Improved cognitive flexibility after aortic valve replacement surgery

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Abstract

OBJECTIVES: Aortic valve replacement (AVR) surgery is associated with potential risk to cerebral injury. On the other hand, improved cardiovascular functioning after the surgery may have positive impact on brain health. The aim of this preliminary study was to investigate the impact of AVR surgery on cognition, specifically on higher cognitive control functions, i.e. executive functions, that are typically implicated in cognitive decline due to vascular origin.

METHODS: Patients (n = 16) undergoing elective AVR surgery due to aortic stenosis were recruited and their cognitive performance was assessed using a computer-based Executive Reaction Time (RT) test. Testing was performed 1 day prior to AVR surgery and \(\sim\)3 months after the surgery. In addition, the Behavior Rating Inventory of Executive Function—Adult Version (BRIEF-A) was used to assess everyday challenges in executive functions and self-regulation. Patient’s postoperative test results were compared with each patient’s preoperative results to determine changes in executive functions.

RESULTS: Subjects’ overall cognitive performance improved after AVR surgery. After surgery, patients responded in the Executive RT test more accurately with the same response speed (change from 297 to 298 ms). Their overall probability to commit an error (total errors) was reduced by 47%, reflecting improved executive functions in general (OR = 0.53, 95% CI = 0.46–0.59, error rate change from 44.8 to 28.0%). Furthermore, one key component of executive functions, inhibitory control, was improved after AVR surgery. This was seen in reduced probability of failing to withhold a response, i.e. making a commission error, by 89% (OR = 0.11, CI = 0.08–0.16, error rate change from 11.8 to 2.6%). The probability of missing a response was reduced by 48%, reflecting improved attention (OR = 0.52, 0.44–0.64, error rate change from 18.1 to 11.0%). No statistically significant differences in BRIEF-A scores were found.

CONCLUSIONS: There was a marked improvement in cognitive performance following AVR surgery, specifically in executive control functions indicating improved cognitive flexibility. Cognitive improvement, as opposed to the typical trajectory of cognitive decline in an elderly population with vascular disease, emphasizes the importance of these results and points to AVR surgery as having potential benefits on brain health in general.


Keywords: Aortic valve replacement • Executive functions • Cognition • Executive reaction time test

INTRODUCTION

Changes in cognition following cardiac surgery are poorly understood, with most studies focusing primarily on the negative post-operative effects of surgery such as postoperative cognitive dysfunction (POCD). For example, in coronary artery bypass graft (CABG) surgery, POCD has been reported in 14–48% of patients [1] and pre- and postoperative MRI comparison of CABG surgery patients has detected new ischaemic lesions in up to 21% of patients without apparent decline in neuropsychological tests [2]. Aortic valve replacement (AVR) surgery has higher POCD risk compared with CABG [3], with an extensive surgical manipulation inside the aorta, increasing risk of emboli or dislodgement of calcified deposits.

Pathogenesis of POCD in general is thought to be multifactorial, traditional theories including hypoperfusion, microemboli, calcified atheroma of the ascending aorta and neurotoxicity of anaesthetic drugs [4]. These have been joined by more recent discoveries...
where immunological and genetic biomarkers suggest that the body’s inflammatory response to surgical trauma is a contributing factor. Taken together, there is a multitude of vascular mechanisms linking cardiac surgery to cognitive performance [5].

In addition to cardiac surgery, persons’ overall circular conditions affect their cognitive performance. Atherosclerosis has been linked with increased risk for dementia, and in individual level, lower cardiac output has been associated with executive function deficits [6]. Furthermore, improved cardiac output after CABG may improve executive functions 6–12 months after the operation [7]. Taken together, there is a clear correlation between the vascular health and cognitive performance.

Executive functions are higher order cognitive functions controlling goal-directed behaviors and allowing successful cognitive performance in daily living. Key processes subserving executive functions and cognitive flexibility are working memory, inhibition and task switching. Working memory is needed for temporarily maintaining information in the brain, while inhibition allows for adaptive and socially appropriate behaviours by suppressing stimuli or behaviours that interfere with the current goals or that are inappropriate in the current situation. Task switching is a prerequisite for flexible behaviours and allows for efficient adaptation to novel situations with overlearned, automated or previously successful behaviours replaced by more appropriate behaviour to the current context. To that end, executive functions are essential in successful and independent living especially when faced with novel situations and carrying out novel, non-automated tasks. While a vast variety of brain disorders and injury may lead to compromised executive functions with significant detrimental impact on daily tasks, objective detection of dysfunction in executive functions remains a challenge [8].

