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ORIGINAL ARTICLE

Assessment of long-term cognitive dysfunction in older patients who undergo heart surgery

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Abstract
Introduction: Older patients are more likely to have cognitive dysfunction, and a great proportion of patients undergone surgical procedures are older adults. Postoperative cognitive dysfunction (POCD) has been shown as a consistent complication after major surgical procedures such as heart surgery.
Aim: To determine the presence of long-term POCD in ≥65-year-old patients undergoing coronary artery bypass grafting and aortic valve replacement, and to establish related risk factors.
Methods: We prospectively and sequentially included 44 patients with coronary disease and aortic stenosis scheduled for heart surgery. Follow-up of all patients was standardized and a neurocognitive evaluation were performed preoperatively and at 1, 6 and 12 months after surgery.
Results: Patients experienced a significantly postoperative cognitive dysfunction (33.5%, 63.4% and 38.9% at 1, 6 and 12 months, respectively) from baseline (20.5%). Patient-associated aspects such as age ($p < 0.01$), history of smoking ($p < 0.01$), arterial hypertension ($p = 0.022$), diabetes mellitus ($p = 0.024$), heart failure ($p = 0.036$) and preoperative cognitive dysfunction ($p < 0.01$), and surgery-associated aspects such as EuroSCORE ($p < 0.01$) and operation time ($p < 0.01$) were identified as related risk factors.

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Conclusions: Older patients who underwent heart surgery had long-term POCD. Both patient- and surgery-related risk factors were established as related risk factors. These findings suggest that the prevalence of cognitive dysfunction after cardiac surgery in older patients could be related to a possible progression to dementia. In addition, many of the risk factors identified may be modifiable but in practice, these patients are not attended to for their possible cognitive impairment.

PALABRAS CLAVE
Deterioro cognitivo posquirúrgico;
Paciente de edad avanzada;
Cirugía cardiaca;
Factor de riesgo;
Evaluación neuropsicológica;
Enfermedad coronaria

Deterioro cognitivo a largo plazo tras cirugía cardiaca en pacientes de edad avanzada

Resumen
Introducción: Los pacientes de edad avanzada tienen más riesgo de sufrir deterioro cognitivo, y son cada vez más frecuentemente sometidos a una cirugía. El deterioro cognitivo posquirúrgico (DCP) tras cirugía cardiaca se ha mostrado como una complicación importante.
Objetivos: Determinar la presencia del DCP a largo plazo en pacientes $\geq$ 65 años intervenidos de derivación coronaria y reemplazo de válvula aórtica, y establecer los factores de riesgo relacionados.
Métodos: Se realizó un estudio en el que se incluyeron de forma prospectiva y secuencial 44 pacientes con enfermedad coronaria y estenosis aórtica programados para cirugía. El seguimiento fue estandarizado y se realizaron evaluaciones neuropsicológicas preoperatoriamente a los 1, 6 y 12 meses postoperatorios.
Resultados: Se observó la presencia de un DCP significativo (33,5, 63,4 y 38,9% a 1, 6 y 12 meses, respectivamente) respecto al nivel basal (20,5%). Se identificaron como factores de riesgo variables asociadas al paciente como la edad ($p < 0{,}01$), el tabaquismo ($p < 0{,}01$), la hipertensión arterial ($p = 0{,}022$), la diabetes mellitus ($p = 0{,}024$), la insuficiencia cardiaca ($p = 0{,}036$) y el deterioro cognitivo preoperatorio ($p < 0{,}01$), y variables quirúrgicas como el EuroSCORE ($p < 0{,}01$) y el tiempo de intervención ($p < 0{,}01$).
Conclusiones: Los pacientes de edad avanzada sometidos a cirugía cardiaca presentaron DCP a largo plazo. Variables asociadas al paciente y quirúrgicas se mostraron como factores de riesgo, muchas de ellas modificables. Estos hallazgos sugieren que la presencia de DCP en pacientes de más edad podría suponer mayor riesgo de evolución a demencia. En la práctica clínica habitual no es evaluado el rendimiento cognitivo.

