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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 during a 15-year period; in 40%, the surgery was a reoperation. Men 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 women. **(*Circulation*. 2011;124:2195-2201.)**

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

Over the past decades, the number of adults with congenital heart disease has increased, and is currently estimated at >1 million in the United States and 1.2 million in Europe.[1–3] As a result of tremendous advancements in cardiothoracic surgery in the past decades, 95% of newborns with congenital heart disease now survive to adulthood.[4] However, despite these major advancements, a significant proportion of this patient population will have to undergo cardiovascular surgery at some point in adulthood, either for first corrective surgery or for reoperations to treat residual defects or long-term complications.[5–9] Although there has been rapid growth recently in interventional cardiology techniques to treat adults with congenital heart disease,[10] surgery remains an important treatment option, with ≈1 of 5 hospital admissions of adults with congenital heart disease being for cardiovascular surgery.[11–13]

Clinical Perspective on p 2201

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.[14–16] 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.[17,18] 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

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Table 1. Basic Characteristics of the Overall CONCOR Population (n=10 300), Patients With a Surgical Intervention (n=2015), Patients With a Percutaneous Intervention (n=808), and Patients Without an Intervention (n=7775) in Adulthood

	CONCOR (n=10 300)	Surgical Intervention (n=2015, 19.6%)				Percutaneous Intervention (n=808, 7.8%)		No Intervention (n=7775, 75.5%)	
		First Surgery in Adulthood (n=1416)		Reoperation in Adulthood* (n=812)					
	n	n	%	n	%	n	%	n	%
Patient characteristics									
Male	5064	745	15	429	9	371	7	3784	75
Female	5236	671	13	373	7	437	8	3991	76
Age, y†	33.1 (18.0–92.2)	49.0 (18.8–90.6)		40.4 (18.1–84.1)		42.5 (18.8–89.7)		29.6 (18.0–92.2)	
Main defects									
VSD	1749	113	6	54	3	63	4	1553	89
ASD	1552	421	27	55	4	258	17	926	60
CoA	1010	118	12	135	13	58	6	754	75
TOF	942	45	5	193	20	101	11	672	71
AoS	929	196	21	116	12	37	4	645	69
PS	784	26	3	27	3	41	5	700	89
BAV	558	130	23	14	3	21	4	419	75
AVSD	478	72	15	43	9	30	6	367	77
Marfan	462	139	30	35	8	7	2	314	68
TGA	451	5	1	24	5	60	13	374	83
PDA	164	11	7	5	3	21	13	132	80
Ebstein	154	23	15	11	7	24	16	109	71
PA+VSD	118	3	3	20	17	7	6	92	78
ccTGA	117	8	7	6	5	19	16	87	74
UVH/DILV	107	6	6	8	7	15	14	83	78
Other	725	100	14	66	9	46	6	548	76

CONCOR indicates Congenital Corvitia; VSD, ventricular septal defect; ASD, atrial septal defect; CoA, aortic coarctation; TOF, tetralogy of Fallot; AoS, aortic stenosis; PS, pulmonary stenosis; BAV, bicuspid aortic valve; AVSD, atrioventricular septal defect (including ASD, primum type); Marfan, Marfan syndrome; TGA, transposition of the great arteries; PDA, patent arterial duct; Ebstein, Ebstein anomaly; PA, pulmonary atresia; ccTGA, congenitally corrected TGA; UVH/DILV, univentricular heart/double-inlet left ventricle; and other, other congenital heart defects with n<100. Percentages are calculated within rows.

*Two hundred thirteen subjects with both first-time surgery and reoperations in adulthood appear in both columns of surgical intervention; 298 subjects with both surgical interventions and percutaneous interventions in adulthood appear in both columns.

†Age is at the time of inclusion and is stated as median with range limits.

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 scheme[20]), 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 severity[21] 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

Table 2. Frequencies of First Operations and Reoperations in Adulthood in All Male and Female Patients per Defect

