The Effect of Coronary Artery Bypass Surgery on Brain Perfusion

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Coronary artery bypass grafting (CABG) is one of the major treatment methods of coronary artery disease. CABG is an open-heart surgery that uses cardiopulmonary bypass (CPB). After CPB, it is well known that neurological and neuropsychological complications may occur. The purpose of this study was to evaluate brain perfusion patterns before and after CPB and to locate brain perfusion changes in patients with neurological and neuropsycological complications after CPB. **Methods:** Twenty-five patients who underwent open-heart surgery (22 CABG, 3 valve replacement) and 5 patients (4 cholecystectomy, 1 periferic vascular surgery) as a control group were included in the study. The ^{99m}Tc-HMPAO injected dose was 925 MBq. Brain perfusion SPECT images were obtained 30–60 min postinjection using a dedicated triple-head brain SPECT camera. Imaging was performed 1 wk before and 4–6 wk after surgery. Technetium-99m-HMPAO brain SPECT slices were evaluated visually and semiquantitatively. **Results:** None of the patients had severe neurologic complications. Neuropsychological deficits occurred in eight patients after CABG. Cognitive deterioration and depressive mood occurred in five patients. Disorientation, agitation and confusion periods were present in another two patients. Frontal hypoperfusion was found in these patients by visual and semiquantitative evaluations ($p = 0.0277$) and left parietal hypoperfusion was also present semiquantitatively ($p = 0.0277$). Visual hallucinations occurred in one patient. Computed tomography of these patients was normal. No perfusion abnormalities were observed in the patient with visual hallucinations and in patients without symptoms after open-heart surgery nor in the control group. Brain SPECT was repeated in two symptomatic patients 5 mo after CABG. Frontal hypoperfusion became normal, and these patients' symptoms disappeared. **Conclusion:** The results of this study indicate that regional cortical hypoperfusion may occur in patients with neuropsychological complications after CABG. Technetium-99m-HMPAO brain SPECT is a useful method to locate and determine brain perfusion changes after CABG.

Key Words: technetium-99m-HMPAO; brain perfusion; SPECT; coronary artery bypass surgery

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Coronary artery bypass grafting (CABG) has become a widely accepted method for the treatment of coronary artery disease. Although mortality after CABG is very low (2%–3%), morbidity resulting from neurological and neuropsychological complications has been relatively high (*1–11*). The reported incidence of major neurological complications such as stroke, seizure and diffuse encephalopathy varies between 2%–5%. The incidence of minor neurological symptoms such as nystagmus, decreased coordination, hyporeflexia and abnormal sensation may occur in 20%–25% of the patients. Neuropsychological complications such as affective changes, depressive mood and decreased attention, and memory and concentration abilities may occur in 20%–75% of the patients after CABG (*1–11*). Hence, there is growing interest in this topic.

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The mechanisms of these neurological and neuropsychological complications are not well understood. It has been reported that micro- and macroemboli, low mean arterial pressure, patient's age, previous neurologic and psychiatric diseases, operation time, pump or cardiopulmonary bypass (CPB) time, type of oxygenator system and pulsatile or nonpulsatile bypass may be contributing factors for these complications. These factors may alter cerebral perfusion during and after CABG (*1,2,5–7,9,10–15*).

The purpose of this study was to investigate: (a) the presence of regional brain perfusion alterations, which can be demonstrated with ^{99m}Tc-HMPAO brain perfusion SPECT before and after CABG; (b) the relationship between neurological and neuropsychological complications and regional brain perfusion abnormalities; and (c) whether these regional brain perfusion alterations are persistent or transient.

MATERIALS AND METHODS

Patients

Twenty-five patients who had open-heart surgery (22 CABG, 3 valve replacement) and 5 patients (4 cholecystectomy, 1 periferic vascular surgery) as a control group were included in the study. The mean age of the patients (10 women and 15 men) was 55.7 ± 6. The mean age of the control group (4 women and 1 man) was 53.8 ± 5.

