Journal of the American Heart Association

EDITORIAL

It's All About the Inflammation

Seth Uretsky, MD; Lillian Aldaia, MD

Cardiovascular disease remains the number 1 killer in the developed world.[1] Coronary artery disease is the most common form of cardiovascular disease, leading to myocardial infarction, heart failure, and death.[1] Inflammation has been implicated as an important linchpin in the atherosclerotic process and promotion of atherogenesis.[2,3] More important, atherogenesis is a diffuse disease process that often affects multiple vascular beds in a given patient.[3] Statin medications, used as lipid-lowering drugs, have been noted to also act as an anti-inflammatory, imbuing these medications with benefits beyond lipid lowering.[4] More importantly, anti-inflammatory drugs, such as statins and canakinumab, treat the entire vascular bed, whereas mechanical interventions, such as coronary artery stenting, treat only the segment of the epicardial coronary artery intervened on. Studies have identified markers of inflammation that are associated with coronary artery disease and outcomes.[3] hs-CRP (high-sensitivity C-reactive protein) is a well-studied marker of inflammation, and increased hs-CRP is associated with increased incidence of coronary artery disease.[5] In CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study), canakinumab, a monoclonal antibody targeting interleukin-1B, resulted in a reduction of cardiovascular events independent of the lipid level.[6] Taken together, these data suggest that inflammation is an important part of the atherosclerotic process and therapies that target inflammation are beneficial in terms of a reduction in cardiovascular events.

See Article by Kanaji et al.

In recent years, the adipose tissue that surrounds blood vessels has been established as metabolically active and an important player in the inflammatory process of atherosclerosis.[7] Perivascular adipose tissue is the adipose tissue that surrounds blood vessels and has an important metabolic and vasoprotective relationship with the blood vessels it surrounds. Perivascular adipose tissue adipocytes secrete adipokines that act in a paracrine or vasocrine manner. In a healthy person, perivascular adipose tissue secretes adipokines that promote vasodilation and have anti-inflammatory effects. In the unhealthy state, perivascular adipose tissue secretes proinflammatory adipokines and cytokines, which affect the surrounding vasculature and promote atherosclerosis. Coronary arteries are embedded in adipose tissue referred to as pericoronary adipose tissue (PCAT). PCAT is readily measured and evaluated using computed tomography (CT). Studies have linked CT-quantified PCAT to the presence and progression of coronary plaque burden, decreased myocardial perfusion, and clinical outcomes.[8–10] Thus, PCAT measured by CT is an important marker in the assessment of the coronary health in patients. This is particularly important given the increased use of coronary CT angiography (CCTA) to evaluate patients with known and suspected coronary artery disease. CCTA allows assessment of atherosclerotic overall burden and stenosis severity, the hemodynamic importance of coronary lesions using either functional flow reserve CT or stress CT, and burden of inflammation by assessing PCAT.

Key Words: Cardiac CT ■ coronary atherosclerosis ■ inflammation ■ pericardial fat

Correspondence to: Seth Uretsky, MD, Department of Cardiovascular Medicine, Gagnon Cardiovascular Institute, Cardiac Administration, Box 5, Morristown Medical Center, 100 Madison Ave, Morristown, NJ 07960. E-mail: seth.uretsky@atlantichealth.org.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

For Disclosures, see page 2.

JAHA is available at: www.ahajournals.org/journal/jaha

In this issue of the *Journal of the American Heart Association* (*JAHA*), Kanaji and colleagues assessed the relationship of PCAT attenuation and global coronary flow reserve (gCFR) in patients who have undergone urgent revascularization for non–ST-segment–elevation myocardial infarction.[11] The patients in this study cohort underwent CCTA before revascularization with PCAT attenuation assessment using CCTA. gCFR was assessed 30 days after revascularization with phase-contrast magnetic resonance imaging of the coronary sinus. The authors found that patients with impaired gCFR 30 days after revascularization had higher PCAT attenuation before revascularization. In a multivariate analysis, only age and mean PCAT attenuation were associated with a gCFR <1.8. This finding has several important applications. First, it links PCAT attenuation to potentially higher-risk patients who have already undergone revascularization. Second, it illustrates the limitations of local therapies, like stents, in a diffuse disease process, such as atherosclerosis. Third, it highlights the importance of therapies that improve vascular health, like statins, via anti-inflammatory pathways and suggests that PCAT metabolism may be a therapeutic target.