Traditional neuropsychological tests used in previous studies are not sensitive in detecting alterations in executive functions. Structured testing environments with neuropsychologist guiding the subject through isolated tests of specific cognitive domains do not efficiently tap into problems of executive functions that manifest in unstructured and unpredictable environments of daily living. Furthermore, traditional neuropsychological tests are not suitable for repeated testing of cognitive functions, e.g., before and after the surgery, because they are vulnerable to significant learning effect when repeated [9]. Additionally, testing is time consuming, labour intensive and expensive, requiring up to several hours of a neuropsychologist’s time to administer the tests. For these reasons, traditional neuropsychological tests may become a bottleneck in clinical assessments. Assessing alterations in executive functions before and after the AVR surgery in a clinical setting calls for a rapid, easily administered, sensitive and repeatable method. Computer-based tests, such as the Executive Reaction Time (RT) test used in this study, are best candidates to fulfill these requirements. The Executive RT test was developed to tap into the real-life cognitive challenges where multiple executive functions need to be engaged simultaneously. It has shown promise as a sensitive method in detecting changes in executive functions in clinical populations, such as patients with mild traumatic brain injury [10] and patients treated with deep brain stimulation due to refractory epilepsy [11].

The aim of this study was to evaluate the general impact of AVR surgery on cognition, specifically on higher cognitive control functions known to be vulnerable to vascular insult. Additionally, we wanted to evaluate the suitability of Executive RT test and standardized questionnaires as tools for perioperative evaluation of cognition in AVR surgery patients. We expected either improvement or impairment in brain health due to cardiac surgery to be reflected in the performance measures of the Executive RT test or in questionnaire scores.

MATERIALS AND METHODS

Patients scheduled to undergo elective AVR surgery because of aortic stenosis at the Tampere University Hospital Heart Centre from spring 2014 to summer 2015 were screened for the study. Patients were excluded if they were under 60 or above 85 years of age, had previous neurological or psychiatric disorder with manifest symptoms, significant visual problem that could not be corrected for, problems with arm/hand use that made the execution of the test difficult or if they declined to participate. Subjects were given information about the study and written consent to participate was obtained. Subject flow through the study is presented in Fig. 1 and participant demographics are in Table 1. Six subjects had AVR surgery, eight subjects had concomitant CABG (AVR + CABG), one concomitant aortic and mitral valve surgery (AVR + MVR) and one combination of all three operations (AVR + MVR + CABG). The study was approved by the local institutional ethics committee and was conducted in accordance with the Declaration of Helsinki.

![Figure 1: Flow of patients through the phases of the study. AVR: aortic valve replacement.](https://academic.oup.com/icvts/article-abstract/23/4/630/2630776)
EXECUTIVE REACTION TIME TEST

Patients performed an experimental computer-based RT test for executive functions, i.e. Executive RT test (see Fig. 2). It is a visual attention task embedded with emotional distractors engaging several executive functions simultaneously such as working memory, controlled attention, inhibition of a prepotent response and rule switching.

Testing started with a grey triangle displayed on the screen for 150 ms, followed by a fixation cross for 150 ms after which a Go/NoGo signal would be presented for 150 ms signalling the subject whether to respond or not. In case of a Go-signal, the subject was supposed to indicate the direction of the previously presented triangle with a button press as fast as possible and in the case of a NoGo signal, the subject was supposed to withhold from responding. Keeping the orientation of the triangle in mind after the triangle disappeared from the screen requires working memory. In a speeded RT test, a NoGo stimulus requires inhibition of a prepotent response.

