Surgery in Adults With Congenital Heart Disease

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Background—A significant proportion of patients with congenital heart disease require surgery in adulthood. We aimed to give an overview of the prevalence, distribution, and outcome of cardiovascular surgery for congenital heart disease. We specifically questioned whether the effects of surgical treatment on subsequent long-term survival depend on sex.

Methods and Results—From the Dutch Congenital Corvitia (CONCOR) registry for adults with congenital heart disease, we identified 10 300 patients; their median age was 33.1 years. Logistic and Cox regression models were used to assess the association of surgery in adulthood with sex and with long-term survival. In total, 2015 patients (20%) underwent surgery for congenital heart disease in adulthood during a median follow-up period of 15.1 years; in 812 patients (40%), it was a reoperation. Overall, both first operations and reoperations in adulthood were performed significantly more often in men compared with women (adjusted odds ratio = 1.4 [95% confidence interval, 1.2–1.6] and 1.2 [95% confidence interval, 1.0–1.4], respectively). Patients with their third and fourth or more surgery in adulthood had a 2- and 3-times-higher risk of death compared with patients never operated on (adjusted hazard ratio = 1.9 [95% confidence interval, 1.0–3.6] and 2.7 [95% confidence interval, 1.1–6.3], respectively). Men with a reoperation in adulthood had a 2-times-higher risk of death than women (adjusted hazard ratio = 1.9; 95% confidence interval, 1.0–3.5).

Conclusions—Of predominantly young adults with congenital heart disease, one fifth required cardiovascular surgery at some point in adulthood, either for first corrective surgery or for reoperations to treat residual defects or long-term complications. Whether there is an effect of sex on surgical treatment and outcome after surgery is still unknown.

Key Words: adults ▪ heart defects, congenital ▪ sex ▪ surgery ▪ outcome assessment

Clinical Perspective on p 000

In recent years, there has been increased attention on sex differences in cardiovascular disease because it has been recognized that men and women differ in clinical manifestation, morbidity, mortality, and the way they are managed. Few data exist on sex differences in adults with congenital heart disease. However, our research group and others have previously shown that men appear to have a higher risk of long-term complications and mortality. Whether there is an effect of sex on surgical treatment and outcome after surgery is still unknown.

We used the Dutch nationwide Congenital Corvitia (CONCOR) registry to give an overview of the prevalence, distribution, and outcome of cardiovascular surgery for congenital heart disease in adulthood. Furthermore, we sought to determine the effects of sex on the risk of
coding scheme20), as well as patient and family history, were classified by use of the European Pediatric Cardiac Code Short List such as demographics, diagnosis, clinical events, and procedures.

Clinical data were obtained from medical records. In case of multiple diagnoses in 1 patient, a prespecified hierarchical scheme founded on consensus-based classification of defect severity21 was used, by means of which the diagnosis with the worst prognosis was established as the main diagnosis. After entry, data on major cardiac events before entry and during follow-up were systematically recorded from the patients' medical letters written by their cardiologist. Quality control of data was performed by randomly verifying 10% of data yearly. Currently, 103 Dutch hospitals are participating, including all 8 tertiary referral centers from which 70% of patients originate.

surgical treatment and on long-term survival after surgery in adulthood.

Methods

CONCOR Registry

The Dutch national registry database has been described in detail elsewhere.19 Briefly, CONCOR aims to facilitate research into the cause of congenital heart disease and on its outcome. From November 2001, patients with congenital heart disease ≥18 years of age (childhood survivors) were recruited and included by 3 independent, permanently employed research nurses through the treating cardiologist or via response to advertisements in local media. Clinical data such as demographics, diagnosis, clinical events, and procedures (classified by use of the European Pediatric Cardiac Code Short List coding scheme20), as well as patient and family history, were obtained from medical records. In case of multiple diagnoses in 1 patient, a prespecified hierarchical scheme founded on consensus-based classification of defect severity21 was used, by means of which the diagnosis with the worst prognosis was established as the main diagnosis. After entry, data on major cardiac events before entry and during follow-up were systematically recorded from the patients' medical letters written by their cardiologist. Quality control of data was performed by randomly verifying ~10% of data yearly. Currently, 103 Dutch hospitals are participating, including all 8 tertiary referral centers from which 70% of patients originate.

