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Attenuation of Regional Cerebral Blood Flow During Memory Processing after Coronary Artery Bypass Surgery

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Abstract

Reports of memory impairment after cardiac surgery are controversial. To address this controversy, we used positron emission tomography to examine changes in regional cerebral blood flow (rCBF) during memory processing before and after elective coronary artery bypass grafting surgery. In postoperative scans we observed significantly reduced rCBF in two of the most important memory processing areas: the medial temporal lobe ($p=0.023$) and the prefrontal cortex ($p=0.002$). The results suggest postoperative attenuation of rCBF in brain areas involved in memory processing. These reductions could be used to evaluate severity of memory impairment after coronary artery bypass grafting surgery in patients at risk.

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Introduction

Although cognitive impairment is found in as many as 69% of patients undergoing cardiac surgery at the time of hospital discharge,¹⁻³ the causes for such impairment are still not established. Memory deficit is a frequent finding⁴⁻⁶ and the most commonly self-reported cognitive symptom⁷ after coronary artery bypass grafting (CABG). Perioperative factors producing global and local impairment to cerebral function have been proposed as potential causes. Observation of intact emotional and social functioning in memory deficient postsurgical patients^{8,9} suggests that the impairment could be limited to memory processing areas. In contrast, it has been suggested that intraoperative global hypoxia could cause memory deficit by affecting regions sensitive to brain ischemia and involved in memory processing such as the hippocampus.^{10,11} An understanding of the cerebral anatomical correlates of memory deficits after cardiac surgery could provide insight into the mechanisms of postoperative cognitive deficits and potentially help in development of therapeutic strategies.

We hypothesized that brain regions associated with memory processing are functionally compromised after CABG. To test this hypothesis, we compared memory-induced changes in regional cerebral blood flow (rCBF) before and after surgery, using positron emission tomography (PET). We were particularly interested in the medial temporal lobe and prefrontal cortex because human memory is predominantly processed in these areas.^{12,13}

Methods

The study was approved by Partner's IRB, Boston, MA, USA. Written informed consent was obtained from all participants. The study involved eight native English-speaking right-handed patients undergoing routine CABG (Table 1). Seven patients underwent on-pump and one off-pump CABG (intraoperative decision). Due to technical reasons, PET data could not be acquired in one patient preoperatively and another postoperatively. Accordingly, we present data on six patients.

Patients were studied twice during performance of an explicit memory task. The first series of scans were performed 1.5 [0.9-10.8] (median [interquartile range]) days before surgery, and the second 6.5 [5.0-16.3] days after surgery. During these scans patients were positioned in the PET camera, where they performed word stem completion tasks.¹²⁻¹⁸ The task began with a study phase outside the scanner in which 135 words (1 word/5s) were presented. Patients were asked to indicate their liking/disliking for each word. At the end of the study phase, patients were scanned under control and test conditions. In the control condition the first 3 letters (word stem) of a word derived from the studied words was presented for 5s and patients were asked to complete the stem using the first word that came to mind (e.g., picture for PIC). In the test condition, similar stems were presented and patients were asked to complete them using specifically the words from the study phase. Two control and two test blocks of 45 stems each were performed. The word lists were counterbalanced across patients. The voice onset latency and accuracy of responses (% correct retrieval) were recorded using a microphone channel connected to a voice-operated relay.

Imaging protocols were similar to previous descriptions.¹⁴⁻¹⁸ Briefly, ¹⁵O labeled CO₂ (¹⁵O-CO₂) was delivered by nasal cannula (2L/min, mean radioactivity 2960 MBq/L) and emission data acquisition started 30 s after beginning the word stem completion task (15-slice whole-body tomograph, Scanditronix PC 4096, General Electric, Milwaukee, WI). Images were reconstructed using measured attenuation correction and Hanning-weighted reconstruction filter set to allow 8-mm in-plane spatial resolution. Corrections were made for scattered positron random coincidences, and counting losses resulting from dead time in the camera.

Anesthetic management included premedication (midazolam 0.02-0.06 mg/kg), induction with propofol (0.5-1.5 mg/kg), fentanyl (10-20 mcg/kg), and muscle relaxation (cisatracurium, vecuronium or pancuronium), and maintenance with isoflurane, fentanyl and a muscle relaxant. Alphastat management was used, patients cooled to 32°C during cardiopulmonary bypass, and rewarmed by bringing the cardiopulmonary bypass machine water jacket to 37.0-38.5°C targeting a final nasopharyngeal temperature of 36.5-37.0°C.

After the PET data were corrected for head movement, images were transformed to a standard stereotaxic space (Montreal Neurological Institute) and analyzed using statistical parametric mapping software (SPM5, Wellcome Department of Cognitive Neurology, London).¹⁹ Scans were then smoothed using a 12×12×12 mm full width at half maximum Gaussian kernel to meet conditions for subsequent SPM statistical analysis. Voxel-wise analysis used proportional scaling with a global mean of 50 ml/min/100 ml. The four conditions of the design matrix for the general linear model used by SPM were the control and test conditions, both before and after CABG. SPM contrasts were formed to localize changes and create corresponding statistical parametric maps. Hypothesis testing was performed using planned contrast ($t=1.96$) at each voxel, following exploratory criteria used in previous imaging studies.^{20,21}

Results

Patients had normal ventricular function and common comorbidities (Table 1). None had perioperative stroke, with the median value of the NIH Stroke scale equal to zero at the time of imaging.

Behavioral data acquired during performance of the memory task indicated that patients appropriately followed instructions. There was greater accuracy (% correct retrieval) in the test versus control condition (Table 2). Postoperatively, patients had more “no responses” in the test condition, potentially suggesting minor postoperative impairment in task performance. There was no significant postoperative change in the accuracy of responses (Table 2).

