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A COMPARISON OF SURGICAL AND MEDICAL THERAPY FOR ATRIAL SEPTAL DEFECT IN ADULTS

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Abstract *Background. The surgical closure of an atrial septal defect is frequently recommended for patients over 40 years of age. However, the prognosis for such patients with unrepaired defects is largely unknown, and the outcome for patients operated on after the fourth decade of life has not yet been compared with that for medically treated patients in a controlled follow-up study.*

Methods. In a retrospective study, we examined the clinical course of 179 consecutive patients with isolated atrial septal defects diagnosed after the age of 40. The 84 patients (47 percent) who underwent surgical repair were compared with the 95 patients (53 percent) who were treated medically. The mean (±SD) follow-up period was 8.9±5.2 years (range, 1 to 26).

Results. Multivariate analysis revealed that surgical closure of the defect significantly reduced mortality from all causes (relative risk, 0.31; 95 percent confidence interval, 0.11 to 0.85). The adjusted 10-year survival rate of surgically treated patients was 95 percent, as compared with 84 percent for the medically treated patients. In addition, surgical treatment prevented functional deterioration, as measured by the New York Heart Association class (relative risk, 0.21; 95 percent confidence interval, 0.08 to 0.55). However, the incidence of new atrial arrhythmias or of cerebrovascular insults in the two groups was not significantly different.

Conclusions. The surgical repair of an atrial septal defect in patients over 40 years of age, as compared with medical therapy, increases long-term survival and limits the deterioration of function due to heart failure. However, surgically treated patients should be followed closely for the onset of atrial arrhythmias so as to reduce the risk of thromboembolic complications. (N Engl J Med 1995;333: 469-73.)

PATIENTS with isolated atrial septal defects may have a benign clinical course. Most of them have minimal, if any, functional limitation during childhood and adolescence.[1] Patients often survive to an advanced age.[2-4] Nevertheless, the life expectancy of patients with unrepaired atrial septal defects is generally thought to be shortened. According to a commonly cited observational report, less than 50 percent of these patients survive beyond the age of 40 years, and only 10 percent reach the age of 60.[5] However, the clinical series that formed the basis for this estimate included only small numbers of middle-aged and elderly patients, and these either were examined on only one occasion[6] or were followed for a mean period that did not exceed five years.[2] Furthermore, although the surgical closure of an atrial septal defect is performed frequently in patients over 40,[7,8] there is a lack of controlled follow-up studies comparing the long-term outcome for such patients with that of a medically treated population with unrepaired defects. The data available in the literature cannot be considered sufficient to demonstrate whether surgical closure or medical treatment is preferable for middle-aged and elderly patients with atrial septal defects.[9]

In the present study, we followed the clinical course of 179 consecutive patients with isolated atrial septal defects diagnosed after the age of 40. The outcome of the 84 patients who were operated on was compared with that of the remaining 95 patients, who were treated medically throughout the follow-up period. The aim of the study was to examine the effect of surgery on long-term survival as well as on the incidence of cardiovascular events during follow-up.

METHODS

Study Population

Between November 1966 and July 1991, 179 patients over 40 years of age were given a diagnosis of atrial septal defect at the Universitätsklinik Freiburg or the Herzzentrum Bad Krozingen. There were 125 women (70 percent) and 54 men (30 percent), with a mean (±SD) age of 56±9 years (range, 41 to 79). Of these patients, 3 (2 percent) had ostium primum defects, 13 (7 percent) had sinus venosus defects of the superior vena caval type, and the remaining 163 (91 percent) had ostium secundum defects. All the patients underwent right heart catheterization, and the ratio of pulmonary to systemic blood flow (Qp:Qs) was determined by oximetry. The study patients had predominant left-to-right interatrial shunt with a Qp:Qs of at least 1.5:1. We excluded from the study patients who had been referred for reoperation of previously repaired atrial septal defects (i.e., those repaired before the age of 40), as well as those with complex congenital cardiac malformations. Patients with angiographical-

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ly confirmed coronary artery disease or severe mitral regurgitation were also excluded.

