Turning the heart off: give it a second try?

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Received Apr 20, 2022; accepted Apr 21, 2022
doi:10.1007/s12350-022-03013-5

See related article, pp. 3256–3262

ROLE OF FDG-PET IMAGING IN INFECTIVE ENDOCARDITIS

The diagnosis of infective endocarditis (IE) is challenging and relies on the association of the detection of lesions typical of cardiac infection on imaging and the presence of biological criteria in favor of systemic bacterial infection.[1] Echocardiography is the first-line imaging modality for the detection of lesions caused by IE. The diagnostic accuracy of echocardiography is, however, lower in patients with a suspicion of prosthetic valve endocarditis (PVE)[2] because echocardiographic images are often hampered by acoustic shadowing and artifacts related to the implanted material. Nuclear imaging is playing an increasing role in the diagnosis of PVE.[3] ^{18}F-Fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) provides high sensitivity for the identification of infectious foci in the heart as well as for the detection of septic emboli, the portal of entry and mycotic aneurysms.[4–6] Several clinical studies have demonstrated that the addition of ^{18}F-FDG-PET imaging to echocardiography improves the detection rate of PVE.[4] Consequently, the presence of infectious foci in the heart on ^{18}F-FDG-PET imaging has been included as a major criterion of IE in patients classified as ''possible PVE'' or ''rejected PVE and high clinical suspicion''[1] in the guidelines on IE published by the European Society of Cardiology in 2015.

PATIENT PREPARATIONS FOR SUPPRESSING FDG MYOCARDIAL UPTAKE

Reducing ^{18}F-FDG myocardial uptake greatly facilitates the detection of small infectious cardiac foci thanks to a decrease in background noise in the valvular region. Myocardial metabolism is based on an adaptive balance between carbohydrates/glucose and free fatty acids (FFA) consumption.[7] When carbohydrates are abundantly available in circulating blood, glucose-based metabolism is preferred resulting in high ^{18}F-FDG myocardial uptake. Circulating glucose is taken up into normal cardiomyocytes mostly through GLUT4 glucose transporters, whereas inflammatory cells relies on GLUT1 and GLUT3 transporters.[8] Complex biochemical adaptive mechanisms known as the Randle cycle explain why myocardial metabolism switches to the preferential consumption of FFA when the concentration of blood glucose is low.[7] High plasmatic concentrations of FFA stimulate the production of ketone bodies by the liver, which are used as primary energy fuel by cardiomyocytes.[7] Predominant consumption of ketone bodies for myocardial metabolism produces high cellular concentrations of fatty acid coenzyme A by-products that strongly downregulate the expression of insulin receptors and GLUT4 glucose transporters by cardiomyocytes but do not modify the levels of expression of GLUT1 and GLUT3 by inflammatory cells.[9] This glucose-FFA balance is influenced by blood levels of glucose and insulin, medications, the duration of fasting, and patient's diet before the injection of ^{18}F-FDG.[9] Consequently, several dietary and pharmacological protocols have been proposed to suppress

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J Nucl Cardiol 2022;29:3263–6.
1071-3581/$34.00

^{18}F-FDG uptake in the heart knowing the mechanisms involved in the regulation of myocardial sugar uptake.

