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Hypercholesterolemia as a Risk Factor for Catheterization-Related Cerebral Infarction — A Literature Review and a Summary of Cases

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1. Introduction

Hypercholesterolemia is one of the major risk factors of atherosclerotic disease. Treatment with statins reduces serum levels of low-density lipoprotein cholesterol, and attenuates atherosclerotic plaque formation in the carotid artery, coronary artery, and thoracic aorta.

During diagnostic angiography or interventions for coronary artery diseases, catheterization can lead to devastating complications, including stroke. Previous studies reported stroke rates of 0.1–0.4% [1-9]. Catheterization-related acute stroke is associated with high in-hospital mortality and prevalence of overall major complications [5,10,11].

Because only new neurological complications are classified as stroke, clinically unapparent cerebral embolisms are not taken into account. Asymptomatic cerebral infarction is thought to be related to the incidence of symptomatic cerebral infarction, cognitive decline, and dementia [12], and may thus represent a significant complication of catheterization procedures.

Here, we summarize our review of published literature, present two case studies in our cardiovascular center, and summarize our data on hypercholesterolemia and catheterization-related stroke.

2. A review of published literature on hypercholesterolemia and catheterization-related stroke

Previously published data on catheterization-related acute stroke is summarized in Figure 1. Previous studies have reported stroke rates of 0.1– 0.4% [1-9], and rates of stroke and

transient ischemia attack (TIA) after catheterization do not appear to have decreased over time (Figure 1). Much of the published data is limited to stroke. Stroke is defined as cerebral infarction or hemorrhage with a neurological deficit lasting >24 h; TIA is a neurological deficit lasting <24 h.

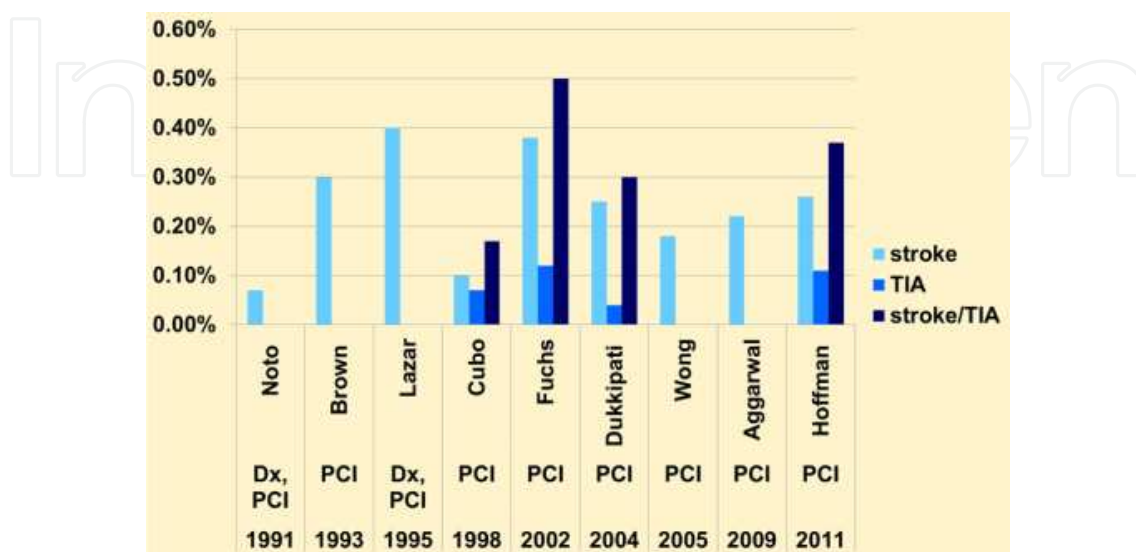


Figure 1. Rates of stroke and transient ischemic attack (TIA) after catheterization have not reduced overtime [1-9].

