# Neurocognitive and neuroanatomic changes after off-pump versus on-pump coronary artery bypass grafting: Long-term follow-up of a randomized trial

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**Objective:** It is unknown whether avoidance of cardiopulmonary bypass during coronary artery bypass grafting affects cerebral injury or long-term neuropsychological function.

**Methods:** Two hundred unselected patients were randomized to off-pump coronary artery bypass or on-pump coronary artery bypass grafting between March 2000 and August 2001. One hundred sixty-eight patients had early postoperative brain magnetic resonance imaging. Eighty-seven returned after a mean of 7.5 years of follow-up; 67 had repeat magnetic resonance imaging, and 76 had neuropsychological testing.

**Results:** There were 26 deaths among patients undergoing off-pump coronary artery bypass and 31 among patients undergoing cardiopulmonary bypass as of March 2009. Seventy-six patients (41 undergoing cardiopulmonary bypass and 35 undergoing off-pump coronary artery bypass) had neuropsychological testing at late follow-up. Groups were similar in age, sex, depression, and IQ. Patients undergoing off-pump coronary artery bypass showed better attention, performing better at tracking and mentally manipulating information ($P = .011$). Patients undergoing off-pump coronary artery bypass demonstrated better cognitive reasoning and made fewer errors in reasoning ($P = .05$); they also showed a trend toward better verbal learning ($P = .064$). There were no domains in which patients undergoing cardiopulmonary bypass outperformed those undergoing off-pump coronary artery bypass. Early magnetic resonance imaging in 168 patients showed no significant differences between groups in temporal or frontal lobe atrophy, subcortical white matter lesions, or acute infarctions. There were no significant differences between groups in atrophy over time or new subcortical white matter lesions or infarctions. Acute perioperative cerebral infarctions were more common and atrophy more progressive during follow-up among diabetic than nondiabetic patients.

**Conclusions:** After a mean of 7.5 years of follow-up, patients undergoing off-pump coronary artery bypass performed better than those undergoing cardiopulmonary bypass in several neuropsychological domains; these differences were small and of uncertain clinical importance. Early brain magnetic resonance imaging showed no significant differences in acute cerebral infarctions between the off-pump coronary artery bypass and cardiopulmonary bypass groups. (J Thorac Cardiovasc Surg 2011;141:1116-27)

In an effort to avoid morbidity attributed to cardiopulmonary bypass (CPB), aortic cannulation/clamping, hypothermic cardioplegic arrest, and systemic hemodilution, off-pump coronary artery bypass (OPCAB) techniques were refined and popularized in the 1990s.[1,2] Despite reports of improved outcomes with OPCAB from numerous centers[3,4] and from the Society of Thoracic Surgeons (STS) National Cardiac Database[5] and the US Veterans Administration database,[6] adoption of OPCAB plateaued at approximately 20% in 2004 and has not changed significantly since that time.[7] This might be due in part to the technically challenging nature of OPCAB and in part due to the lack of compelling reductions in major adverse cardiac events (death, stroke, and myocardial infarction) among the low-risk patients enrolled in small, underpowered randomized controlled trials comparing OPCAB with conventional CABG techniques.[8,9]

One of the strong motivations to explore and adopt OPCAB techniques has been the hope that avoidance of CPB and reduced aortic manipulation would be associated with reduced risk of perioperative stroke and neurocognitive decline associated with coronary artery bypass surgery.[10] Typically enrolling low-risk patients, randomized trials to date have been underpowered to detect a difference in

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**Abbreviations and Acronyms**

CPB = cardiopulmonary bypass
CSF = cerebrospinal fluid
FLAIR = fluid attenuated inversion recovery
MRI = magnetic resonance imaging
OPCAB = off-pump coronary artery bypass
RAVLT = Rey Auditory Verbal Learning Test
ROI = region of interest
SMART = Surgical Management of Arterial Revascularization Therapies
STS = Society of Thoracic Surgeons

perioperative stroke, an infrequently occurring end point.[9,11-15] Nonetheless, risk-adjusted retrospective reviews of numerous large clinical databases have repeatedly demonstrated a clinically and statistically significant reduction in perioperative stroke for patients undergoing OPCAB compared with conventional CABG during CPB.[5,6,16,17] The early studies among these patients were legitimately criticized because of their inability to account for intraoperative conversion of patients from OPCAB to CPB to report an intent-to-treat comparison. This potential source of bias was addressed by the introduction of a data field in the STS National Cardiac Database to report intraoperative conversion and subsequently by the first intent-to-treat analysis of the STS database, which confirmed an adjusted odds ratio for stroke in patients undergoing OPCAB of 0.65 ($P < .001$).[16]