Introduction

Older patients are more likely to have cognitive dysfunction (CD) due to the progressive reduction of brain volume associated with the physiological aging, the higher prevalence of cerebrovascular disease and the possibility for developing degenerative CD such as Alzheimer's disease.[1] Frequently, the CD associated with aging may be influenced by genetic, environmental and individual factors that may modulate the progressive decline.[2]

Due to the increasing average age of the population and new developments achieved in medicine, a large proportion of patients who undergo surgical procedures, including extensive heart procedures, are older, up to 50% of elderly population is estimated to need at least a surgical procedure during its lifetime.[3–5]

Postoperative cognitive dysfunction (POCD) has been shown as a consistent complication after major surgical procedures such as heart surgery.[4] It has been defined as a decrease in cognitive performance respect to preoperative baseline levels and multiple cognitive domains could be affected.[4,5] The incidence of POCD is reported to widely vary depending on timing of postoperative evaluation, type of surgery, and basal patient characteristics.[3–6] Older patients who undergo major procedures may suffer more than 25% of POCD within few weeks and it may be permanent in about 50% of these patients.[3,4,6]

POCD has been traditionally associated with specific factors regarding the extension of surgery technique, or anesthesia.[5,6] However, in last years, patient-related factors such as the presence of cardiovascular risk factors and atherosclerotic cardiovascular disease have been identified as predictors of POCD.[4,6–8]

Despite this evidence, much is still unknown about potential risk factors in older patients who undergo heart surgery. Previously our group has characterized a multidomain long-term postoperative cognitive impairment and a partial neurocognitive recovering in these patients at 12 months follow-up,[6,7] and we have shown that a brief domain-specific cognitive evaluation could be routinely implemented in perioperative care practice to detect postoperative cognitive dysfunction, better than the screening tests.[9] The aims of this study were to determine the presence of long-term POCD in older patients who underwent heart surgery and to establish related risk factors. We hypothesized that older patients would have POCD and both surgery and patient-related factors would be associated with.

Methods

We prospectively and sequentially included 44 patients of ≥65-year-old patients with severe aortic stenosis and extensive coronary disease scheduled for elective heart surgery (coronary artery bypass grafting (CABG) and aortic valve replacement (AVR)) at the Hospital Regional Universitario de Málaga and the Hospital Universitario Virgen de la Victoria.

The Institutional Research Ethics Committee from Málaga approved this study and written informed consent was obtained from each participant. This study was carried out in accordance with the Declaration of Helsinki.

Follow-up of all patients was standardized with recording sociodemographic, clinical and operative-anesthetics data preoperatively (baseline) and at 1, 6 and 12 months after surgery.

All patients underwent a neurocognitive evaluation with a battery of 6 standardized neuropsychological tests before (4.8 [standard deviation (SD) 0.7] days) and after surgery (1, 6 and 12 months postoperatively). All evaluations were performed by the same qualified examiner in an appropriate environment with sufficient lighting and silence in order to develop the cognitive assessments according to Murkin et al's consensus statement on assessment of neurobehavioral outcomes after cardiac surgery.[10] The assessment included measures of attention-executive functions (Trail Making Test (TMT)) and Stroop Color-Word Interference Test (SCWIT), memory (Free and Cued Selective Reminding Test (FCSRT)), verbal fluency (Semantic and Phonological Tests (SVFT and PVFT)) and visuospatial perception (Judgment of Line Orientation Test (JLOT)). Patients' raw cognitive scores on specific-domain cognitive tests were converted to age- and education-adjusted co-normative reference values (scaled score and percentile rank) according to the Spanish Multicenter Normative Studies (NEURONORMA project).[11] CD was defined as a percentile rank equal or less than 10% (a score deterioration in the performance ≥1.5 SD) of any test. POCD was defined as a significant worsening in performance and the percentage of patients with CD after surgery when compared to the patient's preoperative levels.[6,7]

Continuous variables are expressed as means (SD) and qualitative data as absolute values and percentages. The differences between groups were determined using the two-sample Student's *t*-test or the Mann—Whitney—Wilcoxon rank-sum test for continuous variables and Pearson's chi-squared test for categorical variables. The postoperative performances with respect to the preoperative levels were assessed by repeated-measures analysis of variance (ANOVA). After an exploratory data analysis, including baseline sociodemographic, clinical, and surgical characteristics in the models, multiple linear regression analysis was used to identify independent risk factors for POCD. Values were considered to be statistically significant when $p < 0.05$. Statistical analyses were performed using the SPSS for Windows statistical software package version 20.0 (IBM SPSS Statistics, IBM Corporation, Chicago, IL).

