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¹⁸F-florbetapir PET-determined Cerebral β -Amyloid Deposition and Neurocognitive Performance after Cardiac Surgery

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Abstract

Background—Amyloid deposition is a potential contributor to postoperative cognitive dysfunction. We hypothesized that 6-week global cortical amyloid burden, determined by ¹⁸F-florbetapir positron emission tomography, would be greater in those patients manifesting cognitive dysfunction at 6 weeks postoperatively.

Methods—Amyloid deposition was evaluated in cardiac surgical patients at 6 weeks (n=40) and 1 year (n=12); neurocognitive function was assessed at baseline (n=40), 6 weeks (n=37), 1 year (n=13), and 3 years (n=9). The association of 6-week amyloid deposition with cognitive dysfunction was assessed by multivariable regression, accounting for age, years of education, and baseline cognition. Differences between the surgical cohort with cognitive deficit and the Alzheimer's Disease Neuroimaging Initiative cohorts (normal and early/late mild cognitive impairment) was assessed, adjusting for age, education, and APOE4 genotype.

Results—We found that 6-week abnormal global cortical amyloid deposition was not associated with cognitive dysfunction (13/37, 35%) at 6 weeks postoperatively (median standard uptake value ratio [IQR]: cognitive dysfunction 0.92 [0.89–1.07] vs. 0.98 [0.93–1.05]; p=0.455). In post-hoc analyses, global cortical amyloid was also not associated with cognitive dysfunction at 1 or 3 years postoperatively. Amyloid deposition at 6 weeks in the surgical cohort was not different from that in normal Alzheimer's Disease Neuroimaging Initiative subjects but increased over 1 year in many areas at a rate greater than in controls.

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**Neurologic Outcomes Research Group (NORG) collaborators listed in Appendix II

Conclusion—In this study, postoperative cognitive dysfunction was not associated with 6-week cortical amyloid deposition. The relationship between cognitive dysfunction and regional amyloid burden and the rate of postoperative amyloid deposition merit further investigation.

Introduction

Up to 50% of patients undergoing cardiac surgery may experience postoperative cognitive dysfunction at the time of hospital discharge.¹ While there appears to be an initial improvement in the months after surgery, cognitive dysfunction persists in up to 42% at 5 years after surgery¹, resulting in a diminished quality of life and loss of functional independence.²

The mechanisms underlying postoperative cognitive dysfunction remain elusive, although several contributing factors have been proposed: preoperative cognitive impairment, genetic predisposition, transcerebral platelet activation, cerebral microembolism or hypoperfusion during cardiopulmonary bypass (CPB), central nervous and systemic inflammatory responses to surgery, hemodilution, hyperglycemia, hyperthermia, and the unmasking of Alzheimer's disease and acceleration of amyloid deposition associated with inhalational anesthetics (reviewed elsewhere)³. Because cardiac surgery generally takes place in older adults, the possibility exists that cognitive dysfunction after cardiac surgery represents a form of mild cognitive impairment, which also affects older adults. Mild cognitive impairment has been suggested to be a transitional phase between normal aging and dementia and a precursor to Alzheimer's disease⁴. Both mild cognitive impairment and Alzheimer's disease involve the accumulation of β -amyloid in the central nervous system. Laboratory studies have shown that inhalational anesthetics increase β -amyloid generation⁵ and promote β -amyloid oligomerization in cultured cells.⁶ Thus, anesthesia itself may influence β -amyloid processing and play a role in the evolution of cognitive dysfunction in the aging, in common with mild cognitive impairment/Alzheimer's disease. However, human studies have provided conflicting results about whether cerebrospinal fluid (CSF) β -amyloid levels rise, fall, or remain unchanged after anesthesia and surgery.^{7,8} Thus, we attempted to directly measure amyloid deposition in the brain following surgery using the positron emission tomography tracer ¹⁸F-florbetapir.

Positron emission tomography agents have shown great promise in mapping fibrillar amyloid deposition in the brain. ¹⁸F-florbetapir [(E)-4-(2-(6-(2-(2-(¹⁸F-fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-N-methylbenzamine] is a novel imaging agent that binds with high affinity (Kd 3.1 nM \pm 0.7) to β -amyloid peptide fibrils in brain amyloid plaques.^{9,10} In a multicenter study, ¹⁸F-florbetapir was shown to have the highest cortical retention in Alzheimer's subjects, the lowest in cognitively normal subjects, and intermediate retention in those with mild cognitive impairment.¹¹ ¹⁸F-florbetapir has been used in an increasing number of investigations of Alzheimer's disease and has demonstrated comparable or better sensitivity and specificity for diagnosing Alzheimer's disease compared to clinical criteria.¹² Furthermore, ¹⁸F-florbetapir imaging is the modality used in the longitudinal Alzheimer's Disease Neuroimaging Initiative – a multicenter investigation of subjects with normal cognition, varying degrees of mild cognitive impairment, and Alzheimer's disease.¹³

In this study, we utilized ^{18}F -florbetapir imaging to assess the relationship between global cortical and regional amyloid deposition and cognitive dysfunction in patients at 6 weeks after cardiac surgery with CPB. We also conducted follow-up cognitive testing and imaging at 1 and 3 years post-surgery for post-hoc analyses. We hypothesized that 6-week ^{18}F -florbetapir cortical amyloid burden would be greater in those patients manifesting postoperative cognitive dysfunction at 6 weeks and that the amyloid deposition pattern in patients with cognitive dysfunction would be similar to that seen in individuals from the Alzheimer's Disease Neuroimaging Initiative cohort with mild cognitive impairment.

