Alterations of Neuropsychological Function and Cerebral Glucose Metabolism After Cardiac Surgery Are Not Related Only to Intraoperative Microembolic Events

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Background and Purpose—High-intensity transient signals (HITS) during cardiac surgery are capable of causing encephalopathy and cognitive deficits. This study was undertaken to determine whether intraoperative HITS cause alterations of neuropsychological function (NPF) and/or cerebral glucose metabolism (CMRGlc), even in a low-risk patient group, and whether induced changes are interrelated.

Methods—Eighteen patients without signs of cerebrovascular disease underwent elective coronary artery bypass grafting (CABG), and two of these additionally underwent valve replacement in normothermia. Intraoperatively, HITS were recorded by means of transcranial Doppler ultrasonography (TCD). Perioperatively, NPF and CMRGlc were assessed using a standardized complex test battery and positron emission tomography with ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG-PET), respectively.

Results—Intraoperatively, the number of HITS ranged from 90 to 1710 per patient and hemisphere, more on the right side than on the left ($P<.05$). HITS occurred primarily during cardiopulmonary bypass (71.3%) and, to a lesser extent, during aortic manipulation (22.2%). Changes in global and regional CMRGlc between first (one day preoperatively) and second (8 to 12 days postoperatively) FDG-PET scans were mild. No correlations were found between the number of HITS, age of patient, duration of cardiac ischemia or cardiopulmonary bypass and the changes in CMRGlc. In patients with recorded HITS and a postoperative decrease of regional CMRGlc (n=11), the maximal decrease of rCMRGlc in each hemisphere below the individual global change of CMRGlc correlated with the number of HITS ($r=-0.46$, $P<.05$). Limitations in NPF occurred 8 to 12 days postoperatively, resolved within 3 months, and were not found to be correlated to the absolute number of HITS or changes in CMRGlc.

Conclusions—HITS during cardiac surgery can cause alterations of both NPF and CMRGlc, even in a low-risk patient group. However, the number of HITS and changes in NPF and CMRGlc are not necessarily interrelated, which indicates that (1) the location of brain damage related to HITS is more important for the development of NPF than is the absolute number of HITS, and (2) factors in addition to HITS might contribute to surgery-related brain damage. **(*Stroke*. 1998;29:660-667.)**

Key Words: cardiopulmonary bypass ■ cerebral embolism ■ neuropsychological tests ■ tomography, emission computed ■ ultrasonography, Doppler

After cardiac operations, cerebral complications constitute one of the main causes of morbidity and disability. Stroke after CABG occurs at a rate of 0.8% to 5%. However, neuropsychological dysfunction of variable duration and degree, including cognitive deficits and encephalopathy, is observed in up to 80% of patients and can persist for 12 months in one third of patients.[1–3] The causative parameters include subject variables that predate the operation, such as advanced age, concomitant cerebrovascular disease, and severity of cardiovascular symptoms or heart disease[4–6]; and intraoperative variables that are related to the CPB circuit or operative procedures. As previously reviewed by Gilman and others,[7–9] mounting evidence points to ischemic events secondary to microemboli from either the CPB circuit or the aorta as the primary mechanism producing cerebral injury.[1,4,10–13] Further intraoperative cerebrovascular risk factors are related to the duration of extracorporeal circulation,[1,5] the temperature and pH management,[4,5,14–16] the induction of an inflammatory response, and probably also to a low mean arterial pressure (<50 mm Hg) in patients with impaired autoregulation.[1,4,12] Cerebral embolism may occur as a single macroembolus that results in hemiplegia or as multiple microemboli that can be

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Selected Abbreviations and Acronyms

CABG	= coronary artery bypass graft surgery
CMRGlc	= cerebral metabolic rate of glucose
CNS	= central nervous system
CPB	= cardiopulmonary bypass
FDG	= ^{18}F-2-fluoro-2-deoxy-D-glucose
HITS	= high-intensity transient signals
NPF	= neuropsychological function
NTB	= neuropsychological test battery
PET	= positron emission tomography
TCD	= transcranial Doppler ultrasonography

expected to result in a diffuse pattern of CNS injury rather than a focal deficit.[11] Possible sources of macroembolization and microembolization include air from the heart and open aorta or the oxygenator, debris from the aorta or cardiac valves, clots from the left atrium or ventricle, fat from cardiotomy suction, cellular aggregates, and particulate matter of silicone from the bypass pump.[4]