The Go/NoGo stimuli resembled a traffic light with three circles atop one another. The circle in the middle was always grey, and either the top or bottom circles were filled with green or red with the same logic as in conventional traffic lights (red in the top circle, green in the bottom circle). The orientation of the triangle as well as the signal for Go and NoGo alternated randomly. In all trials, a small black distractor was shown in the middle position. The distractor illustrated either a spider acting as a threatening emotional stimulus that might divert attention from the assigned task or a flower acting as a neutral control figure. Both distractor figures were comprised of same visual elements [13]. The test was composed of 16 blocks, ~2 min in length. In half of the blocks, green acted as a Go signal as in normal traffic lights. The remaining half of the blocks had the rule reversed, with green meaning NoGo and red meaning Go. After each block, the rule for responding was changed engaging subject’s task switching ability.

The Executive RT test is designed to test a broad spectrum of executive functions concurrently. Remembering the orientation of the triangle and the response rule requires working memory. Rule switching from green light indicating a Go trial and red light a NoGo trial to an opposite response rule requires the ability to flexibly change response sets. NoGo trials require the ability to inhibit a prepotent response in a speeded RT task and the ability to inhibit a response according to the previous set. A threatening distractor is used to test subject’s emotional reactivity by analysing how it modulates RT and error rates compared with neutral (non-threatening) distractor.

The level of cognitive performance in the Executive RT test is reflected in the speed and accuracy of responses. There are three different error types, i.e. incorrect button press, missing responses and commission errors, all reflecting failures in different executive functions. Incorrect button press to the orientation of the triangle indicates failure in working memory performance. A miss is a failure to respond within the given time, indicating a lapse in attention. A commission error is a failure in withholding a prepotent response during a NoGo trial, indicating inefficient inhibitory control. Total error count reflects the overall executive function performance.

A computer program (Presentation v16.0, Neurobehavioral Systems, Inc., Albany, CA, USA) was used to display the visual stimuli and collect the behavioural response data (see Fig. 2).

Questionnaires

All patients completed the BDI [14] to control for underlying depression, the MMSE [15] to screen for potential cognitive dysfunction and the BRIEF-A to assess subjective challenges in executive functions and self-regulation before and after the AVR surgery. BRIEF-A is a validated questionnaire to assess executive function in everyday life. It assesses nine aspects of executive functioning (inhibit, self-monitor, plan/organize, shift, initiate, task monitor, emotional control, working memory and organization of materials). From these individual aspects, two broader indexes are calculated: Behavioral Regulation Index (BRI) and Metacognition Index (MI). These two together form a summary score, the Global Executive Composite (GEC). BRIEF-A also has three validity scales (negativity, inconsistency and infrequency) to assess subjective bias [16]. The BRIEF-A questionnaire was completed by both the patient and a family member or close relative to provide a third-party opinion about the patient’s executive functions (‘informant’). Informant was defined as a person who sees the patient at least weekly and patients were allowed to recruit informant whom they felt was qualified to answer the questionnaire. A stamped, self-addressed return envelope was provided for informant so that informant could return the questionnaire directly to the researcher. The patient and informant answered the questionnaires independently, without seeing one another’s responses. After the surgery, BRIEF-A was completed at the postoperative control.
meeting by the same informant who filled out the questionnaire preoperatively.

Cardiopulmonary bypass and surgery

Non-pulsatile cardiopulmonary bypass (CPB) at 2.0–3.0 l/min/m² was conducted using membrane oxygenator (D903 Avant Phisio, Dideco, Mirandola, Italy) with normothermia. Mean arterial pressure was maintained at 50–80 mmHg during CPB. Haemodynamics was treated according to a protocol during and after surgery: (i) central venous pressure 10–15 mmHg with fluid administration, (ii) mean arterial pressure 60–90 mmHg with norepinephrine or sodium nitroprusside and (iii) dobutamine if inotropic effect was needed according to cardiac index or echocardiographic evaluation.

All the operations were made through a median sternotomy. If needed, mitral and tricuspid valve procedures were done first and thereafter aortic valve was replaced by a mechanical or bioprosthesis. In cases with concomitant CABG, distal vein anastomoses were sutured first and after AVR proximal vein anastomoses were performed. Lastly, the distal end of internal thoracic artery was sutured when used.

