Published in final edited form as:
AJNR Am J Neuroradiol. 2013 March ; 34(3): 518–523. doi:10.3174/ajnr.A3251.

Blood Brain Barrier Disruption After Cardiac Surgery

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Abstract

Background and purpose—CNS complications are often seen after heart surgery, and post-surgical disruption of the blood-brain barrier (BBB) may play an etiologic role. The objective of this study was to determine the prevalence of MRI-detected BBB disruption (Hyperintense Acute Reperfusion Marker: HARM) and DWI lesions after cardiac surgery.

Materials & methods—All patients had an MRI after cardiac surgery. In half the patients (group 1), we administered gadolinium 24 hours after surgery and obtained high-resolution DWI and FLAIR images 24-48 hours later. In the other half (group 2), we administered gadolinium at the time of the post-operative scan (2-4 days after surgery). Two stroke neurologists evaluated the images.

Results—We studied 19 patients. None of the patients had clinical evidence of a stroke or delirium at the time of the gadolinium administration or the scan, but 9 patients (47%) had HARM (67% in group 1 and 30% in group 2, p=0.18) and 14 patients (74%) had DWI lesions (70% in group 1 and 78% in group 2, p=1.0). Not all patients with DWI lesions had HARM, and not all patients with HARM had DWI lesions (p=0.56).

Conclusions—Almost half the patients undergoing cardiac surgery have evidence of HARM and three quarters have acute lesions on DWI after surgery. BBB disruption is more prevalent in the first 24 hours after surgery. These findings suggest that MRI can be used as an imaging biomarker to assess therapies that may protect the BBB in patients undergoing heart surgery.

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Conflicts of Interest
None

This work was presented in part at the 36th International Stroke Conference in February, 2011.

INTRODUCTION

Between 1% and 6% of patients have clinical evidence of stroke after heart surgery, and the incidence of hyperintense lesions on DWI is even higher (18%-60%). These DWI lesions typically are small, often do not lead to clinical deficits, and their long-term clinical implications are not well understood.[1-7] Because it leads to brain changes, cardiac surgery has been proposed as a model to screen potential neuroprotective agents, particularly when DWI is used to identify incident lesions.[2, 8]

In addition to ischemia due to hypoperfusion and distal embolization, cardiac surgery elicits a systemic inflammatory response that may lead to a disruption of the blood-brain barrier (BBB) and neurological dysfunction.[9] In experimental models the use of cardiopulmonary bypass leads to opening of the BBB.[10, 11] Disruption of the BBB can be seen on MRI as enhancement of the subarachnoid space on post-contrast FLAIR images. Under normal conditions gadolinium-containing compounds do not cross the BBB. Under ischemic conditions, however, an increase in matrix-metalloproteinase-9 (MMP-9) leads to proteolytic breakdown of the BBB integrity that allows passage of gadolinium to the CSF and the parenchyma. Because gadolinium shortens T1, it disrupts the CSF signal suppression of FLAIR, and CSF appears hyperintense. The sensitivity of FLAIR for low-contrast concentrations is >10-fold higher than for T1 imaging, and much lower concentrations of gadolinium are required to see the gadolinium hyperintensity on FLAIR than on T1-weighted images..[12-16]

The enhancement of the CSF on FLAIR, an imaging biomarker called hyperintense acute reperfusion marker (HARM), is seen in 30-40% of patients with acute stroke and around 20% of patients with TIA without DWI lesions on acute MRI, and is more common in patients treated with pharmacologic or mechanical reperfusion therapies.[17, 18] It has been observed in animal models of ischemia, in patients with acute stroke, and in patients undergoing reperfusion procedures, including carotid artery angioplasty and stenting.[12, 13, 17, 19-22] It is associated with age, reperfusion, thrombolysis, endovascular procedures, changes in matrix metalloproteinases, hemorrhagic transformation and poor outcome.[17, 20, 21, 23-26] Recent studies confirm that HARM is due to enhancement of the CSF and not of the parenchyma and that gadolinium in the CSF is the cause of the enhancement.[15, 20] HARM is a biomarker with potential use in proof- of-concept clinical trials of agents that prevent BBB breakdown and consequent brain damage.[27-29]

The purpose of this study was to determine whether BBB disruption occurs after on- and off-pump coronary artery bypass grafting (CABG) or valve repair surgery and, if so, its relationship to incident ischemic lesions.