Clinical studies performed in patients with a suspicion of cardiac sarcoidosis have demonstrated that prolonged fasting, up to 12–18 hours instead of 4–6 hours for oncological indications, decreases blood glucose and insulin concentrations and, hence, stimulates the utilization of FFA as the main source of energy for the heart resulting in low myocardial ^{18}F-FDG uptake.[10] The combination of a dinner with low amounts of carbohydrates (< 3 g) the day before imaging with overnight fasting increases the proportion of patients reaching complete suppression of myocardial ^{18}F-FDG uptake on PET compared with prolonged fasting alone.[11] Low carbohydrate combined with high-fat consumption (> 35 g) diets (LC/HFD) have proven even more effective to suppress myocardial ^{18}F-FDG uptake.[12] The ingestion of fatty intakes, such as vegetable oil, by patients immediately prior to ^{18}F-FDG injection can further reduce myocardial ^{18}F-FDG uptake.[13] When comparing both approaches, a larger proportion of patients showed complete suppression of myocardial ^{18}F-FDG uptake with LC/HFD than with prolonged fasting alone.[14] Prolonged fasting with LC/HFD resulted in an even higher proportion of patients with optimal suppression of myocardial ^{18}F-FDG uptake compared to single approaches.[9] Lastly, pharmacological approaches based on the injection of low-dose heparin or verapamil have been proposed to reduce myocardial ^{18}F-FDG uptake. The injection of low-dose heparin induces an important increase of FFA in the blood due to its intrinsic lipolytic activity independent of its anticoagulant effects.[15] Low-dose heparin in conjunction with LC/HFD reduces myocardial ^{18}F-FDG uptake compared to LC/HFD alone,[16] but the benefits of heparin injection in addition to prolonged fasting (18 hours) remain discussed.[9] Calcium channel inhibitors (CCI) have also been suggested to reduce myocardial ^{18}F-FDG uptake since increased intracellular calcium concentrations facilitate cellular glucose uptake.[17] Nevertheless, this approach was found less efficient than LC/HFD[18] and is therefore not used anymore. Based on the results of these different clinical studies, current recommendations for the preparation of patients referred for the detection of cardiac inflammation or infection with ^{18}F-FDG-PET imaging are to instruct patients to dine with a LC/HFD the day before the exam and then fast 12–18 hours until the exam.[9]

CHALLENGES OF PATIENTS WITH FAILURE TO SUPPRESS MYOCARDIAL FDG UPTAKE

While current protocols for patient preparation are successful in most cases to limit or suppress ^{18}F-FDG uptake in the myocardium, a small number of patients do show persistent high ^{18}F-FDG signal in the myocardium hampering the interpretation of PET images. In patients with a suspicion of IE, the results of the ^{18}F-FDG-PET scan may play an important role in the diagnosis and for guiding clinical decision. In this issue of the *Journal of Nuclear Cardiology*®, Germaini et al[19] have therefore proposed a two-step strategy in this clinical situation. If the first patient preparation with LF/HCD and prolonged fasting failed to suppress myocardial ^{18}F-FDG uptake, the PET scan was repeated the next day after maintaining the patient on a ketogenic diet. Among the 17 patients with definite PVE included in this study and scanned twice with ^{18}F-FDG-PET, 9 patients did not show adequate suppression of myocardial ^{18}F-FDG uptake on the first PET scan after preparation of patients with LF/HCD and 12-hour fasting. On the second PET scan acquired the next day after prolonging the ketogenic diet, SUVmax and SUVmean of the myocardium were significantly lower in 6 patients compared to the first scan facilitating the interpretation of PET images: cardiac infective foci could be identified in three patients and the confidence in image interpretation was improved in another three patients. In two patients, myocardial ^{18}F-FDG uptake remained high on the second scan despite adequate patient preparation. Even though the number of patients evaluated in this study was small, its strength is that only patients with definite IE were included providing the opportunity to assess the impact of this two-step strategy in a group of patients with a high prevalence of cardiac ^{18}F-FDG signal caused by infection on PET. This strategy appears as an elegant additional option to overcome failure to suppress myocardial ^{18}F-FDG uptake, in particular in patients with acute severe diseases such as IE who require a fast answer to guide clinical management. Interestingly, despite the prolonged ketogenic diet, two patients showed persistent ^{18}F-FDG signal in the myocardium. Detailed questioning of patients for whom the cardiac preparation allegedly ‘‘failed’’ often reveals hidden consumption of sweet beverages or food. The success rate of cardiac preparation is frequently higher for outpatients than hospitalized patients, likely because outpatients are more actively informed and involved in the diet. The compliance of outpatients with dietary measures is further improved by a phone call 48 hours before the examination reminding the rules to follow.[20] Another factor that may explain lower success rates to suppress ^{18}F-FDG myocardium uptake specifically in patients with a suspicion of IE is the presence of sugars in the excipients of antibiotics.[21]

The two-step strategy proposed in this work is interesting because prolongation of the diet may be only limited to patients with failure to suppress cardiac ^{18}F-FDG uptake on the first scan. Scheduling a second

scan likely increases the attention of the nursing team on the importance of following adequately the diet and requires only to add another 24 hours of preparation instead of repeating the whole procedure from the beginning. Nevertheless, this strategy requires last-minute available time slots on the PET scanner, the agreement of stakeholders to pay for two consecutive PET scans in this clinical situation, and exposes patients to increased radiation exposure. Furthermore, the added value of this strategy on the diagnostic performance of ^{18}F-FDG-PET imaging in IE needs to be confirmed in a larger population of patients.