Results

A total of 44 patients were initially included in this study. There were 3 postoperative deaths (2 postoperative early deaths and 1 non-cardiovascular death at 8 months). After 12 months follow-up, 41 patients completed all evaluations.

The baseline sociodemographic, clinical, and surgical characteristics are summarized in Table 1. In regards to cognitive characteristics, worse postoperative test scores were recorded on the TMT, SCWIT, FCSRT, SVFT and PVFT when compared to preoperative levels, being maximum at 6-month follow-up. JLOT scores remained unchanged. The percentage of CD had a significant increase (33.5%, 63.4% and 38.9% at 1, 6 and 12 months, respectively) from baseline (20.5%). Preoperative and postoperative test scores, and the

Table 1 Baseline sociodemographic, clinical and surgical characteristics.

	≥65-year-old patients ($n = 44$)
Age (years)	74.2 (1.5)
Male gender	33 (75.0%)
Years of schooling	5.9 (0.7)
Smoking	31 (70.5%)
Arterial hypertension	35 (79.5%)
Dyslipidemia	32 (72.7%)
Diabetes mellitus	35 (79.5%)
Obesity	18 (40.9%)
Heart failure	23 (52.3%)
Peripheral arteriopathy	9 (20.5%)
Chronic kidney disease	7 (15.9%)
Stroke	3 (6.8%)
Atrial fibrillation	5 (11.4%)
Years of Coronary artery disease	5.3 (1.1)
3-vessels coronary artery disease	26 (59.1%)
Left ventricular ejection fraction (%)	59 (5.2)
Cognitive dysfunction	9 (20.5%)
Barthel Index	94.0 (1.2)
EuroSCORE	6.2 (1)
Operation time (min)	274 (14)
Intubation time (min)	659 (55)
Intraoperative complications	11 (25.0%)
Postoperative complications	17 (38.6%)
Length of intensive care unit stay (days)	3.5 (0.2)

EuroSCORE: European System for Cardiac Operative Risk Evaluation.
Continuous variables are shown as mean (SDs) and qualitative data as absolute values and percentages.

Table 2 Preoperative and postoperative test scores and the percentage of patients with cognitive dysfunction.

Test/CD (%)	Preoperative	1-month follow-up	6-month follow-up	12-month follow-up
TMT Part A	72.1 ± 4.5/20.3	78.3 ± 4.9/32.4†	89.5 ± 5.8/46.2‡	81.1 ± 5.2/34.6†
TMT Part B	157.3 ± 11/18.7	161.5 ± 11.5/20.1*	176.9 ± 12.5/33.4†	170.2 ± 12.1/26.1†
SCWIT Part A	78.8 ± 4.1/14.5	71.5 ± 3.8/20.1*	67.1 ± 3.7/24.6†	68.2 ± 3.7/23.1†
SCWIT Part B	54.9 ± 2.8/20.5	50.8 ± 2.6/26.9*	46.2 ± 2.3/32.6†	46.4 ± 2.3/30.9†
SCWIT Part C	27.1 ± 1.8/14.9	22.1 ± 1.5/20.3*	18.2 ± 1.1/24.9†	20.1 ± 1.1/23.5†
FCSRT (TFR)	26.8 ± 1.1/20.4	21.1 ± 1.1/33.5†	15.1 ± 1.0/63.4‡	19.3 ± 1.1/38.9†
FCSRT (TDR)	13.2 ± 0.6/18.2	11.1 ± 0.5/24.6*	8.0 ± 0.4/38.2‡	10.1 ± 0.4/26.9†
FCSRT (TR)	42.5 ± 2.0/17.9	37.5 ± 1.9/23.4*	34.1 ± 1.7/39.9‡	35.2 ± 1.7/31.5†
SVFT	22.3 ± 1.1/2.8	18.1 ± 1.0/7.8*	16.0 ± 1.0/10.3*	16.1 ± 1.0/10.0*
PVFT	16.2 ± 0.9/3.0	13.0 ± 0.9/7.9*	12.1 ± 0.8/11.0*	12.0 ± 0.8/10.7*
JLOT	25.9 ± 1.2/0	25.2 ± 1.1/0.2	25.0 ± 1.0/0.3	25.2 ± 1.1/0.2

