in 12%, 33%, and 55% of the SCD cases, respectively. Clinical variables associated with SCD were supraventricular tachycardia (odds ratio [OR], 3.5; 95% confidence interval [CI], 1.5–7.9; \( P = 0.004 \)), moderate to severe systemic ventricular dysfunction (OR, 3.4; 95% CI, 1.1–10.4; \( P = 0.034 \)), moderate to severe subpulmonary ventricular dysfunction (OR, 3.4; 95% CI, 1.1–10.2; \( P = 0.030 \)), increased QRS duration (OR, 1.34 [per 10-ms increase]; 95% CI, 1.10–1.34; \( P = 0.008 \)), and QT dispersion (OR, 1.22 [per 10-ms increase]; 95% CI, 1.12–1.48; \( P = 0.008 \)).

Conclusions—The clinical parameters found to be associated with SCD in adults with a broad spectrum of CHD, including systemic right ventricles, are similar to those in ischemic heart disease. Moreover, even those patients with mild cardiac lesions are potentially at risk for SCD. This highlights the need for further prospective studies as well as vigilant ongoing follow-up of the adult with CHD. (Circulation. 2012;126:1944-1954.)

Key Words: congenital heart disease ■ death, sudden

Sudden cardiac death (SCD) accounts for 15% of total mortality and 5.6% of annual mortality in the United States, and the vast majority is due to fatal arrhythmia. Similar event rates have also been reported in Europe. Approximately 70% of SCD cases are attributable to coronary heart disease and 10% to acquired or hereditary cardiac diseases.1,2 In patients with ischemic and nonischemic cardiomyopathy, left ventricular ejection fraction (EF) \( \leq 35% \) is the most important predictor of SCD, and implantable cardioverter-defibrillator (ICD) therapy has been proven to be effective in primary and secondary prevention of SCD in these patients.3,4 Similarly, in adults with congenital heart disease (CHD), SCD is a prominent cause of death (19–26%).5,6 During the past few decades, life expectancy has remarkably improved in CHD as a result of better surgical and interventional techniques.5,6 The annual incidence of SCD in the entire CHD population is relatively low (0.09%/y) but much higher than in age-matched controls. When applied to adults with CHD in the United States and Canada, \( \approx 765 \) and 90 SCD events will occur annually, respectively.7,8 Additionally, because the majority of infants born with CHD will now survive into adulthood, the prevalence of SCD will steadily increase. Adults with repaired tetralogy of Fallot (TOF) and/or Mustard or Senning repair for complete transposition of the great arteries (TGA) have been studied previously, and several potential risk factors for SCD have been identified.9,10 Unfortunately, the predictive value of these risk factors is relatively low, and it is uncertain whether these proposed risk factors are relevant to other forms of CHD. Moreover, because the CHD population is growing and aging, the risk profile for SCD may have changed. Therefore, we performed a multicenter case-control study to investigate patients with various types of CHD who died suddenly. Our primary objective was to define clinical parameters associated with SCD. We studied the cause of SCD in this
was completed in March 2011. Information about circumstances of SCD, location, cardiopulmonary resuscitation, or autopsy was collected from general practitioners, relatives, hospitals involved in follow-up, and ambulance care in the region. On the basis of this information, the actual or probable cause of SCD was determined. Medical records were reviewed, and the most recent data before the event were obtained and compared with data on controls at the same time frame. The median time between last outpatient or clinical visit and death was 4 months for the SCD cases (25th percentile, 1 month; 75th percentile, 9 months), and the median time since last outpatient or clinical visit was 2 months for the controls (25th percentile, 0 months; 75th percentile, 12 months). The complexity of the congenital defect was classified as mild, moderate, and complex. Eisenmenger syndrome was defined as the presence of systemic pulmonary arterial pressures or high pulmonary vascular resistance with reversed or bidirectional shunts or in a single ventricle through a large defect between the systemic and pulmonary circulation at ventricular, atrial, or aortopulmonary levels. All patients were considered to have contraindications for cardiac surgery because of high pulmonary vascular resistance. Patients with progressive or severe pulmonary hypertension after surgical repair of defects were not considered to have Eisenmenger syndrome.

Arrhythmias were classified according to the American College of Cardiology/American Heart Association/European Society of Cardiology guidelines. Arrhythmic symptoms included palpitations or (pre)syncope. Rhythm (spontaneous or paced), RR interval, QRS duration, QT interval, and QT dispersion were analyzed manually from standard (25 mm/s and 1 mV/cm) 12-lead ECGs. Moreover, investigators examining the ECGs were blinded to case status. Ventricular paced rhythms for both SCDs and controls were compared. Heart failure symptoms included decreased exercise tolerance, dyspnea, and peripheral edema. Chest x-rays were studied for cardiomegaly (defined as cardiothoracic ratio >50%) and redistribution of the pulmonary flow. Ventricular function was assessed by 2-dimensional echocardiography and classified as normal (EF ≥50%) or mildly (EF, 40%–49%), moderately (EF, 30%–39%), and severely (EF <30%) impaired. Because the aorta does not always arise from the morphological left ventricle, we classified the ventricles as systemic and subpulmonary throughout the article instead of as left and right ventricles. Left ventricular enlargement was defined as end-diastolic diameter ≥60 mm. Right ventricular size was qualitatively assessed as normal or enlarged from the echocardiography reports. Valvular dysfunction was graded as absent or mild, moderate, and severe from continuous wave Doppler tracings and Doppler color flow mapping.