Surgery Data

For all patients, the occurrence, date, and type of intervention for congenital heart disease were collected retrospectively. All interventions for congenital heart disease were divided into surgical (defined as requiring either sternotomy or thoracotomy for cardiac or aortic surgery) or percutaneous interventions. Reoperations were recorded as multiple surgical interventions within the same patient on different dates of surgery. Thus, multiple surgical interventions on the same date of surgery were counted as 1 operation. Moreover, all operations were categorized as corrective or palliative. Corrective operations were defined as surgical interventions with the aim to repair or treat underlying congenital heart defects. Palliative operations were defined as surgical interventions performed to improve clinical tolerance and alleviate serious symptoms of congenital heart defects that could not be repaired otherwise, including bidirectional cavopulmonary anastomosis (Glenn), shunts, and Norwood and Fontan procedures.

Data Analysis

Age at time of inclusion, age at time of surgery, and age at time of death were summarized with medians (range limits). Follow-up death were summarized with medians (range limits). Follow-up.
Results

Of 10,300 adult congenital heart disease patients, 5064 (49%) were male, and the median age was 33.1 years (range limits, 18.0–92.2 years) at the time of inclusion. During a median follow-up period of 15.1 years (range limits, 0.0–74.2 years), a total of 3466 interventions were performed in 2525 patients (24.5%) at adult age. Of these interventions, 2404 (69%) were surgical; these were performed in 2015 patients. Among these patients, 254 (13%) underwent surgery twice in adulthood, 52 (3%) had surgery 3 times, and 10 (0.5%) underwent surgery ≥4 times.

Table 1 shows the basic characteristics of the overall CONCOR population and of patients who had a surgical intervention, who had a percutaneous intervention, and who were without an intervention in adulthood. In total, 2015 patients underwent surgery in adulthood; in 812 patients (40%), it was a reoperation. Approximately one third of patients with an atrial septal defect and Marfan syndrome had surgery in adulthood for the first time ever. Most reoperations in adulthood were seen in tetralogy of Fallot patients (20%); in this group, 37% of reoperations were pulmonary valve surgery. Approximately one third of patients with an atrial septal defect and Marfan syndrome had surgery in adulthood for the first time ever. Most reoperations in adulthood were seen in tetralogy of Fallot patients (20%); in this group, 37% of reoperations were pulmonary valve surgery.
Table 3. Basic Characteristics of Patients Who Underwent Surgery (n=536) During a Median Follow-Up Period of 3.8 Years and of Patients Who Died Perioperatively (n=18, 3.4%)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Operated (n=536)</th>
<th>Perioperative Mortality (n=18, 3.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n%</td>
</tr>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>307</td>
<td>8</td>
</tr>
<tr>
<td>Female</td>
<td>229</td>
<td>10</td>
</tr>
<tr>
<td><strong>Age at death, y</strong></td>
<td></td>
<td>43.4 (20.8–77.8)</td>
</tr>
<tr>
<td>Multiple defects</td>
<td>390</td>
<td>13</td>
</tr>
<tr>
<td><strong>Last surgery</strong></td>
<td></td>
<td>3.3</td>
</tr>
<tr>
<td>Age at surgery, y</td>
<td>34.5 (18.0–77.8)</td>
<td>34.6 (20.8–77.8)</td>
</tr>
<tr>
<td>First surgery</td>
<td>160</td>
<td>3</td>
</tr>
<tr>
<td>Reoperation</td>
<td>376</td>
<td>15</td>
</tr>
<tr>
<td>Second surgery</td>
<td>202</td>
<td>7</td>
</tr>
<tr>
<td>Third surgery</td>
<td>116</td>
<td>4</td>
</tr>
<tr>
<td>Fourth surgery or more</td>
<td>58</td>
<td>4</td>
</tr>
<tr>
<td>Corrective</td>
<td>518</td>
<td>13</td>
</tr>
<tr>
<td>Palliative</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td><strong>Main defects</strong></td>
<td></td>
<td>27.8</td>
</tr>
<tr>
<td>TOF</td>
<td>115</td>
<td>1</td>
</tr>
<tr>
<td>AoS</td>
<td>81</td>
<td>3</td>
</tr>
<tr>
<td>ASD</td>
<td>54</td>
<td>2</td>
</tr>
<tr>
<td>CoA</td>
<td>47</td>
<td>1</td>
</tr>
<tr>
<td>PS</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>Ebstein</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>UVH/DILV</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>BAV</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>TGA</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>50</td>
<td>4</td>
</tr>
</tbody>
</table>