METHODS

Subjects

We enrolled patients who had on- or off-pump CABG or aortic or mitral valve replacement if they were 18 years of age or older and functionally independent (mRS<2). We excluded patients who had dementia, cognitive dysfunction, or a psychiatric disorder; were scheduled for concomitant carotid endarterectomy or pacemaker placement; had a contraindication to MRI; or were pregnant. The Institutional Review Board of the National Institute of Neurological Disorders and Stroke and Suburban Hospital in Bethesda, MD and Washington Hospital Center in Washington, D.C. approved the study and all patients gave informed consent to participate.

Study procedures

Initially we enrolled patients in this study before surgery (patients in group 1). After several months it became clear that it was not practical to enroll and consent patients before surgery: because the time between the decision to operate and the surgery was short, patients were reluctant to enroll in a study that required them to have a pre-operative MRI. We then started enrolling patients after surgery, once they were hemodynamically stable (group 2). Enrolling and imaging patients at different times allowed us to assess the permeability of the BBB at different time-points. We administered gadolinium (0.1 mmol/kg) to patients in group 1 approximately 24 hours after surgery; these patients had a post-operative MRI once they were hemodynamically stable (typically around 48 hours after surgery). The half-life of gadolinium in blood is 1.7 hours yet it remains in the subarachnoid space for several days; any HARM on the post-operative MRI scan therefore reflects the status of the BBB around the time of the injection. Group 1 patients also had a pre-operative MRI. Patients in group 2 received gadolinium at the time of the post-operative MRI and did not have a pre-operative scan. Throughout the study, a neurologist examined the patients and administered the Mini Mental State Examination (MMSE) and the Delirium Rating Scale (DRS) before surgery and at the time of gadolinium administration (group 1), and at the time of the post-operative MRI scan (group 1 and 2).[30]

Imaging and image analysis

Imaging was done in a Philips 3T or a General Electric 1.5T scanner; prior studies have shown that the field strength of the MRI does not affect the HARM detection rate.[31] Typical MRI parameters include 24 cm FOV, 35 contiguous interleaved slices, 3.5-4 mm thick and co-localized across series; trace-weighted DWI images were obtained at b=1000 from a 13-15 direction DTI sequence with an in-plane resolution of 2.5×2.5mm and TR/TE=10s/58ms at 3T or TR/TE=10s/72ms at 1.5T. T2-FLAIR images were obtained with an in-plane resolution of 0.94×0.94 mm, TR/TE=9000/120 ms and TI=2600 ms at 3T or TR/TE=9000/140 ms and TI=2200 ms at 1.5T.

Two stroke neurologists blinded to the clinical and surgical variables read the MRIs, and a third reader settled disagreements. The readers counted the number of lesions on the post-operative DWI and classified them based on location (cortical, subcortical or mixed) and appearance (punctate or confluent). They also reviewed the pre- and post-contrast FLAIR images looking for the presence of HARM and classified it by location (sulcal, ventricular and/or generalized) and severity (mild, moderate or severe) (Figure 1).

Statistical Analysis

The primary outcome measures were evidence of post-operative ischemic lesions on DWI and presence of HARM on FLAIR. We analyzed the outcomes as dichotomous variables. We did the statistical analyses with SPSS for Mac and compared categorical variables using chi-square or Fisher's exact test and means with the independent sample t-test. All p-values are two-tailed.