Methods

Study Population

Following approval by the Duke University Health Systems Institutional Review Board and informed consent, 40 patients aged ≥ 60 years and undergoing cardiac surgery [coronary artery bypass grafting (CABG), CABG+valve, or valve only] with CPB were prospectively enrolled between July 2011 and November 2013. Patients were excluded if they had a history of symptomatic cerebrovascular disease (e.g., prior stroke) with residual deficits, alcoholism (>2 drinks/day), psychiatric illness (any clinical diagnoses requiring therapy), drug abuse (any illicit drug use in the preceding 3 months before surgery), hepatic insufficiency (liver function tests >1.5 times the upper limit of normal), severe pulmonary insufficiency (requiring home oxygen), or renal failure (serum creatinine >2.0 mg/dl). Pregnant or premenopausal women and patients who were unable to read and thus complete the cognitive testing or who scored <24 on a baseline Mini Mental State examination or >27 on the baseline Center for Epidemiological Studies Depression scale were similarly excluded. Patients who received any anti-amyloid therapies or had any radiopharmaceutical imaging in the 7 days prior to the surgery were also excluded.

Elderly control patients and patients with early mild cognitive impairment and late mild cognitive impairment (early vs. late defined by specific cut-offs on the Logical Memory II subscale of the Wechsler Memory Scale – Revised, as defined by ADNI2)¹⁴, who had been previously enrolled and imaged with ^{18}F -florbetapir positron emission tomography through the Alzheimer's Disease Neuroimaging Initiative (adni.loni.usc.edu)^{15,16} were utilized to compare regional patterns of amyloid deposition to our surgical cohort. The Alzheimer's Disease Neuroimaging Initiative was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of the Alzheimer's Disease Neuroimaging Initiative has been to assess whether serial magnetic resonance imaging, positron emission tomography, biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early Alzheimer's disease. ^{18}F -florbetapir imaging was included in the Alzheimer's Disease Neuroimaging Initiative-GO and Alzheimer's Disease Neuroimaging Initiative-2 protocols. All participants gave written informed consent that was approved by the institutional review board of each participating institution.

Surgical Patient Management

Anesthesia was induced with propofol, midazolam, fentanyl, and neuromuscular blocking agents, and isoflurane was used for maintenance. All patients underwent nonpulsatile, hypothermic (30°C - 32°C) CPB with a membrane oxygenator and arterial line filter by a pump primed with crystalloid. Serial hematocrit levels were maintained at 0.21. Before initiating CPB, heparinization (300 - 400 U/kg) was performed to a target activated coagulation time of >480 s. Perfusion was maintained at flow rates of 2 – 2.4 L/min/m² throughout CPB to maintain a mean arterial pressure of 50 – 80 mmHg. Arterial blood gases were measured every 15 – 30 min to maintain the PaCO₂ at 35 – 40 mmHg, unadjusted for temperature (α-stat) and the PaO₂ at 150 – 250 mmHg.

Neuroimaging

Cardiac surgical study participants underwent ¹⁸F-florbetapir positron emission tomography/computerized tomography imaging at the Duke Positron Emission Tomography Center at 6 weeks after surgery. Given funding constraints, imaging was performed at 6 weeks after surgery, since amyloid burden is not expected to change significantly over a 6-week period.¹⁷ Approximately at the midpoint of the study, imaging was added at the 1-year postoperative time point to provide pilot data on the change in amyloid burden over this time interval. A 10 mCi (370 MBq) dose of ¹⁸F-florbetapir (Avid Radiopharmaceuticals, Philadelphia, PA, USA) was assayed with a dose calibrator and administered via bolus injection through a peripheral vein. Once 50 min had elapsed after ¹⁸F-florbetapir injection, patients underwent 10 min of continuous brain positron emission tomography imaging. A low-dose computerized tomography scan was also performed for attenuation-correction of the positron emission tomography images. Positron emission tomography images were immediately reconstructed after the scan, and if any motion was detected another 10-min continuous scan was performed.

For quantitative evaluation, ¹⁸F-florbetapir images were spatially normalized to the stereotactic Montreal Neurologic Institute brain atlas space.¹⁸ A standard uptake value ratio was calculated using an average of six target regions (medial orbital frontal, anterior cingulate, parietal, posterior cingulate, precuneus and lateral temporal) with respect to the whole cerebellum as a reference region. ¹⁸F-florbetapir signal was also measured in the hippocampus, pons, centrum, putamen, and caudate, and the standard uptake value ratio for each region was calculated with respect to the cerebellum. Amyloid burden, as previously described¹⁹, was identified based on standard uptake value ratio values (≥ 1.10 is β-amyloid-positive [abnormal amyloid deposition] and < 1.10 is β-amyloid-negative).

Neurocognitive Testing

Neurocognitive testing was performed at baseline (preoperatively) and at 6 weeks. Post-hoc, 1-year and 3-year follow-up points were added to provide pilot data on the relationship between baseline amyloid burden and long term neurocognitive function. In accordance with the consensus statement on assessment of neurobehavioral outcomes after cardiac surgery²⁰, the following tests were included in the assessment battery: 1) Hopkins Verbal Learning Test²¹, 2) Randt Short Story Memory Test²², 3) Modified Visual Reproduction Test from the

Wechsler Memory Scale²³, 4) Digit Span and Digit Symbol and Vocabulary subtests from the Wechsler Adult Intelligence Scale-Revised²³, and 5) Trail Making Test, Parts A and B²⁴.