Magnetic resonance imaging (MRI) can be used to detect asymptomatic cerebral infarction related to catheterization. Diffusion-weighted MRI (DW-MRI), in particular, represents a highly sensitive tool for detecting acute cerebral ischemic lesions [13,14]. New lesions appear as focal high-intensity cerebral lesions on diffusion-weighted imaging (DWI) and have a low signal on apparent diffusion coefficient (ADC) maps [15].

Several prospective studies of silent cerebral infarction have been performed in a small number of patients. Bendszus et al. used DW-MRI before and after angiography of cerebral vessels to assess embolic events in 100 consecutive angiographies (66 diagnostic and 34 interventional) in 91 patients [16]. In their report, published in *The Lancet* in 1999, they showed that 23% of procedures caused silent embolic cerebral infarction: 42 bright lesions were observed in 23 patients after 23 procedures (17 diagnostic, six interventional), in a pattern consistent with embolic events, and in the absence of any new neurological deficit. More contrast medium, a longer fluoroscopy time, more frequent additional catheters, and having more vessels that were difficult to approach were the risks of silent embolic cerebral infarction. Patients' mean age did not differ between patients with lesions and those without lesions, but their mean age was relatively young (around 50 years old) compared to patients who are receiving cardiac catheterization.

Lund et al. monitored cerebral microemboli during catheterization in 42 unselected patients using multifrequency transcranial Doppler alongside cerebral DW-MRI and neuropsychological assessments. Measurements were taken on the days before and after catheterization [17]. Their report, published in the *European Heart Journal* in 2005, showed that new cerebral lesions

were present in 15.2% of transradial catheterization patients, but in none of the transfemoral catheterization patients. These lesions were significantly associated with a higher number of solid microemboli and a longer fluoroscopy time. Approximately 80% of patients were male and had hyperlipidemia or were statin users; approximately 40% of patients had a previous history of myocardial infarction.

In 2005, Karen et al., using MRI before and after catheterization procedures, reported focal cerebral infarction without any symptoms in 15% of 48 patients [18]. In this prospective study, definitive conclusions could not be drawn owing to the small sample size, but procedure duration appeared to predict cerebral infarction following catheterization. Patients with cerebral infarction were also found to have a history of smoking, hyperlipidemia, hypertension, and obesity.

It is often difficult to acquire MR images before and after procedures in prospective studies. In 2011, Kojuri et al. reported in *BMC Cardiovascular Disorders* the prevalence of retinal emboli after diagnostic and therapeutic catheterization during retinal examination: 6.3% of 300 patients and only 1 patient developed vision disorder [19].

Patients who undergo aortic stenosis (AS) procedures that involve crossing of the aortic valve carry a high risk of cerebral infarction. In 2003, Omran et al. reported in the *Lancet* that 22% of 101 AS patients undergoing retrograde catheterization of the left ventricle had new lesions on MRI, and 3 patients had symptomatic cerebral infarction [20]. A total of 152 patients with AS undergoing cardiac catheterization were randomized to receive catheterization with or without retrograde passage of the aortic valve in a ratio of 2:1. An additional 32 patients without AS were also assessed as healthy controls. In patients without retrograde passage of the aortic valve, and in healthy controls, there was no MRI or clinical evidence of cerebral embolism.

Although these studies used relatively small sample sizes, the incidence of asymptomatic cerebral infarction following catheterization, as assessed by MRI or other methods, appears to remain relatively high. Following improvements in catheter design (rendering them more slender) and in techniques, catheterization-related cerebral infarctions were expected to decrease, though this may be counterbalanced by the increased risk profile of patients who undergo catheterization.

3. Two cases of asymptomatic and symptomatic cerebral infarction related to catheterization

Here we present two cases of cerebral infarction with and without symptoms which was related to cardiac catheterization.

Case 1: A 73-year-old man with hyperlipidemia, hypertension and diabetes underwent percutaneous coronary intervention (PCI) via the right radial artery. An initial diagnostic procedure was performed using 4F catheter; a 6F catheter was subsequently used to perform PCI for the left anterior descending artery (LAD). Due to the tortuosity of the LAD, the

procedure time was 58 min and 275 ml contrast medium was used. MRI was performed 5 days later for MR angiography to detect carotid and intra-cranial lesions. MRI was not performed prior to the procedure; however, new lesions appeared as focal high-intensity cerebral lesions on DWI (Figure 2A) and gave a low signal on ADC maps (Figure 2B). ADC maps represent a useful tool for detecting acute ischemic infarct lesions [16].