RESULTS

We report the imaging findings in 19 patients with mean age of 67.4 years (SD ±10.2). Six patients had off-pump CABG and 13 had surgery with the use of a cardiopulmonary bypass pump (7 CABG and 6 valvular surgery). The mean pump time was 130 minutes (SD ±23, range 82-179 minutes) and the mean cross-clamp time was 101 minutes (SD ±27, range 56-160 minutes). The mean pump time was similar between the 7 patients who had CABG and the 6 who had valve repair (141 [± 22] vs. 120 [±22] minutes, respectively; p=0.13). Similarly, cross-clamp time did not differ between the CABG and the valve repair patients

(109 [±26] vs. 92 [±26] minutes, respectively; p=0.26). Seven patients were examined with a 3T scanner and 12 with 1.5T.

The mean time from surgery to gadolinium administration in patients in group 1 was 21.6 hours [±1.2]; the corresponding value for patients in group 2 was 88.1 hours [±21.2] (p<0.001). The integrity of the BBB was therefore assessed, on average, 21.6 hours after surgery in the first group of patients and 88.1 hours after surgery in the second group. The time from surgery to the post-operative MRI was also shorter in group 1 than in group 2 (52 hours [±15.4] vs. 88.1 hours [±21.2]; p<0.001). The nine patients in group 1 had a pre-operative scan: only one of them (11%) had DWI lesions before surgery. None of the patients had clinical evidence of a stroke after surgery and all had consistently normal neurological examinations and scores in the MMSE and DRS,

We found HARM in 9 patients (47%); of these, seven (78%) also had DWI lesions (table 1). Most patients had mild/moderate HARM and only two had severe sulcal or background HARM; both patients were in group 1 (Figure 2 and 3). There were more than twice as many patients with HARM in group 1 than in group 2 (66.7% vs. 30%; p=0.18). The proportion of patients with HARM was similar in patients who had on-vs. off-pump procedures (38% vs. 50%, p=1.0).

DWI lesions were seen in 14 (74%) of the 19 patients who had a post-operative scan. In these patients, the mean number of lesions was 5.6 (SD ±4.7) and the median was 4 (range 1-18). The proportion of patients with DWI lesions was similar in group 1 and group 2 (78% vs. 70%; p=1.0). The incidence of lesions (as a dichotomous variable) did not differ by type of surgery (valvular, CABG and off-pump CABG, p=0.54). The proportion of patients who had DWI lesions was similar (83% vs. 69%, p=0.63) in those who had off-pump versus on-pump procedures. Not all patients with DWI lesions had HARM, and not all patients with HARM had DWI lesions, and the association between DWI lesions and HARM was not significant (p=0.56; table 1). Among the 7 patients who had DWI lesions and HARM, 3 had background HARM only; 1 had sulcal, background and ventricular HARM; and 3 had sulcal HARM only. The four patients with sulcal HARM had DWI lesions in multiple vascular territories. In 2 of these patients, the HARM was not in the vascular territory of the DWI lesions. In the other 2 patients, there was HARM in at least one of the affected vascular territories, but not all sulcal HARM was contiguous with the DWI lesion (online table).

DISCUSSION

MRI-demonstrated BBB disruption after cardiac surgery occurred in almost half the patients in our sample. The incidence of HARM was higher among patients who received gadolinium within 24 hours of surgery. Because of the short plasma distribution and elimination half-life of gadolinium (0.2 ± 0.13 hours and 1.6 ± 0.13 hours, respectively), our findings suggest that the BBB may open during or soon after heart surgery and close shortly thereafter. Animal studies show that the BBB opens soon after ischemia. In an MCA occlusion (MCAO) rat model, brain sucrose uptake, a marker of BBB disruption, increased 3 hours after reperfusion, was maximal at 48 hours, and persisted for up to 14 days.[32] In another study, gadolinium enhancement of the ventricles ipsilateral to stroke was seen on FLAIR within 1 hour of reperfusion in rats subject to MCAO, suggesting that the blood-CSF barrier can be disrupted within minutes of onset of ischemia, and this enhancement increases by 24 hours. At 48 hours parenchymal enhancement on T1 was evident, suggesting a more widespread BBB opening.[23] In humans with stroke HARM can be seen within the first 6 hours of symptom onset, and persists for up to 5 days.[17]

