Editorial

Unraveling Inflammation and Oxidative Stress in Cardiac Sarcoidosis

Hayan Jouni, MD; Panithaya Chareonthaitawee, MD

Sarcoidosis is an inflammatory disorder of unknown pathogenesis hallmarked by noncaseating granulomas with multiorgan system involvement. In the United States, estimated prevalence of sarcoidosis ranges from 141.4 per 100 000 in blacks, 49.8 per 100 000 in whites, to 21.7 in Hispanics, and 18.9 in Asians.[1] In a series of patients with biopsy-proven extracardiac sarcoidosis and unknown cardiac involvement, 26% seem to have cardiac sarcoidosis (CS) when assessed with cardiac magnetic resonance imaging (CMR),[2] a rate that is consistent with a published US autopsy study.[3] CS may be associated with significant morbidity and mortality, especially in patients with severe left ventricular dysfunction.[4] However, a more recent study suggests that increased awareness, detection, and treatment of CS may be associated with better outcomes.[5]

See Article by Ishiguchi et al

Both fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}FDG PET) and CMR have become pivotal in the diagnosis, monitoring, and prognostication of CS.[6–8] In the largest outcomes study of patients with CS evaluated with PET, Blankstein et al[6] assessed 118 consecutive patients with CS and demonstrated that presence of focal PET myocardial perfusion defects and/or ^{18}FDG abnormality predicts patients at high risk for death or ventricular arrhythmias, with the worst outcomes noted in the group with both perfusion defects and ^{18}FDG abnormality. Likewise, the presence of myocardial gadolinium–delayed enhancement on CMR predicts all-cause mortality and ventricular arrhythmias in patients with known or suspected CS.[8] However, both techniques have their disadvantages. ^{18}FDG PET is limited by complicated dietary preparations, variable suppression of physiological myocardial ^{18}FDG uptake, and uncertain effects of steroids on both physiological and pathological myocardial ^{18}FDG uptake.[7] CMR is relatively contraindicated in patients with cardiac devices which are present in a substantial proportion of patients with CS and has technical challenges in detecting active cardiac inflammation.[9] Therefore, the ability to monitor CS activity remains challenging, and additional markers of disease activity would be useful in patient management.

In this issue of *Circulation: Cardiovascular Imaging*, Ishiguchi et al[10] carefully explore urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) as a predictor for ventricular arrhythmias in 36 patients with active CS as part of an important ongoing effort to find additional markers of disease activity in CS. Oxidative stress results in generation of reactive oxygen species that can cause direct oxidative damage to the DNA. When guanosine is oxidized, cellular DNA repair systems are activated and eventually lead to excretion of this oxidized nucleoside (8-OHdG) which can be measured in serum or urine and is considered a marker of global bodily oxidative stress.[11,12] In a prior study, the authors have demonstrated significantly elevated levels of urinary 8-OHdG in patients with active CS compared with patients with inactive CS, idiopathic dilated cardiomyopathy, and controls.[13] They subsequently showed that before treatment of active CS patients with corticosteroids, urinary 8-OHdG was an independent predictor for cardiovascular death.[12] In the current article,[10] they demonstrate that in CS patients with active inflammation (assessed by ^{18}FDG PET) and sustained ventricular tachycardia (VT), urinary 8-OHdG was significantly elevated compared to patients with active CS without sustained VT or patients with an idiopathic dilated cardiomyopathy. This finding remained significant after multivariate analysis adjusting for other possible confounders, such as left ventricular ejection fraction, New York Heart Association class, and regional wall motion abnormalities (as a surrogate for myocardial scar). After treatment with steroids, previously active CS patients with sustained VT had subsequent lower levels of urinary 8-OHdG in parallel with a reduction in VT burden.

Despite their promising findings, the current study results are tempered by several limitations. First, the study cohort is small, with numerous comparisons between small subgroups ranging from 18 to 27 patients. This limitation is further compounded by the relatively wide range of urinary 8-OHdG levels, especially in the active CS with VT subgroup. Second, the diagnosis of CS in this study was made according to a modified version of the Japanese Ministry of Health and Welfare diagnostic criteria that usually does not include ^{18}FDG PET findings. Like other diagnostic criteria for CS,[14] this set of criteria has not been prospectively validated and has limitations in both sensitivity and specificity for CS diagnosis. Third, ^{18}FDG PET was used to identify active inflammation in this study, but patient preparation for ^{18}FDG PET was limited only to prolonged fasting without additional dietary manipulation for suppression of physiological myocardial ^{18}FDG uptake. The latter may not only decrease the specificity of ^{18}FDG PET for CS diagnosis but

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

From the Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN.