Treatment of the Atrial Septal Defect

Surgically Treated Patients

Surgical closure of the defect was performed in 84 patients (47 percent). The mean age at the time of operation was 56±7 years. Surgical closure of the defect was combined with repair of partial anomalous pulmonary venous drainage in three patients (4 percent) and tricuspid-valve annuloplasty in four (5 percent). Sixty-seven of the 84 patients (80 percent) were referred for surgery within 12 months of confirmation of the diagnosis by cardiac catheterization. The remaining 17 patients in this group (20 percent) were initially treated medically and underwent surgery after a period ranging from 2 to 16 years (mean, 7±4 years), either at the discretion of the physicians caring for them or because of the initial reluctance of the patients to undergo surgery. A complete clinical and hemodynamic follow-up evaluation, including right and left heart catheterization as well as coronary angiography, was performed in all patients before surgery.

Medically Treated Patients

In our study group, 95 patients (53 percent) were given only medical treatment (digitalis, diuretics, or nitrates), which extended throughout the follow-up period; the decision not to operate was based on the judgment of the cardiologists and cardiac surgeons involved in each case. All patients who were not referred for surgical closure of the defect after diagnosis were advised to appear for follow-up examinations at 12-month intervals or as soon as they noticed the onset of new symptoms or the worsening of existing symptoms.

Follow-up Evaluation

The mean follow-up period was 8.9±5.2 years (range, 1 to 26). The current status of all patients was assessed by means of a standardized questionnaire addressed to the referring physician or by direct telephone contact with the patient or a first-degree relative. Complete clinical data included the patient's New York Heart Association (NYHA) functional class, cardiac rhythm (in particular, atrial fibrillation or flutter), specific cardiac symptoms, current medication, and information on the occurrence of cardiovascular events. A cardiovascular event was defined as death due to cardiovascular causes (congestive heart failure, sudden death, massive pulmonary embolism, or stroke), transient ischemic attack or nonfatal stroke, peripheral arterial embolization, a new instance of atrial fibrillation or flutter (whether sustained or paroxysmal), or the need for implantation of a permanent pacemaker. Postoperative cardiovascular events were further classified as early or late, depending on whether they occurred within 30 days of surgery or after this period. Finally, the progression to congestive heart failure was clinically defined as a change in the patient's NYHA ranking to class III or IV, which reflected either the death of the patient due to heart failure or severe functional limitation at the end of the follow-up period.

Death certificates as well as autopsy reports were obtained for all patients who died. Causes of death were classified as either cardiovascular, according to the above definition, or noncardiovascular. In addition, for patients who underwent surgical repair of the defect, perioperative mortality was defined as death within 30 days after the operation.

Statistical Analysis

In the statistical description of the patients, absolute and relative frequencies were calculated for discrete variables; means (±SD) were determined for continuous variables. Differences between the characteristics of the two patient groups — medical and surgical — were tested for significance with Fisher's exact test, for discrete variables, and with the two-sample Wilcoxon rank-sum test, for continuous variables.[10]

Overall survival time for all patients started at the date of right heart catheterization. To avoid waiting-time bias, surgically treated patients were counted as belonging to the medically treated group until the date of closure of the defect.[11] For the surgically treated patients, survival time free of cardiovascular events started at the date of operation. A Cox proportional-hazards model[12] was used to investigate the independent prognostic effect of base-line characteristics on the patients' total and event-free survival. Base-line continuous variables were prospectively dichotomized at clinically relevant cutoff points. The results are presented as estimates of relative risk, with corresponding 95 percent confidence intervals and P values calculated with Wald's test. Because of the high number of cardiovascular events occurring shortly after surgical repair, the corresponding relative risk for surgically treated, as opposed to medically treated, patients is not constant over time and must be interpreted as an average risk during the whole follow-up period. For purposes of graphic presentation, estimates of the probability of overall survival according to treatment group were calculated on the basis of the Cox model.[13] Multiple logistic regression was used to investigate the independent effect of base-line characteristics on the functional deterioration of patients, defined as a change in the patient's status to NYHA class III or IV — severe functional limitation or death due to heart failure — by the end of the follow-up period. The results are presented as odds-ratio estimates with corresponding 95 percent confidence intervals and P values calculated with Wald's test.

All tests of significance were two-tailed, with P values of less than 0.05 assumed to indicate significance.

Table 1. Clinical Characteristics of 179 Consecutive Patients Who Presented with Atrial Septal Defect.