The clinical relevance of HARM in cardiac surgery patients is unclear, as our patients did not have evidence of neurologic or cognitive dysfunction at the time of gadolinium administration -when the integrity of the BBB was evaluated- or at the time of the MRI scan. Further studies are needed to determine if BBB disruption after heart surgery is clinically relevant and if it occurs because of focal or global ischemia, reperfusion injury, changes in the level of matrix metalloproteinases, or inflammatory mechanisms. Our findings suggest that such studies should focus on the first 24 hours after surgery.

The incidence of DWI lesions in our series is higher than previously reported.[1-7] Several features of our MRI sequences may explain this higher incidence: we used thin slices to decrease partial volume averaging with normal tissue on CSF; used short echo time to decrease T2 loss; used a DTI sequence with 13-15 directions instead of a conventional DWI sequence to increase averaging and signal-to-noise; and, on the 1.5 T scanner, used a twice refocused spin echo to decreased eddy currents.

In our patients, most DWI lesions were cortical. The clinical relevance of such small DWI lesions seen after invasive procedures, however, remains unknown.[33] Case studies have shown that over time some of these lesions may become invisible on 3D T1-weighted and FLAIR images, but still lead to a loss of gray matter.[34] These small cortical lesions may be another pathway to cortical atrophy and may explain why some patients undergoing cardiac surgery develop cognitive impairment.

In our study, we did not find an association between HARM and DWI lesions. Cerebral ischemia and reperfusion are associated with opening of the blood brain barrier, which has been described in patients with transient symptoms without DWI lesions.[18] A proposed mechanism for BBB disruption after ischemia of any duration is activation of inflammatory cascades and proteolytic enzymes.[25, 35] The effect of ischemia on BBB disruption may be diffuse.[26] HARM is not always related to the site of ischemia.[17, 21] In addition, in patients undergoing cardiac surgery, the procedure activates a systemic inflammatory response and the production of immune mediators that may contribute the development of acute and chronic neurological dysfunction and disruption of the blood brain barrier, a process also seen in patients with traumatic brain injury and hemorrhagic and ischemic stroke. [36, 37] Future studies are needed to clarify the role of different immune mediators in the genesis of HARM in these patients.

The use of cardiopulmonary bypass (CPB) may lead to disruption of the BBB, perhaps on the basis of a systemic inflammatory response.[9, 11] Case series suggest that neurologic complications are less when the CABG is done off-pump, but clinical trials have not confirmed this observation. [38, 39] In our series, the proportion of patients with DWI lesions and HARM was similar in patients who had an off-pump CABG as those who had an on-pump procedure (CABG or valve replacement). The reasons why patients who have an off-pump procedure have disruption of the BBB are not clear and merit further study looking at serum biomarkers of inflammation and levels of different matrix metalloproteinases.

Our study has some limitations, hence our findings are preliminary and require replication in a larger prospective study. Our sample was small, and the lack of association between HARM and DWI lesions may be a type II error rather than a definitive finding. It is possible that some of the DWI lesions were present before surgery, but only one of the nine participants who had a pre-surgical MRI had DWI lesions at baseline. Breathing high oxygen concentration may lead to CSF hyperintensity on FLAIR due to the T1 shortening effect of oxygen, a phenomenon described only in intubated patients and volunteers breathing 100% O_2, and in that case the CSF enhancement is global and severe. [40, 41] We do not have information about the use of supplemental oxygen in our patients, but we know that

none was intubated or using a non-rebreather mask, so we assume that any HARM was not due to high CSF oxygen concentration. Patients were subject to a variety of surgical procedures, but because of the sample size we cannot determine whether features inherent to each surgery played an etiologic role in the development of brain changes. Finally, we do not have longitudinal follow-up data to determine the clinical implications of BBB disruption shortly after cardiac surgery.