TCD is a useful technique to detect air, platelet, thrombus, atheroma, and fat microemboli as short-duration HITS.[17–20] With the aid of TCD, HITS can be quantified and their source located during CABG,[1,11,13,21–24] carotid endarterectomy,[25,26] angioplasty,[27] or angiography,[28] as well as in patients with carotid stenosis,[29–32] prosthetic cardiac valves,[29,32–36] atrial fibrillation,[36] myocardial infarction, and stroke.[37–39] However, the clinical sequelae of HITS detected by TCD are still under debate. Imaging techniques such as MRI[40] have been used to determine morphological changes after cardiac surgery with CPB, which may be related to the occurrence of microemboli. Also, a concordance between neuropsychological deficits and new postoperative morphological abnormalities has been described.[40]

To further elucidate the clinical significance of HITS occurring during cardiac operations, intraoperative transcranial embolus detection was performed in conjunction with preoperative and postoperative assessment of NPF and CMRGlc. It was hypothesized that the absolute number of HITS is related to changes of NPF and CMRGlc and that induced changes are somehow interrelated. A low-risk patient group was investigated to control for other risk factors known to cause cognitive dysfunction to study specifically the impact of HITS on altering brain function.

Subjects and Methods

Patients

Eighteen patients (mean age, 56.7±7.0 years; range, 42 to 69 years) with coronary heart disease underwent elective CABG in normothermia; of those, additionally, 1 patient had aortic and 1 mitral valve replacement. The following study exclusion criteria were used to control for subject variables: age >69 years, cardiac ejection fraction <50%, left ventricular end-diastolic pressure >15 mm Hg, diabetes mellitus, previous stroke (confirmed by cranial computed tomography), atherosclerosis of the carotid arteries (confirmed by duplex sonography), and stenosis of intracranial arteries (confirmed by TCD). To control for intraoperative cerebrovascular risk factors, arterial P_{O_2}, P_{CO_2}, and pH were kept at normal levels, and the mean arterial pressure was kept above 50 mm Hg throughout the operation. The parameters of the intraoperative management are shown in Table 1. The protocol was approved by the Ethics Committee of the Medical Faculty of the University of Cologne, and participating patients gave signed informed consent.

TABLE 1. Parameters of Intraoperative Management

Neuroleptanalgesia (midazolam, fentanyl)
Continuous bilateral recording of HITS by TCD
Normal values for body temperature, Pa_{O_2}, Pa_{CO_2}, and pH
Mean arterial pressure >50 mm Hg
Cannulation of ascending aorta for orthograde perfusion
Selective cannulation of venae cavae
Infusion of cardioplegic solution separately in aortic root
Aortic vent
Bypass ventilation in head-down position
Membrane oxygenators (0.2 μm; Maxima, Medtronic)
40-μm arterial line filter (No. 40066, Sartorius)

Embolus Detection (TCD)

During the operation, bilateral transcranial detection of HITS within the proximal middle cerebral artery (depth, 50 to 62 mm) was performed continuously from aortic cannulation to bypass discontinuation with use of a 2-MHz pulsed-wave TCD probe (Multidop X, DWL). Bilateral transducers were positioned on the patient's temple with aid of an ear/nose-fixed transducer-holder to fix the probe while allowing optimal positioning. HITS were identified as high-amplitude, unidirectional, transient signals <0.1 second in duration and associated with a characteristic chirping sound.[20] They were recorded on disk for later review and evaluation. Only HITS >8 dB above background were counted. As introduced by Barbut et al,[21] the number of HITS occurring within 4 minutes of the following operative events were registered: aortic cannulation, aortic cross-clamping, aortic cross-clamp release, tangential aortic clamping, opening of central anastomoses, and aortic decannulation. HITS occurring during stable bypass were categorized as interim signals.[21]

Cerebral Glucose Consumption (PET)