All patients were examined 1 wk before and 4–6 wk after the operation. Only one patient was examined 1 wk before, 9 days and 6 wk after the operation. Neurologic, neuropsychologic, echocardiographic and coronary angiographic examinations were performed in patients with open-heart surgery. Carotid doppler ultrasonography (Toshiba, SSH-140A, Toshiba Corp., Tokyo, Japan) was performed in seven patients with clinically and symptomatologically suspected carotid artery obstruction. No significant carotid artery disease was found. Patients who had previous neurologic, psychiatric illnesses and depressed personality features were excluded. The patients who required intra-aortic balloon pumping before CABG and emergent surgery were also excluded. Control patients underwent the same diagnostic workup except coronary angiography and had to be free of cardiac and neurologic diseases. Two patients in the CPB group and one patient in the control group were left-handed. Informed consent was obtained from all patients in this study. Patients' characteristics are summarized in Table 1.

Operation Procedures

CABG and valve replacement (mitral or aortic) were performed in elective conditions. The anesthetic protocol consisted of premedication with diazepam (0.2 mg/kg) and induction with penthotale (3–5 mg/kg), fentanyl (5–6 μg/kg) and norcurone (0.1 mg/kg) and maintenance with isoflurane (% 0.4–0.5 MAC). The anesthetic protocol was similar in the open-heart surgery and control groups.

Patients were given 3 mg/kg of intestinal mucosa heparin, supplemented as needed, to maintain an activated clotting time of at least 400 sec and over. A membranous oxygenator was used.

TABLE 1
Characteristics of Coronary Artery Bypass Surgery, Valve Replacement and Control Group Patients

Variable	CABG (n = 22)	VR (n = 3)	CP (n = 5)
Age (yr)	55.7 ± 6	53 ± 12	53.8 ± 5
LVEF (%)	58.4 ± 8.6	60 ± 5.1	65 ± 2.1
Previous myocardial infarction	6	0	0
Previous neurologic and psychiatric illnesses	0	0	0
Hypertension	6	0	0
Diabetes mellitus	3	0	0

CABG = coronary artery bypass grafting; VR = valve replacement; CP = control patients; LVEF = left ventricular ejection fraction.

Arterial blood gases were sampled every 15 min. The circuit was primed with lactated Ringer's solution (Baxter/Eczacibasi, Istanbul, Turkey), 20 ml/kg, with blood added as necessary to achieve a hematocrit value of approximately 25% during bypass. Before bypass, the priming solution was circulated through a Micropor filter (Microtropper, Miramed, Mirandola, Italy). Nonpulsatile flow was used in 14 patients; pulsatile flow was used in 11 patients. Mean patient body temperature was 28°C. The full-flow was used during CPB. The perfusion pressure was similar in all CPB patients and mean perfusion pressure was 60 mmHg. The average operation parameters are summarized in Table 2.

Imaging Procedures

Brain SPECT imaging was performed concurrently with neurologic and neuropsychological examinations (1 wk before and 4–6 wk after operations). Within 5 min after labeling, 925 MBq (25 mCi) of ^{99m}Tc-HMPAO (Ceretec®, Amersham Medical Limited, Buckingamshire, England) was injected. Radiochemical purity exceeded 90% when tested by instant thin-layer chromatography (Gelman Instrument Co., Ann Arbor, MI). In a quiet dark room, the radiopharmaceutical was injected with the patient's eyes closed and ears covered. Within 30–60 min postinjection, scans were performed with a multidetector SPECT system (Neurocam, GE, Medical Systems, Milwaukee, WI) using high-resolution collimation. Data were acquired over 30 min as 128 projections into 64 × 64 digital matrices (each pixel 4 × 4 mm). These data were preprocessed using a modified Metz filter (based on a Gaussian line spread function with FWHM = 11 mm, order of 4) and were reconstructed by filtered backprojection with a ramp filter. Attenuation correction was applied to the data using the commercially supplied Sorenson method (GE Medical systems, Star 4000 computer, Milwaukee, WI). Oblique reorientation was performed to yield 2-pixel-thick (8 mm) transaxial images parallel to the orbitomeatal line. Visual evaluations of the images were performed independently by two nuclear physicians. There was no disagreement between the physicians. Semiquantitative evaluations were performed by drawing irregular regions of interest (ROIs) in five standardized 8-mm-thick oblique slices corresponding to anatomical levels. ROIs were drawn first on the right hemisphere (10 ROIs), then mirrored ROIs were placed on the left hemisphere (Fig. 1). The ROIs were initially drawn for the preoperative study and then copied for the postoperative study. The cortex:cerebellum mean counts per pixel ROI ratios were obtained from single slices that best depicted these anatomic regions.