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Methods

Study Design and Population

This was an international, retrospective, case-control study of adults (aged ≥18 years) with CHD and proven or presumed arrhythmic death. Cases were defined as adult CHD patients with SCD, and controls were alive adult CHD patients without SCD. Patients with moderate or severe heart failure were not excluded. Those patients with nonarrhythmic causes of sudden death were excluded. For each SCD case, 2 control patients who were alive were matched to (1) age (plus or minus 5 years of corresponding SCD case); (2) gender; (3) diagnosis; (4) type of surgical intervention (eg, prior shunt, palliative or corrective surgery, valve replacements); (5) date of surgical repair (within 5 years of corresponding SCD case); and (6) center (when available). Cases and controls were recruited from the CONCOR (CONgenital CORvitia) database, the Toronto Congenital Cardiac Centre for Adults, and the University Hospital Leuven. CONCOR is a Dutch registry of adults with CHD since 2001 and included 11,535 patients. The Toronto Congenital Cardiac Centre for Adults serves as the adult continuity clinic in Toronto for CHD in Ontario, Canada, and all consecutive patients seen in the clinic have been entered into a database since 1980. This database contains ~8000 adults with CHD. University Hospital Leuven registered ~6255 adults with CHD since 1970. Data collection was completed in March 2011.

Definitions

SCD is historically defined as (1) death due to cardiovascular causes within 1 hour of onset or significant worsening of the symptoms or (2) unwitnessed death during sleep. In this study, SCD included (1) proven or documented arrhythmic death (instantaneous death with documented ventricular fibrillation [VF] or ventricular tachycardia [VT]); (2) arrhythmic death by exclusion (instantaneous death or circumstances compatible with SCD, without severe disease that would lead to death soon and in the absence of a nonarrhythmic cause of death at autopsy); and (3) arrhythmic death by default (abrupt loss of consciousness and disappearance of pulse but no further data). Data analyses were performed with SPSS software for Windows (18.0 for Windows; SPSS Inc, Chicago, IL). For all analyses, 2-tailed

Data Collection

Information about circumstances of SCD, location, cardiopulmonary resuscitation, or autopsy was collected from general practitioners, hospitals involved in follow-up, and ambulance care in the region. On the basis of this information, the actual or probable cause of SCD was determined. Medical records were reviewed, and the most recent data before the event were obtained and compared with data on controls at the same time frame. The median time between last outpatient or clinical visit and death was 4 months for the SCD cases (25th percentile, 1 month; 75th percentile, 9 months), and the median time since last outpatient or clinical visit was 2 months for the controls (25th percentile, 0 months; 75th percentile, 12 months). The complexity of the congenital defect was classified as mild, moderate, and complex. Eisenmenger syndrome was defined as the presence of systemic pulmonary arterial pressures or high pulmonary vascular resistance with reversed or bidirectional shunts or in a single ventricle through a large defect between the systemic and pulmonary circulation at ventricular, atrial, or aortopulmonary levels. All patients were considered to have contraindications for cardiac surgery because of high pulmonary vascular resistance. Patients with progressive or severe pulmonary hypertension after surgical repair of defects were not considered to have Eisenmenger syndrome.

