

Cerebral Microembolism During Cardiac Catheterization and Risk of Acute Brain Injury

A Prospective Diffusion-Weighted Magnetic Resonance Imaging Study

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Background and Purpose—Cerebral microembolism detected by transcranial Doppler occurs systematically during cardiac catheterization, but its clinical relevance remains unknown. Studies suggest that asymptomatic embolic cerebral infarction detectable by diffusion-weighted (DW) MRI might exist after percutaneous cardiac interventions, especially after retrograde catheterization of the aortic valve in patients with valvular aortic stenosis, with a frequency as high as 22% of cases. We investigated the incidence of new ischemic lesions on serial cerebral DW MRI after cardiac catheterization.

Methods—This prospective study involved 46 patients with severe aortic valve stenosis. To assess the occurrence of cerebral infarction, all patients underwent cerebral DW MRI and neurological assessment within 24 hours before and 48 hours after cardiac catheterization and retrograde catheterization of the aortic valve. A subgroup was monitored by transcranial power M-mode Doppler during cardiac catheterization to observe cerebral blood flow and track emboli.

Results—One patient had a focal diffusion abnormality on DW MRI before cardiac catheterization. After catheterization, we detected only 1 additional acute cerebral diffusion abnormality in a single case (2.2%), although cerebral microemboli were detected in all transcranial Doppler-monitored patients during cardiac catheterization, as expected. All patients remained asymptomatic. Based on these results a mid-point incidence of 5.9% (95% CI, 0.01 to 12.5) for abnormalities on DW MRI in asymptomatic cardiac catheterization patients in our center can be assigned.

Conclusions—Unsuspected cerebral infarctions can be detected by DW MRI after cardiac catheterization, but this phenomenon remains infrequent in our series. Further studies are needed to identify factors explaining the discrepancy between these results and those of previous studies. (*Stroke*. 2006;37:000-000.)

Key Words: cardiac catheterization ■ cerebral embolism ■ diffusion magnetic resonance imaging
■ magnetic resonance imaging ■ ultrasonography, Doppler, transcranial

Symptomatic cerebral infarction after cardiac catheterization is rare,^{1,2} but silent brain injury could occur at an unexpectedly high rate.^{3,4,5} One study has found that up to 22% of patients with severe aortic stenosis who have undergone retrograde catheterization of the valve can be identified as having new ischemic lesions as detected by diffusion-weighted (DW) MRI.³ More recently, a surprisingly high rate (15%) of acute brain injury after percutaneous coronary intervention has also been reported.^{4,5} The use of transcranial Doppler (TCD) sonography allows the recording of systematic microemboli entering the middle cerebral artery during various endovascular interventions, including cardiac catheterization.^{6,7} In the case of coronary bypass surgery, evidence indicates that microembolism is related to cognitive impairment, based on the results of neuropsychological testing.⁸ During cardiac catheterization, cerebral microembolism as de-

tected by TCD has frequently been observed, but whether it is clinically relevant remains unknown.^{6,7} However, recent studies mentioned above have suggested that some of these microemboli could be related to silent cerebral embolisms responsible for acute brain injury, as documented by DW MRI.^{3,4,5}

Indeed the high sensitivity of DW MRI suggests that this technique could allow an improved estimate of cerebral ischemic events associated with cardiovascular-catheter procedures.⁹ We therefore performed DW MRI before and after cardiac catheterization to prospectively assess both clinically silent and apparent cerebral embolisms.

Patients and Methods

Study Population

From January 2005 to December 2005, 46 patients with a mean age of 76 (± 8 , SD) years were prospectively and consecutively enrolled

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in the present study after informed consent was obtained. This population represents 76.6% of all the 60 eligible patients screened during the same period in our center. All patients were scheduled for cardiac catheterization because of aortic valve stenosis to assess coronary artery tree and aortic valve disease before surgery. Exclusion criteria were a contraindication to MRI or inability to give written informed consent. Among the 14 patients excluded 4 had unclear echocardiographic findings, 2 had contraindication to MRI and 8 were excluded because of MRI unavailability.