One day preoperatively and 8 to 12 days postoperatively, the CMRGlc was measured by means of FDG-PET, with standard patient positioning. For all PET studies, a positron scanner with 24 detector rings (ECAT EXACT HR [8 patients] or ECAT EXACT [10 patients], Siemens CTI) was used. After intravenous injection of approximately 370 MBq FDG, 47 contiguous transaxial image planes (slice thickness, 3.125 mm [ECAT EXACT HR] or 3.375 mm [ECAT EXACT]) were obtained. The data were reconstructed to a 128×128 matrix by filtered back-projection by application of a Hanning filter with a cutoff frequency of 0.4 cycles/pixel. The transaxial and axial spatial resolution varied between 3.6 mm (ECAT EXACT HR) and 5.8 mm (ECAT EXACT) full width at half maximum at the center.[41] Scans between the 20 and 60 minutes of data acquisition and multiple arterialized blood samples were used to calculate CMRGlc based on the Sokoloff model, with adaption of K_1 to measured activity.[42] Initial and follow-up studies were performed on the same scanner in each patient. With aid of a previously described coregistration procedure,[43] exact three-dimensional alignment of the two PET studies was performed to create follow-up PET brain slices with exact anatomic correspondence. An automated regions of interest evaluation procedure was applied to search for regional changes of CMRGlc between the two PET measurements in 31 cortical and subcortical infratentorial and supratentorial regions of each hemisphere.

Neuropsychological Test Battery

An NTB of 10 tests was used to assess cognitive, mnestic, and personality variables. FDG-PET and NTB were carried out 1 day preoperatively, 8 to 12 days postoperatively, and (NTB alone) 3 months postoperatively using identical or, if available, parallel subtests

TABLE 2. Intraoperative and Perioperative Variables of Interest

Patient	Age, y	Per Anast, n	Cen Anast, n	Cardiac Ischemia, min	CPB, min	HITS, n		Difference in Global CMRGlc, %
						L	R	
1	56	4	3	49	88	. . .	. . .	−3.25
2	55	3	2	78	123	369	319	−13.05
3	69	5	3	97	207	. . .	. . .	−14.48
4	62	5	4	76	144	207	392	−10.72
5	63	3	2	155	225	1685	1710	−2.2
6	59	3	2	56	87	93	125	−5.69
7	65	2	1	39	63	. . .	. . .	−15.84
8	58	3	2	45	84	375	545	−11.18
9	55	2	1	33	48	. . .	. . .	−12.57
10	51	4	3	64	155	349	393	−0.13
11	65	3	2	35	70	. . .	. . .	12.89
12	57	3	2	55	92	. . .	. . .	−10.7
13	45	5	4	86	149	393	505	2.81
14	54	1	1	58	86	1516	1699	−1.36
15	42	4	3	66	103	124	133	37.48
16	51	4	3	53	93	90	106	−5.28
17	60	3	2	46	76	142	172	−15.35
18	53	4	3	65	106	336	876	4.44
Mean	56.7	3.4	2.4	64.2	111.1	473.3	581.3	−3.57
SD	7.0	1.1	0.9	28.5	48.0	540.3	568.9	12.89
Range	42-69	1-5	1-4	33-155	48-225	90-1685	106-1710	P=.05

Per Anast indicates peripheral anastomoses; Cen Anast, central anastomoses.

of NTB. Patients had to avoid taking any anesthetic or analgesic medication at least 2 days before testing and imaging.

Statistics

The primary analysis focused on the absolute numbers of HITS in relation to operative events. The data for CMRGlc are reported as mean±SD of absolute values and as percent differences between the first (preoperative) and second PET measurement (8 to 12 days postoperatively) for 31 supratentorial and infratentorial regions of interest. Statistical analyses for the 2-sided nonparametric Wilcoxon test and Spearman rank correlations were performed with a commercial software package (SPSS 6.0; SPSS, Inc). The mean±SD values of the test scores were determined for each variable of the NTB, and a paired-samples t test was used for statistical analysis.