Statistical analysis

Patient error rates, RTs and the impact of emotional distractor were compared before and after AVR surgery. Prior to data analysis, the data were checked for possible outlier blocks, which were then removed from future analysis. A block was considered as an outlier if the combined number of the missing responses and commission errors was higher than 75% of the all trials in the block (wrong rule block) or the total error rate in a block was >3 SDs above the subject’s mean error rate (outlier block). If the sum of the missing responses and commission errors is higher than 75% of the all trials, it indicates that the subject had been probably answering with the wrong rule. Answering with the wrong rule could be temporary, e.g. lapse in attention, or in the case of being consistent, it can indicate a deficit in the subject’s executive functions. Therefore, in a wrong rule case, we also checked the subject’s overall performance for the possible indication of general rule switching problem. Altogether, there were seven blocks considered as a wrong rule block, three subjects having two of them and one subject one. However, these cases were considered individual occurrences and not indicating general rule switching problem. There were two blocks with exceptionally high error rate for two different patients. In total, 9 blocks were removed out of 144 (18 patients × 8 blocks).

RTs were analysed using a repeated measures analysis of variance (ANOVA) with Test (before, after) and Distractor valence (neutral, emotional) as within-subject factors. Only correct responses were included in RT analysis. For error analysis, a generalized binary logistic regression was used with Test and Distractor valence as fixed effect predictors and Subject as a random effect. Only correct responses’ outcome variable as ‘incorrect’ or ‘other’ (i.e. ‘correct’ or ‘miss’), ‘Missing responses’ outcome variable as ‘miss’ or ‘other’ (i.e. ‘correct’ or ‘incorrect’) and commission errors outcome variable as ‘commission error’ or ‘correct’. Finally, separate models predicting patient’s probability to make an error were created for total errors and for each error type separately.

Results from BDI (total score), the Mini-Mental State test (total score) and the BRIEF-A questionnaires were compared before and after the AVR surgery with Wilcoxon signed rank test. BRIEF-A comparison was done for total score (GEC, MI, BRI and for each subcategory (inhibition, shifting, emotional control, initiation, working memory, planning/organization, organization of materials and monitoring) separately.

All statistical analysis was done using R v3.2.2 with ‘ez’ package v4.2.2 for repeated measures ANOVA, ‘lme4’ package v1.1-9 for regression analysis and ‘coin’ package v1.1-0 for Wilcoxon signed rank test.

RESULTS

After surgery, patients responded in the Executive RT test more accurately with the same response speed than before the surgery. Generalized binary logistic regression found a statistically significant main effect of Test for total errors, missing responses and commission errors, i.e. subjects committed significantly less these errors postoperatively. Subjects’ probability to make an error in general was reduced by 47% (total errors OR = 0.53, 95% CI = 0.46–0.59, error rate changing from 44.8 to 28.0%). probability to miss responding by 48% (missing responses OR = 0.52, 0.44–0.64, error
rate changing from 18.1 to 11.0%) and probability to make a commission error by 89% (OR = 0.11, CI = 0.08–0.16, error rate changing from 11.8 to 2.6%) (see Table 2 and Fig. 3). No statistically significant predictors were found for incorrect responses.

Repeated measures ANOVA found no statistically significant differences in patient RTs (mean RT before = 297 ms, mean RT after = 298 ms measured from the onset of the traffic light). There were no statistically significant differences between any of the questionnaire scores before and after the AVR surgery. Questionnaire scores are presented in Table 3.

While most patients performed at similar or better level postoperatively, one subject performed significantly worse after the surgery and both he and his informant reported increased challenges in executive functions. His total error rate in Executive RT increased from preoperative 12% to postoperative 24%, BRIEF-A Self total score (GEC T score) from 52 to 65 and BRIEF-A informant score from 53 to 58. The increase in BRIEF score corresponded to a change from 60th percentile of the population to 95th percentile after the operation. While his MMSE and BDI scores remained the same, these measures suggested decline in his executive functions postoperatively.

**DISCUSSION**

The current pilot study assessed feasibility of Executive RT Test in measuring alterations in cognitive performance in a cardiac surgery population. On the basis of the results, Executive RT Test is a feasible and a sensitive method in detecting post-cardiac-surgery changes in cognitive performance in comparison with individual pre-surgery baseline level detecting both improvement and impairment at individual level. At the group level, the current study showed significantly improved executive functions three months after AVR surgery when compared with performance before the surgery. To our knowledge, this is the first study suggesting improved cognitive executive functions after AVR surgery. Improved cognitive performance after surgery in a group of patients where cognitive decline due to general vascular disease is a natural trajectory suggests AVR surgery may have a significant positive impact on brain health in general.