	Male Patients						Female Patients					
	CONCOR (n=5064)	First Surgery in Adulthood (n=745, 14.7%*)		Reoperation in Adulthood† (n=439, 8.7%‡)			CONCOR (n=5236)	First Surgery in Adulthood (n=671, 12.8%‡)		Reoperation in Adulthood† (n=373, 7.1%‡)		
Main Defects	n	n	%	n	%	Mean Reoperations	n	n	%	n	%	Mean Reoperations
VSD	767	61	8.0*	34	4.4‡	1.3	982	52	5.3*	20	2.0‡	1.4
ASD	539	147	27.3	19	3.5	1.1	1013	274	27.0	36	3.6	1.2
CoA	605	79	13.1	100	16.5‡	1.2	405	39	9.6	35	8.6‡	1.2
TOF	516	25	4.8	92	17.8	1.3	426	20	4.7	101	23.7	1.3
AoS	588	120	20.4	68	11.6	1.3	341	76	22.3	48	14.1	1.5
PS	318	11	3.5	7	2.2	1.1	466	15	3.2	20	4.3	1.2
BAV	372	101	27.2*	11	3.0	1.6	186	29	15.6*	3	1.6	1.0
AVSD	196	30	15.3	22	11.2	1.3	282	42	14.9	21	7.4	1.2
Marfan	237	88	37.1*	20	8.4	1.6	225	51	22.7*	15	6.7	1.4
TGA	294	4	1.4	15	5.1	1.5	157	1	0.6	9	5.7	1.0
PDA	38	2	5.3	2	5.3	1.0	126	9	7.1	3	2.4	1.0
Ebstein	68	8	11.8*	3	4.4	1.7	86	15	17.4*	8	9.3	1.5
PA+VSD	52	1	1.9	8	15.4	1.6	66	2	3.0	12	18.2	1.3
ccTGA	75	8	10.7	4	5.3	1.3	42	0	0.0	2	4.8	1.0
UVH/DILV	60	2	3.3	5	8.3	1.4	47	4	8.5	3	6.4	1.3
Other	339	58	17.1	29	8.6	1.4	386	42	10.9	37	9.1	1.3

CONCOR indicates Congenital Corvitia; VSD, ventricular septal defect; ASD, atrial septal defect; CoA, aortic coarctation; TOF, tetralogy of Fallot; AoS, aortic stenosis; PS, pulmonary stenosis; BAV, bicuspid aortic valve; AVSD, atrioventricular septal defect (including ASD, primum type); Marfan, Marfan syndrome; TGA, transposition of the great arteries; PDA, patent arterial duct; Ebstein, Ebstein anomaly; PA, pulmonary atresia; ccTGA, congenitally corrected TGA; UVH/DILV, univentricular heart/double-inlet left ventricle; and other, other congenital heart defects with n<100. Percentages are calculated within rows.

*After adjustment for age, defect, multiple defects, and childhood operation, the difference between first surgery in adulthood in male and female patients is significant ($P<0.05$).

†Reoperation in adulthood means a surgery after a first surgery in childhood (male patients, n=314; female patients, n=285) or after a first surgery in adulthood (male patients, n=125; female patients, n=88).

‡After adjustment for age, defect, multiple defects, and number of childhood operations, difference between reoperations in adulthood in male and female patients is significant ($P<0.05$).

duration for surgery in adulthood was calculated from the 18th birthday to the date of inclusion. Follow-up duration for survival was calculated from date of inclusion to either the time of analysis (April 4, 2009) or death. For distribution of congenital heart defects, defects experienced by at least 100 patients were included to give an overview. Frequencies of interventions were calculated in total and by defect. We assessed the association between sex and surgery in adulthood using logistic regression models, from which we present odds ratios and 95% confidence intervals (CIs) after adjustment for age at inclusion, defect, multiple defects, and childhood operations. Furthermore, we assessed the association of surgery in adulthood (first-time surgery and reoperation) with long-term survival and of sex with long-term survival using Cox regression models, from which we present hazard ratios and 95% CIs after adjustment for age at inclusion, defect, and multiple defects. For assessment of long-term survival, reoperations in adulthood were stratified according to the number of surgeries performed in the medical history. Perioperative mortality (death during or within 30 days after surgery) was assessed in a subset of patients using prospective data (n=536). We used SPSS version 17.0 (SPSS Inc, Chicago, IL) for analysis.

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 replacements. More than 15% of patients with congenitally corrected transposition of the great arteries underwent a percutaneous intervention in adulthood, primarily for pacemaker implantation.

Frequencies of first operations and of reoperations in adulthood in men and women are shown in Table 2. Overall,

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)

	Operated (n=536)	Perioperative Mortality (n=18, 3.4%)	
	n	n	%
Patient characteristics			
Male	307	8	2.6
Female	229	10	4.3
Age at death, y	…	43.4 (20.8–77.8)	
Multiple defects	390	13	3.3
Last surgery			
Age at surgery, y	34.5 (18.0–77.8)	34.6 (20.8–77.8)	
First surgery	160	3	1.9
Reoperation	376	15	4.0
Second surgery	202	7	3.4
Third surgery	116	4	3.4
Fourth surgery or more	58	4	6.8
Corrective	518	13	2.5
Palliative	18	5	27.8
Main defects*			
TOF	115	1	0.8
AoS	81	3	3.6
ASD	54	2	3.7
CoA	47	1	2.1
PS	23	1	4.3
Ebstein	15	1	6.7
UVH/DILV	12	3	25.0
BAV	12	1	8.3
TGA	6	1	16.7
Other	50	4	8.0

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.

both first surgery and reoperations in adulthood were performed significantly more often in men compared with women (after adjustment for age, defect, multiple defects, and childhood operations, odds ratio=1.4 [95% CI, 1.2–1.6] for first surgery and 1.2 [95% CI, 1.0–1.4] for reoperations). This higher rate of reoperations in men compared with women was driven primarily by the higher reoperation rate in men with ventricular septal defect (odds ratio=2.3; 95% CI, 1.3–4.1) and aortic coarctation (odds ratio=1.9; 95% CI, 1.3–3.0).