Characteristic	Surgical Group (N = 84)	Medical Group (N = 95)	P Value
	no. (%)		
Sex (F/M)	62/22	63/32	0.33
Age >55 yr	31 (37)	52 (55)	0.02
Cyanosis	18 (21)	31 (33)	0.13
NYHA class III or IV	27 (32)	22 (23)	0.19
Cerebral or peripheral arterial embolism	3 (4)	8 (8)	0.22
Atrial fibrillation or flutter	22 (26)	18 (19)	0.28
Recurrent respiratory infections	12 (14)	10 (11)	0.50
Angina pectoris	29 (35)	38 (40)	0.54
Edema	19 (23)	23 (24)	0.86
Exertional dyspnea	64 (76)	71 (75)	0.86
Systemic arterial hypertension*	30 (36)	34 (36)	1.0
Palpitations	37 (44)	41 (43)	1.0

*Systemic arterial hypertension was defined as arterial pressure persistently above 160/90 mm Hg.

Results

Clinical and Hemodynamic Characteristics at Diagnosis

The symptoms and clinical characteristics of the medically and surgically treated patients at the time of diagnosis are presented in Table 1. The mean age of the patients who subsequently underwent closure of the defect was 54±7 years, whereas the age of those who were treated medically was 57±10 years (P=0.01). There was no significant difference between the two groups with regard to other clinical characteristics. Overall, 168 patients in the study population (94 percent) reported cardiac symptoms at presentation.

Table 2 shows the hemodynamic characteristics of the study group at the time of initial cardiac catheterization. Comparison of pulmonary-artery pressures — systolic, diastolic, and mean — revealed no appreciable difference between the medical and surgical groups. Overall, 121 patients (68 percent) had systolic pulmonary-artery pressures of less than 40 mm Hg, 46 patients (26 percent) had systolic pressures of 40 to 60 mm Hg, and 12 patients (7 percent) had severe pulmonary hypertension with systolic pressures exceeding 60 mm Hg. Surgically treated patients had lower values for pulmonary vascular resistance (Table 2). However,

Table 2. Hemodynamic Characteristics at the Time of Diagnosis.

CHARACTERISTIC	SURGICAL GROUP (N = 84)	MEDICAL GROUP (N = 95)	P VALUE
	mean ±SD (range)		
Pulmonary-artery pressure (mm Hg)			
Systolic	37±14 (17–99)	39±15 (17–88)	0.34
Diastolic	14±7 (5–40)	13±6 (1–40)	0.44
Mean	23±9 (10–65)	23±8 (8–55)	0.92
Qp:Qs ratio	2.9±1.1 (1.5–9.0)	2.3±1.0 (1.5–6.9)	<0.001
PVR (dyn · sec · cm^{-5})*	113±94 (19–527)	141±132 (31–1115)	0.009

*PVR denotes pulmonary vascular resistance.

markedly elevated pulmonary vascular resistance — defined as a value higher than 400 dyn · sec · cm^{-5} — indicating severe pulmonary vascular obstructive disease[14] was present in only four patients (2 percent of the study population), two in each group.

Multivariate Analysis of Factors Affecting Mortality

Cox proportional-hazards analysis revealed a significant decrease in overall mortality after surgical closure of an atrial septal defect. After adjustment for the covariates listed in Table 3, the relative risk of death was 0.31 for patients who underwent surgical closure, as compared with the patients treated medically (P = 0.02). The estimated probability of survival was 98 percent at 5 years after catheterization and 95 percent at 10 years for surgically treated patients, as compared with 93 and 84 percent, respectively, for those treated medically (Fig. 1). Among the clinical and hemodynamic variables, NYHA class III or IV, a systolic pulmonary pressure of 40 mm Hg or more, and a Qp:Qs ratio of more than 2.5:1 at the time of diagnosis were found to be significant independent predictors of death in the study population (Table 3).

There were no perioperative deaths among the patients who underwent surgical closure of the defect. After discharge from the hospital, the 84 patients in this group were followed for a mean of 9.1±5.0 years. Six patients died during the follow-up period. There were three deaths from cardiovascular causes; two of these were due to congestive heart failure. In the third patient, who died suddenly, 24-hour Holter monitoring had indicated the presence of complex ventricular arrhythmias. Two patients died from noncardiovascular causes, one of a metastatic colonic tumor and one of an ovarian tumor. The cause of death of one patient remained unknown.