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Data analyses were performed with SPSS software for Windows (18.0 for Windows; SPSS Inc, Chicago, IL). For all analyses, 2-tailed
Table 1. Characteristics of Sudden Cardiac Death Cases and Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n=165)</th>
<th>Controls (n=310)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>106 (64)</td>
<td>195 (63)</td>
<td>0.773</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>36±15</td>
<td>37±14</td>
<td>0.480</td>
</tr>
<tr>
<td>Documented coronary artery disease</td>
<td>9 (5)</td>
<td>5 (2)</td>
<td>0.018</td>
</tr>
<tr>
<td>Noncardiac diseases</td>
<td>47 (28)</td>
<td>86 (28)</td>
<td>0.864</td>
</tr>
<tr>
<td>Syndrome as cause of defect</td>
<td>11 (7)</td>
<td>18 (6)</td>
<td>0.709</td>
</tr>
<tr>
<td>NYHA functional class III</td>
<td>40 (24)</td>
<td>17 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptoms during last outpatient visit, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure symptoms</td>
<td>62 (38)</td>
<td>42 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arrhythmic symptoms</td>
<td>28 (17)</td>
<td>35 (11)</td>
<td>0.082</td>
</tr>
<tr>
<td>Documented arrhythmias, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>66 (40)</td>
<td>77 (25)</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation/atrial flutter</td>
<td>57 (35)</td>
<td>58 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>29 (18)</td>
<td>30 (10)</td>
<td>0.013</td>
</tr>
<tr>
<td>Sustained VT/VF</td>
<td>5 (3)</td>
<td>3 (1)</td>
<td>0.096</td>
</tr>
<tr>
<td>Nonsustained VT</td>
<td>25 (15)</td>
<td>27 (9)</td>
<td>0.032</td>
</tr>
<tr>
<td>Bradyarrhythmias</td>
<td>23 (14)</td>
<td>33 (11)</td>
<td>0.289</td>
</tr>
<tr>
<td>Arrhythmia treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac medication</td>
<td>115 (70)</td>
<td>180 (58)</td>
<td>0.013</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td>40 (24)</td>
<td>37 (12)</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart failure drugs</td>
<td>69 (42)</td>
<td>44 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pacemaker implantation</td>
<td>34 (21)</td>
<td>50 (16)</td>
<td>0.111</td>
</tr>
<tr>
<td>AICD</td>
<td>2 (1)</td>
<td>6 (2)</td>
<td>0.560</td>
</tr>
<tr>
<td>Ablation of arrhythmia</td>
<td>5 (3)</td>
<td>12 (4)</td>
<td>0.639</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; VT, ventricular tachycardia; VF, ventricular fibrillation; and AICD, automated implantable cardioverter-defibrillator.

P values <0.05 were considered statistically significant. Descriptive statistics for nominal data were expressed in absolute numbers and percentages. After normality was confirmed, mean values and SDs were calculated for normally distributed continuous variables. When frequencies and means were compared, the χ² test and Student t test were used, respectively. To identify clinical parameters associated with SCD, univariate and stepwise multivariate conditional logistic regression models were used. Variables with P values ≤0.10 in univariate analyses were considered in multivariate models (backward stepwise; entry threshold, P=0.05; removal threshold, P=0.10). Holter monitoring and exercise tests were lacking in more than half of the cases and were therefore excluded from the multivariate analysis. The clinical parameters associated with SCD among the different CHD conditions were also assessed. In the present study, no multivariate analysis was performed because of the small number of cases in each underlying CHD condition. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Results

Events

Overall, 1189 of 25 790 adults (5%) died, of whom 213 died suddenly (19%). The causes of sudden death were proven or presumed arrhythmia in 171 (80%), aortic dissection or aneurysm rupture in 19 (9%), cerebrovascular accident in 8 (4%), pulmonary embolism/hemorrhage in 8 (4%), myocardial infarction in 4 (2%), and upper gastrointestinal bleeding in 3 patients (1%). Patients who died from a nonarrhythmic
cause of sudden death were excluded from further analysis. Of the remaining 171 SCDs, 131 (77%) experienced an out-of-hospital cardiac arrest, and cardiopulmonary resuscitation was performed in 84%. One hundred eighteen events (69%) occurred at rest, 19 (11%) during sleep, and only 17 (10%) during exercise. No information was available regarding the circumstances at time of cardiovascular collapse in 17 patients (10%). Autopsy reports were available for 38 SCD cases (22%) and showed known clinical cardiac defects only, with no explanation for sudden death other than a fatal arrhythmia. Rhythm documentation at the time of event was available for 37 patients (22%) and showed VF in 23 (62%), VT in 4 (11%), combined VT/VF in 4 (11%), supraventricular tachycardia (SVT) in 3 (8%), and bradyarrhythmia in 3 (8%) patients.

### Characteristics of SCD Cases Versus Controls

The underlying cardiac lesions were mild, moderate, and severe CHD in 12%, 33%, and 55% of the SCD cases, respectively. The more specific underlying cardiac defects of the 171 SCDs are shown in Figure 1. Characteristics of SCD cases versus controls are summarized in Table 1. For 165 SCDs, 310 suitable control patients were identified. For 20 SCDs we were able to find only 1 control patient, and for 6 SCDs we were able to find none. These 6 SCDs were excluded from further analyses. SCD cases were more often in a worse functional class (24% versus 5%; \( P < 0.005 \)) than controls and subsequently were more likely to be using heart failure drugs (42% versus 14%; \( P < 0.001 \)). Both SVTs (40% versus 25%; \( P = 0.001 \)) and nonsustained VT (15% versus 9%; \( P = 0.032 \)) occurred more frequently in SCD cases than in controls.

