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Comparison of Neurocognitive Functions after Beating-Heart Mitral Valve Replacement without Aorta Cross-Clamping and after Standard Mitral Valve Replacement with Cardioplegic Arrest

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ABSTRACT

Background: The aim of this study was to compare the postoperative long-term neurocognitive functions of patients who underwent beating-heart mitral valve replacement on cardiopulmonary bypass (CPB) without aorta cross-clamping with those of patients who underwent mitral valve replacement via the classic method.

Methods: The study group included 25 randomly selected patients who underwent beating-heart mitral valve surgery. During the same period, 25 patients were randomly selected as controls to undergo mitral valve replacement procedures via the standard ascending aorta–cannulation technique. The clinical and postoperative (2 months) neurocognitive functional data of both groups were compared.

Results: Neurologic deficit was observed in neither group during the postoperative period. There were no statistically significant differences between the control and the study groups with respect to Hospital Anxiety and Depression Scale (HADS) results (HADS: anxiety, $P = .653$; HADS: depression, $P = .225$), in the right hemispheric cognitive function test results (Raven's Standard Progressive Matrices [RSPM] and Line Orientation Test [LOT] tests: RSPM, $P = .189$), and in the left hemispheric cognitive function test results (the Ray Auditory Verbal Learning [RAVL] and Stroop Color-Word Test [SCWT] tests: SCWT 1 time, $P = .300$; SCWT 2 time, $P = .679$; SCWT 3 time, $P = .336$; SCWT 4 time, $P = .852$; SCWT 5 time, $P = .416$; RAVL total verbal learning, $P = .167$; RAVL immediate recall, $P = .791$; RAVL distraction trial, $P = .199$; RAVL retention, $P = .174$; RAVL delayed recall, $P = .111$; RAVL recognition, $P = .282$; SCWT 4 mistake, $P = .306$; SCWT 4 reform, $P = .066$; SCWT 5 mistake, $P = .236$; SCWT 5 reform, $P = .301$).

Conclusions: The technique of mitral valve replacement with normothermic CPB without cross-clamping of the aorta may be safely used for the majority of patients requiring mitral valve replacement without causing deterioration in neurocognitive functions.

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INTRODUCTION

The development of extracorporeal circulation in the late 1960s and the use of cardiopulmonary bypass (CPB) combined with cardioplegia became popular for reparative cardiac surgery in a bloodless and motionless field. Research initiated by curious and concerned surgeons has identified many damaging effects of CPB and cardioplegic arrest [Newman 2001]. Despite the technical improvements in CPB circuits that have produced less systemic activation and consequently a less systemic inflammatory response, cognitive dysfunction appears in 30% to 70% of patients who undergo open heart surgery with CPB [Newman 2001; Zimpfer 2002]. It is generally suspected that postoperative cognitive decline is caused by impaired cerebral perfusion during CPB and by the postoperative systemic inflammatory response, as well as by microembolism and macroembolism [Taylor 1998]. Cognitive dysfunction affects the quality of life and has profound implications, because neurocognitive impairment prolongs hospital stays and increases the use of resources [Roach 1996]. Although the type of cardiac surgery has been known to affect the prevalence of postoperative cognitive dysfunction, our knowledge with regard to postoperative cognitive dysfunction in beating-heart valvular surgery is limited [Ebert 2001; Hong 2008].

Our group adopted a technique of mitral valve replacement during normothermic CPB without cross-clamping the proximal aorta. Our previous reports demonstrated the efficacy, versatility, and simplicity of our beating-heart technique for mitral valve replacement on CPB without cross-clamping the aorta [Cicekcioglu 2008a, 2008b; Karadeniz 2008; Katircioglu 2008]. The aim of the present study was to compare the long-term postoperative neurocognitive functions of patients who underwent beating-heart mitral valve replacement on CPB without cross-clamping of the aorta with those of patients who underwent mitral valve replacement via the classic method.