Blood Sample and APOE Genotyping

One 10-mL sample of peripheral blood was obtained from each patient and stored at 4°C. Genomic DNA were extracted for each sample and stored at the Duke Molecular Physiology Institute at -20°C. Genotyping for apolipoprotein E was performed at the Molecular Genetics Core at the Duke Molecular Physiology Institute following previously described protocols.²⁵

Statistical Analyses

To characterize cognitive function over time while minimizing potential redundancy in the cognitive measures, a factor analysis with oblique rotation (a linear transformation of the data, which allows for correlated factors) was performed on the 14 cognitive test scores from baseline. Scoring coefficients (weights) of each test on each factor were determined using the rotated factor solution from the factor analysis conducted on 508 eligible cardiac patients in our ongoing prospective post-CABG cognitive testing database. Factors of each subject in our cohort were computed for all time points using the same scoring coefficients, so that the cognitive domain structure remained consistent and comparable over time. Factor analysis suggested a 5-factor solution, which accounts for 80% of the variability in the original test scores, and represents 5 cognitive domains: 1) structured verbal memory (i.e., the ability to recall from a list), 2) unstructured verbal memory (i.e., the ability to remember from a narrative), 3) visual memory, 4) executive function, and 5) attention and concentration. Two outcome measures were calculated to represent postoperative cognitive dysfunction: 1) continuous outcome: the change in cognitive score calculated by subtracting the baseline cognitive index (the 5-domain mean) from the follow-up cognitive index (a change score of 0 indicates no change from baseline while a negative score indicates cognitive decline and a positive score indicates cognitive improvement); 2) binary outcome (cognitive deficit): defined as a decline of >1 standard deviation in at least 1 domain.

The relationship between 6-week global cortical amyloid burden (standard uptake value ratio 1.1) and cognition at 6 weeks after surgery was pre-specified as the primary outcome. Secondary outcomes included the relationship between regional amyloid burden and cognition at 6 weeks postoperatively and the relationship between global amyloid burden and cognition at 1 year. We used the χ^2 test, Fisher exact test, or Wilcoxon rank-sum test, as appropriate, to examine differences between patients with and without cognitive deficit. We then computed Pearson's correlation coefficients of amyloid burden with age, years of education, baseline cognitive score, 6-week cognitive score, and change in cognitive score. Finally, multivariable regression was used to test the association of cognitive deficit and mean 6-week cognitive score change with abnormal amyloid deposition (standard uptake value ratio 1.1), accounting for age, years of education, and baseline cognition.

Subject demographics and amyloid burden in our surgical cohort was compared to age- and sex-matched normal, early mild cognitive impairment, and late cognitive impairment subsets

in the Alzheimer's Disease Neuroimaging Initiative database using the 2-sample t-test, Wilcoxon rank-sum test, χ^2 test, or Fisher exact test, as appropriate.

Apolipoprotein E4 genotype was categorized by the presence (homozygous or heterozygous) or absence of the apolipoprotein E- ϵ 4 allele. The association of apolipoprotein E4 status with amyloid burden at 6 weeks was assessed using the two-sample t-test, Wilcoxon rank-sum test, χ^2 test or Fisher exact test, as appropriate. An analysis of covariance (ANCOVA) model was then used to test differences among four cognitive categories: cognitive deficit at 6 weeks in our surgical cohort and normal, early mild cognitive impairment, and late cognitive impairment in the Alzheimer's Disease Neuroimaging Initiative cohort, adjusting for age, years of education, and apolipoprotein E4 genotype.

In the absence of any published data on amyloid deposition in surgical patients, we relied upon preliminary data from a study conducted by a co-investigator (PMD) evaluating amyloid deposition in healthy, mild cognitive impairment, and Alzheimer's disease subjects, where the estimated mean and standard deviation (SD) of the healthy and mild cognitive impairment groups were used for power calculation. Based on these data, we assessed the statistical power for detecting the correlation between cognitive score changes and amyloid burden. Under a linear regression model with the standard deviation of amyloid burden at 0.25 from preliminary data, we estimated that 40 patients in the cardiac surgical group would provide 80% power to detect a correlation between cognitive score changes and amyloid burden at an R-square of 0.171.

All analyses were performed with SAS version 9.4 (SAS Institute Inc.; Cary, NC). $P < 0.05$ was considered significant. Post-hoc analyses of regional amyloid deposition were adjusted for multiple comparisons by computing a false discovery rate.

Results

Neurocognitive outcomes

Of the 40 patients initially enrolled, 37 had complete baseline and 6-week cognitive and neuroimaging data; at 1 year after surgery, 28 patients had complete baseline and 1-year cognitive data and 12 had neuroimaging; and at 3 years after surgery 18 patients completed cognitive testing. The mean (SD) cognitive change score (from baseline) was 0.10 (0.29) at 6 weeks, 0.13 (0.31) at 1 year after surgery, and 0.08 (0.51) at 3 years after surgery. Cognitive deficit, defined as ≥ 1 SD decline in at least 1 cognitive domain, was present in 35% (13/37) of the cardiac surgical patients at 6 weeks after surgery, 57% (16/28) at 1 year, and 44% (8/18) at 3 years. Interestingly, several patients without deficit at 6 weeks went on to develop deficit at 1 year postoperatively, while others recovered. (Supplemental Figure 1, Supplemental Table 1) Table 1 lists the demographic and surgical characteristics of the enrolled patients.

Global cortical amyloid deposition and postoperative cognitive dysfunction at 6 weeks and 1 year

Representative images from our study cohort of normal (A) and abnormal (B) amyloid deposition as measured by ^{18}F -florbetapir imaging are shown in Figure 1. Global cortical

amyloid deposition was measured as standard uptake value ratio 1.03 (0.17) in the 40 patients imaged at 6 weeks and 1.04 (0.20) in the 12 patients imaged at 1 year. Cortical amyloid deposition was considered abnormal (standard uptake value ratio ≥ 1.1) in 7 patients (17.5%) imaged at 6 weeks and in 2 patients (16.7%) imaged at 1 year. The cognitive change score at 6 weeks and 1 year after surgery in patients with and without 6-week abnormal global cortical amyloid deposition was 0.108 (0.186) vs. 0.095 (0.311); $p=0.92$; and 0.193 (0.266) vs. -0.121 (0.325); $p=0.62$, respectively.