Of interest in this study was the lack of correlation between hs-CRP and PCAT attenuation and that PCAT attenuation was an independent predictor of gCFR and hs-CRP was not. Whether PCAT is measuring an inflammatory process not detected using hs-CRP or if it is a more sensitive measure of coronary artery inflammation needs to be investigated further.

As the authors point out in their limitations section, it is unclear if the findings in this study are associated with worse clinical outcomes. In addition, it would have been helpful if the gCFR was known before stenting to assess if those with lower mean PCAT attenuation did not have any increase in the gCFR after revascularization or if the increase in revascularization was lower compared with those with higher mean PCAT attenuation. Another limitation is that the authors did not take into consideration the extent of atherosclerosis, determined by CCTA or coronary artery calcium, or stenosis severity, as determined by CCTA on gCFR. In conclusion, this study by Kanaji and colleagues[11] enhances our understanding of the importance of PCAT in the inflammatory process and links the inflammatory process, as measured by PCAT attenuation, to low gCFR.

ARTICLE INFORMATION

Affiliations

From the Department of Cardiovascular Medicine, Gagnon Cardiovascular Institute, Morristown Medical Center/Atlantic Health System, Morristown, NJ.

Disclosures

None.

REFERENCES

1. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation*. 2019;139:e56–e528.
2. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005;352:1685–1695.
3. Christodoulidis G, Vittorio TJ, Fudim M, Lerakis S, Kosmas CE. Inflammation in coronary artery disease. *Cardiol Rev*. 2014;22:279–288.
4. Liberale L, Carbone F, Montecucco F, Sahebkar A. Statins reduce vascular inflammation in atherogenesis: a review of underlying molecular mechanisms. *Int J Biochem Cell Biol*. 2020;122:105735.
5. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med*. 2000;342:836–843.
6. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377:1119–1131.
7. Lin A, Dey D, Wong DTL, Nerlekar N. Perivascular adipose tissue and coronary atherosclerosis: from biology to imaging phenotyping. *Curr Atheroscler Rep*. 2019;21:47.
8. Goeller M, Tamarappoo BK, Kwan AC, Cadet S, Commandeur F, Razipour A, Slomka PJ, Gransar H, Chen X, Otaki Y, et al. Relationship between changes in pericoronary adipose tissue attenuation and coronary plaque burden quantified from coronary computed tomography angiography. *Eur Heart J Cardiovasc Imaging*. 2019;20:636–643.
9. Mahabadi AA, Berg MH, Lehmann N, Kalsch H, Bauer M, Kara K, Dragano N, Moebus S, Jockel KH, Erbel R, et al. Association of epicardial fat with cardiovascular risk factors and incident myocardial infarction in the general population: the Heinz Nixdorf Recall Study. *J Am Coll Cardiol*. 2013;61:1388–1395.
10. Nomura CH, Assuncao-Jr AN, Guimaraes PO, Liberato G, Morais TC, Fahel MG, Giorgi MCP, Meneghetti JC, Parga JR, Dantas-Jr RN, et al. Association between perivascular inflammation and downstream myocardial perfusion in patients with suspected coronary artery disease. *Eur Heart J Cardiovasc Imaging*. 2020;21:599–605.
11. Kanaji Y, Hirano H, Sugiyama T, Hoshino M, Horie T, Misawa T, Nogami K, Ueno H, Hada M, Yamaguchi M, et al. Pre-percutaneous coronary intervention pericoronary adipose tissue attenuation evaluated by computed tomography predicts global coronary flow reserve after urgent revascularization in patients with non–ST-segment–elevation acute coronary syndrome. *J Am Heart Assoc*. 2020;9:e016504. DOI: 10.1161/JAHA.120.016504.