Case 2: A 69-year-old woman with hyperlipidemia and diabetes underwent diagnostic catheterization for left ventricular systolic dysfunction of unknown etiology, with 45% ejection fraction. On the day after catheterization, the patient complained of dizziness. DW-MRI revealed a spotty high-intensity signal (Figure 2C).

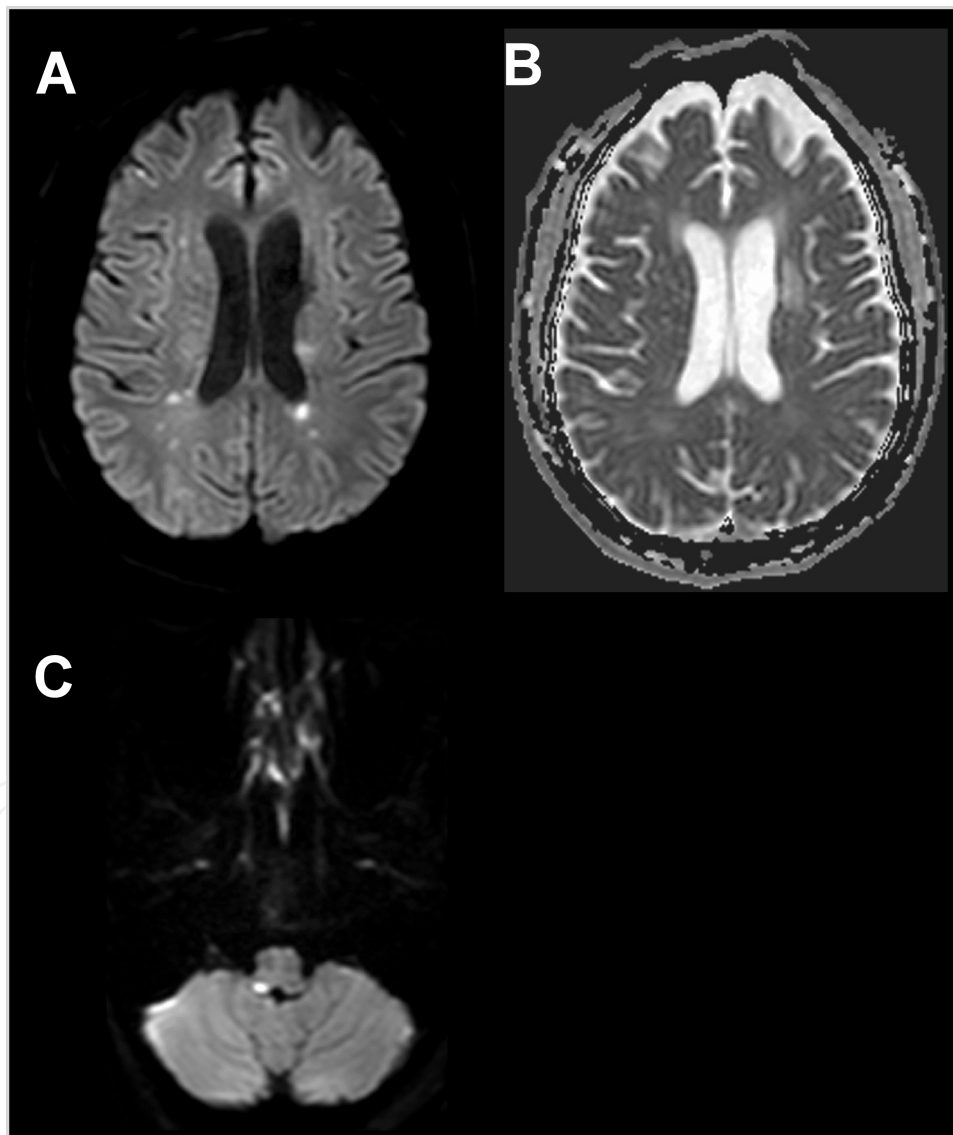


Figure 2. Magnetic resonance imaging (MRI) in two cases of asymptomatic and symptomatic cerebral infarction related to catheterization. (A) Diffusion-weighted MR image of Case 1. (B) Apparent diffusion coefficient (ADC) map of Case 1. (C) DW-MR image of Case 2.