With regard to our primary outcome, 6-week global cortical amyloid deposition was not different in patients with and without cognitive deficit at 6 weeks (median standard uptake value ratio [interquartile range, IQR]: 0.92 [0.89–1.07] vs. 0.98 [0.93–1.05]; $p=0.455$; Table 2), nor was there a difference in the proportion of patients with and without postoperative cognitive dysfunction who had abnormal amyloid deposition (proportion difference: 0.106). Similar patterns were seen at 1 year after surgery (median standard uptake value ratio [IQR]: 0.96 [0.89–1.02] vs. 1.02 [0.97–1.06]). Abnormal 6-week amyloid deposition was seen in 3 patients with cognitive deficit and in 3 patients without deficit at 6 weeks postoperatively ($p=0.644$; Table 3). Similarly, 1 patient with cognitive deficit at 1 year had abnormal global cortical amyloid deposition at 1 year while 1 patient without deficit had abnormal deposition. There were no significant correlations of global cortical amyloid deposition at 6 weeks with baseline, 6-week, 1-year, or 3-year cognitive scores or change scores. In multivariable regression analyses, we found no significant association between 6-week abnormal global cortical amyloid burden and cognitive change scores (beta: 0.09, model R^2 : 0.12) or with the occurrence of postoperative cognitive dysfunction at 6 weeks (odds ratio [OR] 0.47, 95% confidence interval [CI] 0.07–3.43, model R^2 0.09) when controlling for age, years of education, and baseline cognition. There were also no significant associations of 6-week amyloid burden with cognitive outcomes at 1 or 3 years after surgery.

Regional amyloid deposition and postoperative cognitive dysfunction

In post-hoc analyses we found that the frequency of abnormal amyloid deposition (standard uptake value ratio ≥ 1.1) in the hippocampus was significantly different between patients with and without postoperative cognitive dysfunction at 6 weeks postoperatively, although this difference was no longer significant after adjustment for multiple comparisons ($p=0.041$, false discovery rate=0.429; Table 3). Patients who had abnormal 6-week amyloid in the hippocampus showed significantly greater decline in the structured verbal memory domain (median change score [IQR]: -1.08 [-2.05 to -0.69] in patients with standard uptake value ratio ≥ 1.1 vs. -0.075 [-0.82 to 0.46] for patients with standard uptake value ratio <1.1 ; $p=0.019$). Total hippocampal standard uptake value ratio (continuous variable), although higher, was not statistically different between patients with and without deficit (Table 2). The caudate standard uptake value ratio was also greater in patients who had a cognitive deficit at 6 weeks, but this difference was no longer significant after adjustment for multiple comparisons (median [IQR]: Deficit 0.96 [0.85–1.03] vs. No Deficit 0.81 [0.70–0.94]; $p=0.047$, false discovery rate=0.561). Furthermore, the standard uptake value ratios in the caudate failed to meet the ≥ 1.1 threshold for defining abnormal amyloid deposition.

Trajectory of amyloid deposition

While cognitive deficit and the cognitive change score was not associated with abnormal global cortical amyloid deposition in the smaller cohort of 12 patients with 1-year neuroimaging, amyloid deposition increased in many brain regions over time. In these 12 patients, global cortical amyloid deposition increased significantly from 6 weeks to 1 year (mean standard uptake value ratio change: 0.02 ± 0.02 ; $p=0.011$). Statistically significant increases in standard value uptake ration from 6 weeks to 1 year postoperatively were observed in the hippocampus, posterior cingulate, caudate, and occipital regions (Figure 2).

Comparison to Alzheimer's Disease Neuroimaging Initiative cohort

Overall, our cardiac surgical cohort was more similar to the Alzheimer's Disease Neuroimaging Initiative subjects with normal cognition than the age- and sex-matched early or late mild cognitive impairment cohorts, with regard to education and apolipoprotein E4 carrier status (Supplemental Table 2) and global and regional amyloid deposition (Supplemental Table 3 and Supplemental Figure 2).

Abnormal amyloid deposition and cognitive deficit in apolipoprotein E4 carriers

Apolipoprotein E genotype was available for 37 patients in our cohort. Eight patients were found to be apolipoprotein E4 carriers (7 heterozygous, 1 homozygous), and 29 were non-carriers. Of the 8 apolipoprotein E4 carriers, 7 had complete 6-week cognitive testing data; of the 29 non-carriers, 27 had complete 6-week cognitive testing data. Of the 7 apolipoprotein E4 carriers with complete 6-week cognitive testing, 4 (57%) demonstrated cognitive deficit at 6 weeks. This was not statistically different from the deficit rate in the non-apolipoprotein E4 carriers (7/27, 26%; $p=0.178$). Apolipoprotein E4 genotype was, however, significantly associated with worse baseline cognitive score [mean (SD): -0.631 (0.382) vs. 0.001 (0.555) in non-carriers; $p=0.005$), but there was no difference at 6 weeks or in the change score from baseline to 6 weeks between apolipoprotein E4 carriers and non-carriers. Global and regional standard uptake value ratios in apolipoprotein E4 carriers versus non-carriers are shown in Supplemental Table 4. ANCOVA model incorporating the Alzheimer's Disease Neuroimaging Initiative cohort revealed a significant association of global cortical amyloid deposition at 6 weeks with apolipoprotein E4 genotype ($p<0.001$) and age ($p=0.001$) and that the surgical cohort with cognitive deficit at 6 weeks had smaller global cortical amyloid deposition at 6 weeks than the late mild cognitive impairment subjects ($p=0.001$) in the Alzheimer's Disease Neuroimaging Initiative cohort, but not the normal ($p=0.68$) or early mild cognitive impairment patients ($p=0.07$).

When evaluating regional standard uptake value ratio 1.1 in apolipoprotein E4 carriers, only the parietal region was different between the carriers and non-carriers before adjustment for multiple comparisons (38% (3/8) in carriers vs. 3% (1/29) in non-carriers; $p=0.02$, false discovery rate=0.282).

Discussion

We did not find an association between 6-week global cortical amyloid burden and cognitive dysfunction at 6 weeks following cardiac surgery.