TABLE 2
The Average Value of Operation Parameters

Parameter	CABG (n = 22)	VR (n = 3)
Operation time (min)	176.4 ± 65	153.5 ± 28
CPB time (min)	89.3 ± 28	54.3 ± 11
ACC time (min)	45.4 ± 13	44.7 ± 13

CABG = coronary artery bypass grafting; VR = valve replacement; CPB = cardiopulmonary bypass; ACC = aortic cross clamp.

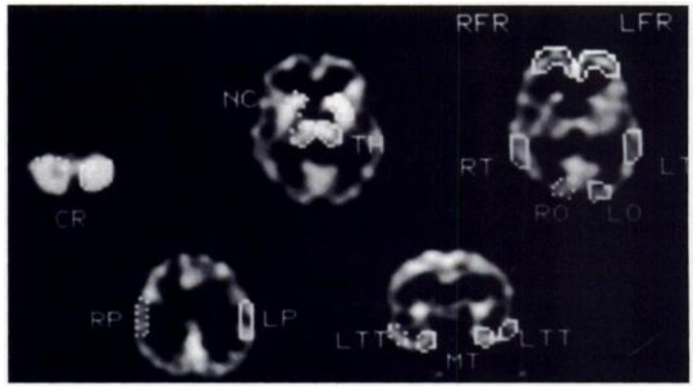

FIGURE 1. Template used to draw regions of interest. CR = cerebellum; RFR = right frontal cortex; LFR = left frontal cortex; RT = right temporal; LT = left temporal; RO = right occipital; LO = left occipital; RP = right parietal; LP = left parietal; TH = thalamus; NC = nucleus caudatus; LTT = lateral temporal; MT = mesial temporal.

All results were expressed as mean ± 1 s.d. The differences between preoperative and postoperative regional cerebral blood flow (rCBF) values were tested with the Wilcoxon test. The operation parameter differences between symptomatic and asymptomatic patients were tested using the Mann–Whitney U-test.

A p value of <0.05 was considered to be significant.

RESULTS

After CABG and valve replacements, severe focal neurological signs did not appear. Three patients demonstrated abnormal sensation in the distribution of the saphenous nerve related to the long saphenous vein removed during the operation. One patient also showed abnormal signs associated with unilateral damage to the lower trunk of the brachial plexus.

Neuropsychological Deficits and Visual Evaluations

Neuropsychological deficits occurred in eight patients. Deterioration of memory, concentration and attention abilities as well as depressive mood occurred in five patients. Visual hallucinations were present in one patient. The symptoms were started on early postoperative periods and these six patients were symptomatic at the time of brain perfusion SPECT. Frontal hypoperfusion was seen in all five patients with cognitive deterioration and depressive mood (Figs. 2 and 3). No perfusion abnormality was found in the patient with visual hallucinations. Five months after the operation, ^{99m}Tc-HMPAO SPECT imaging was repeated in two patients with cognitive deterioration and depressive mood. The symptoms of these two patients disappeared and frontal hypoperfusion became normal (Fig. 3).