Results

All patients had an uneventful postoperative course, without any new neurological abnormalities detected by clinical neurological examination. HITS were detected in all patients and recorded in 10 patients with CABG (range, 90 to 876 counts/hemisphere) and 2 patients with valve replacement (range, 1516 to 1710 counts/hemisphere) (Table 2); in 6 patients recording failed because of operational or software failure. The number of HITS from inception until discontinuation of bypass was highly variable (196 to 3395 per patient), as was the duration of cardiopulmonary bypass (48 to 225 minutes). More HITS were recorded on the right side in 10 patients who underwent CABG only (357±243 versus 248±128 on the left; $P<.05$ by nonparametric Wilcoxon test). As expected, in both patients with combined CABG and valve replacement the number of HITS was significantly higher, with preference to the right hemisphere (patients 5 and 14 in Table 2). HITS were observed most often at the inception of and as interim signals during cardiopulmonary bypass (71.3% of all HITS) but also during aortic cannulation (3.6%) or cross-clamping (3.7%), release of cross-clamp (5.0%), tangential aortic clamping (9.9%), and opening of central anastomoses (4.6%).

Changes in global or regional glucose metabolism between the first and second PET measurement were generally mild (Table 3). Global CMRGlc decreased in all patients by 3.6±12.9% (P=.05; nonparametric Wilcoxon test) and in 8 of 18 patients (44%) by more than 10% (Table 2). Also, a decrease of regional CMRGlc was observed in 16 patients (89%). Regional CMRGlc changes were statistically significant in several cortical areas of both hemispheres (Table 3); no significant regional changes were observed for basal ganglia or most infratentorial regions. Individual maximal rCMRGlc reductions ranged between 1.1% and 27.4%. No correlations were found between the number of HITS, age of patient, duration of cardiac ischemia or CPB, or number of anastomoses and the changes in global or regional CMRGlc. Because cerebral microemboli are expected to cause focal alterations of CMRGlc, the maximal regional CMRGlc reduction below the global CMRGlc change was defined as

$$rCMRGlc_{deltamax} = [(rCMRGlc2-rCMRGlc1)/rCMRGlc1] - [(gCMRGlc2-gCMRGlc1)/gCMRGlc1]$$

TABLE 3. Global and Regional CMRGlc Alterations

	Left					Right				
	1st PET		2nd PET			1st PET		2nd PET		
Region	Mean	SD	Mean	SD	*P*	Mean	SD	Mean	SD	*P*
Global	37.7	4.9	36.0	4.6	.05					
Basal ganglia										
Thalamus	38.7	4.7	37.4	4.4	NS	38.7	5.4	37.4	5.2	NS
Ncl caudatus	41.6	5.0	40.7	5.4	NS	40.8	4.8	39.0	5.0	NS
Ncl lentiformis	41.8	4.8	41.3	4.2	NS	41.8	5.3	40.9	5.2	NS
Frontal lobe										
Gf medialis	41.8	5.9	39.6	5.7	.05	41.0	5.8	39.7	5.5	NS
Gf inferior	41.0	5.0	37.9	5.5	<.05	40.4	5.4	37.5	5.5	.01
Gf medius	42.0	5.4	39.4	5.9	<.05	40.8	5.6	38.3	5.9	<.05
Gf superior	39.7	5.1	37.6	5.6	NS	38.4	5.2	36.8	5.6	NS
G precentralis	39.5	5.1	37.9	5.6	NS	38.7	5.9	37.2	5.4	NS
Parietal lobe										
G postcentralis	37.4	5.3	36.1	4.9	NS	36.2	5.6	35.1	5.1	NS
G supramarginalis	38.0	5.3	35.5	4.7	<.05	37.2	5.6	35.0	5.0	<.05
G angularis	39.1	6.2	36.4	5.9	<.05	37.9	5.5	35.2	5.4	.01
L par superior	35.8	4.8	34.4	4.5	.05	35.5	5.5	33.5	4.8	<.05
Temporal lobe										
G parahippocampalis	32.5	4.6	32.2	3.9	NS	32.1	4.5	31.7	3.5	NS
G fusiformis	35.9	5.5	35.3	5.0	NS	36.1	5.5	35.1	5.0	NS
Gt inferior	35.2	4.6	33.4	4.7	<.05	34.7	5.0	33.0	4.7	<.05
Gt medius	37.7	5.3	35.7	5.1	NS	37.0	5.3	35.3	5.2	NS
Gt superior	35.7	4.6	34.3	4.7	NS	35.2	5.1	34.1	4.7	NS
Insula	39.9	4.8	38.6	4.9	NS	38.6	5.3	37.5	4.9	NS
Occipital lobe										
G lingualis	38.0	6.4	37.4	5.7	NS	37.8	5.8	36.7	5.6	NS
Cuneus	44.4	5.6	41.4	6.1	.01	43.7	5.6	40.9	5.3	<.01
Precuneus	43.6	5.3	41.2	5.6	<.05	43.2	5.4	40.8	5.1	.01
G occipitalis	35.1	5.0	33.5	4.7	<.05	34.6	4.9	33.2	4.7	<.05
Visual	40.7	5.1	39.2	4.8	NS	40.3	5.5	38.7	4.6	NS
G cinguli	40.0	5.0	38.2	5.0	NS	39.3	5.7	37.5	4.7	.05
Infratentorial										
Midbrain	28.7	4.3	28.9	3.4	NS	27.9	4.3	28.2	3.4	NS
Pons	28.3	4.3	28.4	3.5	NS					
Cerebellum	37.3	5.6	35.7	4.9	NS	36.8	5.4	35.2	4.5	<.05
Ncl dentatus	33.3	4.8	33.6	4.5	NS	34.4	4.4	34.5	4.1	NS
Vermis	36.2	5.0	35.4	4.6	NS					