Correspondence to Panithaya Chareonthaitawee, MD, Mayo Clinic, 200 First St, SW Rochester, MN 55905. E-mail Chareonthaitawee.Panithaya@mayo.edu

(*Circ Cardiovasc Imaging*. 2017;10:e007287. DOI: 10.1161/CIRCIMAGING.117.007287.)

***Circ Cardiovasc Imaging* is available at http://circimaging.ahajournals.org**

DOI: 10.1161/CIRCIMAGING.117.007287

also for inflammation.[7] Although the authors did not report any patients with diffuse myocardial ^{18}FDG uptake (described in the Data Supplement), prolonged fasting may explain their somewhat high rate of focal on diffuse ^{18}FDG uptake which was noted in 50% of patients with active CS.

Prior studies suggest that multiple mechanisms of VT may coexist in CS and that the combination of PET perfusion and ^{18}FDG findings may be helpful in identifying those at risk. Tung et al[15] demonstrated that ≈50% of patients with unexplained VT had myocardial ^{18}FDG abnormalities, half of whom also had perfusion defects. Similarly, Blankstein et al[6] also showed that both PET myocardial perfusion defects and myocardial ^{18}FDG abnormalities were associated with increased burden of VT and death in patients with CS. In a systematic review of CMR studies in CS, the presence of myocardial gadolinium–delayed enhancement was predictive of all-cause mortality and ventricular arrhythmias in patients with known or suspected CS.[8] These findings underscore the concept that ventricular arrhythmias in CS are associated not only with inflammation but also with scar tissue. However, the current study by Ishiguchi et al[10] reported only ^{18}FDG PET findings without myocardial perfusion or scar assessment. Furthermore, ^{18}FDG PET was not reassessed after steroid therapy. Therefore, it is possible that the observed decline in urinary 8-OHdG after steroid therapy may signal a more systemic response in oxidative stress rather than a more focal response at the myocardial level. The parallel decrease in VT could be an effect of the small sample size of the study. Although Ishiguchi et al[10] appropriately adjusted for ejection fraction and regional wall motion abnormality scores as surrogates for myocardial scar and demonstrated that urinary 8-OHdG was still significantly associated with VT, it should be noted that regional wall motion abnormalities may not necessarily indicate myocardial scarring which is usually better assessed with PET myocardial perfusion or CMR.

Ishiguchi et al[10] suggest that elevated urinary 8-OHdG levels are specific for myocardial oxidative stress. However, 8-OHdG is a guanosine oxidation product that can be produced by any DNA containing cell under oxidative stress and is not specific to any tissue. The authors propose that the high mitochondrial content of cardiomyocytes and oxidative stress of the mitochondrial DNA could possibly account for the notably elevated levels of urinary 8-OHdG in active CS but not in active pulmonary sarcoidosis (without CS). However, it is noteworthy that 8-OHdG–positive staining was mostly noted involving myocardial nuclei rather than the cytosol in their previous publication.[13] Moreover, somewhat larger published studies have reported elevated serum or urinary 8-OHdG levels in patients with various clinical disorders, such as systolic heart failure (ischemic or idiopathic dilated cardiomyopathy),[16] diabetes mellitus,[17] smokers,[18] and coronary artery disease.[19] Although Ishiguchi et al[10] excluded such patients from the current study, elevated urinary 8-OHdG levels in other disorders and again the wide range of urinary 8-OHdG levels in patients with active CS underscore the potential challenges in interpreting urinary 8-OHdG levels in everyday clinical practice where many confounding variables may be present.

From a histopathologic standpoint, urinary 8-OHdG was significantly associated with fibrosis found in myocardial biopsy samples (24 active CS, 13 nonactive CS, and 21 patients with dilated cardiomyopathy). Patients with active CS also had higher area of their myocardial biopsies with positive 8-OHdG staining. Among the 37 patients diagnosed with CS who underwent endomyocardial biopsy, the authors did not specify how many had diagnostic features of sarcoidosis. CS usually results in focal or patchy involvement of the myocardium, and endomyocardial biopsy typically has a low diagnostic yield for sarcoidosis.[20] The heterogeneous myocardial involvement with sarcoidosis and the histopathologic findings by Ishiguchi et al[10] raise additional questions whether the observed increase in myocardial fibrosis and oxidative stress (as demonstrated by 8-OHdG staining) is restricted to myocardial segments affected by sarcoidosis or is representative of a more generalized myocardial process in the setting of active CS (the low yield of endomyocardial biopsy probably supports the latter). This may suggest that despite the focal nature of CS, additional processes could still contribute to the increased oxidative stress and fibrosis extending to myocardial segments not directly affected by sarcoidosis.