### Table 3. Clinical Variables Associated With SCD in Univariate and Multivariate Analysis in 165 SCD Cases and 310 Matched Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI P</td>
<td>OR 95% CI P</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documented coronary artery disease</td>
<td>6.4 1.34–30.83 0.020</td>
<td>3.5 1.50–7.95 0.004</td>
</tr>
<tr>
<td>Heart failure symptoms</td>
<td>4.2 2.54–6.90 &lt;0.001</td>
<td>4.2 1.50–7.95 0.004</td>
</tr>
<tr>
<td>Arrhythmic symptoms</td>
<td>1.6 0.95–2.86 0.075</td>
<td>1.6 0.95–2.86 0.075</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>2.5 1.50–4.02 &lt;0.001</td>
<td>2.5 1.50–4.02 &lt;0.001</td>
</tr>
<tr>
<td>Nonsustained ventricular tachycardia</td>
<td>2.0 1.09–3.66 0.025</td>
<td>2.0 1.09–3.66 0.025</td>
</tr>
<tr>
<td>Heart failure drugs</td>
<td>5.6 3.24–9.66 &lt;0.001</td>
<td>5.6 3.24–9.66 &lt;0.001</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td>2.5 1.44–4.44 0.001</td>
<td>2.5 1.44–4.44 0.001</td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal heart rhythm nonsinus</td>
<td>4.1 1.90–8.98 &lt;0.001</td>
<td>4.1 1.90–8.98 &lt;0.001</td>
</tr>
<tr>
<td>QRS duration (per 10-ms increase)</td>
<td>1.34 1.22–1.48 &lt;0.001</td>
<td>1.34 1.22–1.48 &lt;0.001</td>
</tr>
<tr>
<td>QRS duration ≥140 ms</td>
<td>4.1 1.44–11.53 0.008</td>
<td>4.1 1.44–11.53 0.008</td>
</tr>
<tr>
<td>QT interval</td>
<td>0.99 0.99–1.00 0.345</td>
<td>0.99 0.99–1.00 0.345</td>
</tr>
<tr>
<td>QTc interval</td>
<td>1.00 0.99–1.01 0.108</td>
<td>1.00 0.99–1.01 0.108</td>
</tr>
<tr>
<td>QT dispersion (per 10-ms increase)</td>
<td>1.34 1.22–1.63 &lt;0.001</td>
<td>1.34 1.22–1.63 &lt;0.001</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately to severely impaired systemic ventricular function</td>
<td>6.3 3.21–12.23 &lt;0.001</td>
<td>6.3 3.21–12.23 &lt;0.001</td>
</tr>
<tr>
<td>Moderately to severely impaired subpulmonary ventricular function</td>
<td>5.5 2.50–12.31 &lt;0.001</td>
<td>5.5 2.50–12.31 &lt;0.001</td>
</tr>
<tr>
<td>Dilated systemic ventricle</td>
<td>2.7 1.54–4.63 &lt;0.001</td>
<td>2.7 1.54–4.63 &lt;0.001</td>
</tr>
<tr>
<td>Dilated pulmonary ventricle</td>
<td>2.0 1.13–3.42 0.016</td>
<td>2.0 1.13–3.42 0.016</td>
</tr>
<tr>
<td>Severe systemic atrioventricular valve regurgitation</td>
<td>3.4 1.15–9.99 0.027</td>
<td>3.4 1.15–9.99 0.027</td>
</tr>
<tr>
<td>Severe LVOT obstruction</td>
<td>10.7 1.30–88.85 0.028</td>
<td>10.7 1.30–88.85 0.028</td>
</tr>
<tr>
<td>Holter findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documented arrhythmias</td>
<td>3.3 1.19–8.99 0.021</td>
<td>3.3 1.19–8.99 0.021</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>2.4 0.94–6.05 0.067</td>
<td>2.4 0.94–6.05 0.067</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>1.3 0.56–3.16 0.512</td>
<td>1.3 0.56–3.16 0.512</td>
</tr>
<tr>
<td>Exercise test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induced arrhythmias</td>
<td>6.6 1.43–30.21 0.016</td>
<td>6.6 1.43–30.21 0.016</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>4.8 1.00–23.24 0.049</td>
<td>4.8 1.00–23.24 0.049</td>
</tr>
</tbody>
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SCD indicates sudden cardiac death; OR, odds ratio; CI, confidence interval; and LVOT, left ventricular outflow tract.
controls, and antiarrhythmic medication was also used more frequently (24% versus 12%; P<0.001). Amiodarone was the most frequently prescribed drug for SCD cases (65%), followed by sotalol (20%). In contrast, controls used sotalol (46%) more frequently than amiodarone (38%). Table 2 shows the clinical parameters of the SCD cases and controls.