MATERIALS AND METHODS

Study Design

We obtained the approval of the Institutional Ethics Committee and consent from each patient. The study group included 25 randomly selected patients who underwent beating-heart

Table 1. Patient Characteristics*

Characteristic	Control Group (n = 25)	Study Group (n = 25)	P
Age, y	43.84 ± 12.07	40.84 ± 10.84	.360
Sex, n			
Male	11 (44%)	13 (52%)	.571
Female	14 (56%)	12 (48%)	
Education, n			
Primary school	20 (80%)	16 (64%)	
High school	4 (16%)	9 (36%)	
College	1 (4%)	0	
Ejection fraction, %	58.3 ± 6.2	55.5 ± 9.4	
Pulmonary artery pressure, mm Hg	45.6 ± 8.6	52.1 ± 19.9	
NYHA functional classification, n			
Class I	—	—	
Class II	13	10	
Class III	9	14	
Class IV	3	1	

*Data are presented as the mean ± SD where indicated. NYHA indicates New York Heart Association.

mitral valve replacement by the same surgeon in the Department of Cardiovascular Surgery of our institution. We also created a control group, which consisted of another group of 25 patients who were randomly selected from those who underwent mitral valve replacement procedures via the standard ascending aorta cannulation technique during the same period. The clinical and postoperative (2 months) neurocognitive functional data of both groups were compared. Criteria for exclusion from the study were a background of low education and central nervous system injury occurring preoperatively.

Demographics

The demographics of the patients are presented in Table 1. In the study group, 48% of the patients were female (n = 12), and the mean age (±SD) was 40.84 ± 10.84 years (range, 21-58 years). In the control group, 56% of the patients were female (n = 14), and the mean age was 43.84 ± 12.07 years (range, 21-71 years). Both groups of patients completed the postoperative neurocognitive evaluation and were included in the study. All patients had rheumatic mitral valve disease.

Surgical Technique

The indications for surgery were valve dysfunction due to a rheumatic process or degeneration. None of the valves were amenable to repair. All procedures were performed via a median sternotomy. Under normothermic conditions (rectal temperature, 35°C-37°C), the CPB flow rate was maintained at the highest level according to the patient's body surface area (2.5 L/min per m^2), with a mean systemic pressure >60 mm Hg. The oxygen flow rate was maintained at 2.5 L/min and 90% concentration (fraction of inspired oxygen) with a Jostra HL 20 pump (Maquet Critical Care, Solna, Sweden) and a D 708 Simplex III oxygenator (Dideco, Mirandola, Italy). Continuous intraoperative electrocardiography monitoring was used to detect any myocardial ischemia. Under normothermic CPB (35°C-37°C), the heart was perfused through the aortic root and allowed to beat physiologically. During the procedure, the heart did not fibrillate, and neither aortic cross-clamping nor cardioplegia was used. Arterial inflow was accomplished via cannulation of the ascending aorta. Venous drainage was obtained by superior and inferior caval cannulas inserted through the right atrium. After CPB with a maximum flow rate and a mean aortic pressure >60 mm Hg was achieved, a left atriotomy incision was performed, and a pump sucker was used to drain the returning blood from the left atrium. Excessive aortic incompetence was an obvious contraindication to this procedure. In addition, we kept patients in the Trendelenburg (head down) position during the operation and continuously vented blood in the aortic root to avoid air embolism. Deairing procedures were maintained until termination of CPB. We used transcranial Doppler and transesophageal echocardiography evaluations to detect air bubbles before we weaned the patient from CPB.

Another group of 25 control patients were randomly selected from those undergoing mitral valve replacement procedures via the standard ascending aorta and bicaval cannulation technique. Aortic cross-clamping and cardioplegia were used. Deairing was done via pulmonary venting and the aortic root.