Cardiac Catheterization

All patients were examined clinically and assessed for any history of previous cerebral embolism. Transthoracic echocardiography, 12-lead surface ECG, and coronary angiography were performed for all patients. Cardiac catheterizations were undertaken by expert interventional cardiologists using a standard Seldinger technique using 5 French (F) catheters. Sheaths were removed immediately after the procedure in all patients. We gave 5000 IU of unfractionated heparin intravenously to all patients at the beginning of the procedure. Retrograde catheterization of aortic valve was attempted in a right oblique projection using a long exchange guide wire (0.035 inch, 260 cm length to ensure exchange of the pigtail catheter) using a left amplatz 1 catheter or a right Judkins catheter. During attempts to cross the aortic valve, the wire was regularly withdrawn and cleaned and the catheter flushed every 2 minutes according to Grossman's recommendations.¹⁰ When the pigtail catheter was placed in the left ventricle, the wire was withdrawn and the catheter vigorously aspirated and pressure measurements performed. After left ventriculography, the catheter was rapidly withdrawn from the left ventricle into the ascending aorta with simultaneous pressure measurements. Maximum and mean pressure gradients were established. We recorded the duration of the whole procedure and fluoroscopic time in all patients.

MRI

MRI was done within 24 hours before and 48 hours after cardiac catheterization. We performed MRI examinations with 1.5 Tesla system (GE Health Care). The imaging protocol included a DW single-shot spin echo echoplanar sequence acquired in the AC-PC (anterior commissure-posterior commissure) plane with 24 contiguous sections (diffusion gradient b values of 0 and 1000 s/mm², repetition time [TR] 6000 ms, echo time [TE] 120 ms, slice thickness 6 mm with no gap, matrix of 128×128 pixels, and field of view of 240 mm); fluid-attenuated inversion recovery (FLAIR; TR/TE 10 000/160 ms, inversion time 2200 ms); and T2-weighted turbo spin echo sequences (TR/TE 3500/94 ms). For DW MRI, the diffusion gradients were successively and separately applied in 3 orthogonal directions for a total acquisition time of 24 seconds. Trace images were then generated and apparent diffusion coefficient maps calculated with a dedicated software tool (Functool; General Electric). The image analysis was performed independently by 2 experienced neuroradiologists (Michèle Hamon, C.O.) who were blinded to the clinical data and were unaware of the technical aspects of the angiographic cardiac procedure. For analysis of DW MRI, the neuroradiologists were asked to determine the presence, size, number, and vascular distribution of any focal diffusion abnormalities (bright lesions) in a pattern consistent with embolic lesions.

TCD

TCD studies for this work were performed with the TCD power M-mode Doppler 100 (PMD100, Spencer Technologies) which calculates a power M-mode Doppler image concurrently with a 2-MHz single-gate spectrogram as previously described.¹¹

Microembolic signals present a unique signature or "track" in the power M-mode Doppler image (slope consistent with the speed of blood flow across the vessel segments in view) which defines them as representing emboli and facilitating exclusion of potential artifacts. In particular, artifacts tend to show significant power signature at all gates simultaneously, whereas true embolic signals have a progression across depth as time changes.¹² The number of micro-

embolic signals for all TCD recordings was assessed by an independent investigator unaware of the DW-MRI results.

Statistical Analysis

Baseline characteristics of the study population are presented as counts and percents for categorical variables and as mean±SD for continuous variables. κ statistic was calculated to determine interobserver agreement. The number of lesions in our population of patients recruited was estimated by the adjusted Wald interval at 95% in accordance with the method recommended by Agresti and Coull.¹³ With small sample sizes, as recommended we have used the mid-point of the adjusted Wald interval instead of the observed proportion.¹⁴ The statistical analyses were performed using SPSS 10.0.7 program.

Results

Baseline characteristics of our study population are listed in Table 1, including the catheterization procedure results. In the 46 patients, the National Institutes of Health Stroke Scale (NIHSS) score was initially 0 and remained 0 after the procedure. Significant carotid stenosis (>50%) as detected by echo-Doppler was found in 8% of the population. No transient change in neurological status was documented for any patient during cardiac catheterization. All patients underwent coronary angiography followed by successful retrograde catheterization of the aortic valve in 100% of cases. As usual, some ectopic ventricular complexes were seen during the placement of the pigtail catheter within the left ventricular chamber, and at the time of crossing the valve with the exchange wire. However, no sustained ventricular tachycardia was induced nor was ventricular fibrillation observed in this population. All procedures were conducted using 5 F catheters and 3.8±0.7 catheters were used successively with a mean duration of procedure of 16±5 minutes and a mean fluoroscopy time of 5.4±3 minutes.