TOF indicates tetralogy of Fallot; AoS, aortic stenosis; ASD, atrial septal defect; CoA, aortic coarctation; PS, pulmonary stenosis; Ebstein, Ebstein anomaly; UVH/DILV, univentricular heart/double-inlet left ventricle; BAV, bicuspid aortic valve; TGA, transposition of the great arteries; and other, other congenital heart defects with n<100. Age at death and age at surgery is stated as median (range limits). Percentages are calculated within rows.

*One hundred twenty-one patients with Marfan syndrome (n=43), ventricular septal defect (n=31), atrioventricular septal defect (n=30), congenitally corrected TGA (n=8), pulmonary atresia with ventricular septal defect (n=6), and patent arterial duct (n=3) were operated on without perioperative deaths.

Discussion

During a median follow-up of 15.1 years, one fifth of patients with congenital heart disease required surgery in adulthood, and in nearly 40%, it was a reoperation. Long-term survival after reoperations in adulthood depends on the number of surgeries performed in the patient’s history. Additionally, this is the first study showing that male patients with congenital heart disease have a higher chance of undergoing surgery in adulthood and, remarkably, have a worse long-term survival after reoperations in adulthood compared with female patients.

A large proportion of patients (70%) who required surgery in adulthood were operated on for the first time ever. In concordance with current literature, these patients were mostly adults with atrial septal defect and aortic stenosis. Furthermore, one third of Marfan patients had their first surgery in adulthood, which also is in agreement with the previously reported data. Focusing on the reoperations, patients with tetralogy of Fallot formed the largest subgroup needing reoperations in adulthood. Although tetralogy of Fallot patients are known for their need of reoperations, none of the previous published literature reported a reoperation rate this high. However, this could be explained by the fact that the follow-up period was longer in this study than in reported series. The overall perioperative mortality was 3.4% in our study, which is comparable to the mortality rates reported previously. The mortality rate was low for corrective surgery but high for palliative surgery, which is also in agreement with current literature.

Even after adjustment for childhood operations, defect, and multiple defects, male patients with congenital heart disease had more surgery in adulthood than female patients for both first-time surgery and reoperation. Sex-related differences in use of procedures have been well documented for adults with acquired cardiovascular disease, but data in the adult congenital heart disease population are sparse. The higher operation rate in men with Marfan syndrome and bicuspid aortic valve compared with women could be a result of biological differences. Both defects are associated with aortic complications, but male patients reach the threshold for elective aortic surgery earlier than female patients because...
the aorta is smaller in female patients.28–31 Furthermore, sex-related complications in adult congenital heart disease patients18,32 could explain the larger reoperation rate in men with aortic coarctation compared with women. Because men with aortic coarctation have a higher prevalence of aortic valve disease than women, they have a higher chance of being operated on.32,33 Other explanations might be genetic, lifestyle, and healthcare behavior differences between male and female patients. Finally, we cannot exclude the possibility that women are in some degree undertreated or alternatively that men are overtreated, as has been suggested in other cardiovascular diseases.14,15

Long-term survival for patients with reoperations in adulthood inversely correlated with the number of surgeries in the patient’s medical history. Furthermore, a new finding was that the risk of long-term mortality after a reoperation in adulthood was higher for male patients compared with female patients, a finding that is supported by the published literature on overall long-term survival in patients with congenital heart disease.13,17,34 An increased incidence of severe congenital heart disease lesions in male patients35 cannot explain these interesting results because we adjusted for underlying defect. However, it is likely that the previously mentioned sex-related complications and perhaps other comorbid conditions play a role in both the higher (re)operation rate and the worse prognosis after reoperation in male patients.