<table>
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<tr>
<th>Table 2: Results of the generalized binary logistic regression</th>
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<td>Predictor</td>
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<td>Intercept</td>
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<td>After x Neutral</td>
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After aortic valve surgery, the probability to make any error was reduced by 47%, probability to miss responding was reduced by 48% and probability to make a commission error was reduced by 89%. There was no change in probability to make an incorrect response.

<table>
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<th>Table 3: Mean questionnaire scores</th>
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<td>Questionnaire/scale</td>
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<tr>
<td>Behavior Rating Inventory of Executive Function—Adult version (BRIEF-A)</td>
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<tr>
<td>Global Executive Composite (GEC)</td>
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<tr>
<td>Behavioral Rating Index (BRI)</td>
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<tr>
<td>Emotional control</td>
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<td>Inhibit</td>
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<td>Initiate</td>
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<td>Metacognition Index (MI)</td>
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<td>Organization of materials</td>
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<tr>
<td>Plan/organize</td>
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<td>Self-monitor</td>
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<td>Shift</td>
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<td>Task monitor</td>
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<td>Working memory</td>
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<td>Mini-Mental State Exam (MMSE)</td>
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<td>Beck Depression Inventory (BDI)</td>
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No statistically significant differences before and after the surgery were observed. BRIEF-A scores are age normalized T scores. Lower BRIEF-A score indicates better executive functions, lower BDI score less depression symptoms and higher MMSE score better cognition. BRIEF-A Subject GEC T score 53 corresponds to 54th percentile in general population and informant GEC T score 50 corresponds to 64th percentile. MMSE ≥ 27 indicates normal cognition and BDI ≤ 13 indicates no depression.
Improved cerebral circulation may be a factor contributing to the improved executive functions after AVR and cardiac surgery in general, since metabolic resources of the brain are dependent on cerebral blood flow, which is determined by cardiac output [17, 18]. Previous studies have concluded that weakened cerebral blood flow can be reversible [19] and improvement of blood flow can lead to improved cognitive function [20]. Cognitive decline after cardiac surgery is likely to be dependent on other factors such as age, pre-existing conditions such as coronary artery disease and cognitive impairment before the surgery rather than the cardiac surgery itself [21, 22].

In Executive RT Test, commission errors reflect the failures in the ability to inhibit prepotent action, i.e. refraining from responding when a ‘NoGo’ rule was displayed. Patients were better able to withhold from responding in ‘NoGo’ cases after the surgery, demonstrating improved inhibitory control. Missed responses in a case where a response was expected (a ‘Go’ case) reflect the patient’s ability to keep attention focused on the current task and response rule. Fewer missed responses suggest better attention control after the surgery. Remembering the orientation of the triangle requires working memory. Subject’s working memory had no improvement after surgery, but stayed at the preoperative level. Taken together, the patients’ ability to perform the test with fewer commission errors and missed responses demonstrates the improved ability of the patient to switch rules, stay on task with the new rule and inhibit from responding when required. In summary, the results indicate improved executive control functions—or more generally improved cognitive flexibility—postoperatively.

No statistically significant changes were found in the BRIEF-A, BDI or MMSE questionnaires before and after surgery. However, there was a trend towards improved MMSE result postoperatively ($P = 0.09$). No change was found in emotional reactivity to evolutionarily and biologically relevant threat stimuli (spiders) nor there were any signs of increase in depressive symptoms in BDI scores after the surgery. Together, these results point towards intact brain circuitry underlying emotional control and mood.

Computer-based Executive RT test is an objective and sensitive method for testing cognitive performance, whereas questionnaires are highly subjective and relatively crude assessment tools. The questionnaire scores always reflect subjective perception patients have of themselves and it may be easier for patients and their relatives to notice a decline or challenge in cognitive functioning than an improvement. Furthermore, the BRIEF-A used in the current study is originally designed to assess subjective challenges and deficits in executive functions, not efficiency or improvement in these functions. Owing to the limitations of questionnaires, to detect a change in cognition using questionnaires, a sample size should be much larger than used in the current study.