Medically treated patients were followed for 8.8±5.3 years after diagnosis of the defect. During this period, 23 patients died. Of 21 deaths due to cardiovascular causes in this group, 15 were due to congestive heart failure; 1 was due to massive pulmonary embolism; and 2 were the result of stroke. In the remaining three patients, who died suddenly of unspecified cardiac disease, an arrhythmogenic cause of death was considered probable on the basis of a history of ventricular arrhythmia. One medically treated patient died of an unknown cause and another patient, who had recurrent respiratory infections, died of pneumonia.

Incidence of Cardiovascular Events

Cardiovascular events occurred in nine (11 percent) of the surgically treated patients during the early postoperative phase, two of whom required implantation of a pacemaker (Table 4). After discharge from the hospital, another 25 patients from this group (30 percent) had late complications. Of the nine patients who had a late transient ischemic attack or stroke, six (67 percent) had atrial fibrillation, which was of new (postoperative) onset in two cases. Only two of the six patients with atrial fibrillation were receiving anticoagulant therapy at the time of the event. In the medically treated group cardiovascular complications occurred in 37 (39 percent) of the patients during long-term follow-up (Table 4). Six medically treated patients had a transient ischemic attack or stroke during this period, but only two of these patients had a history of permanent or paroxysmal atrial fibrillation.

Multivariate analysis showed no independent favorable effect of surgery on the overall incidence of cardiovascular events during follow-up (Table 3). This finding is explained by the lower average duration of event-free survival in the surgically treated group, which was due to the increased incidence of nonfatal cardiovascular complications in the early postoperative period.

Table 3. Relative Risk of Adverse Outcomes According to Treatment and Clinical and Hemodynamic Characteristics at Diagnosis.

VARIABLE*	OVERALL MORTALITY	CARDIOVASCULAR EVENTS	FUNCTIONAL DETERIORATION†
Surgical treatment			
RR (95% CI)	0.31 (0.11–0.85)	1.64 (0.95–2.84)	0.21 (0.08–0.55)
P value	0.02	0.08	0.002
Age >55 yr			
RR (95% CI)	1.87 (0.69–5.06)	1.99 (1.08–3.65)	0.70 (0.27–1.84)
P value	0.22	0.03	0.47
NYHA class III or IV			
RR (95% CI)	2.52 (1.05–6.05)	1.44 (0.82–2.53)	1.48 (0.52–4.21)
P value	0.04	0.20	0.47
Systemic arterial hypertension‡			
RR (95% CI)	0.90 (0.39–2.04)	0.95 (0.56–1.62)	1.36 (0.57–3.24)
P value	0.79	0.86	0.50
Atrial fibrillation or flutter			
RR (95% CI)	0.67 (0.23–1.99)	0.80 (0.41–1.57)	0.64 (0.20–1.99)
P value	0.48	0.51	0.44
Pulmonary-artery systolic pressure >40 mm Hg			
RR (95% CI)	2.77 (1.1–6.99)	1.55 (0.87–2.75)	2.64 (1.01–6.87)
P value	0.03	0.14	0.05
Qp:Qs ratio >2.5:1			
RR (95% CI)	3.56 (1.38–9.18)	1.16 (0.66–2.04)	1.85 (0.75–4.56)
P value	0.009	0.60	0.19
Pulmonary vascular resistance >130 dyn · sec · cm^{-5}			
RR (95% CI)	1.83 (0.77–4.36)	0.87 (0.50–1.52)	1.95 (0.76–5.01)
P value	0.17	0.63	0.17

*RR denotes relative risk, and CI confidence interval.

†Functional deterioration was defined as a change in the patient's status to NYHA class III or IV — reflecting severe functional limitation or death due to heart failure — by the end of the follow-up period.

‡Systemic arterial hypertension was defined as arterial pressure persistently above 160/90 mm Hg.