Perioperative mortality was assessed in 536 patients who had 824 surgeries during a median follow-up of 3.8 years in CONCOR (Table 3). In 160 patients (30%), the operation was their first surgery. Of 536 patients, 27 (5%) died during follow-up; 18 died perioperatively (3.4%). Perioperative mortality was higher after palliative surgery than after corrective surgery ($P<0.001$) and was highest among patients with univentricular heart (25%), transposition of the great arteries (17%), and other defects (8%).

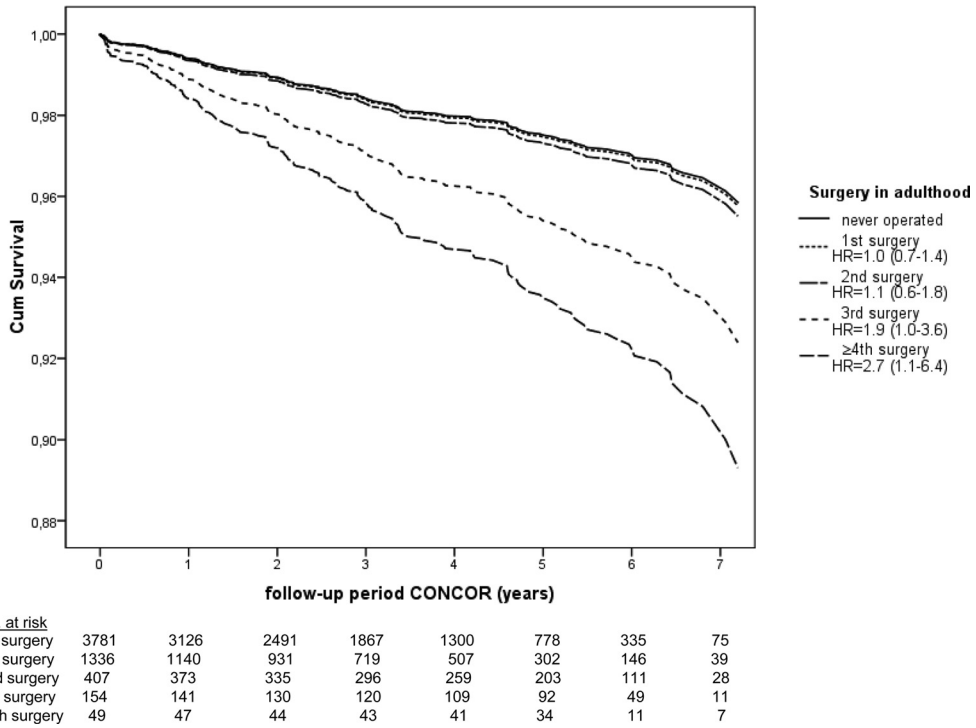
The Figure shows survival curves of adult patients who were never operated on, those who had their first surgery in adulthood, and patients who had their second, third, or fourth or more surgery in adulthood. For patients who had their first surgery in adulthood, the risk of death during a median follow-up period of 3.8 years was comparable to that of patients who were never operated on. For patients who had their third and fourth or more surgery in adulthood, the risk of death was nearly 2 and 3 times higher compared with patients never operated on (hazard ratio=1.9 [95% CI, 1.0–3.6] and 2.7 [95% CI, 1.1–6.3[, respectively). Men with a reoperation in adulthood had a 2-times-higher risk of death compared with women (hazard ratio=1.9; 95% CI 1.0–3.5; Table 4).

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.[5,6] Furthermore, one third of Marfan patients had their first surgery in adulthood, which also is in agreement with the previously reported data.[22] 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[23–25] 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.[5,26,27] The mortality rate was low for corrective surgery but high for palliative surgery, which is also in agreement with current literature.[5,27]

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,[14,15] but data in the adult congenital heart disease population are sparse.[17] 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



No. at risk								
No surgery	3781	3126	2491	1867	1300	778	335	75
1st surgery	1336	1140	931	719	507	302	146	39
2nd surgery	407	373	335	296	259	203	111	28
3rd surgery	154	141	130	120	109	92	49	11
≥4th surgery	49	47	44	43	41	34	11	7

Figure. Survival curves of adult patients who were never operated on (reference group), who had their first surgery in adulthood, and who had their second, third, fourth, or more surgery in adulthood. Hazard ratios (HR) (95% confidence interval) are for a median follow-up period of 3.8 years; they are shown after adjustment for age at inclusion, underlying defect, and multiple defects. CONCOR indicates Congenital Corvitia.

the aorta is smaller is female patients.[28–31] Furthermore, sex-related complications in adult congenital heart disease patients[18,32] 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 patients[35] 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

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

*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.

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Disclosures

None.

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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.