

## Does Cardiac Catheterization Accelerate Decline in Cognitive Function or Serve as an Inflection Point for Evaluation?

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Atherosclerosis is a systemic inflammatory disorder that is most commonly identified by the anatomic location of presentation. Cardiac catheterization is frequently used as part of our diagnostic evaluation of patients with suspected or known coronary artery disease. In the United States in 2010 to 2011, the National Cardiovascular Data Registry reported that 1 110 150 patients underwent diagnostic cardiac catheterization and 941 248 underwent percutaneous coronary intervention.<sup>1</sup> This reinforces the notion that a large number of patients in the United States and worldwide are at risk for the systemic effects of this disease process.

Atherosclerosis is a pan systemic vascular disorder that has the late manifestation of occlusive neointimal plaque formation, as illustrated in the Figure.<sup>2</sup> It is important to remember that the biologic alterations begin with alterations of the endothelial cells, increased resistance to flow involving red blood cells and proteins, and transvessel leakage that presages arterial wall pathological features. These events are more important in small arterioles and may be affected by cardiac catheterization procedures when patients typically are volume depleted because of being labeled nothing by mouth and have altered glucose metabolism because of medications being discontinued; there is also the direct effect of contrast on endothelium. Although this is most commonly associated with acute renal injury, there is reason to suspect that this same process can affect intracerebral arterioles and capillaries as well.

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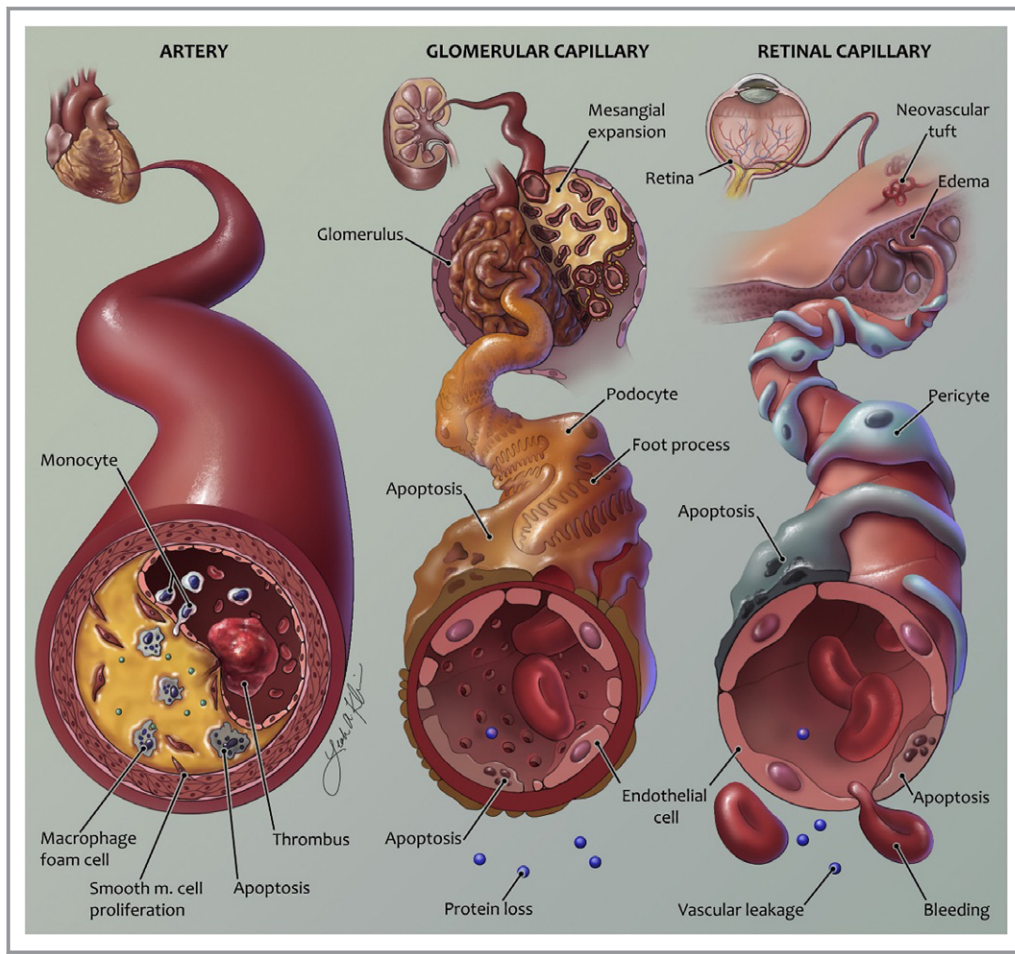
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We often refer to patients as having coronary artery disease, peripheral arterial disease, or cerebrovascular disease, on the basis of their predominant symptom that precipitates their evaluation, forgetting that these same patients have a high prevalence of disease in all vascular beds within the body. The recent publication of the AMERICA (Active Detection and Management of the Extension of Atherothrombosis in High-Risk Coronary Patients in Comparison With Standard of Care for Coronary Atherosclerosis) trial by Collt et al<sup>3</sup> prospectively demonstrated that 5% of this high-risk population had significant carotid artery disease. The AWHs (Aragon Workers' Health Study)<sup>4</sup> recently reviewed >1400 asymptomatic patients, aged 40 to 59 years, who underwent cardiovascular screening using direct imaging using Doppler or computed tomographic calcium scan imaging. This population had atherosclerotic plaques in the femoral arteries (54%), coronary calcification (38%), and carotid plaques (34%).