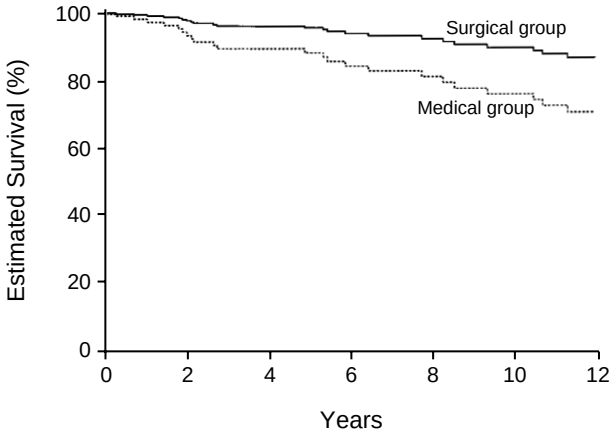

Figure 1. Estimated Probability of Survival for 179 Patients with Isolated Atrial Septal Defects.

The mean follow-up time was 8.9±5.2 years. Survival data have been adjusted for all important prognostic variables. The adjusted relative risk of death was 0.31 for surgically treated patients as compared with medically treated patients (95 percent confidence interval, 0.11 to 0.85; P=0.02).

The functional status of the surgically and medically treated patients at presentation and at the end of the follow-up period is presented in Figure 2. Overall, function, as measured by the NYHA scale, improved in 27 of the surgically treated patients (32 percent) and deteriorated in only 9 patients (11 percent). The favorable effect of surgical treatment was most prominent in the subgroup of patients with severe preoperative heart failure (NYHA class III or IV), since 69 percent of those patients had a long-term improvement in NYHA functional class after defect closure.

In the medically treated group, a deterioration in NYHA class was observed in 32 of the 95 patients (34 percent); only 3 patients (3 percent) had a long-term lessening of the severity of heart failure with medical treatment. Logistic-regression analysis confirmed that the surgical repair of atrial septal defects resulted in a considerable reduction in the risk of functional deterioration (P=0.002) (Table 3).

DISCUSSION

The surgical repair of atrial septal defects has been performed for approximately 40 years.[15] During this time, several investigators have reported on the clinical course of patients who were operated on after the age of 40.[7,8,16-19] However, none of these studies compared the outcome of surgical treatment with that of medical treatment in an age-matched control group with unrepaired defects. In addition, Murphy et al. recently pointed out that patients who undergo surgery after the age of 40 are at increased risk for postoperative cardiovascular complications, whereas surgically treated children and young adults have an excellent prognosis.[20] In accord with these findings, we found no favorable effect of operation on the survival of elderly patients with atrial septal defects and concomitant cardiac diseases, such as coronary atherosclerosis or mitral regurgitation.[21] In the light of such findings, the traditional recommendation of routine surgical treatment for middle-aged and elderly patients with atrial septal defects and substantial left-to-right shunts[7,22] has recently been called into question.[9]

*Table 4. Cardiovascular Events during Follow-up.**

EVENT	SURGICAL GROUP (N=84)		MEDICAL GROUP (N=95)
	EARLY	LATE	
Death	0	3	21
TIA or stroke	3	9	6
New-onset atrial fibrillation or flutter	6	13	16
Implantation of pacemaker	2	9	2
Total no. of events	11	34	45
Total no. (%) of patients with ≥1 event	9 (11)	25 (30)	37 (39)

*Events occurring within 30 days after surgery were considered early.
TIA denotes transient ischemic attack.

In our present study the clinical course of 179 consecutive patients with isolated atrial septal defects diagnosed after the age of 40 was followed over a mean period of 8.9±5.2 years. Nearly half the patients (47 percent) underwent surgical repair of the defect, whereas the remaining patients received only medical treatment, which extended throughout the follow-up period. Multivariate analysis showed a significant reduction in overall mortality after surgical closure of the defect. For the surgical group as compared with the medically treated group, the relative risk of death during the follow-up period was 0.31. Our results suggest that the surgical repair of atrial septal defects substantially increases the long-term survival of middle-aged and elderly patients. There were no perioperative deaths in our study group, and the estimated 10-year survival rate after surgery was 95 percent, as compared with a rate of 84 percent for medically treated patients.