Clinical Parameters Associated With Sudden Arrhythmic Death

Univariate and multivariate analyses are summarized in Table 3. Clinical parameters associated with SCD in multivariate analysis were documented SVTs (OR, 3.5; 95% CI, 1.5–7.9; P=0.004), QRS duration (OR, 1.34 [per 10-ms increase]; 95% CI, 1.10–1.34; P=0.008), QT dispersion (OR, 1.22 [per 10-ms increase]; 95% CI, 1.22–1.48; P=0.008), moderately to severely impaired systemic ventricular function (OR, 3.4; 95% CI, 1.1–10.4; P=0.034), and moderately to severely impaired subpulmonary ventricular function (OR, 3.4; 95% CI, 1.1–10.2; P=0.030). Neither heart failure symptoms, worse New York Heart Association functional class, nor documented ventricular arrhythmias and antiarrhythmic medication altered the risk of SCD. Cardiac surgery with subsequent ventriculotomy with myocardial scar was not found as a specific risk factor for SCD because this was a matching criterion for controls.

SVTs were more common in the SCD cases before death than in controls. SVT was documented during cardiopulmonary resuscitation in 3 patients. Patient 1 had a repaired TOF, accessory pathway, and atrial tachycardia and used propafenone for his arrhythmias. This patient also showed pauses of >2.1 seconds during Holter monitoring but did not have any protection for bradycardia. Patient 2 had a univentricular heart and documented nonsustained VTs and SVTs but used only digoxin for arrhythmia management. Patient 3 also had a univentricular heart but without documented arrhythmias or antiarrhythmic medication use in the patient’s history. Given these data, we are not able to draw any firm conclusions with respect to drugs used to control SVT resulting in unprotected bradycardia leading to VT or VF or ischemia and SCD.

Figure 2A depicts the QRS duration and Figure 2B depicts the QT dispersion in individual SCD cases and controls (with ventricular pacing excluded). Mean QRS duration was significantly longer in SCD cases than in controls (129±30 versus 114±25 ms; P=0.001). A complete right bundle-branch block was present in 34% versus 23% of SCD cases and controls, respectively. Even when these patients were eliminated from the analysis, mean QRS duration was still significantly increased in SCD cases compared with controls (P=0.007). A complete left bundle-branch block was rare in SCD cases and controls (4% versus 1%). In patients with ventricular paced rhythms (25 SCD cases and 39 controls), the mean QRS duration in SCD cases (177±29) and controls (188±34) was not significantly different (P=0.161). QT
dispersion was increased ($\geq 70$ ms) in 50% of SCD cases and in only 16% of controls ($P<0.001$). Figures 3 and 4 show that mean QRS duration and QT dispersion were greater in SCD cases than in controls regardless of ventricular function.

We also analyzed the patients with proven SCD (n=37) and presumed (n=128) SCD separately. The determinants for SCD were the same in proven and presumed SCDs.

Clinical Parameters Associated With Sudden Arrhythmic Death Among Various CHD Conditions

Table 4 summarizes the statistically significant factors associated with SCD among the various cardiac conditions in univariate analysis. Results of exercise testing and 24-hour Holter monitoring, of which the majority were performed in TOF and (congenitally corrected) TGA patients, were not associated with the risk of SCD. Figure 5 shows the age at time of death according to underlying cardiac defects. Overall, 33 SCD cases (58% male) had Eisenmenger syndrome. Eisenmenger syndrome resulted predominantly from septal defects (58%) and univentricular heart physiology (27%).

The underlying cardiac defects were complete TGA in 18 SCD cases (70% male) and congenitally corrected TGA in 12 patients. Fifteen of the 18 complete TGA patients (83%) were treated with Mustard or Senning repair, 2 with an arterial switch procedure (11%), and 1 with a Rastelli procedure (1%). Seven of the 18 complete TGA patients (39%) also had repaired ventricular septal defect. Nine of the 12 congenitally corrected TGA patients (75%) had associated cardiac defects (7 with ventricular septal defect and pulmonary stenosis and 2 with Ebstein-like malformation of the tricuspid valve). Of these, 6 patients were treated with ventricular septal defect closure and 5 also with a left ventricular-to-pulmonary artery conduit. After surgical repair, 27 of the 30 SCD cases with complete TGA or congenitally corrected TGA (90%) had a systemic right ventricle.

Overall, 26 patients with SCD (69% male) had surgically repaired TOF, of whom 12 had a previous palliative shunt (46%). Surgical repair took place at a mean age of 12±14 years, and pulmonary valve replacement with a homograft was performed in 31% of the patients during follow-up. Four of 26 TOF patients had complete atrioventricular block requiring permanent pacemakers in the late postoperative period. A history of complete atrioventricular block was not associated with the risk of SCD ($P=0.439$).