Disorientation, agitation and confusion periods were present in another two patients. Disorientation, agitation and confusion periods appeared on the 2nd postoperative day and continued for 3 days in one patient. This patient could not be imaged during the symptomatic period because of immobilization. Six weeks after the operation, there was no abnormal finding in brain perfusion SPECT of this patient. In another patient, these symptoms appeared on the 4th postoperative day and continued for 10 days. Brain perfusion SPECT performed 9 days after CABG showed marked frontal and temporoparietal hypoperfusion in the symptomatic period. Six weeks after the operation, frontal and parietal cortical perfusion increased and symptoms improved in this patient (Fig. 4).

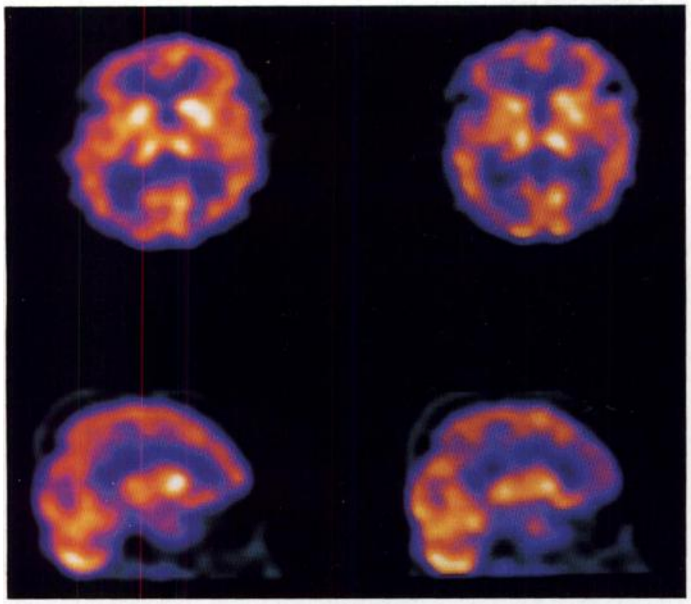

FIGURE 2. Technetium-99m-HMPAO SPECT images of a 53-yr-old patient with CABG. Axial (top) and sagittal (bottom) images. Left column before surgery and right column after surgery. Frontal hypoperfusion is seen after surgery.

All symptomatic patients' CT scans were normal. There was no regional brain perfusion alterations in a patient who had visual hallucinations, in asymptomatic patients and in controls.

Symptoms did not correlate with perfusion and operation time. However, a significant correlation existed between the aortic cross clamp times ($U = 27.0$, $p = 0.05$) and the age of the patients ($U = 24.0$, $p = 0.0316$). Table 4 further illustrates these findings.

Semiquantitative Evaluations

In semiquantitative evaluations, the frontal cortex:cerebellum ratio significantly decreased in symptomatic patients ($z = -2.2014$, $p = 0.027$). There was also a decreased left parietal: cerebellum ratio in these patients ($z = -2.2014$, $p = 0.027$) (Table 4).

DISCUSSION

It has been well documented that neurological and neuropsychological complications may occur after CABG (*1–11*). In this study, although there was no patient with major focal neurological complications, there were five patients with minor neurologic signs (20%) and eight patients with neuropsychological complications (32%). The incidence of these complications was consistent with the previously reported data (*3,5,6,8*).