These results are similar to the excellent survival rates reported by Horvath et al.[8] in a group of patients who were younger than our study population and also had less severe symptoms at the time of operation. On the other hand, our findings do not agree with a recent study that found that the closure of an atrial septal defect in adult life does not significantly alter the patient's prognosis.[23] However, as noted by its authors, that study included only patients who had minimal, if any, cardiac symptoms at presentation, as well as normal pulmonary-artery pressures. It is therefore not possible to extrapolate those results to an unselected adult population with unrepaired defects.

In contrast to the clear long-term survival benefit of surgical treatment, the incidence of nonfatal cardiovascular complications during the follow-up period was not reduced by surgical closure of the defect. This was mostly a result of the occurrence of early postoperative complications in nine (11 percent) of the patients who underwent surgery. During long-term follow-up, atrial fibrillation or flutter developed in 15 percent of the surgically treated patients, an incidence similar to that observed in the medically treated group (17 percent). Furthermore, paroxysmal or permanent atrial fibrillation was present in the majority of the patients — six of nine — who had a transient ischemic attack or stroke during the late postoperative phase. Thus, our observa-

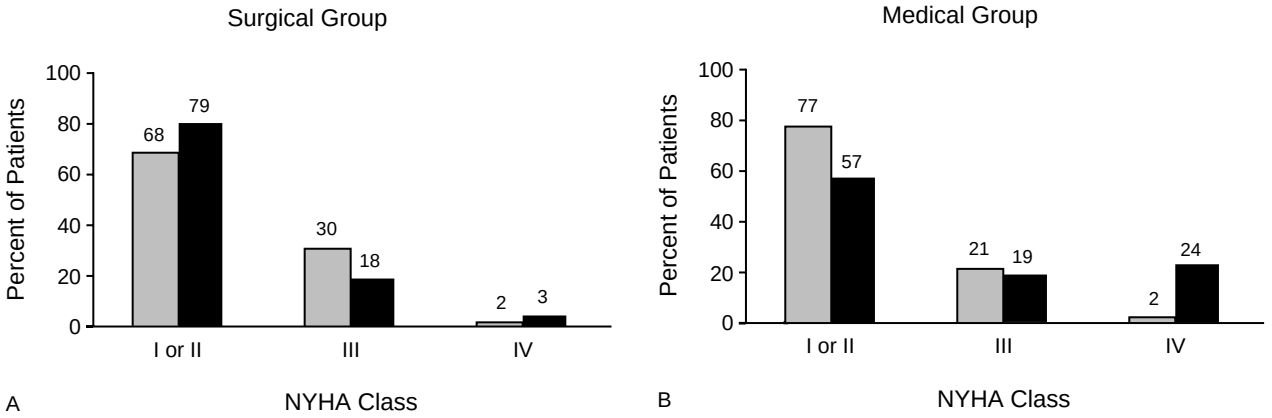

Figure 2. New York Heart Association (NYHA) Functional Class of Patients at the Time of Diagnosis (Gray Bars) and at the End of the Follow-up Period (Black Bars).

Panel A shows patients in the surgical group and Panel B those in the medical group. The numbers above the bars are percentages of patients.

tions are consistent with the conclusions reached by other researchers that the repair of atrial septal defects late in life does not significantly reduce the development of atrial fibrillation or the morbidity associated with thromboembolic complications.[20,23]

The functional status (NYHA class) of the patients followed in our study improved dramatically after surgical, as compared with medical, treatment of the defect. Of the surgically treated patients, 32 percent reported a long-term reduction in the severity of symptoms related to heart failure, as opposed to only 3 percent of those treated medically. Of even greater clinical importance is the fact that there was functional improvement in 69 percent of the patients who had had severe heart failure (NYHA class III or IV) before surgery.

A limitation of this study is the retrospective, nonrandomized assignment of patients to the two treatment groups. With such an observational design, selection bias cannot be excluded. In the present study, we observed three variables that were unequally distributed between the surgically and medically treated groups: age, pulmonary vascular resistance, and the Qp:Qs ratio. Surgically treated patients were younger and had lower values for pulmonary vascular resistance than those treated medically; on the other hand, the group that underwent surgery had greater left-to-right shunts. When these differences are taken together, they do not indicate a more favorable prognosis for one group over the other. Nevertheless, in order to adjust for the biasing effects of any measured confounding factors, all our analyses were based on multivariate regression models that took into account all important prognostic factors. In addition, patients with either concomitant coronary artery disease or severe mitral regurgitation that required surgical treatment were excluded from the study.

