^{18}F-FDG for imaging microvascular injury

Prakash Harikrishnan, MD,[a] Perry Gerard, MD, FACR,[b] and Diwakar Jain, MD, FACC, FASNC[a]

[a] Division of Cardiology in the Department of Medicine, New York Medical College at Westchester Medical Center, Valhalla, NY
[b] Department of Radiology, New York Medical College at Westchester Medical Center, Valhalla, NY

Received Apr 15, 2017; accepted Apr 17, 2017
doi:10.1007/s12350-017-0955-3

See related article, pp. 433–440

Atherosclerosis is an inflammatory process where oxidation of low-density lipoproteins (LDL) in the arterial wall causes initiation and progression of the atherosclerotic plaque by attracting macrophages.[1] The necrotic core of the vulnerable atherosclerotic plaque is rich in free cholesterol crystals derived from apoptotic lipid-laden macrophages and from the membranes of red blood cells which enter the core during intraplaque hemorrhage.[2] Vulnerable plaque is more prone to rupture. The plaque rupture triggers macrophage activation, tissue factor release, platelet aggregation, thrombus formation, thromboembolization, cholesterol embolization, arterial obstruction, end organ ischemia and necrosis. Atherosclerosis is a dynamic process and many of its clinical manifestations such as myocardial infarction, ischemic stroke, transient ischemic attack, acute mesenteric ischemia, acute limb ischemia, and renal injury occur as a consequence of rupture of the vulnerable atherosclerotic plaque. So it is very important to understand the various mechanisms behind the distal organ injury caused by acute plaque rupture.

Cholesterol crystal embolization (CCE) is one known mechanism of organ injury from atherosclerotic plaque rupture and it may happen spontaneously or by the endothelial trauma during instrumentation of an artery.[3] The prevalence of cholesterol crystal embolism in autopsy studies in unselected patients ranges from 0.7% to 4%.[4] This has also been shown to occur spontaneously in 1% of patients with transesophageal echocardiography-confirmed extensive thoracic aortic athersosclerotic disease when followed over 3 years.[5] CCE occurs in 3% of patients who underwent infrarenal aortic and infrainguinal vascular surgery or angiographic manipulation,[6] in 0.8% of patients undergoing cardiac catheterization,[7] and in 0.2% of patients undergoing cardiac surgery.[8] CCE causes organ injury by multiple mechanisms. In this issue of the Journal of Nuclear Cardiology, Pervaiz MH et al[9] examine the non-obstructive, non-ischemic, direct toxicity of cholesterol crystals as a cause of left thigh muscle inflammation and injury in a controlled animal study after injecting cholesterol crystals, polystyrene microsphere control, or saline control into the left femoral artery of rabbits. Thigh muscle inflammation and injury was assessed by ^{18}F-FDG PET/CT and angiography, which were then correlated with inflammatory markers such as tissue macrophage infiltration density and muscle injury markers such as creatine phosphokinase (CPK) levels. There was more muscle inflammation and injury in the cholesterol crystal group compared to the control groups as demonstrated by high maximum standardized uptake values of the left thigh muscles by PET/CT (0.40 ± 0.16 vs 0.21 ± 0.11 and 0.23 ± 0.06; $P = .038$ and $P = .036$, respectively), high CPK levels at 24 hours (7.46 ± 4.32 vs 1.57 ± 0.84 and 1.43 ± 0.57; $P = .007$ and $P = .023$, respectively), and high macrophage density in the muscle biopsy.

CCE may cause organ injury by multiple mechanisms such as macrovascular obstruction, microvascular obstruction, direct toxicity to cells by the nature of its physical structure, and by activating inflammatory response. In this study by Pervaiz et al, arterial obstruction by cholesterol crystal or thromboembolism was ruled out by angiography, direct visualization of the blood vessels during autopsy, and histology, and thereby the

Reprint requests: Prakash Harikrishnan, MD, Division of Cardiology in the Department of Medicine, New York Medical College at Westchester Medical Center, Macy Pavilion, 100 Woods Road, Valhalla, NY 10595; *hprakash.aiims@gmail.com*
J Nucl Cardiol 2018;25:441–2.
1071-3581/$34.00

muscle inflammation and injury were attributed to probable direct toxicity of CCs to the tissue. A physiological intracellular free cholesterol-to-phospholipid ratio is necessary to maintain the normal fluidity of plasma membrane and for maintaining the normal function of integral membrane proteins.[10] A high free cholesterol-to-phospholipid ratio can cause cell injury by affecting the integrity of certain cellular proteins like Na^+/K^+ ATPase, adenylate cyclase, alkaline phosphatase, Na^+/Ca^{++} transporter in the sarcoplasmic reticulum, the ATP-ADP transporter in the inner mitochondrial membrane, and UDP-glucuronosyltransferase.[11] Direct cell toxicity of CCs can also be due to intracellular cholesterol crystallization, conversion to oxysterol,[12] and inducing apoptosis.[13] Intracellular cholesterol crystals can also cause direct cell injury by physically disrupting the integrity of intracellular structures.[14] Whether cholesterol crystal tissue injury observed in this study by Pervaiz et al was related to mechanical injury from sharp needle-like structure of cholesterol crystals or due to its direct biochemical toxicity cannot be answered by this study. Perhaps, if some other inert substance like carbon, polystyrene, or silica shaped similar to cholesterol crystal structure had been used instead of the microsphere control, we would have known whether tissue inflammation and injury was caused by the mechanical injury due to the cholesterol crystal or by its biochemical toxicity.