In conclusion, almost half the patients undergoing cardiac surgery have evidence of HARM and three quarters have acute lesions on DWI after surgery, and BBB disruption is more prevalent in the first 24 hours after surgery. These findings suggest that MRI can be used as an imaging biomarker to assess therapies that may protect the BBB in patients undergoing heart surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to acknowledge the assistance of the Peter C. Hill MD and the cardiac surgery and NIH Stroke Teams at Suburban Hospital and Washington Hospital Center in the performance of this study.

Funding

The Division of Intramural Research of the National Institute of Neurological Disorders and Stroke of the National Institutes of Health supported this research.

Abbreviation key

CABG	Coronary Artery Bypass Grafting
CPB	Cardiopulmonary Bypass
DRS	Delirium Rating Scale
HARM	Hyperintense Acute Reperfusion Marker
MMSE	Mini-mental State Examination
mRS	Modified Rankin Scale

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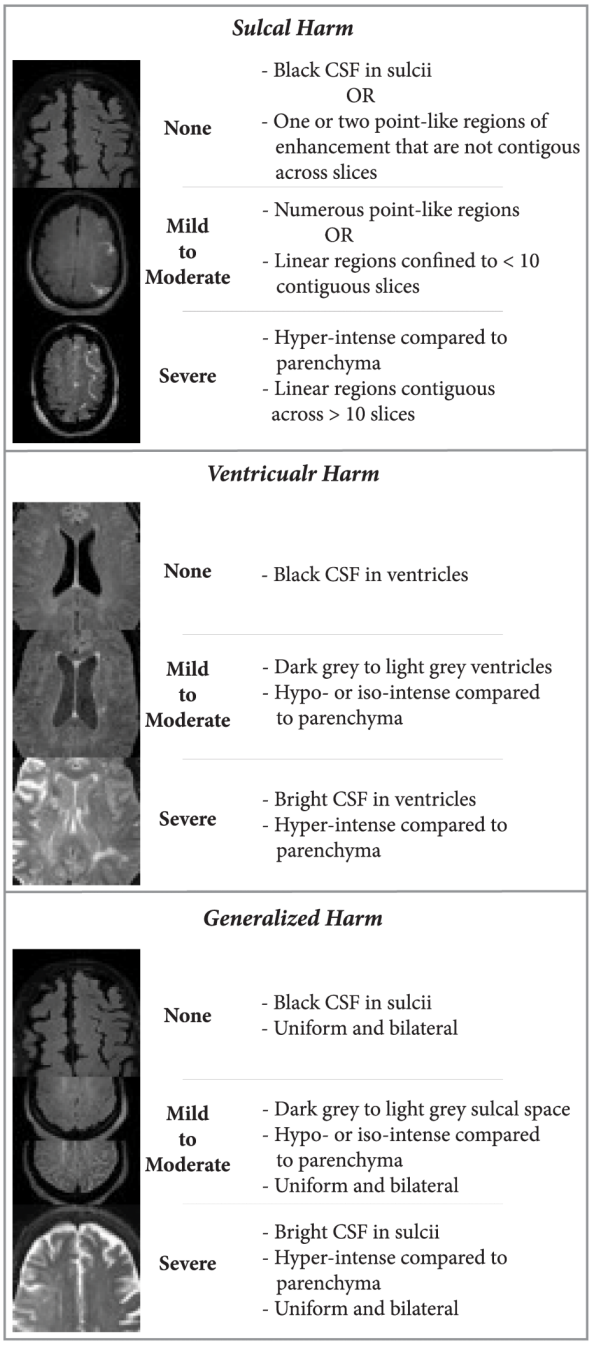

Figure 1.
Classification of HARM by location and severity. Definitions used for HARM classification.