Successful transcranial Doppler recordings were made in the final 12 consecutive patients in the series (26%). In all patients with TCD recordings, we identified systematic cere-

TABLE 1. Baseline Characteristics of the Study Population

No. of patients	46
Male	27 (59%)
Age, years	76±8
BMI, kg/m ²	25.8±3.8
Hypertension	28 (61%)
Diabetes mellitus	4 (9%)
Hypercholesterolemia	21 (45%)
Smokers	18 (39%)
Family history of CAD	4 (9%)
Prior stroke	2 (4.5%)
Associated CAD	28 (61%)
Atrial fibrillation	12 (27%)
Mean Doppler gradient, mm Hg	51±14
AVA, cm ²	0.83±0.31
Invasive LVEF, %	69±13
No. of catheters used per procedure	3.8±0.7
Fluoroscopy time, min	5.4±3.0
Procedure duration, min	16.0±5.0

CAD indicates coronary artery disease; BMI, body mass index; LVEF, left ventricular ejection fraction; AVA, average valve area.

TABLE 2. Comparison of Recent Studies Exploring Brain Injury Using Serial DW at MRI After Cardiac Catheterization.

	n	Heparin	Fluoroscopy Time (min) DWI+/DWI-	Catheter Size (French)	Serial DW MRI	New Cerebral Infarction Observed %	New Cerebral Infarction Mid-Point [95% CI]	Indication
Omran 2003 ³	101	5000 IU	6.1/2.9	6 F-7 F	100%	22%	23% [15–31]	Aortic stenosis
Lund 2005 ⁵	47	5000 IU	11.3/5.2	6 F	89%	13.5%	15.7% [6–26]	CAD
Busing 2005 ⁴	48	2500 IU	10.1/7.4	5 F-6 F-7 F	94%	15%	17% [7–28]	CAD
Hamon 2006	46	5000 IU	7.0/5.4	5 F	100%	2.2%	5.9%* [0.01–12.5]	Aortic stenosis

CAD indicates coronary artery disease.

*Only 1 new cerebral infarction in our consecutive series of 46 patients was documented (2.2%, observed proportion). The mid-point of the adjusted Wald interval and 95% CI is calculated for all studies. It is noteworthy that by comparison to previous studies a lower rate of new cerebral infarction was documented by DW MRI in our series ($P < 0.02$) and especially by comparison with the results of Omran et al³ ($P < 0.002$).

bral microembolism with a mean of 72 ± 37 high-intensity transient signals per procedure.

A total of 92 DW MRI were evaluated blindly. All patients underwent cerebral DW MRI (5 ± 2 hours) before and (13 ± 10 hours) after cardiac catheterization. Before cardiac catheterization, 1 patient had a hyperintense focal lesion on DW MRI. After the procedure only 1 new acute focal bright cerebral diffusion abnormality was found in a single case. This case was an 82-year old woman with normal left ventricular ejection fraction without carotid stenosis or atrial fibrillation but with prior history of hypertension, hypercholesterolemia and diabetes. The duration of the catheterization procedure was 22 minutes with a fluoroscopic time of 7 minutes.

No diffuse alterations in DW MRI or pattern of watershed ischemia were found in any patient. Subsequent comparison of pre- and postcardiac catheterization studies by the 2 readers indicated 98% agreement with a κ value of 0.93 (given the small and focal lesion documented in only 1 case mutual assessment was required for full agreement). Statistical analysis yielded an upper boundary of 12.5% for the incidence of abnormalities on DW MRI in asymptomatic patients who had undergone cardiac catheterization with retrograde catheterization of severe aortic valve stenosis in our center; this value can be assigned with 95% confidence with a mid-point of 5.9% and is significantly different compared with previous studies ($P < 0.02$; Table 2) especially in patients explored for aortic valve stenosis ($P < 0.002$).

Discussion

According to previous studies, the rate of stroke after cardiac catheterization ranges from 0.11% to 0.4%.^{1,2,15} However, these studies on the risks of cardiac catheterization have included only obvious new neurological deficits as complications. Clinically unapparent damage, related to microscopic air embolism or to thromboembolism, were not taken into account. With the advent of cerebral DW MRI, which is very sensitive in detecting acute ischemic lesions early after onset, it has been shown that asymptomatic embolic events might be far more frequent than the apparent neurological complication rate would indicate.^{3,4,5,9}

Based on a previous study of Omran et al³ in patients with aortic stenosis who had undergone retrograde catheterization of the aortic valve, a 22% rate of silent cerebral infarction was expected in our series of patients. However, in our prospective evaluation including 46 patients and using serial cerebral DW MRI, we identified only 1 asymptomatic patient (2.2%)

with such an event in association with retrograde catheterization of the aortic valve.