^{18}F-FDG PET/CT is being clinically used as a non-invasive diagnostic tool in cardiovascular medicine to detect myocardial viability, myocardial ischemia, cardiac inflammation, and infections.[15-18] PET/CT is also being studied as a tool in demonstrating vascular inflammation in patients with vasculitis[19,20] and in identifying vulnerable plaques in atherosclerotic cardiovascular disease.[21] This study by Pervaiz et al adds another potential use of ^{18}F-FDG PET/CT for imaging the inflammation and injury to the muscle and possibly other organ systems from CCE.

As the longevity of the population increases, the prevalence of atherosclerotic cardiovascular diseases also increases and is a cause of significant morbidity and mortality. CCE is one of the manifestations of the wide spectrum of atherosclerotic cardiovascular diseases, which is difficult to study and diagnose. Studies focusing on the mechanisms of tissue injury caused by CCE and finding new diagnostic tools to demonstrate tissue injury will help us in understanding more about the pathogenesis of atherosclerotic cardiovascular diseases.

Disclosures

All the three authors do not have any disclosures.

References

1. Endemann G, Stanton LW, Madden KS, Bryant CM, White RT, Protter AA. CD36 is a receptor for oxidized low density lipoprotein. J Biol Chem. 1993;268(16):11811-6.
2. Kolodgie FD, Gold HK, Burke AP, Fowler DR, Kruth HS, Weber DK, et al. Intraplaque hemorrhage and progression of coronary atheroma. N Engl J Med. 2003;349(24):2316-25.
3. Kronzon I, Saric M. Cholesterol embolization syndrome. Circulation. 2010;122(6):631-41.
4. Cross SS. How common is cholesterol embolism? J Clin Pathol. 1991;44(10):859-61.
5. Tunick PA, Nayar AC, Goodkin GM, Mirchandani S, Francescone S, Rosenzweig BP, et al. Effect of treatment on the incidence of stroke and other emboli in 519 patients with severe thoracic aortic plaque. Am J Cardiol. 2002;90(12):1320-5.
6. Sharma PV, Babu SC, Shah PM, Nassoura ZE. Changing patterns of atheroembolism. Cardiovasc Surg. 1996;4(5):573-9.
7. Fukumoto Y, Tsutsui H, Tsuchihashi M, Masumoto A, Takeshita A. Cholesterol embolism study (CHEST) investigators. The incidence and risk factors of cholesterol embolization syndrome, a complication of cardiac catheterization: A prospective study. J Am Coll Cardiol. 2003;42(2):211-6.
8. Doty JR, Wilentz RE, Salazar JD, Hruban RH, Cameron DE. Atheroembolism in cardiac surgery. Ann Thorac Surg. 2003;75(4):1221-6.
9. Pervaiz MH, et al. PET/cta detection of cholesterol crystal emboli that can trigger muscle inflammation without arterial obstruction. J Nucl Cardiol. 2017. doi:10.1007/s12350-017-0826-y.
10. Simons K, Ikonen E. How cells handle cholesterol. Science. 2000;290:1721-6.
11. Yeagle PL. Modulation of membrane function by cholesterol. Biochimie. 1991;73:1303-10.
12. Brown AJ, Jessup W. Oxysterols and atherosclerosis. Atherosclerosis. 1999;142:1-28.
13. Tabas I. Free cholesterol-induced cytotoxicity. A possible contributing factor to macrophage foam cell necrosis in advanced atherosclerotic lesions. Trends Cardiovasc Med. 1997;7:256-63.
14. Tabas I. Consequences of cellular cholesterol accumulation: Basic concepts and physiological implications. J Clin Investig. 2002;110(7):905-11.
15. Dilsizian V, Bacharach SL, Beanlands RS, Bergmann SR, Delbeke D, Dorbala S, et al. ASNC imaging guidelines/SNMMI procedure standard for positron emission tomography (PET) nuclear cardiology procedures. J Nucl Cardiol. 2016;23(5):1187-226.
16. Jain D, He ZX. Direct myocardial ischemia imaging with exercise (18)FDG. J Nucl Cardiol. 2015;22:111-4.
17. Jain D, He ZX, Lele V. Cardiac hot spot imaging with (18)FDG. Semin Nucl Med. 2014;44:375-85.
18. Jain D, He ZX. Direct imaging of myocardial ischemia: A potential new paradigm in nuclear cardiovascular imaging. J Nuc Cardiol. 2008;15:617-30.
19. Lariviere D, Benali K, Coustet B, Pasi N, Hyafil F, Klein I, et al. Positron emission tomography and computed tomography angiography for the diagnosis of giant cell arteritis: A real-life prospective study. Medicine (Baltimore). 2016;95(30):e4146.
20. Pugliese F, Gaemperli O, Kinderlerer AR, Lamare F, Shalhoub J, Davies AH, et al. Imaging of vascular inflammation with [11C]-PK11195 and positron emission tomography/computed tomography angiography. J Am Coll Cardiol. 2010;56(8):653-61.
21. Tavakoli S, Vashist A, Sadeghi MM. Molecular imaging of plaque vulnerability. J Nucl Cardiol. 2014;21(6):1112-28.