In summary, Ishiguchi et al[10] carefully demonstrate that urinary 8-OHdG may be a promising biomarker for CS. Their preliminary data are encouraging, but larger studies are clearly needed to further explore the role of urinary 8-OHdG in monitoring CS disease activity and predicting detrimental ventricular arrhythmias and outcomes of patients with CS.

Disclosures

None.

References

1. Baughman RP, Field S, Costabel U, Crystal RG, Culver DA, Drent M, Judson MA, Wolff G. Sarcoidosis in America. Analysis based on health care use. *Ann Am Thorac Soc*. 2016;13:1244–1252. doi: 10.1513/AnnalsATS.201511-760OC.
2. Patel MR, Cawley PJ, Heitner JF, Klem I, Parker MA, Jaroudi WA, Meine TJ, White JB, Elliott MD, Kim HW, Judd RM, Kim RJ. Detection of myocardial damage in patients with sarcoidosis. *Circulation*. 2009;120:1969–1977. doi: 10.1161/CIRCULATIONAHA.109.851352.
3. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. *Circulation*. 1978;58:1204–1211.
4. Yazaki Y, Isobe M, Hiroe M, Morimoto S, Hiramitsu S, Nakano T, Izumi T, Sekiguchi M; Central Japan Heart Study Group. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. *Am J Cardiol*. 2001;88:1006–1010.
5. Kandolin R, Lehtonen J, Airaksinen J, Vihinen T, Miettinen H, Ylitalo K, Kaikkonen K, Tuohinen S, Haataja P, Kerola T, Kokkonen J, Pelkonen M, Pietilä-Effati P, Utrianen S, Kupari M. Cardiac sarcoidosis: epidemiology, characteristics, and outcome over 25 years in a nationwide study. *Circulation*. 2015;131:624–632. doi: 10.1161/CIRCULATIONAHA.114.011522.
6. Blankstein R, Osborne M, Naya M, Waller A, Kim CK, Murthy VL, Kazemian P, Kwong RY, Tokuda M, Skali H, Padera R, Hainer J, Stevenson WG, Dorbala S, Di Carli MF. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. *J Am Coll Cardiol*. 2014;63:329–336. doi: 10.1016/j.jacc.2013.09.022.
7. Chareonthaitawee P, Beanlands RS, Chen W, Dorbala S, Miller EJ, Murthy VL, Birnie DH, Chen ES, Cooper LT, Tung RH, White ES, Borges-Neto S, Di Carli MF, Gropler RJ, Ruddy TD, Schindler TH, Blankstein R. Joint SNMMI-ASNC expert consensus document on the role of (18)F-FDG PET/CT in cardiac sarcoid detection and therapy monitoring. *J Nucl Cardiol*. 2017;24:1741–1758. doi: 10.1007/s12350-017-0978-9.
8. Coleman GC, Shaw PW, Balfour PC Jr, Gonzalez JA, Kramer CM, Patel AR, Salerno M. Prognostic value of myocardial scarring on