Neurocognitive Assessment

Cognitive function was assessed with 4 standardized cognitive tests, which are summarized in Table 2. We selected these tests because of their frequent and acceptable application in previous studies, consensus among authors for their use, adequacy of psychometric assessment, published norms, ease of use, and brevity [Raven 1989; Blumenthal 1995]. Postoperative anxiety and depression were evaluated with the Hospital Anxiety and Depression Scale (HADS), which measures the effect of anxiety and depression on subsequent neurocognitive

Table 2. Neurocognitive Tests and Their Cognitive Functions and Specialty

Neurocognitive Test	Cognitive Function	Specialty
Raven's Standard Progressive Matrices (RSPM)	Perceptual relation, generalized ability	Right hemisphere, right parietal lobe
Ray Auditory Verbal Learning (RAVL)	Verbal memory, learning	Left temporal lobe, hippocampus
Stroop Color-Word Test (SCWT)	Attention, mental speed, and control	Dominant frontal lobe
Line Orientation Test (LOT)	Visuospatial capacity	Right hemisphere, right parietal lobe

Table 3. Hospital Anxiety and Depression Scale (HADS) Results*

	Control Group (n = 25)	Study Group (n = 25)	*P*
HADS: anxiety	5.84 ± 4.77	5.28 ± 3.94	.653
HADS: depression	4.36 ± 4.73	5.72 ± 2.91	.225

*Data are presented as the mean ± SD.

Table 4. Right Hemispheric Cognitive Function Tests Result (RSPM and LOT Tests)*

	Control Group (n = 25)	Study Group (n = 25)	*P*
RSPM score	36.12 ± 6.57	38.84 ± 7.80	.189
RSPM time, min	53.80 ± 5.26	49.12 ± 4.94	.002
LOT score	24.20 ± 1.89	25.92 ± 2.02	.003

*Data are presented as the mean ± SD. *P* values <.05 are statistically significant. RSPM indicates Raven's Standard Progressive Matrices; LOT, Line Orientation Test.

Table 5. Left Hemispheric Cognitive Function Test Results (RAVL and SCWT Tests)*

	Control Group (n = 25)	Study Group (n = 25)	*P*
SCWT 1 time, s	10.48 ± 2.30	11.24 ± 2.76	.300
SCWT 2 time, s	11.45 ± 2.36	11.79 ± 3.25	.679
SCWT 3 time, s	13.71 ± 2.54	14.54 ± 3.46	.336
SCWT 4 time, s	19.96 ± 4.50	19.72 ± 4.53	.852
SCWT 5 time, s	28.76 ± 5.81	27.30 ± 6.71	.416
RAVL total verbal learning	42.52 ± 6.14	45.60 ± 9.09	.167
RAVL immediate recall	5.48 ± 1.42	5.60 ± 1.76	.791
RAVL distraction trial	5.72 ± 1.28	6.24 ± 1.54	.199
RAVL retention	8.80 ± 2.26	9.72 ± 2.46	.174
RAVL delayed recall	8.88 ± 2.51	9.96 ± 2.19	.111
RAVL recognition	18.84 ± 4.92	20.32 ± 4.69	.282

*Data are presented as the mean ± SD. SCWT indicates Stroop Color-Word Test; RAVL, Ray Auditory Verbal Learning.

testing [Snaith 1986]. Sociodemographic characteristics, including age, sex, and education level, were also recorded. Each patient was evaluated by the same psychologist at the second month after the operation and afterwards.

Statistical Analysis

Before starting the analysis, we evaluated whether the data were consistent with certain hypotheses. We used the Kolmogorov-Smirnov test to analyze the approximation of the data to a normal distribution and tested for homogeneity of variances with the Levene test. The applicable test chosen for subsequent analysis depended on the results of these tests. To compare mean values for patient age, the Line Orientation Test (LOT), Raven's Standard Progressive Matrices (RSPM) test, RSPM time, the Stroop Color-Word Test (SCWT), the Ray Auditory Verbal Learning (RAVL) test, and HADS (anxiety and depression) for the patient and the control groups, we used the independent-samples Student *t* test. Continuous variables were expressed as the mean ± SD. To compare the 2 groups with respect to sex, educational status, SCWT 4 mistake, SCWT 4 reform, SCWT 5 mistake, and SCWT 5 reform, we used the Pearson chi-square test. The statistical software package SPSS 16.0 (SPSS, Chicago, IL, USA) was used for the statistical analyses in this study. A *P* value <.05 was considered statistically significant.