Left-sided outflow tract lesions were present in 21 SCD cases. These included isolated aortic valve stenosis (n=9; mean age, 33±8 years), isolated bicuspid aortic valve (n=5; mean age, 46±23 years), and coarctation of the aorta (n=7; mean age, 35±18 years). All coarctation of the aorta cases were complex; 5 had bicuspid aortic valve, and 2 had ventricular septal defect. Overall, 18 of 21 patients had undergone surgery for severe aortic valve stenosis. The incidence of moderate to severe aortic valve stenosis was similar for SCD cases and controls. In this subgroup, no clinical variables associated with SCD were found.
Nineteen SCD cases (11%) had septal defects, including atrial septal defect (n=11), ventricular septal defect (n=9), and atrioventricular septal defect (n=2). Thirteen patients had surgical closure, and 4 patients had percutaneous closure of the defect. Only 2 patients (1 atrial septal defect, 1 ventricular septal defect) were untreated because their shunt was not hemodynamically relevant. Patients with atrial septal defect were older (mean age, 60±21 years) than patients with a ventricular septal defect or atrioventricular septal defect (mean age, 29±8 years), and 2 of them had documented coronary artery disease. Postoperative atrioventricular block was present in 3 SCD cases and was not associated with SCD. Moderately to severely impaired systemic ventricular function and subpulmonary ventricular function were present in 18% and 1% of SCD cases and controls, respectively.

Overall, 25 SCD cases had a cyanotic cardiac condition without Eisenmenger physiology, of which 7 were palliated with a Fontan procedure (4%; 86% male). There was no significant difference in baseline characteristics and clinical parameters between SCD cases and controls with a Fontan procedure. Of the remaining 18 cyanotic SCD cases (11%; 61% female), 7 were palliated with an aortopulmonary shunt and 3 with a bidirectional cavopulmonary anastomosis.

Discussion

To the best of our knowledge, this is the largest international study investigating the circumstances of SCD in adults with CHD. This study defines clinical parameters associated with SCD in a large cohort of adults with CHD and among various cardiac defects. The majority of patients were male and died suddenly at rest; only 10% died during active physical exertion. The rhythm most often recorded at time of sudden cardiac arrest was VF. Not only were adults with severe cardiac conditions at risk of SCD but also adults with less complex CHD such as septal defects and left ventricular outflow tract obstruction. Clinical parameters independently associated with SCD were documented prior SVTs (predominantly atrial flutter or fibrillation), increased QRS duration, QT dispersion, and moderately to severely impaired systolic function of the systemic and/or subpulmonary ventricle. The clinical variables associated with SCD differed among the various underlying cardiac defects.

Ventricular Dysfunction

The relationship between left ventricular systolic dysfunction and death due to heart failure and ventricular arrhythmias in patients with ischemic heart disease is well established. This study shows that systemic ventricular dysfunction is associated with SCD in a general CHD population, particularly in adults with (congenitally corrected) TGA, cyanotic patients with or without Eisenmenger physiology, and surgically repaired TOF patients. Published results of the predictive value of systemic ventricular dysfunction in repaired TGA are conflicting. In the present study, impaired
The systolic function of the systemic and subpulmonary ventricle was associated with SCD in Eisenmenger syndrome patients and surgically repaired TOF patients. In one of the largest cohorts of subjects with Eisenmenger syndrome \( n=11005 \), impaired ventricular function, neither systemic nor subpulmonary, was predictive of death. In that study, 20 patients died, of whom 11 died suddenly.26 The association of impaired systolic function of the systemic and subpulmonary ventricle with SCD has been described earlier in TOF patients.14 Left ventricular dysfunction in TOF may be explained in part by older age at repair with longer periods of volume overload and chronic hypoxemia, right ventricular dysfunction leading to left ventricular dysfunction, and regurgitation of the aortic or mitral valve. However, further studies are needed to identify the exact mechanism of left ventricular dysfunction in these patients.

In this study, none of the SCD cases with moderately to severely impaired systemic ventricular function who may have been considered at “high risk” of SCD received an ICD for primary prevention of SCD. This may be attributable in part to the era in which these deaths occurred. Secondary ICD prophylaxis for SCD via the transvenous route has been available since the mid-1990s, and the benefit of primary prophylaxis for SCD was appreciated with the publication of the results of the Multicenter Automatic Defibrillator Implantation Trial (MADIT)4 and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)27 over the past decade. The lack of evidence-based criteria for prophylactic ICD implantation in CHD may explain in part the conservative approach to ICD implantation in more recent years. Left ventricular EF 35% is a powerful prognostic factor and indication for ICD therapy in adults with ischemic and dilated cardiomyopathy. In CHD, the right ventricle is often impaired and might create an arrhythmogenic substrate. In this study, left or right ventricular dysfunction was associated with an at least 3-fold increased risk of SCD. Therefore, ICD therapy should be considered in adults with CHD and an at least moderately impaired ventricular function after elimination of reversible causes of ventricular dysfunction.