FCSRT: Free and Cued Selective Reminding Test; JLOT: Judgment of Line Orientation Test; PVFT: Phonologic Verbal Fluency Test; SCWIT: Stroop Color-Word Interference Test; SVFT: Semantic Verbal Fluency Test; TDR: Total Delayed Recall; TFR: Total Free Recall; TMT: Trail Making Test; TR: Total Recall.

* $p < 0.05$.

† $p < 0.01$.

‡ $p < 0.001$.

Continuous data are shown as means (SDs). Statistical significance was established comparing preoperative and postoperative scores. TMT score derived for each trail is the number of seconds required to complete the task. SCWIT, FCSRT, SVFT, PVFT and JLOT are based on the number of successes.

Table 3 Related risk factors for postoperative cognitive dysfunction.

	OR	95% CI	*B* coefficient	*p*-Value
Age (years)	3.5	1.7—6.9	0.567	<0.01
History of smoking	2.3	1.4—5.0	0.520	<0.01
Arterial Hypertension	1.7	1.1—3.2	0.500	0.022
Diabetes mellitus	1.6	1.1—3.1	0.496	0.024
Heart failure	1.4	1.1—2.9	0.482	0.036
Cognitive dysfunction	2.6	1.5—5.5	0.529	<0.01
EuroSCORE	1.9	1.2—3.4	0.512	<0.01
Operation time (min)	3.0	1.7—5.9	0.538	<0.01

95% CI: 95% confidence interval; EuroSCORE: European System for Cardiac Operative Risk Evaluation; OR: odd ratio.
Multiple linear regression analyses for postoperative cognitive performance.

percentage of patients who presented CD are presented in Table 2.

Age ($p < 0.01$), history of smoking ($p < 0.01$), arterial hypertension ($p = 0.022$), diabetes mellitus ($p = 0.024$), heart failure ($p = 0.036$), preoperative cognitive dysfunction ($p < 0.01$), EuroSCORE ($p < 0.01$), and operation time ($p < 0.01$) were identified as related risk factors. Other clinical and surgical variables were not significant. These data are shown in Table 3.

Discussion

This study found that older patients who underwent heart surgery had long-term POCD, as observed on mental flexibility and inhibitory control, memory, and verbal fluency. The maximum CD was observed at 6 months following surgery and remained significant at 12 months. The cognitive performance observed in this age group was higher than that observed in the younger group (data not shown). Clinical factors such as age, history of smoking, arterial hypertension, diabetes mellitus, heart failure, preoperative CD, EuroSCORE, and operation time were identified as related risk factors.

Older patients had lower cognitive performance, at although the time of evolution of the symptoms was similar to that of the younger patients,[12] plus they are vulnerable to CD after heart surgery[8] and furthermore, they may be at higher risk for POCD.[13,14] Approximately, a 25% of all older patients who have major surgery will experience POCD and half of them will have permanent dysfunction.[13] The evidence regarding the presence of CD in older patients after heart surgery is limited and heterogeneous.[14–16]

To present less education and more presence of cardiovascular risk factors, coronary heart disease, are associated with poorer cognitive performance.[17] Traditionally, surgery- and anesthesia-factors have been associated with POCD. A combination of embolism, hypoperfusion, and inflammatory response after major surgeries lead to cerebral consequences in older patients.[4,5,7,18] However, patient-related factors, including age and other cardiovascular risk factors, have been also associated with POCD.[3,6,7,18] All these contributory factors together would diffusely alter the cerebral hemodynamic status, predisposing to multi-domain CD for longer periods of time after surgery.[7,18] In this study, we shown the surgical risk (EuroSCORE) and operation time and several cardiovascular risk factors were established as predictors of POCD. Also, the presence of preoperative CD had a significant contribution to POCD.