The results of the present study indicate that the surgical repair of atrial septal defects in middle-aged and elderly patients is superior to medical treatment as regards both long-term survival and the lessening of functional limitation due to heart failure. However, the risk of atrial arrhythmia is not reduced by closure of the defect, and surgically treated patients should be followed closely for the onset of atrial fibrillation or flutter in order to prevent or reduce morbidity resulting from cerebral thromboembolism.

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References

1. Campbell M, Neill C, Suzman S. The prognosis of atrial septal defect. BMJ 1957;1:1375-83.
2. Markman P, Howitt G, Wade EG. Atrial septal defect in the middle-aged and elderly. Q J Med 1965;34:409-26.
3. Rodstein M, Zeman FD, Gerber IE. Atrial septal defect in the aged. Circulation 1961;23:665-74.
4. Perloff JK. Ostium secundum atrial septal defect — survival for 87 and 94 years. Am J Cardiol 1984;53:388-9.
5. Campbell M. Natural history of atrial septal defect. Br Heart J 1970;32:820-6.
6. Craig RJ, Selzer A. Natural history and prognosis of atrial septal defect. Circulation 1968;37:805-15.
7. Magilligan DJ Jr, Lam CR, Lewis JW Jr, Davila JC. Late results of atrial septal defect repair in adults. Arch Surg 1978;113:1245-7.
8. Horvath KA, Burke RP, Collins JJ Jr, Cohn LH. Surgical treatment of atrial septal defect: early and long-term results. J Am Coll Cardiol 1992;20:1156-9.
9. Ward C. Secundum atrial septal defect: routine surgical treatment is not of proven benefit. Br Heart J 1994;71:219-23.
10. Bailar JC III, Mosteller F, eds. Medical uses of statistics. 2nd ed. Waltham, Mass.: NEJM Books, 1992:261-9, 281-91.
11. Crowley J, Hu M. Covariance analysis of heart transplant survival data. J Am Stat Assoc 1977;72:27-36.
12. Cox DR. Regression models and life-tables. J R Stat Soc [B] 1972;34:187-220.
13. Makuch RW. Adjusted survival curve estimation using covariates. J Chronic Dis 1982;35:437-43.
14. Saksena FB, Aldridge HE. Atrial septal defect in the older patient: a clinical and hemodynamic study in patients operated on after age 35. Circulation 1970;42:1009-20.
15. Rahimtoola SH, Kirklin JW, Burchell HB. Atrial septal defect. Circulation 1968;38:Suppl V:V-2–V-12.
16. Fiore AC, Naunheim KS, Kessler KA, et al. Surgical closure of atrial septal defect in patients older than 50 years of age. Arch Surg 1988;123:965-7.
17. Nasrallah AT, Hall RJ, Garcia E, Leachman RD, Cooley DA. Surgical repair of atrial septal defect in patients over 60 years of age: long-term results. Circulation 1976;53:329-31.
18. St John Sutton MG, Tajik AJ, McGoon DC. Atrial septal defect in patients ages 60 years or older: operative results and long-term postoperative follow-up. Circulation 1981;64:402-9.
19. Foster-Smith KW, Murphy JG, Bailey KR, et al. Secundum atrial septal defect (ASD): clinical profile and surgical experience in septuagenarians and older. J Am Coll Cardiol 1994;Special Issue:465A. abstract.
20. Murphy JG, Gersh BJ, McGoon MD, et al. Long-term outcome after surgical repair of isolated atrial septal defect: follow-up at 27 to 32 years. N Engl J Med 1990;323:1645-50.
21. Konstantinides S, Geibel A, Kasper W, Bubenheimer P, Görnandt L, Just H. Atrial septal defect in patients over 40 years of age: effect of surgical repair on the long-term clinical course. Circulation 1994;90:Suppl:I-172. abstract.
22. Robb GH. Management of atrial septal defect in middle age. Am Heart J 1973;85:837-8.
23. Shah D, Azhar M, Oakley CM, Cleland JGF, Nihoyannopoulos P. Natural history of secundum atrial septal defect in adults after medical or surgical treatment: historical prospective study. Br Heart J 1994;71:224-8.