In this study, one fifth of the SCD cases had pacemaker implantation for complete atrioventricular block. Chronic

### Table 4. Factors Associated With SCD Among Various Cardiac Defects in Univariate Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Eisenmenger (33 SCD Cases vs 58 Controls)</th>
<th>(cc) TGA* (27 SCD Cases vs 52 Controls)</th>
<th>TOF (26 SCD Cases vs 52 Controls)</th>
<th>Left-Sided Outflow Lesions (21 SCD Cases vs 39 Controls)</th>
<th>Septal Defects (19 SCD Cases vs 39 Controls)</th>
<th>Cyanotic Non-Eisenmenger† (18 SCD Cases vs 32 Controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heart failure symptoms</td>
<td>2.7 (1.12–6.45)</td>
<td>4.0 (1.22–13.07)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>6.6 (1.41–30.97)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heart failure drugs</td>
<td>3.0 (1.20–7.56)</td>
<td>.</td>
<td>3.9 (1.20–12.96)</td>
<td>.</td>
<td>.</td>
<td>18.2 (2.3–141.94)</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>3.4 (1.02–11.48)</td>
<td>.</td>
<td>.</td>
<td>.</td>
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<tr>
<td>Documented arrhythmias</td>
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<tr>
<td>Atrial fibrillation/atrial flutter</td>
<td>.</td>
<td>3.2 (1.07–9.66)</td>
<td>7.2 (1.51–34.56)</td>
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<tr>
<td>Nonsustained ventricular tachycardia</td>
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<td>ECG</td>
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<tr>
<td>QRS duration (per 10-ms increase)</td>
<td>1.34 (1.03–1.76)</td>
<td>.</td>
<td>.</td>
<td>1.52 (1.04–2.22)</td>
<td>1.72 (1.01–2.92)</td>
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</tr>
<tr>
<td>QT dispersion (per 10-ms increase)</td>
<td>.</td>
<td>.</td>
<td>1.99 (1.13–3.46)</td>
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<tr>
<td>Echocardiogram</td>
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<tr>
<td>Impaired systemic ventricular function</td>
<td>8.2 (1.79–37.87)</td>
<td>3.8 (1.18–12.27)</td>
<td>8.5 (0.98–74.91)</td>
<td>7.4 (1.58–34.81)</td>
<td></td>
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</tr>
<tr>
<td>Impaired pulmonary ventricular function</td>
<td>5.0 (1.35–18.73)</td>
<td>.</td>
<td>11.7 (1.42–95.92)</td>
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<tr>
<td>Chest x-ray</td>
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<tr>
<td>Cardiopheratic ratio &gt;0.5</td>
<td>.</td>
<td>.</td>
<td>8.7 (1.08–70.86)</td>
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<tr>
<td>Pulmonary edema</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>11.1 (1.33–92.54)</td>
<td></td>
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<tr>
<td>Laboratory findings</td>
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<tr>
<td>Increased creatinine (per 10-μmol/L increase)</td>
<td>1.12 (1.12–2.46)</td>
<td>...</td>
<td>...</td>
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</table>

SCD indicates sudden cardiac death; (cc) TGA, (congenitally corrected) transposition of great arteries; TOF, tetralogy of Fallot; OR, odds ratio; and CI, confidence interval.

*Excluding patients with arterial switch and Rastelli procedure.
†Excluding patients with Fontan circulation.
right ventricular pacing may contribute to left ventricular
dysfunction. One might speculate that biventricular pacing
may improve ventricular function and prevent SCD in CHD.

QRS Duration and QT Dispersion
Increased QRS duration is associated with an increased risk
of all-cause mortality and SCD in patients with ischemic
cardiomyopathy.28 In adults with CHD, an association be-
tween QRS duration and SCD was reported in patients with
TOF, TGA, and Eisenmenger syndrome.12,13,26 Although
QRS duration was significantly increased in SCD cases, we
were not able to demonstrate an association between QRS
duration and SCD in TOF and TGA, which might be
explained by the low number of SCDs in these subgroups.

In healthy control subjects, QT dispersion ranges from 10
to 70 ms. However, overlaps in values between healthy
controls and cardiac patients or between patients with and
without adverse outcome have been reported.29 Prognostic
information on QT dispersion in CHD is limited.30 In this
study, increased QT dispersion was associated with SCD and
was above the normal range in 50% of SCD cases. The QT
dispersion was within the normal range in the majority of
controls (84%).

Documented Arrhythmias
In the present study, atrial flutter or fibrillation was associated
with SCD, especially in patients with TGA and TOF. This
association has been described earlier in patients with TGA
but not in those with TOF.13 Further studies are needed to
clarify whether atrial tachyarrhythmias are a surrogate marker
for SCD or a consequence of ventricular dysfunction. Docu-
mented nonsustained VTs were uncommon in SCD cases
(18%) and not associated with SCD. Antiarrhythmic drugs
were used more often by the SCD cases than controls because
arhythmias were more often present in SCD cases. One
might speculate that lack of back-up pacing in these patients
might have been a contributing factor, with bradycardia-
induced ventricular arrhythmias leading to SCD.