The predisposing risk factors for atherosclerosis have been associated with increased risks of altered and worsening mental function in prior investigations. The recent publication from Lourenco et al<sup>5</sup> from 33 580 individuals identified in the Survey of Health, Ageing and Retirement in Europe (SHARE) database reported that cardiovascular risk factors, including smoking, physical inactivity, hypertension, and previous diagnosis of diabetes mellitus or hyperglycemia, were independent variables associated with cognitive impairment, even in the absence of a prior heart attack or stroke. Marioni<sup>6</sup> evaluated the relationship of inflammation to age-related cognitive decline. He used prospective cognitive assessment from the AAA (Aspirin for Asymptomatic Atherosclerosis) trial (N=29 147), the ET2DS (Edinburgh Type 2 Diabetes Study) (N=1252), the Edinburgh Artery Study (N=534), and the 1936 Lothian Birth Cohort (N=3686). He assessed inflammation using C-reactive protein and fibrinogen, and he used genetic testing, including apolipoprotein E analysis. These cohorts demonstrated an inverse relationship of cognitive function and C-reactive protein. Apolipoprotein E e4e4 carriers had poorer cognitive scores but lower C-reactive protein values. Diabetes mellitus, particularly those with hyperglycemia, was demonstrated by Hwang et al<sup>7</sup> to correlate with altered



**Figure.** Pathogenesis of vascular disease in atherosclerosis. Reprinted from Rask-Madsen and King<sup>2</sup> with permission. Copyright ©2013, Elsevier Inc.

cognition when assessed by magnetic resonance imaging during testing. This further correlated with small-vessel end organ damage, such as retinopathy and neuropathy. Collectively, these studies reinforce the fact that inflammation, which is enhanced by the risk factors for atherosclerosis, correlates with declines in cognitive function. In addition, there is a constellation of clinical and imaging abnormalities that represent structural abnormalities of the perforating arterioles, capillaries, and venules of the brain that is termed the “cerebral small-vessel disease” syndrome.<sup>8</sup> These changes result in decreased cerebral blood flow and are associated with age, hypertension, hypercholesterolemia, smoking, and diabetes mellitus.

In this issue of *Journal of the American Heart Association (JAHA)*, Scott et al<sup>9</sup> evaluated a cohort of 455 older patients scheduled for elective cardiac catheterization. They were recruited from 2 tertiary centers over a 5-year period ending in 2012 and evaluated using a standard battery of tests examining cognition, including written and computerized tests to identify mild cognitive impairment (MCI). The methods were extraordinarily detailed and included tests administered at

home and occurring at multiple time points, including 24 hours, 7 days, and 90 days after catheterization. The primary end point was defined as baseline MCI correlated to subsequent cognitive function at 3 months. The secondary end point was to correlate clinical management with cognitive function. The finding from the written test that 51.7% of this cohort had MCI at baseline is consistent with the systemic nature of atherosclerosis affecting cognition and concerning for the frequency that was documented. Given that patient recruitment ended in 2012, this investigation would have been enhanced if a later time point (>12 months) would have been included in the assessment.

A major weakness of this study design was the control group that was recruited from an osteoarthritis study. These patients were older, included more women, and, most important, had less diabetes mellitus, smoking, hypercholesterolemia, and prior cardiovascular events, so comparing the 2 groups includes multiple confounding variables. More important, we were not told about baseline renal function, diabetic medication, hemoglobin A1C values, or hemoglobin values. Prior studies have demonstrated that hypertension,

hyperglycemia, and altered rheology<sup>10</sup> decrease cognitive function. The categorization of the extent of coronary disease also lacked objectivity. The use of the Syntax score<sup>11</sup> and scoring of the adventitial calcium would have enhanced the assessment of atherosclerotic burden. Attributing changes in MCI to catheterization alone using this control group is tenuous based on sample size, differences in patient comorbidities, and interactions of the risk factors. A cohort chosen from patients undergoing computed tomographic angiographic imaging of coronary arteries would have been more likely to allow us to isolate the contribution of the catheterization procedure to subsequent cognitive impairment.

The small number of patients and short duration of follow-up limit the ability to draw conclusions from the patients who underwent percutaneous or surgical revascularization.

It is clear that the nexus between alteration of mental function and cardiovascular disease is just beginning to be explored. Prior investigations from Searle and Rockwood<sup>12</sup> and Rogers et al<sup>13</sup> reinforce the interrelationship of altered cognition and frailty. The objective assessment of both frailty and MCI<sup>14</sup> may allow us to better identify a high-risk patient population. Finally, we agree with Scott et al<sup>9</sup> that we should consider further investigation into the benefit of a focused evaluation for MCI in patients who present for anatomic definition of coronary artery disease in the same manner that we have adopted frailty scores in assessing patient risk.

## Disclosures

None.

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