A recent and large study by Giovannetti et al.[16] on cognitive outcomes in older adults 1 year after AVR found that just 12.4% of patients had POCD 4—6 weeks after surgery and observed complete cognitive recovery after 12 months in most patients. By contrast, we found greater percentage of patients with POCD, reaching its maximum level at 6 months and remained significant at 12 months. These differences can be explained by the fact that our patients underwent a more extensive heart procedure (both CABG and AVR) with higher operative risk, and had a riskier cardiovascular profile at baseline.

Jensen et al.[19] conducted a randomized trial in order to evaluate the effect of cardiopulmonary bypass on cognitive function at 3 months postoperatively compared with preoperative levels in older high-risk patients. They found that 7.4% and 9.8% of patients had cognitive dysfunction after off-pump and on-pump CABG, respectively, without significant differences between the groups. In contrast to our work, Jensen et al.'s study only explored short-term POCD and patients only underwent a CABG.

The notable differences showed between studies could be due to the different neurocognitive assessment used and its different timing, the lack of consensus in the definition of POCD, the statistical method performed for comparing groups and the variety of high-risk cardiovascular profile and surgical procedures studied.[4,5,20] This important heterogeneity limits the ability to compare POCD amongst studies.

The strengths of our study include its prospective design, the extensive clinical and procedural data collected, its adequate long-term neurocognitive evaluation and multiple regression analysis, and the fact that it examined two groups of patients with advanced cardiac disease and high cardiovascular risk, beside, as far as we know, this is the first study that have characterized the long-term POCD after heart surgery in the Spanish population. The potential limitations of our study include the relatively small number of patients included, and the lack of neuroimaging and inflammatory biochemical markers correlation. In addition, although the proportion of patients with CD was relevant in our study, the practice effect associated with repeated neurocognitive evaluations can underestimate it.[10] We also used a battery of test for multi-domain neurocognitive evaluation based on our routine clinical practice, validation of the test in our country and the evidence from previous research studies. Thus, our findings may not be completely extrapolated to other studies that use a different battery of test.[5—7] Finally, despite a multiple regression analysis, the possibility of residual, unmeasured confounding factors cannot be excluded. Further research is necessary to confirm these results, identify other predictors, and improve the stratification of surgical risk and the follow-up on these patients.

To date, no perioperative strategies for the prevention of POCD have been established as part of routine clinical practice.[15] Given that older patients are at special risk for POCD,[16,19] the focus of the preoperative evaluation of older patients should include awareness of the age-specific physiologic factors, a determination of risk for developing POCD, complementing the comprehensive cognitive and neurological evaluation performed on patients scheduled for major heart procedures, and the implementation of perioperative strategies in order to reduce the neurocognitive impact. The prevention of vascular risk factors not only reduces the risk of suffering a cardiovascular event, it could also reduce the risk of suffering cognitive deterioration.[21] These patients could be relevant for neurology visits/practices because, as authors concluded, the prevalence of dementia at several years after CABG surgery is greatly increased compared to population prevalence.[20] Recently, authors have recommended that it would be necessary to establish the most suitable procedure for early detection and confirmation of cognitive impairment, and for follow-up of patients with a high risk of progression to dementia,[22] within those patients may be patients after heart surgery, such as those in our study.

In conclusion, older patients had long-term POCD after extensive heart surgery and related risk factors included both patient- and surgery-associated aspects. These findings suggest that the prevalence of CD after cardiac surgery in older patients could be related to a possible progression to dementia, so it would be necessary to perform a comprehensive long-term cognitive evaluation. In addition, many of the risk factors identified may be modifiable but in practice, these patients are not attended to for their possible cognitive impairment.

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Conflict of interest

The authors have no conflicts.

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