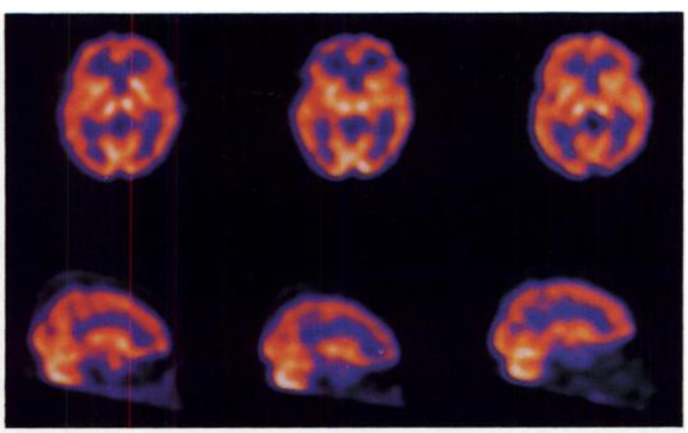

FIGURE 3. Technetium-99m-HMPAO SPECT images of a 55-yr-old woman with CABG. Axial (top) and sagittal (bottom) images. Left column before surgery, middle column 6 wk after surgery and right column 5 mo after surgery. She had cognitive deterioration and depressive mood at 6 wk after surgery. Frontal hypoperfusion is seen at this time. Five months after surgery, the patient was asymptomatic and frontal perfusion increased.

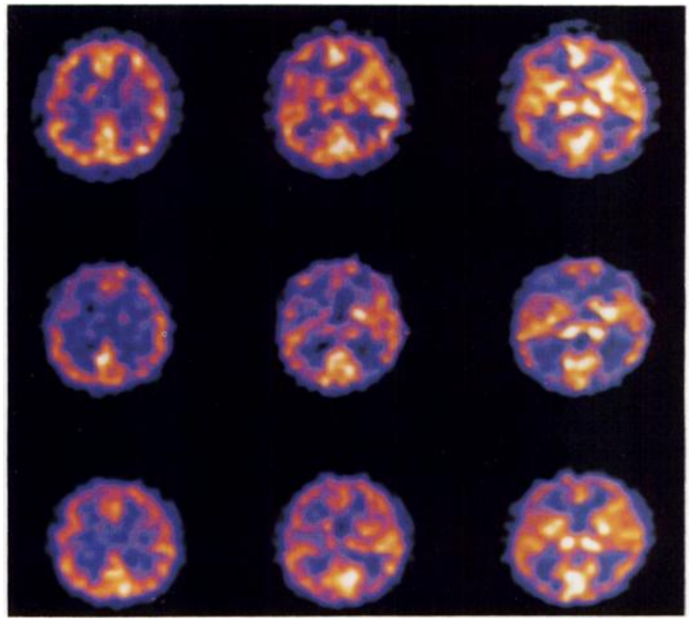

FIGURE 4. Technetium-99m-HMPAO SPECT axial images of a 58-yr-old patient with CABG. Upper row before surgery, middle row 9 days after surgery and lower row 6 wk after surgery. Bilateral parietal and frontal hypoperfusion is seen 9 days after surgery. (The patient had disorientation, confusion and agitation attacks at this time.) Six weeks after surgery, bilateral parietal and frontal perfusion increased and the patient's symptoms improved.

The mechanisms of these complications are not well understood. Most authors suggest cerebral dysfunction after CABG as a feature of cerebral damage, which occurs during surgery (*1,5,9–11*). Long bypass time, the presence and duration of low levels of mean arterial blood pressure and the patient's age contribute the most to these complications. Micro- and macroemboli, types of flow, oxygenator and acid-base system are other reported factors. Cerebral perfusion changes during bypass may be a more important cause of neuropsychological complications than focal neurologic deficits. Low cerebral blood flow during CPB may cause transient and reversible diffuse neuronal derangement rather than permanent cell death (*5*). Schmidt et al. investigated whether there is any relationship between silent focal ischemic lesions on MRI and encephalopathy after CABG. They did not find any relationship between silent focal ischemic lesions and encephalopathy after CABG and reported that the only MRI finding was ventricular enlargement after CABG (*16*). In our study, CT scans of patients with

TABLE 3
Comparison of Ages and Operation Parameters of Symptomatic and Asymptomatic Patient Populations

Parameter	Patients with symptoms	Patients without symptoms
Age (yr)	$59.6 \pm 2.7^{\dagger}$	53.2 ± 7.0
Operation time (min)	181.7 ± 91.9	175.4 ± 40.4
CPB time (min)	95.7 ± 32.5	74.2 ± 22.5
ACC time (min)	$53.5 \pm 11.2^{*}$	42.6 ± 13.3

*U = 27.0, p = 0.05.
†U = 24.0, p = 0.0316.
CPB = cardiopulmonary bypass; ACC = aortic cross clamp.