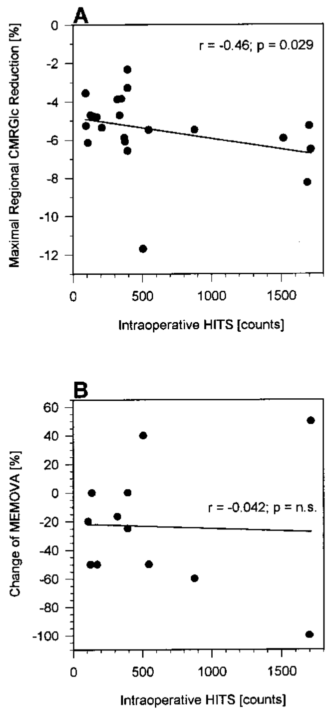
Ncl indicates nucleus; Gf, gyrus frontalis; G, gyrus; L par, lobus parietalis; and Gt, gyrus temporalis.

where 1 and 2 indicate the first and second PET measurement and r and g the regional and global CMRGlc values, respec-tively. In patients with recorded HITS and regional CMRGlc depression (n=11), the maximal decrease of rCMRGlc in each hemisphere below the individual global change of CMRGlc ($rCMRGlc_{deltamax}$) correlated with the number of HITS (by Spearman's rank correlation coefficient, $r=-0.46$, $P<.05$; Fig 1A).

Alterations of NPF were present 8 to 12 days postoperatively and involved the verbal long-term memory (MEMOVA), the visuospatial memory (Corsi block span), and the speed of cognitive information processing, which recovered within 3 months (see Table 4). Verbal memory and concentration scores as well as nonverbal long-term memory improved after 3 months above the preoperative level. The changes in NPF were not correlated with the number of HITS (Fig 1B) or the observed metabolic changes.

Discussion

HITS detected by TCD are common during cardiac operations, even in low-risk patients. They are related to the



A, Significant correlation between the maximal regional CMRGlc reduction below the global CMRGlc change ($rCMRGlc_{deltamax}$) and the number of HITS. B, No significant correlation between the percent change for the test for verbal long-term memory (MEMOVA; see Table 4) between the first and second measurements (columns A and B in Table 4) and the number of HITS detected over the right MCA. Similar results were obtained for the other neuropsychological tests listed in Table 4. r indicates Spearman's rank correlation coefficient.