RESULTS

There were no statistically significant differences between the control and study groups with respect to educational status (*P* = .208) and demographic data. There was no operative mortality in this series, nor were there any major central nervous system complications. The patients in both groups underwent uneventful operations and intensive care unit stays. The mean CPB time in the study group was 56.1 ± 11.4 minutes, and the mean hypothermia temperature was 36.2°C ± 1.1°C (range, 35°C-37°C). Patients in the study group were discharged from the hospital on the sixth postoperative day. In the control group, the mean CPB time was 123 ± 21 minutes (range, 58-165 minutes), the mean aortic cross-clamp time was 70 ± 31 minutes (range, 21-112 minutes), and the mean hypothermia temperature was 28°C ± 1°C (range, 27°C-30°C). Patients of the control group were discharged from the hospital at a mean of 6.2 ± 1.53 days after the operation (range, 4-11 days).

HADS Results

There were no statistically significant differences between the control and study groups with respect to HADS (anxiety) scores (*P* = .653) and HADS (depression) scores (*P* = .225) (Table 3).

Right Hemispheric Cognitive Function Test Results (RSPM and LOT Tests)

There were no statistically significant differences between the control and study groups with respect to RSPM scores (*P* = .189). The mean RSPM time for the study group was significantly shorter than that of the control group (*P* = .002). The mean LOT score of the study group was higher than that of the control group (*P* = .003; Table 4).

Left Hemispheric Cognitive Function Test Results (RAVL and SCWT Tests)

There were no statistically significant differences between the control and study groups with respect to scores for SCWT 1 time (*P* = .300), SCWT 2 time (*P* = .679), SCWT 3 time (*P* = .336), SCWT 4 time (*P* = .852), SCWT 5 time (*P* = .416), RAVL total verbal learning (P = .167), RAVL immediate recall (*P* = .791), RAVL distraction trial (*P* = .199), RAVL retention (*P* = .174), RAVL delayed recall (*P* = .111), and RAVL recognition (*P* = .282) (Table 5).

Table 6. SCWT 4 Mistakes versus Groups*

	0 Mistakes	1-2 Mistakes	Total
Control group, n	18	7	25
Study group, n	21	4	25
Total, n	39	11	50

*SCWT indicates Stroop Color-Word Test.

Table 7. SCWT 4 Reform versus Groups*

	0 Reform	1 Reform	Total
Control group, n	18	7	25
Study group, n	23	2	25
Total, n	41	9	50

*SCWT indicates Stroop Color-Word Test.

There were no statistically significant differences between the control and study groups with respect to scores for SCWT 4 mistake (P = .306), SCWT 4 reform (P = .066), SCWT 5 mistake (P = .236), and SCWT 5 reform (P = .301) (Tables 6 and 7).