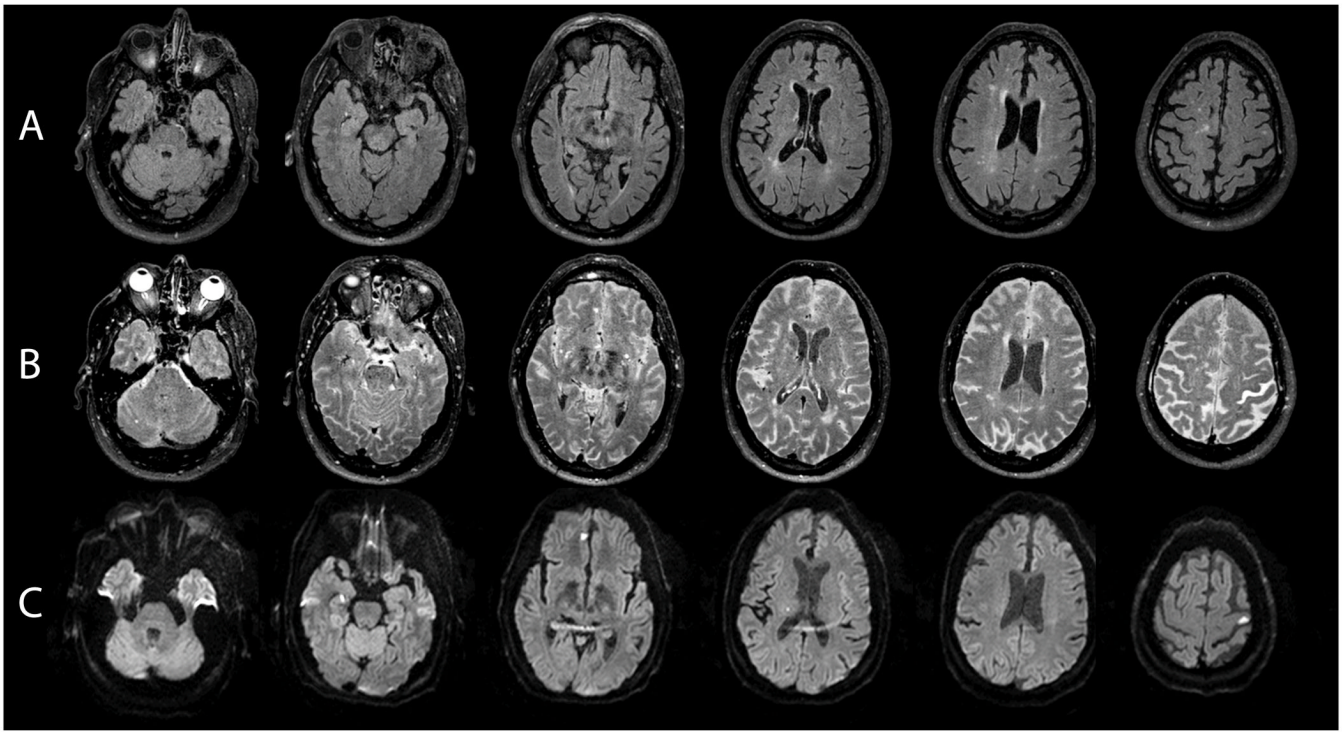

Figure 2.
Generalized HARM 74-year old man who underwent off-pump CABG. A. Baseline FLAIR obtained before surgery. B. Post-gadolinium scan. Gadolinium was administered 20 hours after surgery, and a 3T MRI was done 20 hours later. Post-gadolinium FLAIR shows enhancement throughout the subarachnoid space (severe sulcal and background HARM). The CSF in the ventricles appears gray (mild/moderate ventricular HARM). Gadolinium enhancement is also seen in the eye. C. DWI obtained after surgery. Patient had 4 DWI lesions.