Other groups have recently documented that silent acute brain injury can also be associated with percutaneous cardiac interventions (PCI), with possible cognitive impairment for patients in whom new lesions are identified on DW MRI.^{4,5} It seems that only the length of the procedure or the procedural fluoroscopy time can be independently associated with the risk of cerebral infarction in these studies. These 2 parameters are related to the overall influence of the catheter manipulation, including additional periods of time required while the catheter acts as a embolic source; this factor may lead to thrombus formation or affect the vessel wall during manipulation or placement in patient's vascular system. In addition, as previously assumed, plaque debris broken off from the aorta or the aortic arch, blood clots from the tip of the catheter, or air embolism risk must also be considered in assessing microembolism during heart catheterization. It appears likely that all these well-recognized risks of cerebral embolism for patients who undergo heart catheterization can be related to the duration of the procedure. It is notable that in our study the mean fluoroscopy time needed to cross the aortic valve was shorter than in the study of Omran et al.

All our catheterization procedures were performed at a high-volume center (>3000 diagnostic and 1300 interventional procedures per year) with standard techniques that appear similar to those recently reported and that are associated with a high rate of acute brain injury, as documented by DW MRI.^{3,4,5} All reported studies (see Table 2) used heparin during the procedure with standard commercially available materials for catheters and contrast media. The only characteristic that could have influenced the results in addition to the length of the procedure is the size of catheters used; in previous studies, catheters were 6 F and sometimes 7 F for PCI. Smaller catheters, such as the 5 F used in all our cases, could have minimized the risk of arterial injury and the source of embolism during retrograde passage of the aortic valve.

Because all cardiac catheterizations are associated with microembolism as detected by TCD (confirmed in our substudy analysis), it has been suggested that most of these microembolisms are likely benign microbubbles.^{6,7} However, some recent studies have raised the possibility that some microparticles embolized during heart catheterization could be responsible for acute brain injuries.^{3,4,5} In fact, the most likely sources of embolic material are catheters and guidewires that dislodge atheromatous material from the aortic arch. Visible aortic debris

may be seen on withdrawal of catheters during PCI cases. Patients with a large atherosclerotic burden in the aorta (such as those with advanced coronary artery disease), as documented by transesophageal echocardiography, have an increased risk of cardiac catheterization-induced stroke.^{16,17,18} The more extensive coronary artery disease and longer fluoroscopy times identified in previous studies as risk factors for stroke can be considered as surrogate markers of prolonged, complex catheter manipulations in a severely atherosclerotic aorta. It has been shown that patients with cardiac catheterization-induced stroke often have multiple acute lesions (often tiny, cortical, and in different vascular territories) on DW MRI distinct from the occasional symptomatic lesion and consistent with a shower of embolic material. Given the rate of these unsuspected lesions and the potential consequences related to cognitive impairment, other studies are warranted to determine the risk factors associated with these deleterious effects of heart catheterization.

Among potential limitations of the present study one could argue that differences might exist in the interpretation of cerebral DW MRI. Such differences in MR image interpretation between centers seem unlikely because DW MRI has been routinely used for diagnosis of infarcted brain tissue for several years now and all images were evaluated by experienced neuroradiologists. Another issue is related to the delay between the cardiac catheterization and the postprocedural DW MRI. Indeed the optimal time to detect potential ischemic lesions using DW MRI is unknown. However, it has been documented that 24- to 48-hour DW MRI did not increase diagnostic accuracy in any case in which the 2- to 4-hour study was negative suggesting that early assessment could be performed in asymptomatic patients.¹⁹ Finally, given the number of high-intensity transient signals observed during each catheterization procedure we cannot exclude diffuse and subtle brain injury undetectable by DW MRI in some cases. The ability of neuropsychological tests to address this specific issue warrants further study.

In conclusion, in this prospective study we confirm that cerebral microembolism as detected by TCD occurs for all patients during cardiac catheterization without correlation with the risk of brain injury. Even after retrograde catheterization of valvular aortic stenosis, new cerebral lesions on DW MRI are infrequent in our center. Further studies are warranted to identify factors—including catheterization methods, pharmacological environment, and selection of materials^{20,21}—that could explain this discrepancy with previous studies. Finally, performing pre- and postprocedure DW MRI could be used to monitor the procedure-related frequency of ischemic lesions and to assess the benefit of changes in practice to improve the safety of cardiac angiography and catheterization.

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