CONCLUSIONS

Important progresses have been made during the past 10 years in defining the best patient preparations to suppress physiological cardiac ^{18}F-FDG uptake, resulting in a significant improvement of the quality of PET images for the detection of inflammatory and infective processes in the heart. Education and adherence of patients and of the nursing team for hospitalized patients to the rules of LC/HFD are key to reach high success rates of ^{8}F-FDG myocardial suppression on PET images. Several radiopharmaceuticals targeting more specifically inflammatory or infectious activities than ^{18}F-FDG are emerging[22,23] and would greatly facilitate the acquisition and interpretation of PET images in patients with a suspicion of IE.

Disclosures

NM and FH have no conflict of interest to disclose in relation to this manuscript.

References

1. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F. 2015 ESC guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015;36:3075-128. https://doi.org/10.1093/eurheartj/ehv319.
2. Habets J, Tanis W, Reitsma JB, van den Brink RB, Mali WP, Chamuleau SA, et al. Are novel non-invasive imaging techniques needed in patients with suspected prosthetic heart valve endocarditis? A systematic review and meta-analysis. Eur Radiol 2015;25:2125-33. https://doi.org/10.1007/s00330-015-3605-7.
3. Hyafil F, Rouzet F, Le Guludec D. Nuclear imaging for patients with a suspicion of infective endocarditis: Be part of the team! J Nucl Cardiol 2017;24:207-11. https://doi.org/10.1007/s12350-015-0369-z.
4. Mikail N, Hyafil F. Nuclear imaging in infective endocarditis. Pharmaceuticals (Basel) 2021. https://doi.org/10.3390/ph15010014.
5. Mikail N, Benali K, Mahida B, Vigne J, Hyafil F, Rouzet F, et al. (18)F-FDG-PET/CT imaging to diagnose septic emboli and mycotic aneurysms in patients with endocarditis and cardiac device infections. Curr Cardiol Rep 2018;20:14. https://doi.org/10.1007/s11886-018-0956-0.
6. Mikail N, Benali K, Ou P, Slama J, Hyafil F, Le Guludec D, et al. Detection of mycotic aneurysms of lower limbs by whole-body (18)F-FDG-PET. JACC Cardiovasc Imaging 2015;8:859-62. https://doi.org/10.1016/j.jcmg.2014.10.019.
7. Lopaschuk GD, Karwi QG, Tian R, Wende AR, Abel ED. Cardiac energy metabolism in heart failure. Circ Res 2021;128:1487-513. https://doi.org/10.1161/circresaha.121.318241.
8. Mochizuki T, Tsukamoto E, Kuge Y, Kanegae K, Zhao S, Hikosaka K, et al. FDG uptake and glucose transporter subtype expressions in experimental tumor and inflammation models. J Nucl Med 2001;42:1551-5.
9. Osborne MT, Hulten EA, Murthy VL, Skali H, Taqueti VR, Dorbala S, et al. Patient preparation for cardiac fluorine-18 fluorodeoxyglucose positron emission tomography imaging of inflammation. J Nucl Cardiol 2017;24:86-99. https://doi.org/10.1007/s12350-016-0502-7.
10. Langah R, Spicer K, Gebregziabher M, Gordon L. Effectiveness of prolonged fasting 18f-FDG PET-CT in the detection of cardiac sarcoidosis. J Nucl Cardiol 2009;16:801-10. https://doi.org/10.1007/s12350-009-9110-0.
11. Coulden R, Chung P, Sonnex E, Ibrahim Q, Maguire C, Abele J. Suppression of myocardial ^{18}F-FDG uptake with a preparatory ''Atkins-style'' low-carbohydrate diet. Eur Radiol 2012;22:2221-8. https://doi.org/10.1007/s00330-012-2478-2.
12. Soussan M, Brillet PY, Nunes H, Pop G, Ouvrier MJ, Naggara N, et al. Clinical value of a high-fat and low-carbohydrate diet before FDG-PET/CT for evaluation of patients with suspected cardiac sarcoidosis. J Nucl Cardiol 2013;20:120-7. https://doi.org/10.1007/s12350-012-9653-3.
13. Cheng VY, Slomka PJ, Ahlen M, Thomson LE, Waxman AD, Berman DS. Impact of carbohydrate restriction with and without fatty acid loading on myocardial ^{18}F-FDG uptake during PET: A randomized controlled trial. J Nucl Cardiol 2010;17:286-91. https://doi.org/10.1007/s12350-009-9179-5.
14. Harisankar CN, Mittal BR, Agrawal KL, Abrar ML, Bhattacharya A. Utility of high fat and low carbohydrate diet in suppressing myocardial FDG uptake. J Nucl Cardiol 2011;18:926-36. https://doi.org/10.1007/s12350-011-9422-8.
15. Persson E, Nordenström J, Nilsson-Ehle P, Hagenfeldt L, Wahren J. Plasma lipolytic activity and substrate oxidation after intravenous administration of heparin and a low molecular weight heparin fragment. Clin Physiol 1990;10:573-83. https://doi.org/10.1111/j.1475-097x.1990.tb00449.x.
16. Scholtens AM, Verberne HJ, Budde RP, Lam MG. Additional heparin preadministration improves cardiac glucose metabolism suppression over low-carbohydrate diet alone in ^{18}F-FDG PET imaging. J Nucl Med 2016;57:568-73. https://doi.org/10.2967/jnumed.115.166884.
17. Gaeta C, Fernández Y, Pavía J, Flotats A, Artigas C, Deportos J, et al. Reduced myocardial ^{18}F-FDG uptake after calcium channel blocker administration. Initial observation for a potential new method to improve plaque detection. Eur J Nucl Med Mol Imaging 2011;38:2018-24. https://doi.org/10.1007/s00259-011-1873-2.
18. Demeure F, Hanin FX, Bol A, Vincent MF, Pouleur AC, Gerber B, et al. A randomized trial on the optimization of ^{18}F-FDG myocardial uptake suppression: Implications for vulnerable coronary plaque imaging. J Nucl Med 2014;55:1629-35. https://doi.org/10.2967/jnumed.114.138594.