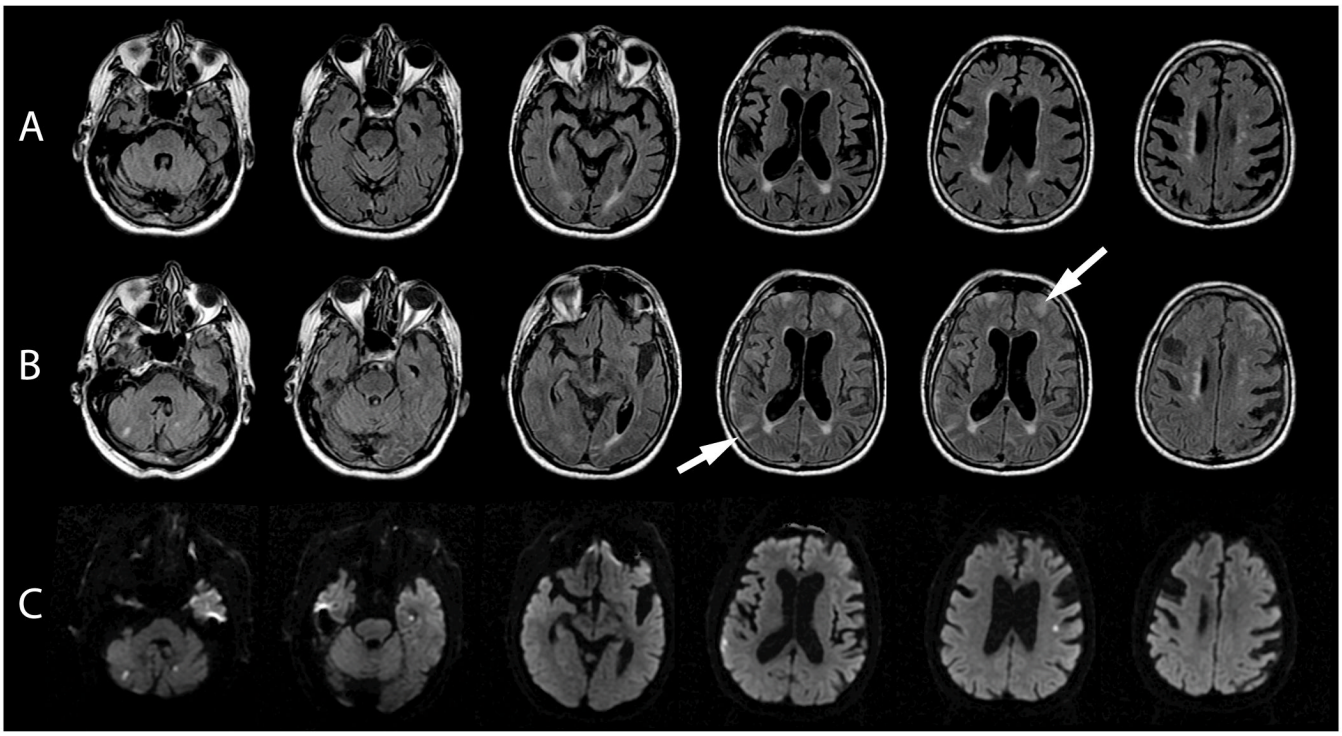

Figure 3.
Sulcal HARM 86-year old man who underwent CABG. A: Baseline FLAIR done before surgery. B. Post-gadolinium FLAIR. Gadolinium was administered 23 hours after surgery and the 1.5T MRI was obtained 27 hours later. Post-gadolinium FLAIR shows bright enhancement in the right frontal and left parietal subarachnoid space (severe sulcal HARM, arrows). C. Postoperative DWI. The patient had six DWI lesions. .

Table 1

Association of HARM and DWI lesions

		HARM		
		Yes	No	Total
DWI lesion	Yes	7	7	14 (74%)
	No	2	3	5
	Total	9 (47%)	10	19