Cognitive dysfunction after cardiac surgery remains a significant problem without a clear etiology. Given that cardiac surgery predominantly takes place in the aged, the possibility exists that the cognitive decline seen in some patients is similar to mild cognitive impairment, which in many will eventually progress to Alzheimer's disease. Both diseases are believed to involve the accumulation of β -amyloid and tau proteins in the brain. While the role of β -amyloid oligomers in the pathogenesis of Alzheimer's disease remains controversial²⁶, there is evidence that β -amyloid can lead to synaptic dysfunction and memory deficits in animals²⁷. CPB is known to disrupt the blood-brain barrier²⁸, and blood-brain barrier dysfunction is associated with increased entry of amyloid into the brain.²⁹ Alzheimer's-type neurodegeneration is accelerated by neuroinflammation³⁰, raising the possibility that perioperative inflammation could stimulate/accelerate β -amyloid-mediated neurologic degeneration, which could contribute to postoperative cognitive dysfunction. Finally, cardiac surgical patients share many of the risk factors for Alzheimer's disease³¹, and there is a known intersection between Alzheimer's and cardiovascular/cerebrovascular disease.³² While there is no evidence that cardiovascular disease severity directly affects amyloid burden³³, it is plausible that some component of postoperative cognitive dysfunction may be related to cardiovascular risk factors that accelerate the progression towards Alzheimer's-type cognitive decline.

To investigate the relationship between postoperative cognitive dysfunction and β -amyloid protein deposition in patients undergoing cardiac surgery, we utilized the novel positron emission tomography tracer, ¹⁸F-florbetapir, which binds with high affinity to β -amyloid fibrils and has been shown to differentiate cerebral β -amyloid deposition between cognitively normal and deficient subjects.³⁴ With regard to our primary outcome, we did not find a significant association between 6-week global cortical amyloid burden and cognitive dysfunction at 6 weeks. 6-week amyloid burden was also not associated with cognitive dysfunction at 1 or 3 years postoperatively, although our sample size at these time points was very small.

In post-hoc analyses of regional amyloid deposition, we found an increased proportion of patients with cognitive dysfunction at 6 weeks with abnormal 6-week amyloid deposition in the hippocampus, which was associated with a verbal memory deficit. While these results were not significant after adjustment for multiple comparisons, the unadjusted findings may point to regions that deserve closer scrutiny in future studies. The hippocampus is an intriguing region because it plays an important role in the acquisition and storage of episodic memories³⁵ – those related to unique personal experiences – and has been linked with postsurgical cognitive changes in animals³⁶. Hippocampal synapse loss occurs early in Alzheimer's and to a greater extent than in other brain regions in advanced Alzheimer's. Furthermore, hippocampal damage correlates better with cognitive impairment in Alzheimer's disease than the presence/quantity of β -amyloid plaques or neurofibrillary tangles.³⁷ Finally, Badgaiya et al. previously showed significant decreases in memory-related regional cerebral blood flow within the hippocampus and parahippocampus after cardiac surgery,³⁸ which may indicate regions of the brain that are more vulnerable to ischemic blood-brain barrier dysfunction and consequent cerebral deposition of circulating amyloid after cardiac surgery.²⁹

We also observed that amyloid deposition significantly increased from 6 weeks to 1 year after surgery in many regions of the brain and that this rate of increase was greater than that reported elsewhere. In a study by Palmqvist et al.³⁹ the mean global standard uptake value ratio change/year in non-demented subjects with normal positron emission tomography scans was 0.0024 (95% CI: 0.0010–0.0039), while that for subjects with abnormal CSF and scan results was 0.011 (95% CI: 0.0083–0.013). Similarly, in the longitudinal Alzheimer's Disease Neuroimaging Initiative cohort, the mean standard uptake value ratio change in 154 control subjects with a normal baseline scan was 0.0027 (0.0100) but was 0.0160 (0.0161) in 61 controls with abnormal baseline scans (Susan Landau, PhD, personal communication). In comparison, the mean (SD) global cortical standard uptake value ratio change in our surgical patients was 0.02 (0.02), nearly 10-fold that seen in scan-negative non-surgical patients and just slightly higher than that in scan-positive non-surgical patients. When we removed patients with abnormal 6-week amyloid deposition (n=2) from our analyses, the rate of change in our surgical cohort remained higher at 0.014 (0.018). Percent standard uptake value ratio change, which discounts variation in reference regions, may be more informative; in the Palmqvist study³⁹, the percent global standard uptake value ratio change/year was 0.35% (95% CI: 0.14%–0.56%) compared to $1.9 \pm 2.0\%$ in our surgical cohort. However, our study sample is limited, and changes over the course of a year are small.

This trajectory of amyloid at 1 year after surgery raises the question of how surgery and/or anesthesia may impact cerebral amyloid deposition and longer term cognitive outcomes. Several in vitro and animal studies have established a link between anesthetic agents and enhanced β -amyloid formation, aggregation, and β -amyloid-induced cytotoxicity.^{5,6} Human studies have demonstrated that low preoperative ratios of β -amyloid/Tau proteins in the CSF are associated with postoperative delirium and cognitive decline, although this is thought to predict a predisposition to cognitive dysfunction due to preclinical Alzheimer's disease rather than a direct anesthetic effect.⁴⁰ Surgery may also have an independent effect on the risk of Alzheimer's development in the postoperative setting.⁴¹ Tang et al.⁷ and Berger et al.⁸ both demonstrated a CSF change in the ratio of β -amyloid/Tau in patients undergoing surgery consistent with that seen in Alzheimer's and correlated with perioperative neuroinflammatory mediator release. The association of perioperative inflammatory changes and Alzheimer's-like cognitive decline may be particularly relevant in the highly inflammatory milieu of cardiac surgery. Cardiac surgery with CPB has been shown to produce an intense cerebral inflammatory response in conjunction with Alzheimer's-like changes in CSF β -amyloid.⁴² Vascular dysfunction and inflammation, both hallmarks of cardiac surgery, have also been associated with amyloid deposition⁴³. Thus, one concern has been whether cardiac surgery itself could increase the rate of amyloid deposition as a consequence of blood-brain barrier disruption²⁸.