TABLE 4
Relative Regional Perfusion: Regions of Interest: Cerebellum Average Ratios Before and After Surgery in Patients with Symptoms and without Symptoms

Region of interest	Patients with symptoms		Patients without symptoms	
	Before surgery	After surgery	Before surgery	After surgery
Right frontal	0.80 ± 0.07	0.73 ± 0.03*	0.80 ± 0.06	0.80 ± 0.05
Left frontal	0.82 ± 0.05	0.77 ± 0.04*	0.82 ± 0.06	0.81 ± 0.05
Right temporal	0.81 ± 0.04	0.80 ± 0.04	0.82 ± 0.07	0.80 ± 0.06
Left temporal	0.84 ± 0.05	0.83 ± 0.06	0.81 ± 0.06	0.82 ± 0.05
Right parietal	0.79 ± 0.05	0.78 ± 0.05	0.80 ± 0.07	0.81 ± 0.03
Left parietal	0.83 ± 0.05	0.79 ± 0.05*	0.82 ± 0.07	0.82 ± 0.05
Right occipital	0.90 ± 0.07	0.91 ± 0.05	0.93 ± 0.08	0.92 ± 0.09
Left occipital	0.91 ± 0.07	0.92 ± 0.05	0.94 ± 0.09	0.91 ± 0.06
Right thalamus	0.89 ± 0.08	0.89 ± 0.05	0.87 ± 0.11	0.90 ± 0.06
Left thalamus	0.91 ± 0.05	0.90 ± 0.09	0.87 ± 0.08	0.90 ± 0.06
Right nucleus caudatus	0.93 ± 0.11	0.90 ± 0.14	0.90 ± 0.07	0.87 ± 0.11
Left nucleus caudatus	0.92 ± 0.09	0.89 ± 0.14	0.89 ± 0.08	0.90 ± 0.06
Right mesial temporal	0.76 ± 0.04	0.75 ± 0.04	0.73 ± 0.14	0.78 ± 0.09
Left mesial temporal	0.77 ± 0.05	0.76 ± 0.06	0.75 ± 0.11	0.79 ± 0.08

*z = −2.2014, p = 0.0277 (p ≤ 0.05 is accepted as significant).

neuropsychological deficits were normal. These findings may support the assertion that low cerebral blood flow during CPB may cause reversible diffuse neuronal derangement rather than permanent cell death.

Gökgöz et al. reported regional brain perfusion changes in nine patients, six of whom were diagnosed to be in delirium state on psychiatric examination after CABG (*24*). They found that right and left anterior parietotemporal, right frontal, left occipital and right and left temporoparietal cortices demonstrated significant postoperative hypoperfusion on the 4th postoperative day. They reported that on the 15th postoperative day, although cerebral perfusion of four patients having left anterior temporoparietal hypoperfusion improved slightly, the decrease in cerebral perfusion remained and the cerebral perfusion of the other five patients increased. In our study, only one patient with confusion, agitation and disorientation attacks was imaged in early postoperative period (9 days after operation). This patient had bilateral frontal and temporoparietal hypoperfusion. Six weeks after the operation, the symptoms of the patient improved and the perfusion of frontal and temporoparietal cortices increased.

Our study showed frontal and parietal hypoperfusion in patients with cognitive deterioration and depressive mood both visually and semiquantitatively. Frontal hypoperfusion disappeared in two patients and the symptoms of these two patients also improved 5 mo after CABG. These SPECT findings might be consistent with the patients' symptoms because frontal cortex hypometabolism and decreased blood flow are reported in the patient with depression and in some patients with dementia (*17–23,25*). On the other hand, it is difficult to explain whether frontal and parietal hypoperfusion is a reflection of transient derangement of neuronal cells due to CABG or decreased metabolic activity resulting from depression. Depression after CABG may also be due to patients' physical and emotional condition related to a major surgical procedure and postoperative status (*3,8*).