4. A single center retrospective analysis of catheterization-related cerebral infarction

We next present the summarized results of a single center analysis of catheterization-related cerebral infarction in our cardiovascular center. A total of 84 patients who had undergone 1237 consecutive catheterizations with follow-up MRI within 14 days, between 2010 and 2011, were retrospectively analyzed. Of these, 10 symptomatic patients underwent MRI to check for cerebral infarction. The remaining 74 patients were asymptomatic, and underwent MRI for preliminary assessment before coronary artery bypass graft (35%), valvular surgery (18%), or aortic repair (6.8%). MRI revealed cerebral infarction in 5 out of 10 symptomatic patients (50%), and in 22 out of 74 asymptomatic patients (29.7%). Patient background characteristics are presented in Tables 1 and 2. In univariate analysis, the prevalence of dyslipidemia, the number of atherosclerotic risk factors, the number of catheters used, the procedure time, urgent settings, and reasons for intervention differed significantly between patients with and without cerebral infarction (Tables 1 and 2). Dyslipidemia and the number of catheters used were identified as predictive of catheterization-related cerebral infarction by multivariate analysis (odds ratio [OR], 4.66; 95% CI, 1.32–20.2; P=0.02 and OR, 2.04; 95% CI 1.02–4.35; P=0.04, respectively). Overall, the rate of asymptomatic catheterization-related cerebral infarction detected by DW-MRI was high (29.7%). This may be partially due to selection bias because MRI was performed in candidates for cardiac surgery for atherosclerotic disease. The rate of catheterization-related symptomatic ischemic stroke recorded in this study (0.24%) is roughly equivalent to those reported in previous studies [1-9].

	Infarction group (n=27)	No infarction group (n=57)	P value
Age, yr	74.1±6.6	70.4±9.4	0.08
Male, %	66.7	59.6	0.54
Risk factors			
Hypertension, %	77.8	71.9	0.57
Dyslipidemia, %	81.5	52.6	0.01
Diabetes, %	55.6	36.8	0.11
Smoking, %	63	57.9	0.66
Family history, %	29.6	15.8	0.14
No. of risk factors	3.03±1.26	2.32±1.19	0.014

Table 1. Baseline characteristics

	Infarction group (n=27)	No infarction group (n=57)	P value
No. of catheters used	2.85±1.1	2.12±0.9	0.003
Catheter size, F	4.44±0.8	4.25±0.6	0.3
Contrast volume, ml	128±55	120±55	0.48
Fluoroscopy time, min	22.7±14	17.1±12	0.04
LV angiogram, %	48.2	43.9	0.71
Aortic angiogram, %	11.1	14	0.71
Urgent, %	22.2	7	0.04
IABP, %	3.7	0	0.14
Purpose of procedure			
Diagnostic, %	74.1	91.2	0.04
Interventional, %	25.9	8.8	0.04
Approach site			
Radial or brachial, %	81.5	80.7	0.93
Femoral, %	18.5	19.3	0.93

Table 2. Procedural characteristics

5. Conclusions

Despite improvements in procedural techniques and catheter design, patients undergoing catheterization remain at greater risk of atherosclerosis. While ischemic or hemorrhagic stroke is the most debilitating complication of such procedures, conferring significant comorbidity and mortality, asymptomatic cerebral infarction, which has been associated with cognitive decline, is also a significant complication. Intervention against atherosclerotic risk factors is needed along with careful procedural planning, in order to reduce rates of catheterization-related cerebral infarction. Hypercholesterolemia is one of risks of catheterization-related cerebral infarction.

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