Our finding that some patients experienced cognitive decline over time while others improved also merits further study and correlation with observed changes in the trajectory of global and regional cortical amyloid deposition. Cognitive improvement over time after surgery is certainly a recognized phenomenon and can be seen either globally or in select cognitive domains⁴⁴. However, no mechanistic explanation has yet been uncovered as to why some patients improve while others continue to decline/recover more slowly.

It is important to interpret our findings in the context of our sample size limitations. Without any prior studies on amyloid burden in surgical patients, our initial sample size estimation was based on the hypothesis that patients with postoperative cognitive dysfunction would have amyloid deposition to individuals with mild cognitive impairment. For our primary outcome, comparison of the binary variables of abnormal amyloid deposition and postoperative cognitive dysfunction demonstrated a proportion difference of 0.106; we are only powered to detect a proportion difference of 0.5, thus we cannot conclusively exclude an association between 6-week abnormal amyloid deposition and a clinically meaningful decline in cognitive function after cardiac surgery. Furthermore, we estimate that we have 80% power to detect a mean standard uptake value ratio difference of 0.16 between patients with and without postoperative cognitive at 6 weeks postoperatively; thus, our detected standard uptake value ratio difference of 0.06 falls below this threshold. Based on these data, we estimate that 117 patients would be needed to achieve 80% power in a future study (see Supplement I).

The lack of baseline imaging and longer term (> 3 years) follow-up are further limitations of our study. While the existing literature indicates a longer time course for change in amyloid¹⁷, we cannot say with certainty that surgery does not produce changes in amyloid deposition in the immediate postoperative period. Future studies should include a baseline assessment of brain amyloid prior to surgery as well as longer duration of follow-up. Based on the existing literature in mild cognitive impairment subjects, the time course of clinically significant β -amyloid deposition needed to produce cognitive decline may be significantly longer.^{45,46} Finally, we are limited by the relatively younger and male-dominated nature of our surgical cohort. Older age has been shown to increase the risk for postoperative cognitive dysfunction⁴⁷ and Alzheimer's disease, and multiple studies have indicated that females have a higher prevalence and incidence of Alzheimer's disease⁴⁸ and mild cognitive impairment progression over time than men⁴⁹. Future studies should include an older surgical group that more closely matches the Alzheimer's Disease Neuroimaging Initiative mild cognitive impairment cohort.

In conclusion, this study employed amyloid imaging using ¹⁸F-florbetapir to investigate 6-week and evolving brain amyloid burden in patients undergoing cardiac surgery with CPB. We observed that postoperative cognitive dysfunction was not associated with 6-week global cortical amyloid deposition, but the rate of amyloid deposition following surgery was greater than what has been reported in normal elderly subjects. The findings from this study support further investigation of 1) the relationship between hippocampal amyloid deposition and early postoperative cognitive dysfunction and 2) the significance of amyloid deposition increases within 1 year of cardiac surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest/Disclosures

PMD has received research grants (through Duke University) from Avid, Lilly, Neuronetrix, Avanir, Alzheimer's Drug Discovery Foundation, Forum, and has received speaking or advisory fees from Anthrotronix, Cognoptix, Takeda, Genomind, Sonexa, Targacept, Neurocog Trials, Forum, T3D Therapeutics, Alzheimer's Association, Hints, MindLink, Global Alzheimer's Platform, and University of Miami. PMD owns shares in Maxwell Health, Muses Labs, Anthrotronix, Evidation Health, Turtle Shell Technologies, and Advera Health Analytics. PMD is a co-inventor on patents relating to dementia biomarkers that are unlicensed.

Appendix I

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Brief Summary Statement

Cerebral amyloid deposition as measured by ¹⁸F-florbetapir PET/CT was not associated with changes in cognitive performance in patients after cardiac surgery.