cardiopulmonary bypass and, to a minor degree, to specific operative procedures, eg, aortic manipulation. In this study, the absolute number of HITS did not correlate with alterations of neuropsychological function or global cerebral glucose metabolism but did correlate with regional changes of CMRGlc. The individual regions maximally involved were located in different areas of the brain for each patient. This might be due to individual differences in vascular anatomy and the fact that the number of HITS occurring in one area depends on selective streaming in individuals.[44] The significant right-to-left difference of the number of HITS in our study supports this hypothesis in that emboli caused by cardiac operations may follow preferably the right brachiocephalic trunk. Taken together, the findings from this study indicate that cognitive changes after cardiac surgery depend more on the location of HITS-related brain damage than on the number of HITS alone. Furthermore, the lack of a correlation between the number of HITS and alterations of gCMRGlc and NPF points to additional factors that might influence postoperative differences. We tried to control for many of the above-mentioned subject and intraoperative variables, which are known to cause cognitive dysfunction after cardiac surgery and which might also alter CMRGlc, by avoiding hypotension in patients during surgery and discontinuing analgesic and anesthetic medications at least 2 days before PET imaging. Still, confounding variables could include early postoperative brain swelling,[45] late effects from anesthesia,[46] or changes in cardiac output. Unfortunately, control PET studies of CMRGlc after noncardiac surgery, to assess specifically the influence of anesthesia on postoperative brain function, are not available.

In accordance with findings in previous studies,[21,47] HITS were observed in all patients. The number of HITS recorded from the inception to discontinuation of bypass was highly variable; however, their relation to operative events was similar. HITS were observed most often at the inception of and as interim signals during extracorporal circulation (71.3%). Less frequently, they occurred during aortic manipulation (22.2%). This is in accordance with Baker et al,[23] who found the rate of HITS to be highest at the onset of bypass. They stated that a significant number of microembolic events must arise from the bypass circulation at this stage. In contrast, Barbut et al[21] detected the majority of HITS during aortic manipulation, especially during removal of the aortic cross-clamp. These different observations can be explained by the differences in age and atherosclerotic state of the patient population under investigation. Whereas HITS detected at aortic manipulation are thought to represent dislodgement of fragments of atheromatous plaques from the aortic wall, HITS at the inception and during extracorporal bypass are presumed to result from air bubbles or platelet clumps in the bypass equipment.[21]

Postoperatively, global and regional changes of CMRGlc were generally mild. In 44% of patients, the mean reduction of global CMRGlc was below a previously reported 10% limit of change in global CMRGlc between two PET measurements within 24 hours in normal subjects.[48] Moody et al[10] could demonstrate the presence of numerous capillary and small arterial dilatations in the penetrating vessels of the brain in patients after cardiac surgery, which appeared to reflect the ghosts of microemboli. The characteristic features were those of sausage-like dilatations along the penetrating small vessels with intact capillary or arteriolar walls and empty lumens. These were calculated to be in the millions in number, but most of them cleared by 1 week after operation. In their vicinity, focal vacuolation, neuronal loss, and gliosis were found. If disseminated equally throughout the brain, they might be the cause of a global reduction in glucose metabolism; if accumulated locally, a regional depression of CMRGlc would exceed the global one. In this study, a correlation between the number of HITS and the maximal regional CMRGlc depression ($rCMRGlc_{deltamax}$) below the global CMRGlc depression was present, indicating that a high number of HITS may be the cause of regional CMRGlc alterations. However, the missing relation between HITS and changes in global CMRGlc points to additional factors influencing postoperative differences (see above). Furthermore, the histological findings of Moody et al[10] suggest that only a small proportion of all microemboli (0.1% to 1.0%) may be detected as HITS by TCD. Microemboli may well be quite small during surgery, producing no HITS and small ischemic lesions beyond the resolution of PET and being responsible for the lack of correlation between the above-mentioned parameters.