CMR in patients with cardiac sarcoidosis. *JACC Cardiovasc Imaging*. 2017;10:411–420. doi: 10.1016/j.jcmg.2016.05.009.
9. Ohira H, Tsujino I, Ishimaru S, Oyama N, Takei T, Tsukamoto E, Miura M, Sakaue S, Tamaki N, Nishimura M. Myocardial imaging with 18F-fluoro-2-deoxyglucose positron emission tomography and magnetic resonance imaging in sarcoidosis. *Eur J Nucl Med Mol Imaging*. 2008;35:933–941. doi: 10.1007/s00259-007-0650-8.
10. Ishiguchi H, Kobayashi S, Myoren T, Kohno M, Nanno T, Murakami W, Oda S, Oishi K, Okuda S, Okada M, Suga K, Yano M. Urinary 8-hydroxy-2'-deoxyguanosine as a myocardial oxidative stress marker is associated with ventricular tachycardia in patients with active cardiac sarcoidosis. *Circ Cardiovasc Imaging*. 2017;10:e006764. doi: 10.1161/CIRCIMAGING.117.006764.
11. Hayakawa H, Hofer A, Thelander L, Kitajima S, Cai Y, Oshiro S, Yakushiji H, Nakabeppu Y, Kuwano M, Sekiguchi M. Metabolic fate of oxidized guanine ribonucleotides in mammalian cells. *Biochemistry*. 1999;38:3610–3614. doi: 10.1021/bi9823611.
12. Myoren T, Kobayashi S, Oda S, Nanno T, Ishiguchi H, Murakami W, Okuda S, Okada M, Takemura G, Suga K, Matsuzaki M, Yano M. An oxidative stress biomarker, urinary 8-hydroxy-2'-deoxyguanosine, predicts cardiovascular-related death after steroid therapy for patients with active cardiac sarcoidosis. *Int J Cardiol*. 2016;212:206–213. doi: 10.1016/j.ijcard.2016.03.003.
13. Kobayashi S, Myoren T, Oda S, Inari M, Ishiguchi H, Murakami W, Fukuda M, Tanaka T, Okuda S, Nao T, Doi M, Yamada J, Okamura T, Hoshii Y, Suga K, Matsuzaki M, Yano M. Urinary 8-hydroxy-2'-deoxyguanosine as a novel biomarker of inflammatory activity in patients with cardiac sarcoidosis. *Int J Cardiol*. 2015;190:319–328. doi: 10.1016/j.ijcard.2015.04.144.
14. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, Judson MA, Kron J, Mehta D, Cosedis Nielsen J, Patel AR, Ohe T, Raatikainen P, Soejima K. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm*. 2014;11:1305–1323. doi: 10.1016/j.hrthm.2014.03.043.
15. Tung R, Bauer B, Schelbert H, Lynch JP 3rd, Auerbach M, Gupta P, Schiepers C, Chan S, Ferris J, Barrio M, Ajijola O, Bradfield J, Shivkumar K. Incidence of abnormal positron emission tomography in patients with unexplained cardiomyopathy and ventricular arrhythmias: the potential role of occult inflammation in arrhythmogenesis. *Heart Rhythm*. 2015;12:2488–2498. doi: 10.1016/j.hrthm.2015.08.014.
16. Kobayashi S, Susa T, Tanaka T, Wada Y, Okuda S, Doi M, Nao T, Yoshiga Y, Yamada J, Okamura T, Ueyama T, Kawamura S, Yano M, Matsuzaki M. Urinary 8-hydroxy-2'-deoxyguanosine reflects symptomatic status and severity of systolic dysfunction in patients with chronic heart failure. *Eur J Heart Fail*. 2011;13:29–36. doi: 10.1093/eurjhf/hfq178.
17. Hinokio Y, Suzuki S, Hirai M, Chiba M, Hirai A, Toyota T. Oxidative DNA damage in diabetes mellitus: its association with diabetic complications. *Diabetologia*. 1999;42:995–998. doi: 10.1007/s001250051258.
18. Loft S, Vistisen K, Ewertz M, Tjønneland A, Overvad K, Poulsen HE. Oxidative DNA damage estimated by 8-hydroxydeoxyguanosine excretion in humans: influence of smoking, gender and body mass index. *Carcinogenesis*. 1992;13:2241–2247.
19. Kroese LJ, Scheffer PG. 8-hydroxy-2'-deoxyguanosine and cardiovascular disease: a systematic review. *Curr Atheroscler Rep*. 2014;16:452. doi: 10.1007/s11883-014-0452-y.
20. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, Levine GN, Narula J, Starling RC, Towbin J, Virmani R; American Heart Association; American College of Cardiology; European Society of Cardiology; Heart Failure Society of America; Heart Failure Association of the European Society of Cardiology. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. *J Am Coll Cardiol*. 2007;50:1914–1931. doi: 10.1016/j.jacc.2007.09.008.

KEY WORDS: Editorials ■ biomarkers ■ oxidative stress ■ positron-emission tomography ■ sarcoidosis

Unraveling Inflammation and Oxidative Stress in Cardiac Sarcoidosis

Hayan Jouni and Panithaya Chareonthaitawee

Circ Cardiovasc Imaging. 2017;10:
doi: 10.1161/CIRCIMAGING.117.007287
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-9651. Online ISSN: 1942-0080