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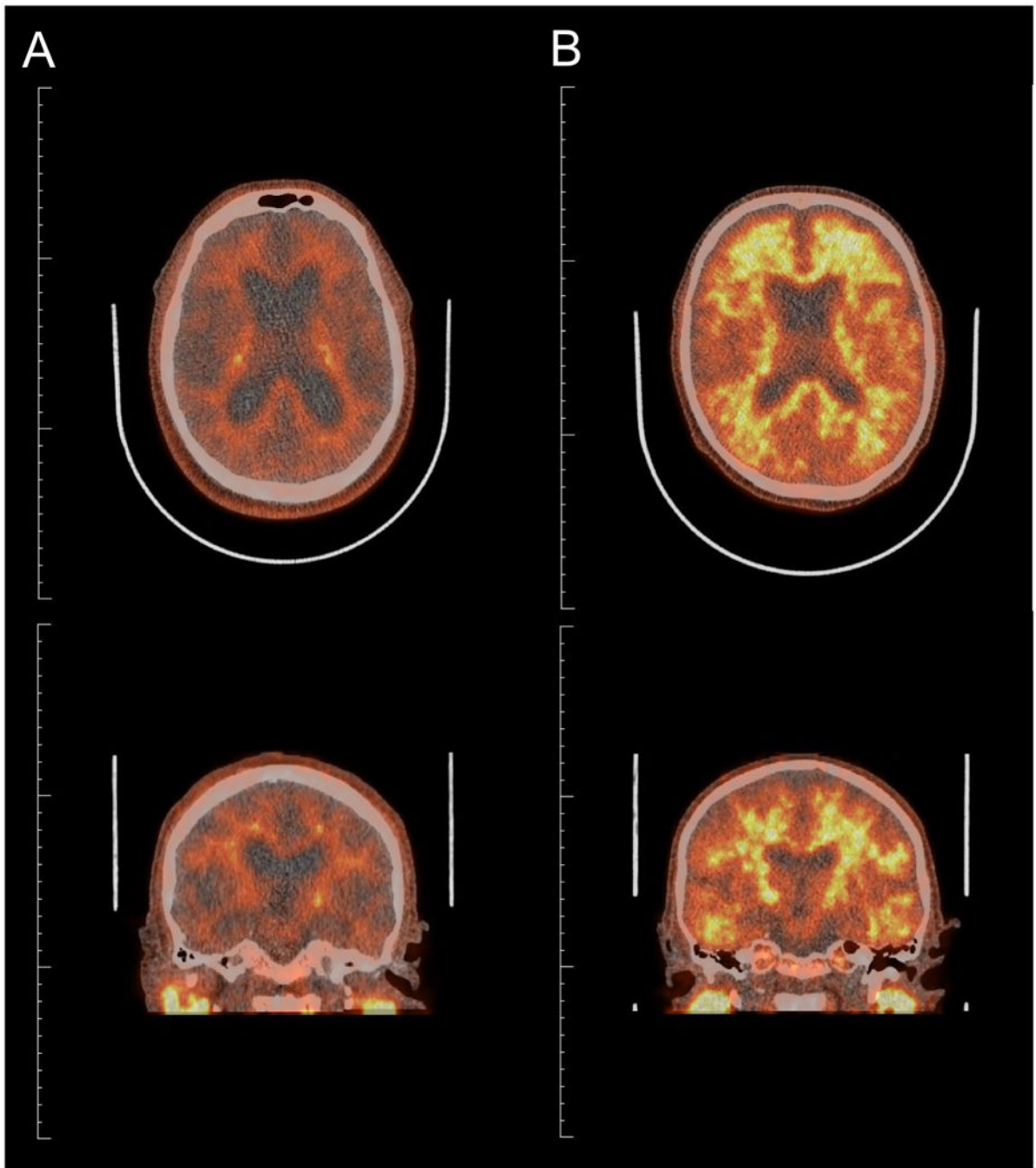


Figure 1. Images of patients with normal (A) and abnormal (B) amyloid deposition by ^{18}F -florbetapir PET imaging. The brighter orange to yellow colors indicate greater amyloid deposition.

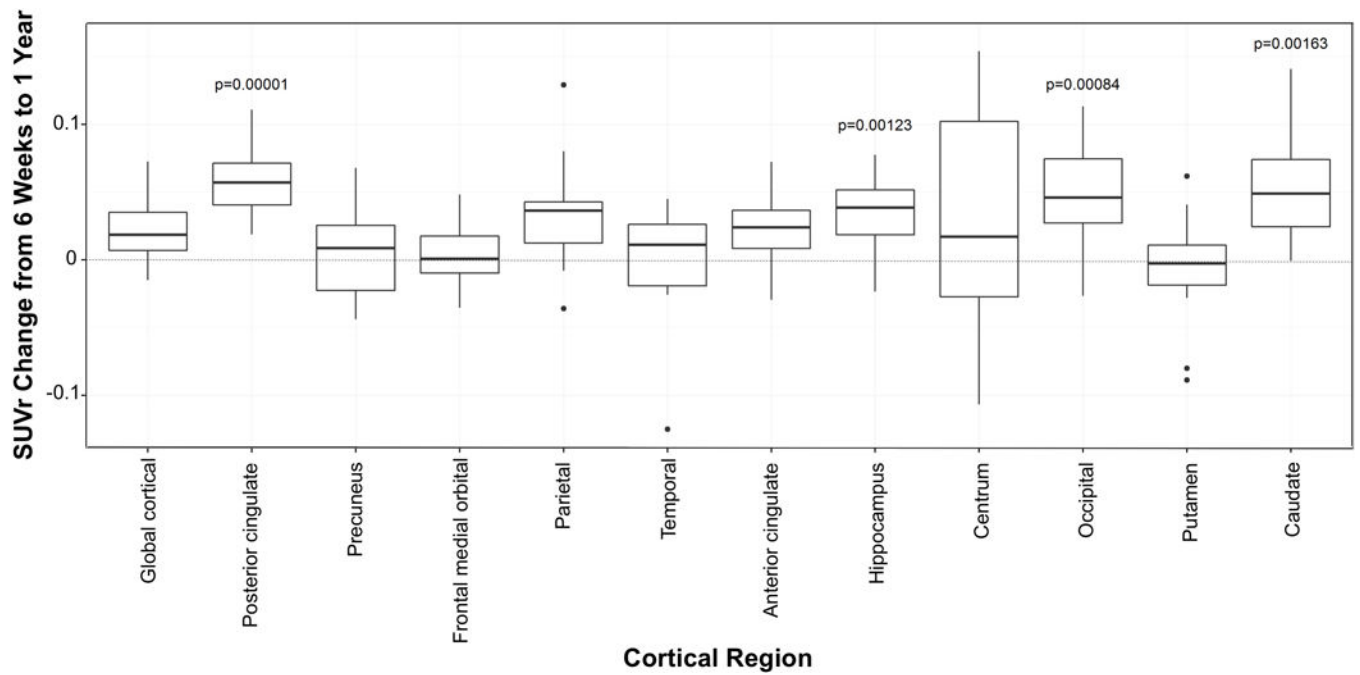


Figure 2.

Box plots showing median (IQR) change in SUVr in each imaged brain region from 6 weeks to 1 year postoperatively. Positive values represent increase in SUVr, while negative values represent decrease in SUVr. N=12.