Unlike the Executive RT test, traditional neuropsychological tests are mostly designed to isolate dysfunction of a single cognitive domain at a time. In addition to assessing the efficiency of different executive functions, the Executive RT test examines emotional reactivity and allows the assessment of emotion–executive function interaction [23]. Successful performance on the test requires intact working memory, controlled attention, task switching and the ability to inhibit prepotent responses as well as the ability to inhibit emotional distraction. All these components of cognitive control contribute to cognitive flexibility required in successful everyday living. To that end, improved performance in the Executive RT test can be assumed to reflect generally improved cognitive flexibility supporting successful daily living.

Comparable findings of improved cognitive performance have been reported for CABG. In a study by Selnes et al., cognitive performance was investigated between CABG and a non-surgical group at 1 and 3 years. They found that while both groups improved in cognitive testing compared with the baseline tests, cardiac surgery patients demonstrating significantly greater improvement over non-surgery controls, suggesting that improvement is due to better circulatory conditions of the brain after the surgery [24].

In this study, most subjects improved their performance in Executive RT test after the operation, but one subject had a significant decline. Closer examination of subject’s medical records revealed some risk factors for cognitive decline including previous neurological symptoms suggestive of TIA and slightly longer operation time than average, but no other obvious reason was identified. The patient was discharged from the hospital normally and no apparent cognitive decline was observed in the clinical setting.

Main limitations of this study include potential effect of stress during the first test, small sample size combined with concomitant operations, lack of control group and potential learning effect. Preoperative testing 1 day before major open-heart surgery might be reflected on the preoperative test result due to potential stress related to forthcoming operation, but the effect is difficult to evaluate. On the one hand, significant stress can reduce performance, on the other hand, mild stress has a positive effect on performance, and furthermore, different people react differently to stressful situations.

While the study had a small patient population and there was no control group, these concerns are compensated by ‘within-subject’ design, where patients serve as their own controls and where within-subject design increases statistical power. While we cannot assess the incidence of POCD due to the small sample size, statistically significant improvement in cognitive performance in a small group of patients presents strong evidence for the fact that AVR surgery in general, when no complications occur, improves cognitive flexibility.

AVR was the common operation done for all subjects in this study, but some subjects had concomitant operations. We screened those patients for this study who had isolated AVR planned, but in some cases, another procedure was added after the cardiological evaluation. As this is not exceptional, we decided to keep those patients in the study. It is our belief that the resulting study population is more representative of AVR patients in general. Since concomitant procedures add to overall complication risk and despite this, a cognitive improvement of the executive functions was detected, results are better generalizable than if all subjects had only AVR and this emphasizes the significance of the result.

Some studies report that there might be an amount of practice effect involved in the neuropsychological tests when the same tests are performed more than once by the same subject [9]. Previous studies of practice effect have concentrated mainly on questionnaires and traditional neuropsychological tests [25], but it is feasible to assume that the same effect could be observed with the Executive RT test when performed twice, before and after the surgery. However, the practice effect is assumed to be marginal in a computer-based test where the response rule is changed repeatedly and the stimuli are presented randomly and rapidly, in the order of milliseconds. Furthermore, learning effect is minimized when there is no one-to-one mapping between stimuli and correct response that could be learned. Additionally, if a learning effect was significant, learning could be expected to be found at all the levels of the test including improved RTs and working
memory performance. This, however, was not the case. Future studies are needed to elucidate the amount of potential learning effect. Learning in general is vulnerable to insult on brain circuits independent of aetiology. Thus, even if improved performance in the Executive RT test would be partly explained by learning, it would still point towards well-functioning brain circuits after AVR surgery in an elderly patient population with cardiovascular risk factors predisposing to a trajectory of cognitive decline.

CONCLUSIONS

In conclusion, the Executive RT test proved to be a promising tool for the assessment of cognitive function in cardiac patients. The test was able to show a general improvement in executive functions after AVR surgery, while it pinpointed a case with significant executive function decline, which was not detected as part of normal procedure at the time of hospital discharge. With the paradigm employed in this study, the patient testing requires ~30 min, providing a significantly less resource-consuming method compared with traditional neuropsychological tests. We also demonstrated that AVR surgery is associated with marked improvement in cognitive performance in a task requiring cognitive flexibility. Improved cognitive flexibility after AVR surgery points towards improved brain health possibly due to enhanced cardiovascular health and cerebral perfusion conditions.

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