COMMENTS

The exact etiology of CPB-associated neurologic injury is unknown, but a number of contributing factors are likely to play a role. Postoperative neurologic deficits can be divided into 2 categories [Eagle 1999]. Type 1 deficits include major focal neurologic events, stupor, and coma. Type 2 deficits include cognitive deficits that are more global, such as deterioration in intellectual function, memory, and confusion, without evidence of focal injury. Type 1 deficits are usually caused by identifiable sources of cerebral hypoxia due to intraoperative hypoperfusion or embolic phenomena. In contrast, the etiology of type 2 deficits is unclear and likely multifactorial, with such factors as hypoxia, time on CPB, advanced age, low education level, diabetes, severity of atherosclerotic disease, type of surgery, preoperative creatinine levels, and the perioperative inflammatory response having been implicated in its pathophysiology [Murkin 1999; Ramlawi 2006]. Neurocognitive deficit after open heart surgery with CPB has been discussed intensively as having tremendous social and economic impacts. It is known to affect the quality of life and to prolong stays in the hospital, as well as to increase the use of resources [Grimm 2003]. Cardiac valve replacement surgery with the heart beating on normothermic CPB (without the deleterious effects of ischemia-reperfusion injury of the heart due to cardioplegic arrest) may have some benefits over conventional hypothermic arrested-heart surgery [Gersak 2002; Kaplon 2002; Karadeniz 2008]. Recently, the use of beating-heart surgery has gained popularity for treating heart valvular diseases [Thompson 2003; Cicekcioglu 2008a, 2008b; Karadeniz 2008; Katircioglu 2008]. Postoperative blood loss, inotropic drug requirements, and ventilation times are significantly reduced, possibly leading to better recoveries and fewer complications in the postoperative period [Ghosh 2004; Ramphal 2004]. Although beating-heart valve replacement is supposed to be a good method for myocardial protection, little is known about the neurologic outcomes obtained with this technique. Because the aorta is not cross-clamped and hypothermia is not used, cerebral embolization and poor cerebral protection may be expected to be greater than with the conventional technique. Emboli are implicated as an important source of brain injury during CPB. During cardiac surgery, showers of emboli are frequently associated with cross-clamp removal and rewarming. A common embolization process is the generation of a much smaller number of particulate microemboli, either caused by surgical manipulation of an atheromatous aorta or generated by the unique characteristics of components of the pump circuit [Edmonds 1996; Motallebzadeh 2005]. We adopted a technique for mitral valve replacement during normothermic CPB that does not involve cross-clamping of the proximal aorta. In addition, mitral valve replacement without cross-clamping of the aorta may reduce the micro- and macroembolic load occurring during aorta manipulation. The only situation in which a potential hazard may occur with this technique is excessive aortic incompetence, but that is an obvious contraindication to this procedure.

Additionally, we kept patients in the Trendelenburg position during the operation to avoid air embolism. We used transcranial Doppler and transesophageal echocardiography evaluations to detect air bubbles before we weaned the patient from CPB.

Investigators have suggested that on-pump beating-heart valve surgery without cross-clamping of the aorta causes more air emboli [Abu-Omar 2004]. In our previous study, however, we detected no significant evidence of cerebral injury, and a preoperative and postoperative comparison of beating-heart mitral valve replacement without cross-clamping of the aorta revealed no deleterious effects on the neurocognitive functions of the right and left hemispheres [Cicekcioglu 2008a, 2008b; Karadeniz 2008; Karticioglu 2008]. We reported on our preoperative and postoperative comparison of the effects of beating-heart mitral valve replacement on neurocognitive functions [Cicekcioglu 2008a]. This study was designed to postoperatively compare beating-heart mitral valve replacement without cross-clamping of the aorta and standard mitral valve replacement with cardioplegic arrest (cross-clamping of the aorta) with respect to the neurocognitive functions of the right and left hemispheres. We detected no postoperative deterioration in any of the neurocognitive tests. Both right and left hemispheric tests demonstrated that no deterioration had occurred after the procedure. Moreover, we observed significant improvements in HADS anxiety and depression levels over those of our previous pilot study [Cicekcioglu 2008a]. In this study, the RSPM time of the study group was shorter than that of the control group (P = .002). The LOT score of the study group was greater than that of the control group (P = .003). It was thought that this finding was because the number of patients with a higher educational level was greater in the study group than in the control group.

The mean CPB time was 56.1 ± 11.4 minutes in the study group, versus 123 ± 21 minutes in the control group. The higher mean CPB time in the control group was due to the cooling and warming periods. The patients in the study group required no cooling or warming periods, which was a great advantage of our study group

In conclusion, our findings suggest that there were no differences in neurocognitive test results between the patients who underwent beating-heart mitral valve replacement without cross-clamping of the aorta and the patients who underwent standard mitral valve replacement with cardioplegic arrest. This technique offers a simple, effective, and safe alternative to cardioplegic techniques. Hypothetically, an increased risk of air embolism was not observed because of a physiologically closed aortic valve, which is like an aortic cross-clamp in that it offers a secure guarantee against air embolism. Furthermore, this technique is likely to be advantageous, especially in elderly patients with a calcified aorta.

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