Sudden Arrhythmic Death in Septal Defects
Although repaired septal defects are considered benign and
ventricular arrhythmias or SCDs have been reported as
uncommon,31 in the present cohort, 11% of SCD cases had
septal defects (89% were closed). The few untreated septal
defects were not hemodynamically relevant. Patients with
atrial septal defect repair were older, and potentially coronary
artery disease rather than CHD might have been the cause of
SCD. Almost half of the SCD cases with ventricular septal
defect/atrioventricular septal defect had pacemaker insertion
for complete atrioventricular block, and the remaining cases
had associated cardiac anomalies.

Study Limitations
This study has limitations inherent to any retrospective study.
Data collection was limited to data in medical records.
Rhythm documentation at the time of event or autopsy reports
was not available for all SCD cases, and thus it is not possible
to ascertain that their deaths were solely arrhythmic in nature.
On the other hand, the actual incidence of SCD might have
been underestimated because of the strict definitions applied
in this study. Data on syncope were lacking in the majority of
the SCD cases and could therefore not be used for risk
stratification. Patients were retrieved from 3 databases with
different inclusion periods, which precluded determination of
the annual incidence rate of SCD in the general CHD
population. Moreover, the prognosis of patients and thus the
incidence of SCD might have been influenced by changes in
treatment recommendations during the study period. Assess-
ment of ventricular function may be challenging in CHD
because of abnormal ventricular geometry. Cardiac magnetic
resonance imaging is more accurate in measuring EF in some
cardiac lesions (eg, the systemic right ventricle). Unfortu-
nately, quantification of ventricular EF by cardiac magnetic
resonance imaging was frequently lacking in this study, in
which case qualitative data were used. Furthermore, a cutoff
value for pulmonary arterial blood pressure to define Eisen-
menger syndrome was not used in this study. The number of
patients among the various cardiac defects was small, and
therefore multivariate analyses were not performed for these
subgroups. A prospective analysis of the risk factors reported
here would be preferable but is extremely difficult to achieve
because of the low incidence of SCD and the heterogeneity
within the CHD population.

Conclusions
We have identified several clinical parameters associated
with SCD in adults with a broad spectrum of CHD including
systemic right ventricles. These parameters may be helpful
for identifying high-risk patients and may guide clinicians in
their treatment strategy. The identified clinical parameters are
similar to the risk factors for SCD in ischemic cardiomyop-
athy and include documented SVTs, impaired ventricular function, increased QRS duration, and prolonged QT dispersion. It is important to be aware that SCD occurs at a relatively young age in patients with CHD. The treating cardiologist should focus on preserving ventricular function as a means of reducing the risk of SCD. Reversible causes of ventricular dysfunction should also be treated at a young age. Although patients with repaired cyanotic and left-sided outflow lesions have previously been identified as at risk for SCD, this study reveals that a broader spectrum of adults with CHD, even those with cardiac lesions traditionally considered mild, are potentially at risk for SCD. This highlights the need for further prospective studies as well as vigilant ongoing follow-up of the adult with CHD.

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Disclosures
None.

References
CLINICAL PERSPECTIVE

Sudden cardiac death (SCD) is a major cause of mortality in adults with congenital heart disease (CHD). As this population ages, the population at risk and the risk factors associated with SCD may be changing. Therefore, we conducted a multicenter case-control study to determine the adult CHD population at risk of SCD and the clinical parameters associated with SCD. From 3 databases including 25,790 adults with CHD, 1189 deaths (5%) were identified, of which 213 patients (19%) died suddenly. The cause of sudden death was proven or presumed arrhythmia in 171 of 1189 patients (14%; 64% male; mean age, 36±15 years). Most cases of SCD occurred at rest (69%) or during sleep (11%). The underlying cardiac lesions were mild, moderate, and severe CHD in 12%, 33%, and 55% of the SCD cases, respectively. We have identified several clinical parameters associated with SCD in adults with CHD that may be helpful in identifying high-risk patients and may guide clinicians in their treatment strategy. The identified clinical parameters are similar to the risk factors for SCD in ischemic cardiomyopathy and include documented supraventricular tachycardias, impaired ventricular function, prolonged QRS duration, and increased QT dispersion. Although patients with repaired cyanotic and left-sided outflow tract lesions have been identified previously as at risk for SCD, this study reveals that a broader spectrum of adults with CHD, even those with cardiac lesions traditionally considered mild, are potentially at risk for SCD. This highlights the need for further prospective studies as well as vigilant ongoing follow-up of the adult with CHD.

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Sudden Cardiac Death in Adult Congenital Heart Disease

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