Roine et al. (*26*) found frontal hypoperfusion in 77% of patients 24 ± 2 hr after cardiac arrest with ^{99m}Tc-HMPAO SPECT. They reported that while frontal hypoperfusion improved in parallel with recovery, it was persistant in most of patients during follow-up. Most regional perfusion defects that are described in this study were not observed in later neuroradiological examinations, that is, they did not lead to completed infarction. In another trial, generalized decrease in glucose metabolism was demonstrated in 12 patients, 1–6 mo after cardiac arrest by PET (*27*). DeVolder et al., found frontomesial hypometabolism in 5 of 12 patients whereas parietooccipital hypometabolism was more common. The physiopathologic conditions should be quite different in postanoxic syndrome after true cardiac arrest than after cardiac arrest during cardiopulmonary bypass. Blood circulation is supported by the extracorporal circulation system in cardiac arrest during CPB whereas exact circulatory arrest occurs during true cardiac arrest. It is of interest that decreased (during CPB) or interrupted (during cardiac arrest) cerebral blood flow may lead to frontal hypoperfusion.

Long aortic cross clamp time, age and nonpulsatile flow are the possible risk factors for neuropsychological complications in this study. The risk factor increases as the aortic cross clamp time and patient age increases. We did not find any relationship between operation time, pump time and the symptoms, but aortic cross clamp time was significantly longer in symptomatic patients than in asymptomatic patients and control subjects. Pulsatile flow was used in 11 asymptomatic patients and only 1 symptomatic patient. Use of pulsatile CABG has been reported to reduce neuropsychological complication rates and to prevent intraoperative hypothalamic and pituitary stress responses. It also enhances intraoperative cerebral blood flow and metabolism (*6,28,29*).

CONCLUSION

Regional brain perfusion abnormalities may occur in patients with neuropsychological complications after CABG. These abnormalities may be demonstrated with ^{99m}Tc-HMPAO brain SPECT imaging. Our findings suggest that regional brain perfusion alterations in patients with neuropsychological complications may be reduced by using shorter aortic cross clamp times and by using pulsatile flow. The regional brain perfusion alterations might be related to symptoms of patients with neuropsychological complications, but further studies are needed.

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Dual Spillover Problem in the Myocardial Septum with Nitrogen-13-Ammonia Flow Quantitation

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Conventional cardiac PET modeling techniques for [^{13}N]ammonia flow determination do not fully account for the effects of spillover of activity from the right ventricle (RV) onto the activity in the myocardial septum. The purpose of this study was to investigate and to quantitatively account and correct for this effect. **Methods:** Simulations were performed to determine the error introduced by conventional quantitation using septal time-activity curves, which only account for left ventricle (LV) spillover. Furthermore, we explored two separate methods to account for the dual spillover problem: direct estimation of the RV and LV spillover fractions incorporated into the [^{13}N]ammonia model by using the LV and RV input functions in the fit and estimation of the relative dispersion and time shift between the LV and RV input functions by fitting using only the LV input function. The simulated curves were fitted using a two-compartment [^{13}N]ammonia model. Flow estimates from the conventional model and the models including either of the two correction procedures were compared with canine microsphere data. **Results:** The influence of RV spillover on flow estimation in the septum is determined by several parameters (e.g., dispersion between the RV and LV input function). Depending on the value of these parameters, the septal flow may be underestimated by 0%–30%. The applied methods for correction of the dual spillover problem were comparable and allow for more accurate quantitation in the septum. The canine microsphere data revealed that flow underestimation in the septum is small but significant. **Conclusion:** Dual spillover in the myocardial septum can introduce significant errors in the estimation of flow by the conventional [^{13}N]ammonia model fitting method, which does not properly account for the RV spillover. Adjusting for the RV spillover in one of the two proposed methods allows for more accurate quantitation of myocardial septal flow with [^{13}N]ammonia PET data.

Key Words: PET; myocardial blood flow; septum; nitrogen-13-ammonia

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