Table 1

Characteristics of the Cardiac Surgical Cohort

Variable	Baseline (n=38)*	6 weeks (n=40)**	1 year (n = 12)**	3 years (n = 18)*
Age, y	69 (6)	69.4 (6)	71 (5)	71 (6)
Sex, % female	9 (23%)	8 (22%)	2 (17%)	4 (22%)
Race, % white	34 (85%)	32 (86%)	11 (92%)	15 (86%)
Weight, kg	85 (17)	86 (18)	83 (17)	85 (16)
History of hypertension	33 (83%)	31 (84%)	9 (75%)	15 (84%)
Diabetes mellitus	22 (55%)	20 (54%)	4 (33%)	9 (54%)
Previous MI	13 (33%)	13 (35%)	3 (25%)	4 (35%)
Ejection fraction (%)	51 (9)	51 (9)	52 (8)	54 (4)
Years of education	14 (4)	14 (3)	16 (5)	15 (4)
Preoperative statins, %	28 (80%)	27 (82%)	9 (90%)	14 (82%)
Preoperative platelet inhibitors, %	30 (86%)	29 (88%)	7 (70%)	16 (88%)
Surgical procedure, %				
CABG	24 (60%)	23 (62%)	8 (67%)	11 (62%)
CABG+valve	8 (20%)	7 (19%)	2 (17%)	3 (19%)
Valve only	8 (20%)	7 (19%)	2 (17%)	4 (19%)
No. of grafts, % ***				
1	6 (19%)	6 (20%)	2 (20%)	3 (21%)
2	5 (16%)	4 (13%)	1 (10%)	2 (14%)
3	10 (31%)	10 (33%)	5 (50%)	5 (36%)
>3	11 (34%)	10 (33%)	2 (20%)	4 (29%)
Cross-clamp time, min	90 (34)	87 (33)	90 (30)	84 (34)
CPB time, min	145 (49)	141 (44)	136 (35)	142 (46)
Baseline cognitive score	-0.17 (0.57)	-0.15 (0.56)	-0.19 (0.48)	-0.17 (0.64)
6-week cognitive score	-0.07 (0.61)	-0.05 (0.62)	-0.06 (0.64)	-0.09 (0.69)

Values are mean (SD) unless otherwise indicated. CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass.

* N represents the number of patients with cognitive testing data at these time points.

** N represents the number of patients with imaging at these time points.

*** Only includes patients undergoing CABG or CABG+valve procedures. Differences in demographics and comorbidities between baseline/6-week and the 1- and 3-year time points are due to patient loss to follow-up.

Global cortical and regional SUVR values in patients with and without cognitive deficit at 6 weeks

Table 2

Brain Region	No Deficit (n = 24)		Deficit (n = 13)		P Value	FDR	Mean Difference [95% CI]
	SUVR (median[IQR])	SUVR (median[IQR])	SUVR (median[IQR])	SUVR (median[IQR])			
Global cortical	0.98 [0.93–1.05]	0.92 [0.89–1.07]	0.455	0.754	-0.06 [-0.23–0.10]		
Posterior cingulate	0.98 [0.88–1.04]	0.87 [0.84–1.08]	0.514	0.754	-0.04 [-0.21–0.13]		
Precuneus	1.09 [1.02–1.15]	0.99 [0.94–1.20]	0.417	0.754	-0.05 [-0.24–0.15]		
Frontal medial orbital	0.89 [0.87–0.93]	0.88 [0.85–0.92]	0.691	0.754	-0.06 [-0.18–0.07]		
Parietal	0.90 [0.82–1.03]	0.89 [0.81–1.09]	0.622	0.754	-0.09 [-0.26–0.09]		
Temporal	1.07 [1.01–1.13]	1.06 [1.00–1.16]	0.787	0.787	-0.07 [-0.22–0.07]		
Anterior cingulate	1.01 [0.95–1.10]	0.96 [0.93–1.07]	0.417	0.754	-0.08 [-0.29–0.12]		
Hippocampus	1.05 [1.01–1.09]	1.10 [1.02–1.12]	0.417	0.754	0 [-0.06–0.06]		
Centrum	1.67 [1.59–1.78]	1.62 [1.56–1.71]	0.301*	0.754	0.04 [-0.05–0.13]		
Occipital	1.00 [0.86–1.04]	0.94 [0.90–1.08]	0.763*	0.754	-0.02 [-0.14–0.09]		
Putamen	1.19 [1.15–1.30]	1.18 [1.13–1.24]	0.417	0.754	0.01 [-0.08–0.09]		
Caudate	0.81 [0.70–0.94]	0.96 [0.85–1.03]	0.047	0.561	-0.12 [-0.25–0]		

SUVR, standard uptake value relative to cerebellum; IQR, interquartile range; FDR, false discovery rate; CI, confidence interval.

* P-value determined by t-test. All other P-values determined by Wilcoxon rank sum test.

Table 3

Frequency of abnormal global cortical and regional amyloid deposition at 6 weeks in patients with and without cognitive deficit

Brain Region	No Deficit (n = 24)		Deficit (n = 13)		P Value ^{†‡}	FDR
	SUVr	1.1 (%)	SUVr	1.1 (%)		
Global cortical	3 (12.5)		3 (23.1)		0.644 [†]	0.787
Posterior cingulate	3 (12.5)		3 (23.1)		0.644 [†]	0.787
Precuneus	9 (37.5)		5 (38.5)		0.954 [‡]	1
Frontal medial orbital	0 (0)		2 (15.4)		0.117 [†]	0.429
Parietal	2 (8.3)		2 (15.4)		0.602 [†]	0.787
Temporal	7 (29.2)		6 (46.2)		0.302 [‡]	0.787
Anterior cingulate	5 (25.0)		6 (46.3)		0.108 [†]	1
Hippocampus	5 (20.8)		7 (54.8)		0.041 [‡]	0.429
Occipital	3 (12.5)		3 (23.1)		0.644 [†]	0.787
Putamen	23 (95.8)		10 (76.9)		0.115 [†]	0.429
Caudate	2 (8.3)		0 (0)		0.532 [†]	0.787

SUVr, standard uptake value relative to cerebellum; FDR, false discovery rate. P-value determined by

[†]Fischer exact test or

[‡]Chi-square test.