In contrast to Toner et al,[40] who described a concordance between postoperative morphological changes on MRI and

TABLE 4. Neuropsychological Test Battery

Task	A	B	C	P<.05
Memory				
Verbal Selective Reminding Task	6.3	6.3	7.0	A & B < C
(max 10 words)	(0.9)	(1.2)	(1.0)	
Delayed recall (MEMOVA)	5.3	4.2	5.5	A > B (<C)
(max 10 words)	(1.9)	(2.5)	(2.6)	
Rey-Osterrieth Figure				
Copy	33.3	33.9	34.8	NS
(max 36 points)	(3.2)	(3.4)	(1.3)	
Delayed reproduction	17.1	21.3	20.8	A < B & C
(max 36 points)	(6.2)	(5.5)	(6.4)	
Corsi Block Span (~7±2)	5.2	4.7	5.0	A > B (<C)
	(0.8)	(1.0)	(0.9)	
Language				
FAS Test (words)	27.6	29.5	34.4	A < C
	(6.5)	(8.4)	(11.3)	
General intelligence				
Leistungsprüfsystem (C score)	5.5	5.5	5.9	A & B < C
	(1.3)	(1.4)	(1.2)	
Information processing				
Modification of Trail-Making Test	126.4	118.8	114.6	C < A
(in seconds)	(34.0)	(29.9)	(33.4)	
Digit Symbol Test (WAIS-R)	35.2	32.8	36.9	(A >) B < C
(items)	(8.3)	(9.2)	(10.3)	
Attention/concentration				
Concentration Endurance Test (d2),	343.2	362.8	373.3	NS
PR=50	(76.2)	(65.5)	(79.0)	
Mood				
Beck Depression Inventory	6.3	6.6	5.8	NS
(mild depression >18.7)	(4.9)	(4.4)	(3.7)	
State Trait Anxiety Inventory (20-80)	37.0	33.7	33.8	NS
	(8.5)	(7.8)	(8.0)	

Max indicates maximum; MEMOVA, verbal long-term memory test; NS, not statistically significant; FAS, fluency test; WAIS-R, Wechsler Adult Intelligence Scale-Revised; and PR, percent range. Values in parentheses indicate standard deviations.

neuropsychological deficits in a small patient group, Schmidt et al[49] failed to demonstrate CABG-related microembolic lesions on postoperative MRIs. We also did not find a correlation between neuropsychological deficits and the HITS-induced changes of $rCMRGlc_{deltamax}$, which might have two reasons. First, although neurobehavioral testing provides a sensitive, objective, reliable, and valid means[50] to evaluate the function of the brain to determine the presence of trauma, the severity of behavioral dysfunction does not necessarily correlate with the extent of structural damage. The location of the lesion is generally more important than the volume of tissue disrupted for predicting the social consequences of the CNS insult.[50] Second, the smallest emboli are widely distributed and are likely to be the cause of rather general neuropsychologic changes[12]; they cause microstructural damage,[10] which may be easily missed by any available imaging method. On the other hand, NPF reveals only brain damage of functionally important areas, whereas imaging methods such as PET or MRI are able to reveal the "true" in vivo imageable extent of structural damage after cardiac surgery. Therefore, the measurement of the cerebral glucose metabolism seems to be a complementary tool for demonstrating the possible extent of damage induced by a cardiac operation, which might not be directly related to functional or behavioral impairment but reveals clinically subtle brain damage.

As discussed previously,[9] our results support the views that the two major etiologic factors of neurological dysfunction after CABG, emboli and hypoperfusion, are not exclusive but interrelated, and that they may operate concurrently in every patient, although to different and somewhat unpredictable proportions.

In summary, the causes and mechanisms of CNS injury after cardiac operations are complex and multifactorial and include not only the occurrence of HITS or cerebral emboli, respectively, but also differences in vascular anatomy and other factors, such as postoperative brain swelling and/or effects from anesthesia. With respect to HITS, two variables seem to influence the occurrence of neurological complications: the number of HITS (as shown in previous studies) and the location of HITS-related brain damage (as demonstrated in this study). In patients without signs of generalized atherosclerosis, the HITS detected by TCD during cardiac surgery are primarily related to the CPB and only to a minor degree to aortic manipulation. They might be the cause of a postoperative diminution of regional CMRGlc, superimposing a multifactorial global CMRGlc reduction. As the occurrence of HITS and alterations of NPF and CMRGlc seem to be only partly related to each other, the use of behavioral tools for the assessment of brain function after cardiac surgery should be complemented by other measures of CNS functional integrity such as PET, which can reveal additional, clinically subtle, brain damage.

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