In preoperative scans, rCBF increased during memory processing (control vs test) in the medial temporal lobe and superior frontal gyrus (Table 3). Postoperatively, these changes were attenuated and control versus test comparison revealed a smaller extent of rCBF increase in the right temporal lobe and the medial frontal cortex (Table 3) with only two regions showing increases in rCBF in contrast to four found preoperatively. We did not

observe a change in the superior frontal gyrus that met our significance criteria. A comparison of the rCBF changes observed before and after surgery revealed significant attenuation in several areas after surgery (Table 4; Fig. 1). Within the medial temporal lobe, the rCBF reductions in the postoperative scans as compared to preoperative scans were localized to the left parahippocampal and right hippocampal areas.

Discussion

After CABG surgery, we found significant attenuation of memory-related rCBF changes in the medial temporal lobe, prefrontal cortex, extrastriate, thalamus, and putamen. Since these areas are involved in memory processing, the attenuation could be a neural signature for postoperative impairment of explicit memory. Accordingly, our results are consistent with localized impairment of processing areas as the mechanism for memory deficits. They are also in line with observations of isolated postoperative memory dysfunction with normal performance in non-memory tasks also dependent on intact frontal cortex (e.g., emotions, social interaction).^{8,9} If our findings resulted from a global insult, we would expect brain areas sensitive to hypoxia to be predominantly affected. Whereas the reduced activation in the medial temporal lobe was consistent with this expectation,²² the absence of postoperative rCBF changes in the hypoxia sensitive cerebellum^{10,23} and the finding of a significant change in the relatively less sensitive prefrontal cortex argues against a global insult. The significance of the reduced rCBF in the left putamen and thalamus in postoperative scans is unclear at this time. It is, however, interesting to note that left putamen activation has been observed in both implicit and explicit memory tasks.²⁴ Thus, the observations might suggest a postoperative shift and enhancement of the basal ganglia-mediated memory system. Of note, our findings of changes in memory processing areas occurred with quite subtle impairment in task performance suggesting that functional (memory paradigm) rCBF imaging could be a sensitive marker of postoperative memory deficits. Further studies with larger sample sizes will be required to establish the mechanisms of those findings and the value of early rCBF changes as predictors of severity of long-term cognitive deficit.

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Figure 1.

Contrast of regional cerebral blood flow (rCBF) changes observed before and after coronary artery bypass surgery during memory processing. The rCBF was significantly attenuated in postsurgical scans in several brain areas including the left (A) and right (B) medial temporal lobe and left prefrontal cortex (C). These areas are involved in explicit memory processing.

Table 1
Demographic and Clinical Data

Age (Yrs)	63 ± 13
Gender (M/F)	6/0
Hypertension (Y/N)	6/0
Smoking (Y/N)	3/3
Diabetes Mellitus (Y/N)	1/5
Hypercholesterolemia (Y/N)	6/0
Left ventricular ejection fraction (%)	62 ± 7
Numbers of grafts	3.3 ± 1.4
Cross-clamp duration (min)*	121 ± 30
Cardiopulmonary bypass duration (min)*	152 ± 47
Medications (# patients)	
Angiotensin-converting-enzyme inhibitors	4
Angiotensin receptor blocker	2
Aspirin	4
β-blockers	6
Calcium channel blockers	1
Diuretics	3
Nitrates	1
Statins	5

* Data obtained from 5 patients

Table 2
Memory task results

		Preoperative	Postoperative
Mean Response Time (ms)	Control	1761±276	1734±179
	Test	1816±261	1767±209
Mean Correct Retrieval (%)	Control	13±2	14±4
	Test	27±5*	24±12 [#]
Mean 'No Response' (%)	Control	5.6±4.9	8.4±7.2
	Test	7.9±4.9	12.4±10.0 [§]

Data are presented as mean ±SD.

Control: word stem completed with the first word that came to mind.

Test: word stem completed with a word presented in the study phase.

Correct retrieval (%): % of responded words present in the list provided in the study phase.

control versus test contrasts:

*
p=0.0006

§
p=0.062

[#]
p=0.071

Table 3
Brain areas with increased regional cerebral blood flow (rCBF) during performance of the explicit memory task (test condition) as compared to the rCBF observed during performance of the control task (control condition)

Region	MNI (x,y,z)	t-value	p-value
Preoperative			
Right superior frontal gyrus (BA 9)	24,42,26	3.31	0.001
Right superior frontal gyrus (BA 9)	30,42,12	2.67	0.004
Right medial temporal lobe	32,10,-30	1.97	0.024
Right medial temporal lobe	50,-50,-2	1.97	0.024
Postoperative			
Right medial temporal lobe	46,-28,-12	3.84	0.001
Medial frontal gyrus (BA 9)	14,26,24	3.75	0.004

MNI = Montreal Neurological Institute coordinates

Table 4
Brain areas with a significant reduction in postoperative versus preoperative regional cerebral blood flow (rCBF) during performance of an explicit memory task

Region	MNI (x,y,z)	t-value	p-value
Left middle frontal gyrus (BA 9)	14;50;24	3.13	0.002
Right superior frontal gyrus (BA 9)	26;44;28	2.27	0.014
Left medial temporal lobe	-20;0;-28	2.05	0.023
Right medial temporal lobe	34;-16;-6	1.90	0.031
Right inferior frontal gyrus (BA 47)	26;36;-14	2.22	0.016
Left middle frontal gyrus (BA 11)	-4;42;-24	2.22	0.016
Left extrastriate cortex (BA 19)	-52;-60;2	2.65	0.006
Left putamen	-28;-6;20	3.48	0.001
Thalamus	0;-30;-4	2.32	0.010

MNI = Montreal Neurological Institute coordinates