19. Germaini M, Boursier C, Goehringer F, Selton-Suty C, Lefevre B, Roch V, et al. The detection of infectious endocarditis may be enhanced by a repeat FDG-PET while maintaining patients on a ketogenic diet. J Nucl Cardiol 2022. https://doi.org/10.1007/s12350-022-02921-w.
20. Christopoulos G, Jouni H, Acharya GA, Blauwet LA, Kapa S, Bois J, et al. Suppressing physiologic 18-fluorodeoxyglucose uptake in patients undergoing positron emission tomography for cardiac sarcoidosis: The effect of a structured patient preparation protocol. J Nucl Cardiol 2021;28:661-71. https://doi.org/10.1007/s12350-019-01746-4.
21. Ionova Y, Wilson L. Biologic excipients: Importance of clinical awareness of inactive ingredients. PLoS ONE 2020;15:e0235076. https://doi.org/10.1371/journal.pone.0235076.
22. Pinkston KL, Gao P, Singh KV, Azhdarinia A, Murray BE, Sevick-Muraca EM, et al. Antibody guided molecular imaging of infective endocarditis. Methods Mol Biol 2017;1535:229-41. https://doi.org/10.1007/978-1-4939-6673-8_15.
23. Kircher M, Lapa C. Infection and inflammation imaging: Beyond FDG. PET Clin 2020;15:215-29. https://doi.org/10.1016/j.cpet.2019.11.004.