Although it seems logical that elimination of CPB and reduction in aortic manipulation should reduce the risk of embolic and ischemic stroke,[18] it must also be acknowledged that the specific technique for performing (or avoiding) proximal anastomoses on the ascending aorta (including single, double, or no aortic clamp) can have a significant effect on stroke risk, especially in patients with atherosclerosis of the ascending aorta, independent of the use or avoidance of CPB during surgical coronary revascularization.[19]

Whether CABG causes neurocognitive decline[20-22] is contested, and several studies have reported similar change from baseline neurocognitive function in risk-matched[23] or randomized[24] patients undergoing CABG versus percutaneous coronary intervention or CABG versus noncardiac surgical procedures.[25] Measures of neurocognitive or neuropsychological function are inherently imprecise and prone to a variety of systemic biases and confounders. Moreover, there is no general agreement on which of the many available tests are most appropriate,[26] what would constitute a clinically significant decline,[27] or even how to best perform statistical comparisons of test scores across multiple neuropsychological domains.[28] Perhaps as a result of this methodological imprecision, single-center prospective studies have reported "significant" decline relative to that seen in control subjects in neuropsychological performance ranging from zero percent[23] to 53%[20] of patients after conventional CABG during CPB.

Magnetic resonance imaging (MRI), especially with diffusion-weighted techniques, has been the preferred imaging modality to demonstrate acute cerebral emboli. Nonetheless, the resolution of presently available scanners is such that defects smaller than 1 mm are not detectable. Moreover, the correlation between detection of new brain lesions on MRI scanning and the appearance of new decline in neurocognitive function has been disappointingly weak in at least 1 previous small clinical series.[29]

The Surgical Management of Arterial Revascularization Therapies (SMART) trial was conceived to rigorously compare completeness of revascularization, clinical outcomes, and resource use in unselected patients referred for elective primary CABG randomly assigned to undergo OPCAB or conventional CABG during CPB. Similar graft patency was demonstrated between groups by means of coronary angiographic analysis before hospital discharge and at the 1-year follow-up and by means of computed tomographic angiographic analysis at a mean of 7.5 years of follow-up.[13,30,31] The principal secondary end points of the SMART trial were neuroanatomic and neurocognitive outcomes, as measured by using early and late diffusion-weighted brain MRI and neuropsychological testing at late follow-up. These results are the subject of this report.

## MATERIALS AND METHODS

Between March 2000 and August 2001, 297 unselected patients with multivessel coronary artery disease were approached for voluntary enrollment in the SMART trial. Two hundred of these 297 patients were randomly assigned to undergo off-pump or on-pump coronary artery bypass grafting by a single surgeon (J.D.P.). A single crossclamp was used in the CPB group; partial occlusion clamping of the ascending aorta was used for proximal anastomoses in the OPCAB group, when intraoperative epiaortic ultrasound scanning of the ascending aorta revealed less than grade 3 atherosclerosis. The sample size for the SMART trial was chosen for the ability to detect a 5% absolute difference between groups in the primary end point of graft patency.

After a mean of 7.5 years (range, 6.8–8.4 years), 87 of the original participants volunteered to return for late follow-up. As of March 30, 2009, there were 26 deaths from all causes among patients undergoing OPCAB and 31 among patients undergoing CPB since initial enrollment. Reasons for loss of patients to follow-up are listed in the consort flow diagram (Figure 1).

### Neuropsychological Testing

Of the 87patients who returned for late follow-up, 76 (41 undergoing CPB and 35 undergoing OPCAB) underwent a focused battery of neuropsychological tests to determine whether the surgical groups differed with respect to cognitive function. The trained and certified neuropsychological test administrators were blinded to treatment assignment. Table 1 lists the neuropsychological test by domain. Each test is briefly described below.

I. Attention.

A. *Wechsler Memory Scale–3 Digit and Spatial Span*: Patients listened to sequences of digits and viewed sequences of spatial positions,