Table 4. Sex Differences in Risk of Death in Patients Who Were Never Operated on, Who Had Their First Surgery in Adulthood, and Who Had Their Second or Third or More Surgery in Adulthood

<table>
<thead>
<tr>
<th>Surgery in Adulthood</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No surgery at all</td>
<td>1.84 (1.21–2.78)</td>
</tr>
<tr>
<td>First-time surgery</td>
<td>0.97 (0.60–1.59)</td>
</tr>
<tr>
<td>Reoperation</td>
<td>1.89 (1.02–3.50)</td>
</tr>
<tr>
<td>Second surgery</td>
<td>1.10 (0.47–2.55)</td>
</tr>
<tr>
<td>Third or more surgery†</td>
<td>3.78 (1.33–10.79)</td>
</tr>
</tbody>
</table>

*Hazard ratio (HR) (95% confidence interval [CI]) for a median follow-up period of 3.8 years, males vs females. HRs are shown after adjustment for age of inclusion, underlying defect, and multiple defects. †Because of the small number in the category of 4 surgeries, this category could not be validly analyzed separately; therefore, it was combined with the category of 3 surgeries.

Implications

One fifth of patients with congenital heart disease underwent surgery in adulthood. However, taking into account the low median age of the patients with no intervention in adulthood, it is to be expected that the prevalence of surgery in adulthood will be even higher with longer follow-up. The high rate of reoperations supports the hypothesis that corrective surgery is not necessarily curative surgery, and thorough follow-up is needed in these patients. Furthermore, our data indicate that male and female patients born with a congenital heart defect differ in the way they are (surgically) managed, at least in frequency. Cardiologists should be aware of this existing difference in treatment. Whether this relates to biological, genetic, or behavioral differences between male and female patients with congenital heart disease remains uncertain, but large prospective studies are necessary to confirm our findings, to assess underlying mechanisms, and to assess whether this is appropriate clinical practice.
Although long-term survival after a patient’s first and second surgeries in adulthood is relatively high, long-term survival for patients with after ≥3 surgeries in adulthood is reduced. Interestingly, long-term survival after reoperations seems worse for men compared with female patients. Whether this is a reflection of the natural clinical course in male and female patients with congenital heart disease or of other underlying mechanisms that are playing a role needs to be investigated further. Data from international databases on congenital heart surgery could be of additional value.36

Limitations
The patients included in CONCOR form a survival cohort because patients who died before enrollment could not be included. The results of this study should be interpreted in this context. Furthermore, this study covers a long period of time, during which treatment algorithms, follow-up, and surgical and perioperative management changed considerably. Finally, the association of sex with surgery and long-term survival may be a reflection of sex-linked characteristics not included in the CONCOR database, such as healthcare behavior or comorbid conditions. However, in another study (A.C.Z., unpublished data, 2011), we found no differences in smoking status, diabetes mellitus, and obesity between male and female patients, suggesting a limited contribution of these comorbid conditions to the association found.

Conclusions
Of predominantly young adults with congenital heart disease, one fifth required surgery during 15 years of follow-up, and in nearly 40%, this surgery was for reoperations. Overall, long-term survival after reoperations in adulthood depended on the number of past surgeries. Male patients with congenital heart disease have a higher chance of undergoing surgery in adulthood and have a consistently worse long-term survival after reoperations in adulthood compared with female patients.

Sources of Funding
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Disclosures
None.

References
CLINICAL PERSPECTIVE

A significant proportion of patients with congenital heart disease require surgery in adulthood. In the Congenital Corvitia (CONCOR) national registry of adults with congenital heart disease, one fifth required surgery during 15 years of follow-up, and in nearly 40%, surgery was for reoperations. This is the first study showing that men with congenital heart disease have a 40% higher chance of undergoing first surgery and a 20% higher chance of undergoing reoperations in adulthood compared with women. Furthermore, men have a 2-times-higher risk of mortality after reoperations in adulthood compared with women. This study supports the existing evidence for sex differences in the prognosis of adults with congenital heart disease, and these findings underscore the need for further research on the mechanisms underlying these differences.
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